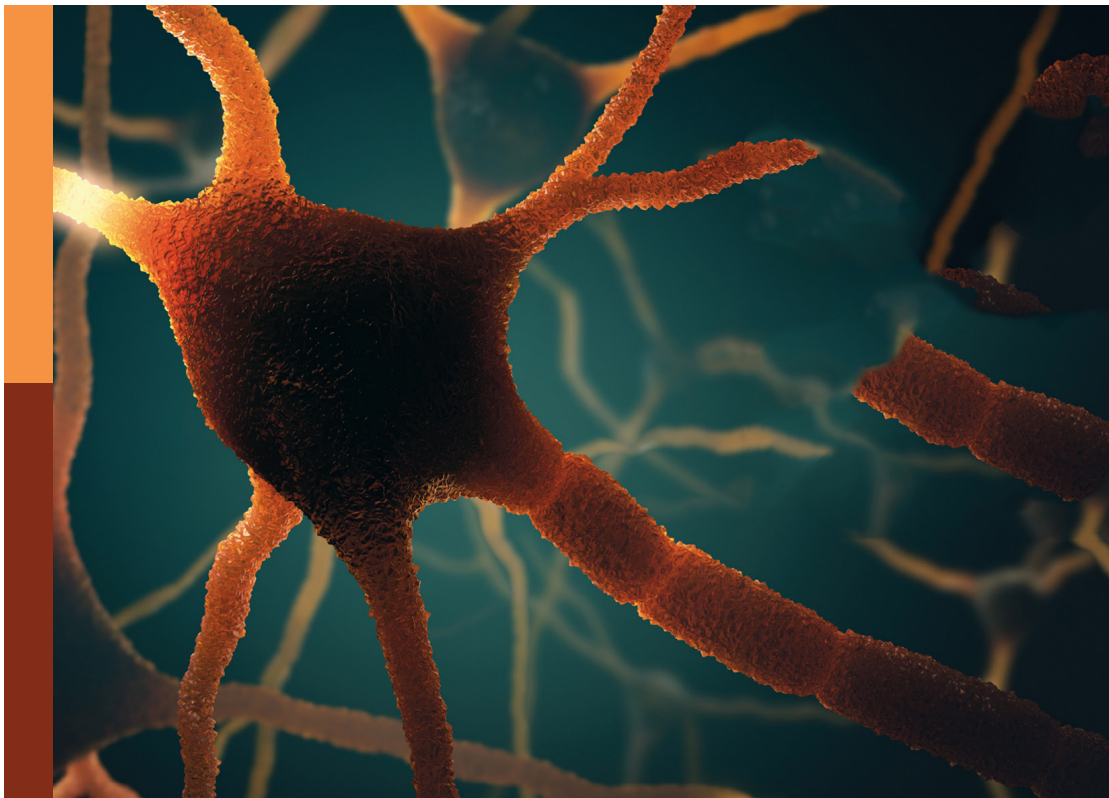
frontiers | Research Topics

The heart-brain connection in emotions, cognition, and dementia

Edited by
Knut Asbjorn Hestad, Ivana Hollan, Helene Girouard and Knut Engedal

Published in
Frontiers in Aging Neuroscience



ISSN 1664-8714
ISBN 978-2-83250-993-7
DOI 10.3389/978-2-83250-993-7

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

The heart-brain connection in emotions, cognition, and dementia

Topic editors

Knut Asbjorn Hestad — Hedmark University of Applied Sciences, Norway
Ivana Hollan — Norwegian University of Science and Technology, Norway
Helene Girouard — Montreal University, Canada
Knut Engedal — Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Norway

Citation

Hestad, K. A., Hollan, I., Girouard, H., Engedal, K., eds. (2022). *The heart-brain connection in emotions, cognition, and dementia*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-993-7

Table of contents

frontiers | Frontiers in Aging Neuroscience

TYPE Editorial
PUBLISHED 24 November 2022
DOI 10.3389/fnagi.2022.1074280

OPEN ACCESS

EDITED AND REVIEWED BY
Kristy A. Nielson,
Marquette University, United States

*CORRESPONDENCE
Knut A. Hestad
knut.hestad@inn.no

SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 19 October 2022
ACCEPTED 01 November 2022
PUBLISHED 24 November 2022

CITATION
Hestad KA, Engedal K, Hollan I and Girouard H (2022) Editorial: The heart-brain connection in emotions, cognition, and dementia. *Front. Aging Neurosci.* 14:1074280. doi: 10.3389/fnagi.2022.1074280

Editorial: The heart-brain connection in emotions, cognition, and dementia

Knut A. Hestad[1,2]*, Knut Engedal[3,4], Ivana Hollan[5] and Hélène Girouard[6,7,8,9]

[1]Department of Research, Innlandet Hospital Trust, Brumunddal, Norway, [2]Department of Health and Nursing Science, Faculty of Health and Social Sciences, Inland Norway University of Applied Sciences, Elverum, Norway, [3]Norwegian National Centre for Aging and Health, Vestfold Hospital Trust, Tønsberg, Norway, [4]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway, [5]Norwegian University of Science and Technology, Gjøvik, Norway, [6]Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [7]Groupe de Recherche Universitaire sur le Médicament (GRUM), Groupe de Recherche sur le Système Nerveux Central (GRSNC), Université de Montréal, Montréal, QC, Canada, [8]Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA), Université de Montréal, Montréal, QC, Canada, [9]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), Montréal, QC, Canada

KEYWORDS

heart, brain, connection, dementia, Alzheimer's

Editorial on the Research Topic
The heart-brain connection in emotions, cognition, and dementia

Introduction

The heart-brain axis to explain cognition, emotions, and the development of dementia remains largely unknown. Conversely, the influence of the brain on the heart, especially in old age also needs to be further explored.

Therefore, we initiated this Research Topic which includes six original and four review papers. They complemented each other, showing the influence the cardiovascular system has on the brain. Our goal was to provide insights into the possible psychological, social, and biological factors involved in the heart-brain interactions that can contribute to sickness and health. The manuscripts examined the pathophysiological impacts of high blood pressure, arterial stiffness, and the influence of heart function on brain and cognition. Two manuscripts also examined the involvement of the autonomic nervous system on the heart-brain connection. Studies presented in this Research Topic suggest that hypertension might not be directly responsible for Alzheimer's disease (AD), but that cerebrovascular damage reduces resistance to cognitive impairment and Alzheimer's disease.

Blood and pulse pressures as risk factors

It is well-known that blood pressure changes over time are related to age, and that high blood pressure in people aged 50–70 is a risk factor for dementia later in life. Hypertension is also the most important risk factor for stroke. Selbaek et al. have evaluated blood pressure in older people over a period of 35 years with four measurements [1984–86 (HUNT1 study), 1995–97 (HUNT2), 2006–08 (HUNT3), and 2017–19 (HUNT4)]. The aim of this study was to compare trajectories of systolic blood pressure (SBP) in people with and without a diagnosis of dementia at the time of the fourth SBP measurement. At the 4th time point, 9,720 participants in a community survey were assessed. Compared to those without dementia, the participants with dementia had higher systolic blood pressure (SBP) at the first and second measurement, but lower SBP at the last measurement. The differences at first and second measurement compared with the last measurement were especially pronounced among women. Regarding dementia subtypes, those with vascular dementia had a higher SBP than those with the Alzheimer's type of dementia at the second and third measurement. Age trajectories in SBP showed that the dementia group experienced a steady increase in SBP until about 65 years of age and a decrease from 70 to 90 years. SBP in the group without dementia increased until 80 years before it leveled off from 80 to 90 years. Thus, it might be "normal" to have a steady raise in SBP until the age 80 before it levels off. However, those who had the highest blood pressure earlier were more likely to have a dementia diagnosis 10 years later. The results point to the importance of treating high blood pressure early in life. Earlier studies have indicated that the brain may adjust to the raise in pressure, but if a subsequent fall in SBP is too big, it may accelerate brain damage. A sudden and big SBP drop itself may be harmful to the brain. However, the cause-effect relationship is still uncertain. Does a significant drop in blood pressure create the brain damage, or does the brain damage create the blood pressure drop? With an increase in vascular pathology in the brain, manifestations of Alzheimer's disease can increase. The brain of a person with longstanding hypertension may therefore be more vulnerable to and have less reserves to compensate for development of Alzheimer's disease pathologies. Hypertension does not cause Alzheimer's disease, but may reduce the brain reserves the individual needs to function as a healthy person. Alzheimer's disease develops over years and does not manifest before the brain capacity is reduced to a point where it cannot compensate for the underlying pathology anymore.

Badji, Pereira et al. compared brain structure, cognitive performances, and cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease and neurodegeneration, between normotensive and hypertensive (controlled, uncontrolled, and untreated) in a cohort of 70-year-old adults. The aim of this study was to examine whether controlling hypertension exerts beneficial effects on the brain. They found more white matter pathology (lower fractional anisotropy, more white matter hyperintensities, and enlarged perivascular space) in hypertensive individuals compared to their normotensive counterparts (highest in the uncontrolled participants). No significant difference was found in MRI or CSF markers of Alzheimer's disease pathology when normotensives were compared with hypertensive participants, nor among the hypertensive groups. This supports the fact that hypertension is not responsible for Alzheimer's disease, but, highly responsible for cerebrovascular damages leading to reduced brain reserves to withstand development of plaques and tangles that are responsible for dementia of the Alzheimer's type.

To understand the pathomechanisms by which vascular dysfunctions alter brain integrity, we need to know which parameters in the vascular system impact the brain's function. In a second contribution to this Research Topic, Badji, Cohen-Adad et al. studied the relationship between arterial stiffness index (ASI) measured with infrared light (photoplethysmography), pulse pressure (PP), and MRI markers of white matter integrity in 17,984 participants aged 63.09 $\pm$ 7.31 years from the UK Biobank. They concluded that brachial PP is a better predictor of white matter integrity than ASI. This was seen in those individuals younger than 75 years. No significant relationship was found between neither peripheral PP nor ASI and white matter integrity in the individuals older than 75 years of age. Comparing these findings with those reported by Selbaek et al., there seems to be an evidence for a shift at the age of about 75–80 regarding the relationship between vascular dysfunctions and cognition. One possible explanation is that a decline in blood pressure happens as a result of brain damage after the age of 75. This important decline in BP can further damage cerebrovascular integrity leading to dementia.

Pathological mechanisms of the heart impacts the brain

It is known that areas around the hippocampus usually are the first ones to be involved in the neuropathological processes in Alzheimer's disease. It is also known that the hippocampus is very sensible to oxygen deficiency due to circulation failure, as often seen in overdoses of heroin. Niu et al. examined neural connectivity by analyzing MRI degree centrality in the hippocampus of patients with coronary artery disease (CAD). They found, in the CAD patients, a reduced connectivity in the right hippocampus, the right lingual gyrus and the left middle frontal gyrus. These observations correlated with the cognition scores. Niu et al. concluded that reduced cerebral

neural connectivity may contribute to the cognitive impairment in CAD patients. The next manuscripts also examined the influence of heart pathology and cognitive deficits.

In a review, Myers et al. underline that atrial cardiopathy (a structural and functional disorder of the left atrium that may manifest as atrial fibrillation or heart failure) may contribute to cognitive impairment. This is an important Research Topic that has gained much interest in the literature and clinical practice especially because arterial cardiopathy can cause stroke.

Hagberg et al. summarized knowledge regarding consequences of out-of-hospital cardiac arrest (OHCA) on the brain. This is clearly in line with how oxygen deficiency to the brain may influence cognitive performance. After successful resuscitation, concerns regarding acquired brain injury and its sequels on cognitive functioning are relevant. Diffuse cortical and deep gray matter lesions are the most common findings with neuroimaging. Cognitive domains affected by OHCA are specifically executive functions, memory, and processing speed. Nevertheless, cognitive functions of OHCA survivors are not routinely assessed, and there is a lack of consensus that screening methods for cognitive changes should be applied. However, the authors emphasize that there is a need for an appropriate assessment as up to 50% of OHCA survivors develop cognitive decline.

The autonomic nervous system: A cornerstone in the heart-brain connection

The autonomic nervous system is involved in the heart-brain connection. The two next studies looked at different aspects of the results of the autonomic nervous systems influence of the heart. Dolphin et al. reviewed the research to date investigating the cognitive effects of a non-invasive transcutaneous (t-VNS) device, and its impact on neuro-cardiovascular stability. How do t-VNS devices offer equivalent therapeutic potential as invasive devices without the surgical risks? They conclude that t-VNS shows promise as a neuro-modulatory technique in cognitive decline, and this may be *via* its ability to regulate both cardiac autonomic functions and to enhance cerebral perfusion.

Nicolini et al. studied heart rate variability as a predictor of cognitive decline in subjects with normal cognition or Mild Cognitive Impairment (MCI). This was a longitudinal study with ∼3-year follow-up of a previous cross-sectional study. The participants were outpatients aged $\geq$ 65 when enrolled. They found that MCI patients had a greater response to a sympathetic challenge at baseline, related to steeper decline in episodic memory. A higher response to a parasympathetic challenge predicted a lesser decline in executive functioning. Thus, these intriguing results point to the impact of the autonomic nervous system on cognition.

Depression: The cardiovascular link

Hakim addressed interconnections between depression and dementia. It is common knowledge that depression is related to shorter life expectancy, and that older people who suffer from depression have a higher risk than others to develop dementia in the future. People with depression usually die from the same diseases as others, mainly of cardiovascular diseases. It is also known that several people with psychiatric illnesses, including depression have an unhealthy lifestyle including sedentary lifestyle and smoking. The conclusion of the review is that depression may activate pro-inflammatory mediators, which may lead to cerebral small vessels impairment, with a consequent reduction in cerebral blood flow, causing cognitive deficits. Inflammation is a Research Topic where a lot has been done related to depression and heart disease. There are also data indicating a role for inflammation in dementia.

Diabetes and sex-related brain vulnerability

Thomas et al. examined how diabetes is associated with brain structure and function in geriatric patients. They examined 893 patients (50% female) with MRI or CT scan and a thorough neuropsychological examination. They found that diabetes was associated with increased incidence of cerebral lacunes and brain atrophy in women compared to men. Thus, this study further supports differences in pathophysiological processes between men and women as seen in the study of Selbaek et al..

Taken together, the presented manuscripts bring further evidence for a close connection between the cardiovascular and the central nervous system and shed light on some of the potential mechanisms. Knowledge gained from these studies contributes to develop preventive approaches to protect two vital systems, including the reduction of their dysfunctional interactions.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 12 January 2022
doi: 10.3389/fnagi.2021.777475

Cerebrospinal Fluid Biomarkers, Brain Structural and Cognitive Performances Between Normotensive and Hypertensive Controlled, Uncontrolled and Untreated 70-Year-Old Adults

Atef Badji[1,2,3], Joana B. Pereira[3], Sara Shams[4,5,6], Johan Skoog[7], Anna Marseglia[3], Konstantinos Poulakis[3], Lina Rydén[7], Kaj Blennow[7,8], Henrik Zetterberg[7,8,9,10,11], Silke Kern[7], Anna Zettergren[7], Lars-Olof Wahlund[3], Hélène Girouard[12,13,14,15], Ingmar Skoog[7†] and Eric Westman[3†]*

[1] NeuroPoly Lab, Institute of Biomedical Engineering, Polytechnique Montréal, Montréal, QC, Canada, [2] Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [3] Division of Clinical Geriatrics, Centre for Alzheimer Research, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, Stockholm, Sweden, [4] Department of Radiology, Karolinska University Hospital, Stockholm, Sweden, [5] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [6] Department of Radiology, Stanford Medicine, Stanford, CA, United States, [7] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Centre for Ageing and Health (AgeCap) at the University of Gothenburg, Gothenburg, Sweden, [8] Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden, [9] Department of Neurodegenerative Disease, UCL Institute of Neurology, London, United Kingdom, [10] UK Dementia Research Institute at UCL, Mölndal, Sweden, [11] Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong SAR, China, [12] Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [13] Groupe de Recherche sur le Système Nerveux Central (GRSNC), Université de Montréal, Montréal, QC, Canada, [14] Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA), Université de Montréal, Montréal, QC, Canada, [15] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM), Montréal, QC, Canada

OPEN ACCESS

Edited by:
Eszter Farkas, University of Szeged, Hungary

Reviewed by:
Benjamin Cretin, Hôpitaux Universitaires de Strasbourg, France
Corinne Pettigrew, Johns Hopkins University, United States

***Correspondence:**
Atef Badji
atef.badji@ki.se

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *15 September 2021*
Accepted: *30 November 2021*
Published: *12 January 2022*

Citation:
Badji A, Pereira JB, Shams S, Skoog J, Marseglia A, Poulakis K, Rydén L, Blennow K, Zetterberg H, Kern S, Zettergren A, Wahlund L-O, Girouard H, Skoog I and Westman E (2022) Cerebrospinal Fluid Biomarkers, Brain Structural and Cognitive Performances Between Normotensive and Hypertensive Controlled, Uncontrolled and Untreated 70-Year-Old Adults. Front. Aging Neurosci. 13:777475. doi: 10.3389/fnagi.2021.777475

Background: Hypertension is an important risk factor for Alzheimer's disease (AD). The pathophysiological mechanisms underlying the relationship between AD and hypertension are not fully understood, but they most likely involve microvascular dysfunction and cerebrovascular pathology. Although previous studies have assessed the impact of hypertension on different markers of brain integrity, no study has yet provided a comprehensive comparison of cerebrospinal fluid (CSF) biomarkers and structural brain differences between normotensive and hypertensive groups in a single and large cohort of older adults in relationship to cognitive performances.

Objective: The aim of the present work was to investigate the differences in cognitive performances, CSF biomarkers and magnetic resonance imaging (MRI) of brain structure between normotensive, controlled hypertensive, uncontrolled hypertensive, and untreated hypertensive older adults from the Gothenburg H70 Birth Cohort Studies.

Methods: As an indicator of vascular brain pathology, we measured white matter hyperintensities (WMHs), lacunes, cerebral microbleeds, enlarged perivascular space (epvs), and fractional anisotropy (FA). To assess markers of AD pathology/neurodegeneration, we measured hippocampal volume, temporal

cortical thickness on MRI, and amyloid-β_{42}, phosphorylated tau, and neurofilament light protein (NfL) in cerebrospinal fluid. Various neuropsychological tests were used to assess performances in memory, attention/processing speed, executive function, verbal fluency, and visuospatial abilities.

Results: We found more white matter pathology in hypertensive compared to normotensive participants, with the highest vascular burden in uncontrolled participants (e.g., lower FA, more WMHs, and epvs). No significant difference was found in any MRI or CSF markers of AD pathology/neurodegeneration when comparing normotensive and hypertensive participants, nor among hypertensive groups. No significant difference was found in most cognitive functions between groups.

Conclusion: Our results suggest that good blood pressure control may help prevent cerebrovascular pathology. In addition, hypertension may contribute to cognitive decline through its effect on cerebrovascular pathology rather than AD-related pathology. These findings suggest that hypertension is associated with MRI markers of vascular pathology in the absence of a significant decline in cognitive functions.

Keywords: CSF (cerebrospinal fluid), hypertension, brain, MRI, white matter, aging

INTRODUCTION

Hypertension is considered to play an important role in cognitive deficits, being mediated by microvascular dysfunction and cerebrovascular pathology (Iadecola, 2014). Cerebral small vessel disease has a constellation of clinical and radiological manifestations among which white matter hyperintensities (WMHs), lacunes, cerebral microbleeds and enlarged perivascular spaces have been associated with hypertension (Veglio et al., 2009; Brown et al., 2018). Advances in neuroimaging techniques with diffusion tensor imaging (DTI) have further improved our knowledge about the effects of hypertension on brain microstructure (Maillard et al., 2014; de Groot et al., 2015; Badji et al., 2019). For instance, high blood pressure was found to be associated with reduced fractional anisotropy (FA) in numerous white matter tracts in adults aged 46–100 years (mean 63.8) (de Groot et al., 2015). Interestingly, DTI metrics can capture microstructural changes related to hypertension before the appearance of irreversible white matter damage. Indeed, these metrics can capture microstructural changes within WMHs that are not yet visible on standard T2 fluid attenuation inversion recovery (FLAIR) images (Maillard et al., 2014).

Several studies have supported the vascular hypothesis of Alzheimer's disease (VHAD) throughout the years. It is now more and more recognized that the critical steps that turn normal aging into a cognitively dysfunctional vortex starts with the acquisition of vascular risk factors such as hypertension (Baumgart et al., 2015; de la Torre, 2018). Vascular risk factors are responsible for the sustained cerebral hypoperfusion that follows (Baumgart et al., 2015; de la Torre, 2018). Mechanistically, once reached a critical threshold of cerebral hypoperfusion, hemodynamic deterioration will damage endothelial cells, thereby cerebral blood flow reactivity, vessel tone and vessel compliance as well as affecting the signaling pathways between astrocytes and neurons which in turns, ultimately lead to decline in brain metabolism and cognitive function (de la Torre, 2018).

Midlife hypertension is particularly associated with an increased risk of developing both Alzheimer's disease (AD) and vascular dementia. Neuropathological studies showed that individuals with high blood pressure often have large areas of white matter hyperintensity, ventricular enlargement and silent infarcts, which can lead to cognitive dysfunction. A large autopsy-based neuropathological study importantly revealed that 80% of patients diagnosed with AD and no evidence of mixed dementia has vascular pathology including cortical infarcts, lacunes, and cerebral microbleeds (Toledo et al., 2013), supporting the concept that cerebrovascular dysfunction is prominent in AD and lowers the threshold for dementia for a given AD pathology burden (de la Torre, 2018).

Moreover, hypertension increases pulsatile aortic stress which promotes elastin fragmentation (Mitchell, 2014). These structural arterial changes successively lead to functional changes in CBF that have been associated with the rate of accumulation of cerebral AB over time (Hughes et al., 2014; Avolio et al., 2018). This means that overall there is a significant overlap between hypertension, cerebrovascular lesions and cerebral AB pathologies.

Because hypertension is a modifiable risk factor, blood pressure control has become an important candidate for the prevention of cerebrovascular pathology and cognitive impairment (Gorelick et al., 2017). Although several studies have assessed the impact of hypertension on markers of cerebral small vessel disease, white matter integrity, AD pathology or cognitive function, none have yet compared these markers between normotensive vs. different hypertensive groups (controlled, uncontrolled, and untreated hypertensives) in a single cohort of older adults. The aim of the present

work is to study the clinical, MRI and CSF differences between normotensive, controlled hypertensive, uncontrolled hypertensive and untreated hypertensive older individuals aged 70 years old. In particular, we hypothesized that uncontrolled and untreated hypertensive participants have more vascular pathology, AD pathology and poorer cognitive performance than normotensive and hypertensive controlled participants.

MATERIALS AND METHODS

Study Participants

As part of the Gothenburg H70 Birth Cohort Studies, 1,203 participants (559 men and 644 women, mean age 70.5 years) born in 1944 and registered as residents in Gothenburg agreed to participate (Rydberg Sterner et al., 2019). This means that all patients were assessed at ∼70 years of age. A previously published paper by Rydberg Sterner et al. (2019) contains all procedures for the baseline examination of the Birth cohort 1944, conducted in 2014–2016, represented in several key flow charts. For the current study, participants were excluded if they had a dementia diagnosis or mini-mental state examination score < 24 ($n = 37$), other neurological diseases (e.g., Parkinson and multiple sclerosis) ($n = 15$), or missing data in MRI or neuropsychological tests ($n = 628$). This left 523 individuals for the present study. However, only a subset number of these participants ($n = 322$) underwent CSF sampling via lumbar puncture. After removing participants according to our exclusion criteria stated above and the ones with missing variables, a total of 280 participants were included in all CSF analysis.

A general health interview was performed by a research nurse or a medical doctor, and consisted of questions about medical history, including questions regarding hypertension, diabetes, stroke, cardiac and neurological diseases, and present treatment. The interviews also contained questions regarding educational level, alcohol consumption and smoking. Physical examinations were carried out by research nurses and included measurement of blood pressure, anthropometry (i.e., height and weight), and an ECG. Systolic and diastolic blood pressure (SBP and DBP, respectively) were recorded in the right arm in the sitting position after 5 min rest using a standard cuff (Umedico) (Rydberg Sterner et al., 2019). The 12-lead ECG was coded according to the Minnesota Code (MC) by a biomedical analyst working at the cardiac laboratory at Sahlgrenska University Hospital.

Ethical approval was obtained from the Regional Ethical Review Board in Gothenburg (Approval Numbers: 869-13, T076-14, T166-14, 976-13, 127-14, T936-15, 006-14, T703-14, 006-14, T201-17, T915-14, 959-15, T139-15), and by the Radiation Protection Committee (Approval Number: 13-64) in accordance with the 1964 Helsinki declaration and its later amendment. Study participants provided written informed consent prior to examinations.

Hypertension Classification

Participants were classified into four groups:

1) Normotensive (NT), $n = 181$.
   i) No history of hypertension and normal blood pressure with SBP <140 mmHg and DBP <90 mmHG at the examination ($n = 102$).
   ii) Previous history of hypertension but not taking antihypertensive medication and SBP <140 mmHg and DBP <90 mmHg at the examination ($n = 79$).
2) Hypertensive controlled (HTC), $n = 46$.
   History of hypertension, currently on anti-hypertensive treatment and SBP <140 mmHg and DBP <90 mmHg at the examination.
3) Hypertensive treated uncontrolled (HTU), $n = 63$.
   History of hypertension, currently on antihypertensive medication and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg at the examination.
4) Hypertensive untreated (HU), $n = 233$.
   i) History of hypertension, not taking antihypertensive medication and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg at the examination ($n = 90$).
   ii) No history of hypertension and either SBP ≥ 140 mmHg or DBP ≥ 90 mmHg at the examination ($n = 143$).

Blood Sampling

Blood samples were drawn by a research nurse after an overnight fast. Level of total serum cholesterol, LDL, HDL and blood glucose were analyzed at the laboratory of the Department of Clinical Chemistry at Sahlgrenska University Hospital in Gothenburg with the use of standard routine clinical laboratory procedures as fully described by Rydberg Sterner et al. (2019). DNA was extracted from individual samples of whole blood according to standard procedures at LGC Genomics in Berlin (Germany). All the DNA samples have been genotypes at the University College London (UK) using the Neuro Consortium Array (neurox2) from Illumina[1] as described in previous publications (Rydberg Sterner et al., 2019; Najar et al., 2021).

Neurocognitive Assessments

Cognitive examination was performed by a psychiatric research nurse, a psychiatrist, or a medical doctor under supervision of a neuropsychologist. Participants underwent a series of tests covering a broad range of cognitive domains including memory (memory-in-reality + free recall, Thurston's picture memory, ADAS-Cog word memory list, and delayed recall), attention and processing speed (figure identification, digit span forward, and supra-span test), executive function (digit span backward and SRBII – figure logic), verbal fluency (category fluency and letter fluency), and visuospatial abilities (Koh's Block test). A detailed description of all cognitive tests and their respective scoring can be found in **Table 1**.

Cerebrospinal Fluid Sampling

All CSF samples were collected through lumbar puncture by a consultant neurologist/psychiatrist at the Neuropsychiatric outpatient department at the Sahlgrenska University Hospital. 10 ml of CSF was collected in a polypropylene tube following centrifugation at 1800 RCF (Relative Centrifugal Force) at

[1] www.illumina.com

TABLE 1 | Description of neuropsychological tests.

	Description	Score
Memory		
Word List, free recall	The participants are asked to remember 12 objects shown five minutes previously	Total number of objects the participants remembered [0–10]
Thurstone's picture memory	Participants are shown 28 pictures and are then asked to recognize the correct picture among 3 others	Total number of pictures the participants recognized [0–28]
Memory-in-reality, delayed recall	Participants are shown objects and are prompted to recall the items in any order after 30 min	Total number of words the participants remembered [0–10]
Attention/processing speed		
Figure identification	The participants are shown similar one figure and five additional ones and should mark the identical figures among four others	Total number of images the participants correctly identified [0–60]
Digit span forward	Participants hear a sequence of numerical digits and are asked to recall the sequence correctly	Total number of "numbers" the participants were able to say [0–9]
Supra-span test	Participants hear a 10-words list related to clothing and are asked to recall as many words as possible	Total number of words the participants were able to remember [0–10]
Executive function		
Digit span backward	Participants hear a sequence of numerical digits and are asked to recall the sequence backward	Total number of "numbers" the participants were able to say [0–10]
Figure logic	Participants are shown five figures and need to say which one is different from the four others	Total number of images the participants correctly identified [0–30]
Verbal fluency		
Category fluency	Participants should name as many animals as possible within 1 min	Total number of animals the participants were able to say [0-]
Letter fluency	Participants should produce as many words as possible that begin with the letters F, A, and S within 1 min	Total number of object's name the participants were able to say [0-]
Visuospatial abilities		
Koh's block test	The participants are asked to assemble 4–16 blocks so that their upper surfaces replicate pattern as shown in seven subsequent figures	Total number of pattern the participant were able to reproduce [0–42]

20°C for 10 min and stored at −70°C pending experimental use. CSF phosphorylated tau at threonine 181 (P-TAU) was determined using a sandwich enzyme-linked immunosorbent assay (ELISA) [INNOTEST® htau Ag and PHOSPHO_TAU (P-TAU)], (Fujirebio, Ghent Belgium), as previously described (Blennow et al., 1995; Vanmechelen et al., 2000). CSF amyloid-β42 (Aβ42) was measured using a sandwich ELISA (INNOTEST® β-amyloid 1–42), specifically constructed to measure amyloid-β peptides starting at amino acid 1 and ending at amino acid 42 (Sjögren et al., 2000). CSF Neurofilament light protein (NFL) was determined using a sandwich ELISA (UmanDiagnostics, Umeå, Sweden). The limit of detection for NFL was 125 ng/L. Laboratory procedures were accredited by the Swedish Board for Accreditation and Conformity and performed by board-certified laboratory technicians blinded to clinical data.

Brain Magnetic Resonance Imaging Analysis

Magnetic Resonance Imaging Acquisition

All participants were scanned on a 3.0T Philips Achieva system (Philips Medical Systems) at the Aleris Clinic in Gothenburg. The imaging protocol included a 3D T1-weighted Turbo Field Echo (TFE) sequence to assess structural changes, a FLAIR sequence for detection of cerebral small vessel disease (e.g., white matter intensities and lacunes), a DTI sequence to assess white matter microstructural integrity, a venus bold sequence (VenoBOLD) for detection of microbleeds and a T2 weighted sequence for detection of enlarged perivascular spaces.

The T1w acquisition was done with sagittal slices of 1.0 mm isotropic resolution, Echo Time (TE) = 3.2 ms, Repetition Time (TR) = 7.2 ms and field of view (FOV) = 256 mm × 256 mm, flip angle = 9°, number of slices = 160. The FLAIR acquisition was done with sagittal slices of 2.0 mm isotropic resolution, TE = 280 ms, TR = 4,800 ms and FOV = 250 mm × 250 mm, flip angle = 90°, number of slices = 140. DTI data were acquired with axial slices of 3.0 mm isotropic resolution, encoded with 1 *b*-value shell: 800 k s/mm^2, along with 32 directions and 1 b = 0 image. Other acquisition parameters were: TE = 83 ms, TR = 7,340 ms and FOV = 224 mm × 224 mm, flip angle = 90°, 32 volumes. The venus bold acquisition was done with 300 slices of 1.0 mm isotropic resolution, TE = 20,59–24,99 ms, TR = 14,59–17,60 ms, and FOV = 220 mm × 220 mm and finally, the T2w acquisition was done with transversal slices of 4.0 mm isotropic resolution, TE = 80 ms, TR = 3,000 ms and FOV = 230 mm × 230 mm.

Magnetic Resonance Imaging Data Processing

Magnetic resonance imaging data management and processing were done with our database system, the HiveDB (Muehlboeck et al., 2014).

T1w Processing

T1-weighted images underwent pre-processing with the Freesurfer pipeline (version 6.0.0) which include several steps described in the following link[2] including correction of motion artifacts and spatial distortions, removal of non-brain tissue, alignment to the Talairach standard space, field intensity normalization, skull stripping, surface alignment, segmentation of subcortical white matter and deep gray matter structures, and cortical thickness estimation as the shortest distance between each vertex on gray matter/white matter surface and the gray matter/CSF (pial) surface (Fischl and Dale, 2000). The Freesurfer output underwent manual visual QC to ensure optimal estimation of thickness and volumes. For this study, the right and left hippocampal volumes were averaged and then adjusted for total intracranial volume. In addition, we calculated a meta temporal ROI as the mean cortical thickness of the entorhinal, inferior temporal, middle temporal and fusiform gyri (Jack et al., 2017).

Diffusion Tensor Imaging Processing

Diffusion-weighted images were analyzed using the FMRIB's Diffusion Toolbox from FSL (Behrens et al., 2007). First, the data was corrected for distortions caused by eddy currents and head motion using the b0 non-diffusion data as a reference volume (Andersson and Skare, 2002). The resulting images were skull-striped and a diffusion tensor model was fitted at each voxel to obtain FA maps for each subject (Beaulieu and Allen, 1994). The FA maps were then submitted to a Tract-Based Spatial Statistics (Smith et al., 2007) analysis, which aligned these maps to standard space using non-linear registrations and merged them into a single 4D file. The mean of all FA images was fed into a skeletonization procedure to obtain a mean FA skeleton, which was thresholded with a FA value of 0.2. This skeleton represents the centers of all white matter tracts common to the group. Finally, all FA images were projected onto the thresholded mean FA skeleton, assigning the maximum FA value of the FA images to the skeleton voxel, and obtaining an image that contains the projected skeletonized FA data. Then, the mean FA values for each participant was computed within the FA skeleton mask and used in our analyses. As such the FA measure in the white matter included in our study is the mean FA of all voxels included in the FA skeleton and can be considered as a measure of global FA. The mean FA in the cingulum was also obtained directly from the ICBM-DTI-81 atlas (Mori et al., 2008) containing the right and left ventral aspect of the cingulum, referred to as the parahippocampal cingulum bundle.

Fluid Attenuation Inversion Recovery, T2w, and Venus Bold Processing

All MRI images were analyzed according to the recently proposed Standards for Reporting Vascular Changes on Neuroimaging and standardized scales (Gregoire et al., 2009; Wardlaw et al., 2013) by a trained radiologist (S.S). WMHs were classified from 0 to 3 (none or single punctate; multiple punctate; early confluent; and large confluent), according to the Fazekas scale (Fazekas et al., 1991). Lacunes were defined as having CSF signal on FLAIR (hypointense), T2 (hypertensive), and T1 (hypotensive), and be 3–15 mm in size. Cerebral microbleeds were rated according to the microbleed anatomical rating scales (MARS) and were defined as round hypointense dots on the venoBOLD acquisition. Microbleeds were only rated as present or absent (Gregoire et al., 2009). Care was taken to avoid cerebral microbleeds mimics (e.g., mineralization in the globus pallidus, hemorrhage, partial volume artifact etc.). Enlarged perivascular spaces were rated on T2 sequences in the centrum semiovale and basal ganglia as follows: 0 = none, 1 = 1–10, 2 = 11–20, 3 = 21–40, and 4 =>40, according to the validated enlarged perivascular space rating scale (MacLullich et al., 2004; Doubal et al., 2010; Potter et al., 2015).

Statistical Analysis

To detect potential outliers, we visualized the histograms of all variables and computed their mean and median. Using the 1.5 interquartile rule, 26 outlier participants were excluded from all CSF analysis. To assess differences in demographics, clinical, MRI, neuropsychological and CSF variables between our four groups [(i) normotensive, (ii) hypertensive controlled, (iii) hypertensive uncontrolled, and (iv) hypertensive untreated], the Wilcoxon test was used for non-normally distributed variables. Chi-squared tests were used for binary variables.

Prior to analysis, the hippocampal volume where detrended for sex and intracranial volume, the neuropsychological variables were detrended for sex and education and the CSF variables were detrended for sex as done previously (Voevodskaya et al., 2014; Falahati et al., 2016). The detrending algorithm fits a generalized linear model (GLM) to each cognitive (CSF or MRI) variable in the control group (normotensive) to measure the effects of the covariates (education, sex, or intracranial volume) on the outcome in the absence of the group effect. This allows us to model the covariates-related changes as linear drift. Then, the regression coefficient of the resulting GLM model (linear drift) is used to remove the covariates-related changes from all participants and obtain corrected values. In order to do that, the detrended variable was first computed by summing the residual of the model with the mean of the prediction. Finally, a linear regression was performed on the detrended outcome over the group variable using the whole dataset. Age was not covaried for any of the variables since all subjects were assessed at around 70 years old. Before running the detrending algorithm, a preliminary GLM was performed to determine which covariates should be included. The sex was not found to predict hippocampal volume ($p = 0.439$) in our cohort and was therefore not included as covariate in the algorithm. In contrast, sex predicted 7 out of 12 specific tests for different cognitive functions and was therefore added to the detrending algorithm ($p < 0.05$). All statistical tests were implemented in R version 3.5.2. Correction for multiple comparisons was performed using the false discovery rate (FDR) procedure as described in Benjamini and Hochberg (1995) in SPSS (IBM SPSS 25 Statistics, Chicago, IL, United States). Since the p-threshold adjustment for significance under the Benjamini–Hochberg procedure not only depends on the number of tests but also on the calculated p-value for each test, original/uncorrected p-values

[2]http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferAnalysisPipelineOverview

were reported and only the significant ones after correction were highlighted in bold. The adjusted threshold under which a *p*-value is declared significant after the FDR correction is shown in caption legend. The FDR correction was based on the number of cognitive assessments within each cognitive domain, and the number of MRI metrics within each type of markers/sequences.

RESULTS

Table 2 shows the demographic and clinical characteristics of participants of the four groups (NC, HTC, HTU, and UT). As expected, SBP and DBP differed between the groups (**Table 2**). However, no significant differences were found in disease duration between the HTC and HTU groups. In general HTC, HTU, and HU had higher BMI and lower HDL cholesterol than NT. Interestingly HTC was found to have lower cholesterol than NT which could be explained by the fact that 43.5% of participants in HTC were on anti-cholesterol medication.

Normotensive Versus Hypertensive Participants

Magnetic Resonance Imaging Markers of Alzheimer's Disease, Neurodegeneration and Vascular Pathology

Hypertensive participants were found to have more white matter pathology than NT (**Table 3**). For instance, HTC had more lacunes (p = 4.45e-4) than NT. HTU had more lacunes than NT, but also lower FA (p = 3.08e-4). HTU had more WMHs and epvsCS than NT (p = 1.29e-4 and p = 0.026, respectively), however, the latter was not significant after FDR corrections. In contrast, no differences were found between NT and HU regarding any MRI markers. HTU had more lacunes (p = 3.03e-4), more WMHs (p = 0.022) than HU. HTU was also found to have lower FA (p = 0.02) and more microbleeds (p = 0.037) than HU, although these results were not significant after FDR.

No significant differences were found in MRI markers of AD/neurodegeneration pathology between normotensives and the hypertensive groups.

Cerebrospinal Fluid Markers of Alzheimer's Disease Pathology and Neurodegeneration

Hypertensives groups had comparable levels of P-TAU, NFL, and Aβ42, compared to NT (**Table 4**), and their were no differences in any CSF variables between the hypertensive groups.

Cognition

The cognitive performance between NT and hypertensive participants was in general comparable (**Table 5**). However, HTC performed significantly worse than HU in MMSE (**Table 5**, p = 0.008). Interestingly, HTC was also found to perform worse than HU in the Supra-span test (**Table 5**, p = 0.012) and Koh's Block test (**Table 5**, p = 0.011), which assess attention/processing speed and visuospatial performance, respectively. However, the former results were not significant after FDR correction. In addition, HTU participants had lower performance than HU in delay recall memory test (p = 0.047), although this result was not significant after FDR correction.

DISCUSSION

We examined the clinical, neurochemical and radiological differences between normotensives and those with controlled, uncontrolled or untreated hypertension, using MRI markers of vascular pathology (WMHs, lacunes, microbleeds, enlarged perivascular space, and FA), MRI and CSF markers of AD pathology/neurodegeneration, as well as cognitive tests in a cognitively healthy population-based sample of 70-year-olds.

Firstly, we observed a higher vascular burden in uncontrolled hypertensive participants compared to the other groups. Secondly, participants with treated but uncontrolled hypertension had more vascular pathology than those with untreated hypertension. This suggests that treatment of hypertension may not be enough to prevent further cerebrovascular pathology, good control of blood pressure may also be necessary. Thirdly, CSF and MRI markers of AD pathology/neurodegeneration did not differ between normotensive and hypertensive participants, nor between hypertensive subgroups, suggesting that hypertension may be associated with cognitive changes in late life through cerebrovascular pathology rather than AD related pathology. Finally, in this sample of dementia-free participants, cognitive function did not differ between normotensive and hypertensive participants, nor between the hypertensive groups, suggesting that MRI markers of vascular pathology can capture cerebrovascular changes that have not yet translated into cognitive symptoms.

Pathogenesis of Hypertensive Brain Damage

The negative effects of hypertension on cognitive function are best understood in terms of the brain's need for a certain constant perfusion threshold for optimal function. Indeed, the brain is a highly vascularized organ, making continuous regulation of blood flow critical to meet its high metabolic demand (Cipolla, 2009). A high blood pressure can alter the structure and molecular composition of cerebral blood vessels, which ultimately compromises oxygen and glucose delivery for proper neural function as well as removal of metabolic waste and toxin protein such as amyloid-β plaques and P-TAU (Iadecola, 2010; Pires et al., 2013). These alterations render the brain more vulnerable to ischemic injury, small vessel disease, and the development of neurodegenerative pathologies, such as AD (Faraco and Iadecola, 2013; Sörös et al., 2013).

Cerebrovascular Pathology

Normotensive vs. Hypertensive Treated Controlled

Cerebral WMHs are more common and extensive in patients with cardiovascular risk factors such as hypertension, diabetes mellitus and heart disease (Pantoni and Garcia, 1995; Skoog, 1998; Debette and Markus, 2010; Habes et al., 2018). WMHs have

TABLE 2 | Demographic and clinical characteristics.

Characteristic	Normotensive NT (*n* = 181)	Hypertensive treated (*n* = 115) Controlled HTC uncontrolled HTU (*n* = 46) (*n* = 63)		Hypertensive untreated HU (*n* = 233)	*P*-value
Female	94 [51.93%]	18 [39.13%]	26 [41.26%]	126 [54.07%]	/
Age (y)	70.54 ± 0.27	70.54 ± 0.231	70.51 ± 0.266	70.53 ± 0.245	/
Education (elementary school)	170 [93.92%]	41 [89.13%]	52 [82.53%]	209 [89.69%]	NT vs. HTU (p = 0.01383)
SBP (mmHg)	124.34 ± 8.63	125.56 ± 8.13	152.03 ± 14.52	152.34 ± 14.68	**NT vs. HTU (p = 2.2e-16). NT vs. HU (p = 2.2e-16). HTC vs. HTU (p = 2.2e-16). HTC vs. HU (p = 2.2e-16).**
DBP (mmHg)	74.01 ± 6.99	74.54 ± 5.91	84.28 ± 10.52	83.467 ± 8.019	**NT vs. HTU (p = 7.34e-16). NT vs. HU (p = 2.2e-16). HTC vs. HTU (p = 3.82e-16). HTC vs. HU (p = 2.31e-16),**
Hypertension DD (y)	0	13.85 ± 10.57	11.66 ± 10.37	NA	/
APOE-ε4 status					**/**
One allele	55 [30.38%]	16 [34.78%]	13 [20.63%]	71 [30.47%]	**/**
Two alleles	2 [1.10%]	2 [4.34%]	6 [9.52%]	6 [2.57%]	**NT vs. HTU (p = 4.36e-4).** HTU vs. HU (p = 0.023)
Vascular risk factors					
Diabetes	18 [9.94%]	6 [13.04%]	14 [22.22%]	27 [11.58%]	NT vs. HTU (p = 0.023). HTU vs. HU (p = 0.050).
Current smoking	18 [9.94%]	5 [10.86%]	2 [3.17%]	12 [5.15%]	/
Alcohol risk consumption (grams per week)	93.41 ± 92.31	104.39 ± 100.48	72.85 ± 69.71	87.82 ± 96.16	/
BMI (km/m^2)	24.84 ± 3.87	26.74 ± 3.26	28.17 ± 4.75	26.01 ± 4.20	**NT vs. HTC (p = 3.92e-5). NT vs. HTU (p = 4.42e-07). NT vs. HU (p = 2.94e-4). HTU vs. HU (p = 1.02e-4).**
Medical conditions					
Ischemic heart diseases	19 [10.49%]	7 [15.21%]	9 [14.28%]	14 [6.00%]	/
Heart failure	2 [1.10%]	2 [4.34%]	2 [3.17%]	2 [0.85%]	/
Atrial fibrillation	14 [7.73%]	7 [15.21%]	3 [4.76%]	13 [5.57%]	HTU vs. HU (p = 0.030)
Stroke					
Lipid profile					
Tot cholesterol, mmol/L	5.57 ± 1.18	4.99 ± 1.25	5.23 ± 1.05	5.68 ± 1.20	**NT vs. HTC (p = 3.70e-4).** NT vs. HTU (p = 0.035). **HTC vs. HTU (p = 7.50e-5). HTU vs. HU (p = 6.840e-4).**
LDL cholesterol, mmol/L	3.53 ± 1.06	3.16 ± 1.05	3.27 ± 0.92	3.63 ± 1.04	NT vs. HTC (p = 0.039). **HTC vs. HU (p = 8.39e-4). HTU vs. HU (p = 0.015).**
HDL cholesterol, mmol/L	1.74 ± 0.55	1.50 ± 0.43	1.51 ± 0.40	1.76 ± 0.52	**NT vs. HTC (p = 6.89e-4). NT vs. HTU (p = 3.38e-4). HTC vs. HTU (p = 1.80e-4). HTU vs. HU (p = 3.01e-5).**
Anti-cholesterol medication, number, and (%)	33 (18.2%)	20 (43.5%)	34 (53.96%)	39 (16.7%)	**NT vs. HTC (p = 6.28e-4). NT vs. HTU (p = 1.097e-7). HTC vs. HU (p = 1.129e-4). HTU vs. HU (p = 3.265e-09).**

Data are presented as means ± standard deviations or number [proportion%]. y, years; SBP, systolic blood pressure; DBP, diastolic blood pressure; DD, disease duration; APOE-ε4, apolipoprotein ε4 allele; Tot, total; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Ischemic heart diseases are defined by either myocardial infarction or angina pectoris. Information about diabetes was ascertained based on self-report medical history, use of hypoglycemic medications (diet, oral hypoglycemic agents, or insulin), or fasting blood glucose ≥ 7.0 mmol/L or non-fasting blood glucose (noFBG) ≥ 11 mmol/L as suggested by the American Diabetes Association's (American Diabetes Association, 2019). Only results with uncorrected $p < 0.05$ are shown. Significant results after FDR are in bold. Adjusted threshold with FDR are $p = 0.008$ for education, APOE-ε4, diabetes and atrial fibrillation, $p = 0.033$ for SBP, DBP, BMI, and HDL cholesterol, $p = 0.016$ for LDL cholesterol and $p = 0.025$ for total cholesterol.

TABLE 3 | Differences in MRI variables among normotensive and hypertensive participants (treated controlled, uncontrolled, or untreated).

	Normotensive NT (*n* = 181)	**Hypertensive treated (*n* = 115) Controlled HTC (*n* = 46) uncontrolled HTU (*n* = 63)**		**Hypertensive untreated HU (*n* = 233)**	***P*-value**
Gray matter					
Temporal thickness	2.91 ± 0.14	2.89 ± 0.13	2.92 ± 0.14	2.92 ± 0.12	/
Hippocampal volume	3951.373 ± 384.478	3792.429 ± 431.198	3926.912 ± 454.671	3898.523 ± 417.834	NT vs. HTC (p = 0.0308). HTC vs. HU (p = 0.0405).
Microstructure					
FA cingulum	0.23 ± 0.05	0.22 ± 0.02	0.23 ± 0.02	0.23 ± 0.05	/
FA white matter	0.40 ± 0.06	0.39 ± 0.06	0.39 ± 0.05	0.40 ± 0.05	**NT vs. HTU (p = 3.08e-4).** HTU vs. HU (p = 0.020).
cSVD markers					
Microbleed	0.24 ± 1.04 [0–12]	0.24 ± 0.97 [0–6]	0.81 ± 3.04 [0–22]	0.18 ± 0.83 [0–8]	HTU vs. HU (p = 0.037)
WMHs	0.99 ± 0.57 [0–3]	1.06 ± 0.71 [0–3]	1.30 ± 0.73 [0–3]	1.08 ± 0.63 [0–3]	**NT vs. HTU (p = 1.29e-4).** HTU vs. HU (p = 0.022).
epvsCS	1.95 ± 0.74 [1–4]	NA	2.21 ± 0.81 [1–4]	1.97 ± 0.82 [0–4]	NT vs. HTU (p = 0.026).
epvsBG	1.24 ± 0.52 [1–3]	NA	1.35 ± 0.63 [1–4]	1.25 ± 0.56 [0–3]	**/**
Lacunes	0.05 ± 0.28 [0–3]	0.17 ± 0.44 [0–2]	0.25 ± 0.59 [0–2]	0.073 ± 0.32 [0–3]	**NT vs. HTC (p = 4.45e-4).** **NT vs. HTU (p = 3.35e-5).** HTC vs. HU (p = 0.03). **HTU vs. HU (p = 3.02e-4).**

Data are presented as means ± standard deviations [range] is added for non-continuous variables. FA, fractional anisotropy; cSVD, cerebral small vessel disease; WMHs, white matter hyperintensities; epvs, enlarged perivascular space; CS, centrum semiovale; BG, basal ganglia. Only results with uncorrected $p < 0.05$ are shown. Significant results after FDR are in bold. Adjusted threshold with FDR are $p = 0.008$ for white matter microstructure and cerebral microbleeds and $p = 0.011$ for all cSVD markers.

TABLE 4 | Differences in CSF variables among normotensive and hypertensive participants (treated controlled, uncontrolled, or untreated).

	Normotensive NT (*n* = 81)	**Hypertensive treated (*n* = 60) Controlled HTC (*n* = 22) uncontrolled HTU (*n* = 38)**		**Hypertensive untreated HU (*n* = 113)**	***P*-value**
P-tau	44.41 ± 12.02	48.95 ± 15.24	44.37 ± 12.07	47.80 ± 12.48	/
NFL	723.69 ± 270.94	702.38 ± 224.34	724.70 ± 271.42	728.20 ± 219.70	/
AB42	717.87 ± 280.68	721.84 ± 229.71	731.19 ± 281.78	726.39 ± 226.15	/

Data are presented as means ± standard. P-TAU, phosphorylated TAU; NFL, neurofibril, AB42. Only results with uncorrected $p < 0.05$ are shown. Significant results after FDR are in bold.

been characterized by different pathologies, including axonal and myelin loss, astrogliosis, reduction of oligodendrocytes, microglial activation and white matter infarction (Braffman et al., 1988; Fazekas et al., 1993). This explains why the different mechanisms contributing to the heterogeneous pathology within WMHs have not been completely elucidated yet (Joutel and Chabriat, 2017). Cerebral hypoxia due to stenosis or occlusion of vessels caused by hypertension is considered as the major contributor of WMHs (Iadecola, 2013; Badji et al., 2019). However, we found no differences in WMHs load between normotensives and treated controlled hypertensives. This suggests that at least some of the WMHs may reflect benign, age-associated changes, such as partial loss of the ependymal lining (Mito et al., 2019).

Elevated blood pressure is associated with microatheromatosis and atherosclerosis, giving rise to thickening of the vessel wall or, in severe cases, to vessel wall necrosis, which may lead to rupture (Alistair, 2002; Martí-Vilalta et al., 2011). These morphological alterations facilitate the appearance of lacunes, which were more common in participants with controlled hypertension compared to the normotensives as also found by others (Dozono et al., 1991; Kombate et al., 2012).

Normotensive vs. Hypertensive Treated Uncontrolled

Previous studies reported that hypertension is associated with reduced microstructural integrity in most white matter tracts, as assessed by DTI metrics in both younger and older adults (Maillard et al., 2012; Rosano et al., 2015). We found that uncontrolled hypertensive participants had more lacunes than normotensives, but also a lower FA, suggesting that uncontrolled blood pressure leads to further microstructural damage. A recent study assessed the microstructural integrity of 9 white matter tracts in a cohort of middle-aged adults with hypertension (age range 56,7–65.6 years) (McEvoy et al., 2015). In contrast to our findings, this study reported that white matter alterations were more often observed in both controlled and uncontrolled

TABLE 5 | Differences in cognitive performances among normotensive and hypertensive participants (treated controlled, uncontrolled, or untreated).

	Normotensive NT (n = 181)	Hypertensive treated (n = 115) Controlled HTC (n = 46)	Hypertensive treated (n = 115) uncontrolled HTU (n = 63)	Hypertensive untreated HU (n = 233)	*P*-value
General cognition					
MMSE score	29.16 ± 1.14	28.62 ± 1.31	29.16 ± 1.17	29.14 ± 1.06	**NT vs. HTC (p = 0.001). HTC vs. HTU (p = 0.013). HTC vs. HU (p = 0.008).**
Memory					
Word list and free recall	8.44 ± 1.51	8.30 ± 2.00	8.51 ± 1.62	8.70 ± 1.39	/
Thurstone's picture memory	21.60 ± 4.34	21.92 ± 4.73	22.57 ± 3.79	22.59 ± 3.27	/
Memory-in-reality and delay recall	7.41 ± 1.77	7.54 ± 1.71	7.20 ± 1.81	7.61 ± 1.89	HTU vs. HU (p = 0.047)
Attention/processing speed					
Figure identification	28.82 ± 8.06	27.15 ± 7.21	26.84 ± 7.94	28.07 ± 7.60	/
Digit span forward	6.05 ± 1.13	5.92 ± 1.16	5.75 ± 1.09	5.98 ± 1.15	**/**
Supra-span test	7.54 ± 1.48	7.28 ± 1.21	7.52 ± 1.44	7.69 ± 1.36	HTC vs. HU (p = 0.012)
Executive function					
Digit span backward	4.43 ± 1.13	4.19 ± 0.87	4.38 ± 1.23	4.40 ± 1.22	/
Figure logic	20.23 ± 4.16	19.54 ± 4.23	19.87 ± 4.50	20.07 ± 3.98	**/**
Verbal fluency					
Category fluency	24.45 ± 6.01	24.20 ± 6.13	24.65 ± 7.55	23.93 ± 5.55	/
Letter fluency	40.99 ± 13.32	40.65 ± 14.93	38.23 ± 12.95	40.27 ± 11.99	/
Visuospatial abilities					
Koh's block test	7.45 ± 2.17	7.04 ± 1.85	7.59 ± 2.34	7.80 ± 2.18	HTC vs. HU (p = 0.011)

Data are presented as means ± standard deviations. Only results with uncorrected $p < 0.05$ are shown. Significant results after FDR are in bold. Adjusted threshold with FDR is $p = 0.025$ for general cognition, $p = 0.002$ for memory and attention/processing speed, and $p = 0.008$ for visuospatial abilities.

hypertensives compared to normotensives. However, this study only examined men, who may be more vulnerable to the effect of hypertension (Reckelhoff, 2001). The Third National Health and Nutrition Examination survey (NHANES III) reported that despite an increased prevalence of hypertension in middle-aged men compared to woman, men seems to receive less treatment for hypertension compared to woman (Burt et al., 1995; August, 1999). Thus, only 19% of men had their blood pressure controlled compared to 28% of women (McEvoy et al., 2015).

We even found that uncontrolled hypertensive participants had more WMHs and more enlarged perivascular spaces than properly controlled treated hypertensive participants. However, this result was not significant after corrections for multiple comparisons. Similar findings have been found in the literature. For instance, Kuller et al. (2010) found that woman above age 65 years, who were treated for hypertension, but had uncontrolled blood pressure, had the greatest amount of total WMHs volume and number of regions containing WMHs than women with controlled hypertension (with or without treatment). This suggests that uncontrolled blood pressure may trigger mechanisms responsible for the appearance of WMHs. For instance, increased blood brain barrier permeability in hypertension may lead to water shift and vasogenic edema (Farrall and Wardlaw, 2009; Maclullich et al., 2009). Fluid stagnation may further lead to enlargement and distortion of perivascular spaces (Brown et al., 2018), in line with our results. Future studies using more advanced diffusion models, such as the single-shell 3-Tissue CSD (SS3T-CSD) methodology, available in MRtrix3Tissue[3], a fork of the MRtrix3 software framework), proposed by Dhollander and Connelly (2016) and Dhollander et al. (2017) may help us better understand the impact of hypertension on the micro-structural properties of normal-appearing WM as well as other tissues and fluids (free water). Our result further suggests that treatment of hypertension may not be enough to slow down WMHs progression and additional cerebrovascular pathology. Blood pressure may need to be efficiently controlled as well, for adequate cerebrovascular protection. Future studies may combine measures of blood pressure variability of 24 h and the SS3T-CSD methodology to better understand the impact of uncontrolled hypertension on white matter integrity.

[3]https://3Tissue.github.io

Hypertensive Treated Uncontrolled vs. Hypertensive Untreated

Our finding of an overall better white matter integrity in untreated hypertensives compared with those treated but uncontrolled may seem contradictory. One explanation could be that misclassification occurred in the untreated group. Some of these participants did not receive a diagnosis of hypertension by a physician and were classified as "untreated hypertensive" based on a single measurement of office blood pressure. In some participants, blood pressure could have been elevated due to a white coat effect. Another possibility is that hypertension disease duration may be shorter in the untreated group. Consequently, the untreated hypertensive participants enrolled in this study may not exhibit the accompanying white matter changes because they are either not truly hypertensive or do not have significant white matter damage yet due to a shorter disease duration.

Nevertheless, such discrepancy is also found in other studies. For instance, Gons et al. (2012) reported a higher structural integrity of the corpus callosum in untreated hypertensive participants compared with treated controlled and uncontrolled individuals, which is in line with our findings. These results emphasize that both treatment and optimal control of blood pressure may be critical for efficient cerebrovascular protection.

Magnetic Resonance Imaging and Cerebrospinal Fluid Biomarkers Reflecting Alzheimer's Disease Pathophysiology and Neurodegeneration

Few studies have examined the association between hypertension and MRI manifestations of AD in non-clinical populations (Skoog and Gustafson, 2006). For instance, Lane et al. (2019) showed that increased SBP in middle age (age 36–43) was associated with smaller hippocampal volumes at age 69–71 years. In addition, in the Honolulu-Asia Study and the Rotterdam study, participants with untreated hypertension had an increased risk for hippocampal atrophy (Korf et al., 2004; den Heijer et al., 2005). However, we found no significant differences in hippocampal volumes between normotensive and hypertensive individuals (controlled, uncontrolled with medication or untreated). A recent study also showed no significant hippocampal atrophy in treated but uncontrolled hypertensive older adults compared to normotensive individuals (Wiseman et al., 2004), which is in agreement with our findings. Differences in MRI protocol, means of hippocampal delineation (manual vs. automatic) and hypertensive group characterization may explain these discrepancies. Another potential explanation is that hippocampal atrophy could be a later sign of cognitive decline. In contrast, white matter pathology may represent the underlying factor associated with cognitive decline when hypertension occurs. This hypothesis is strengthened by results of longitudinal studies showing that although long-term exposure to high blood pressure predicts the appearance of markers of cerebral small vessel disease, it does not predict hippocampal atrophy (Allan et al., 2015).

In addition, we did not find a relationship between hypertension and the pathological CSF hallmarks of AD. A few evidence exists to support that hypertension is associated to amyloid plaques and neurofibrillary tangles in the brain (Roberts et al., 2008; Gottesman et al., 2010; Shah et al., 2012; Lane et al., 2019), however, no consensus has yet been reached.

Cognition

Hypertension has been associated with mild cognitive deficits in many studies (Longstreth et al., 1996; Harrington et al., 2000). However, most studies assessed cognitive performance in older adults by comparing normotensive individuals to untreated hypertensive individuals (Asmar et al., 1995; Harrington et al., 2000; Wysocki et al., 2012; Desjardins-Crépeau and Bherer, 2016). Although several reports suggest that the use of antihypertensive drugs may reduce the incidence of cognitive decline and AD (Skoog et al., 1996; Guo et al., 1999; Hajjar et al., 2005; Khachaturian et al., 2006), the positive impact of antihypertensive medications on the risk of cognitive decline and dementia has not yet reached a consensus. It is thus important to compare the cognitive performance of normotensive and different hypertensive groups (controlled, uncontrolled, and untreated) in older adults. Our study suggests that, in general, the cognitive performance of normotensive and hypertensive groups were similar in 70-year-olds which suggest that MRI markers of cerebral small vessel disease are able to identify white matter changes that do not yet translate into a decline in cognition. A recent study compared cognitive performance in controlled hypertensive and normotensive individuals aged 60–75 years, who were free from dementia (Noriega de la Colina et al., 2019). In that study, controlled hypertensives participants had a lower performance in immediate and delayed recall and total number of words in the Rey Auditory Verbal Learning test compared to normotensives. This is consistent with similar other findings in the literature (Swan et al., 1998; Fitri and Rambe, 2018). After dividing the hypertensive groups into controlled and uncontrolled hypertensive patients in individuals who received antihypertensive medication for at least 6 months, Spinelli et al. (2014) found that uncontrolled individuals performed worse in tests evaluating attention and executive function. One should consider the fact that such an effect may be due to the antihypertensive drugs themselves which can affect mood or attention, in particular when combined, or withdrawn abruptly, resulting in orthostatic hypotension and decline in cognitive function (Johansen et al., 2012; Moonen et al., 2016). However, results from the SPRINT-MIND study showed that intensive SBP control to reduce SBP to 120 mmHg in comparison to standard antihypertensive protocol aiming to control the SBP to 140 mmHg significantly reduced the rate of mild cognitive impairment by 19% (Sprint Mind Investigators for the Sprint Research Group et al., 2019). This means that not only treatment, but treatment protocol has an impact on cognitive function. Further studies are needed to demystify not only the relative contribution of treatment and treatment regimen but also should include other factors such as age and duration of hypertension.

Strengths and Limitations

To our knowledge, this is the first large study investigating clinical, CSF, MRI, and cognitive differences between

normotensive and controlled, uncontrolled and untreated hypertensive individuals in a population-based sample of 70-year-olds. A strength of our study is the use of several MRI markers (WMHs, lacunes, microbleeds, enlarged perivascular space, FA, hippocampal volume, and temporal thickness), which captures a broad range of AD-related cerebrovascular pathology. In addition, we used various neuropsychological tests (**Table 1**) sensitive to different cognitive functions (memory, attention/processing speed, executive function, verbal fluency, and visuospatial abilities). As mentioned above, a strength of this study is the inclusion of CSF measures, though relatedly, a limitation is that the sample size for the CSF analyses was much smaller.

An important limitation of this study is the use of static rather than 24-h ambulatory blood pressure measurements, which are more closely related to end-organ damage. Another limitation is the use of a single blood pressure measurement, which is less reliable than multiple measurements. Thus, the hypertensive untreated group contains 90 true untreated hypertensive participant (with a previous history of hypertension, but not taking antihypertensive drugs and with SBP $\geq$140 mmHg or DBP $\geq$90 mmHg), and 143 potential previously unknown hypertensive participants (no history of hypertension and either SBP $\geq$140 mmHg or DBP $\geq$90 mmHg). The reason to merge the two groups is that a single blood pressure is not a reliable estimate of hypertension disease therefore this sub-group cannot be considered as a reliable hypertensive unknown group. Moreover, as mentioned in the discussion, misclassification could have occurred in this group. A third limitation is the cross-sectional design, which limits conclusions regarding directions of associations. Comparing subgroups based on hippocampal atrophy, pathological results in cognition or CSF changes suggestive of AD would have been interesting, however, due the limited sample size in certain groups (i.e., 46 participants in HTC) and its associated statistical caveat, we refrained from doing such comparison. Nevertheless, we provided a **Supplementary Table 1** presenting qualitative information on such comparisons. However, a follow-up study using a much larger sample size, will focus on the cerebrovascular differences between HTC and HTU using the SS3T-CSD methodology mentioned in the manuscript and will also include the comparisons mentioned above. Finally, differences in APOE4 have not been discussed considering the difficulty to draw any accurate conclusion from our results.

CONCLUSION

This study is the first to provide a comprehensive investigation of the clinical, MRI and CSF differences between normotensive, controlled hypertensive, uncontrolled hypertensive and untreated hypertensive older individuals aged 70 years old. Using several different markers of cerebrovascular pathology, this work provides evidence that hypertensive participants controlled with medication have more subcortical infarcts, such as lacunes, than normotensives. Uncontrolled blood pressure despite medication seems to trigger additional mechanisms that translate into changes in the white matter microstructure, fluid stagnation and enlargement of perivascular spaces. These results stress that not only treatment, but good control of blood pressure is essential for efficient cerebrovascular protection. Considering the strong interplay between hypertension and decline in cerebrovascular integrity, the present work further emphasizes the need for novel interventions aiming to preserve the white matter and cerebrovascular integrity. Finally, our results show no differences in any MRI or CSF markers of AD and neurodegeneration between the normotensive and hypertensive groups. This suggests that the general hypertensive population, including the one that is uncontrolled despite medication, does not translate into differences in AD-related neuropathology in 70-year-olds.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethical Review Board in Gothenburg (Approval Numbers: 869-13, T076-14, T166-14, 976-13, 127-14, T936-15, 006-14, T703-14, 006-14, T201-17, T915-14, 959-15, and T139-15) and by the Radiation Protection Committee (Approval Number: 13-64) in accordance with the 1964 Helsinki declaration and its later amendment. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB: design of the study, analysis, statistics, writing, and revision of the article. JP, L-OW, and EW: design of the study, analysis, and revision of the article. SS and AM: analysis and revision of the article. JS and LR: collecting data, analysis, and revision of the article. KP: statistics and revision of the article. KB, HZ, SK, and AZ: collection of data and revision of the article. IS: design of the study and revision of the article. All authors contributed to the article and approved the submitted version.

FUNDING

AB was supported by a Doctoral TransMedTech excellence scholarship, a Mitacs Globalink Research Award and a Training Course Abroad scholarship from the Québec Bio-Imaging Network. HZ was a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), United States (#201809-2016862), the European Union's Horizon 2020 Research and Innovation Program under the Marie Skłodowska-Curie grant agreement

No 860197 (MIRIADE), and the UK Dementia Research Institute at UCL. KB was supported by the Swedish Research Council (#2017-00915), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), and the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986). This study was financed by grants from the Swedish state under the agreement between the Swedish Government and the county councils, the ALF-agreement (ALF 716681), the Swedish Research Council (2012-5041, 2015-02830, 2019-01096, 2013-8717, and 2017-00639), Swedish Research Council for Health, Working Life and Welfare (2013-1202, 2018-00471, AGECAP 2013-2300, and 2013-2496), Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, Hjärnfonden (FO2014-0207, FO2016-0214, FO2018-0214, FO2019-0163, and FO2020-0235), Alzheimerfonden (AF-554461, AF-647651, AF-743701, AF-844671, AF-930868, and AF-940139), Eivind och Elsa K:son Sylvans stiftelse.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.777475/full#supplementary-material

REFERENCES

Alistair, D. G. (2002). Hypertensive cerebral small vessel disease and stroke. *Brain Pathol.* 12, 358–370. doi: 10.1111/j.1750-3639.2002.tb00450.x

Allan, C. L., Zsoldos, E., Filippini, N., Sexton, C. E., Topiwala, A., Valkanova, V., et al. (2015). Lifetime hypertension as a predictor of brain structure in older adults: cohort study with a 28-year follow-up. *Br. J. Psychiatry* 206, 308–315. doi: 10.1192/bjp.bp.114.153536

American Diabetes Association (2019). 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. *Diabetes Care* 42 (Suppl. 1), S13–S28. doi: 10.2337/dc19-S002

Andersson, J. L. R., and Skare, S. (2002). A model-based method for retrospective correction of geometric distortions in diffusion-weighted EPI. *Neuroimage* 16, 177–199. doi: 10.1006/nimg.2001.1039

Asmar, R., Benetos, A., Topouchian, J., Laurent, P., Pannier, B., Brisac, A. M., et al. (1995). Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 26, 485–490. doi: 10.1161/01.hyp.26.3.485

August, P. (1999). Hypertension in men. *J. Clin. Endocrinol. Metab.* 84, 3451–3454.

Avolio, A., Kim, M. O., Adji, A., Gangoda, S., Avadhanam, B., Tan, I., et al. (2018). Cerebral haemodynamics: effects of systemic arterial pulsatile function and hypertension. *Curr. Hypertens. Rep.* 20:20. doi: 10.1007/s11906-018-0822-x

Badji, A., Sabra, D., Bherer, L., Cohen-Adad, J., Girouard, H., and Gauthier, C. J. (2019). Arterial stiffness and brain integrity: a review of MRI findings. *Ageing Res. Rev.* 53:100907. doi: 10.1016/j.arr.2019.05.001

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., and Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement.* 11, 718–726. doi: 10.1016/j.jalz.2015.05.016

Beaulieu, C., and Allen, P. S. (1994). Determinants of anisotropic water diffusion in nerves. *Magn. Reson. Med.* 31, 394–400. doi: 10.1002/mrm.1910310408

Behrens, T. E. J., Johansen Berg, H., Jbabdi, S., Rushworth, M. F. S., and Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* 34, 144–155. doi: 10.1016/j.neuroimage.2006.09.018

Benjamini, Y., and Hochberg, Y. (1995). Controling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 39, 289–300.

Blennow, K., Wallin, A., Agren, H., Spenger, C., Siegfried, J., and Vanmechelen, E. (1995). Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? *Mol. Chem. Neuropathol.* 26, 231–245. doi: 10.1007/BF02815140

Braffman, B. H., Zimmerman, R. A., Trojanowski, J. Q., Gonatas, N. K., Hickey, W. F., and Schlaepfer, W. W. (1988). Brain MR: pathologic correlation with gross and histopathology. 2. Hyperintense white-matter foci in the elderly. *Am. J. Roentgenol.* 151, 559–566. doi: 10.2214/ajr.151.3.559

Brown, R., Benveniste, H., Black, S. E., Charpak, S., Dichgans, M., Joutel, A., et al. (2018). Understanding the role of the perivascular space in cerebral small vessel disease. *Cardiovasc. Res.* 114, 1462–1473. doi: 10.1093/cvr/cvy113

Burt, V. L., Whelton, P., Roccella, E. J., Brown, C., Cutler, J. A., Higgins, M., et al. (1995). Prevalence of hypertension in the US adult population. Results from the third national health and nutrition examination survey, 1988-1991. *Hypertension* 25, 305–313. doi: 10.1161/01.hyp.25.3.305

Cipolla, M. J. (2009). *Control of Cerebral Blood Flow*. San Rafael, CA: Morgan & Claypool Life Sciences.

de Groot, M., Ikram, M. A., Akoudad, S., Krestin, G. P., Hofman, A., van der Lugt, A., et al. (2015). Tract-specific white matter degeneration in aging: the Rotterdam study. *Alzheimers Dement.* 11, 321–330. doi: 10.1016/j.jalz.2014.06.011

de la Torre, J. (2018). The vascular hypothesis of Alzheimer's disease: a key to preclinical prediction of dementia using neuroimaging. *J. Alzheimers Dis.* 63, 35–52. doi: 10.3233/JAD-180004

Debette, S., and Markus, H. S. (2010). The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 341:c3666. doi: 10.1136/bmj.c3666

den Heijer, T., Launer, L. J., Prins, N. D., van Dijk, E. J., Vermeer, S. E., Hofman, A., et al. (2005). Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 64, 263–267. doi: 10.1212/01.WNL.0000149641.55751.2E

Desjardins-Crépeau, L., and Bherer, L. (2016). "Hypertension and age-related cognitive decline," in *Hypertension and the Brain as an End-Organ Target*, ed. H. Giruouard (Berlin: Springer), 21–38.

Dhollander, T., and Connelly, A. (2016). "A novel iterative approach to reap the benefits of multi-tissue CSD from just single-shell (+ b= 0) diffusion MRI data," in *Proceedings of the 24th International Society of Magnetic Resonance in Medicine*. (Melbourne VIC: University of Melbourne).

Dhollander, T., Raffelt, D., and Connelly, A. (2017). "Towards interpretation of 3-tissue constrained spherical deconvolution results in pathology," in *Proceedings of the 25th International Society of Magnetic Resonance in Medicine*, Honolulu, HI, 1815.

Doubal, F. N., MacLullich, A. M. J., Ferguson, K. J., Dennis, M. S., and Wardlaw, J. M. (2010). Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke* 41, 450–454. doi: 10.1161/STROKEAHA.109.564914

Dozono, K., Ishii, N., Nishihara, Y., and Horie, A. (1991). An autopsy study of the incidence of lacunes in relation to age, hypertension, and arteriosclerosis. *Stroke* 22, 993–996. doi: 10.1161/01.str.22.8.993

Falahati, F., Ferreira, D., Soininen, H., Mecocci, P., Vellas, B., Tsolaki, M., et al. (2016). The effect of age correction on multivariate classification in Alzheimer's disease, with a focus on the characteristics of incorrectly and correctly classified subjects. *Brain Topogr.* 29, 296–307. doi: 10.1007/s10548-015-0455-1

Faraco, G., and Iadecola, C. (2013). Hypertension: a harbinger of stroke and dementia. *Hypertension* 62, 810–817. doi: 10.1161/HYPERTENSIONAHA.113.01063

Farrall, A. J., and Wardlaw, J. M. (2009). Blood–brain barrier: ageing and microvascular disease–systematic review and meta-analysis. *Neurobiol. Aging* 30, 337–352. doi: 10.1016/j.neurobiolaging.2007.07.015

Fazekas, F., Kleinert, R., Offenbacher, H., Payer, F., Schmidt, R., Kleinert, G., et al. (1991). The morphologic correlate of incidental punctate white matter hyperintensities on MR images. *AJNR Am. J. Neuroradiol.* 12, 915–921.

Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., et al. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 43, 1683–1689. doi: 10.1212/wnl.43.9.1683

Fischl, B., and Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11050–11055. doi: 10.1073/pnas.200033797

Fitri, F. I., and Rambe, A. S. (2018). Correlation between hypertension and cognitive function in elderly. *IOP Conf. Ser. Earth Environ. Sci.* 125:012177. doi: 10.1088/1755-1315/125/1/012177

Gons, R. A. R., van Oudheusden, L. J. B., de Laat, K. F., van Norden, A. G. W., van Uden, I. W. M., Norris, D. G., et al. (2012). Hypertension is related to the microstructure of the corpus callosum: the RUN DMC study. *J. Alzheimers Dis.* 32, 623–631. doi: 10.3233/JAD-2012-121006

Gorelick, P. B., Furie, K. L., Iadecola, C., Smith, E. E., Waddy, S. P., Lloyd-Jones, D. M., et al. (2017). Defining optimal brain health in adults: a presidential advisory from the American heart association/American stroke association. *Stroke* 48, e284–e303. doi: 10.1161/str.0000000000000148

Gottesman, R. F., Coresh, J., Catellier, D. J., Sharrett, A. R., Rose, K. M., Coker, L. H., et al. (2010). Blood pressure and white-matter disease progression in a biethnic cohort: atherosclerosis risk in communities (ARIC) study. *Stroke* 41, 3–8. doi: 10.1161/STROKEAHA.109.566992

Gregoire, S. M., Chaudhary, U. J., Brown, M. M., Yousry, T. A., Kallis, C., Jäger, H. R., et al. (2009). The microbleed anatomical rating scale (MARS): reliability of a tool to map brain microbleeds. *Neurology* 73, 1759–1766. doi: 10.1212/WNL.0b013e3181c34a7d

Guo, Z., Fratiglioni, L., Zhu, L., Fastbom, J., Winblad, B., and Viitanen, M. (1999). Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. *Arch. Neurol.* 56, 991–996. doi: 10.1001/archneur.56.8.991

Habes, M., Sotiras, A., Erus, G., Toledo, J. B., Janowitz, D., Wolk, D. A., et al. (2018). White matter lesions. *Neurology* 91, e964–e975. doi: 10.1212/wnl.0000000000006116

Hajjar, I., Catoe, H., Sixta, S., Boland, R., Johnson, D., Hirth, V., et al. (2005). Cross-sectional and longitudinal association between antihypertensive medications and cognitive impairment in an elderly population. *J. Gerontol. A Biol. Sci. Med. Sci.* 60, 67–73. doi: 10.1093/gerona/60.1.67

Harrington, F., Saxby, B. K., McKeith, I. G., Wesnes, K., and Ford, G. A. (2000). Cognitive performance in hypertensive and normotensive older subjects. *Hypertension* 36, 1079–1082. doi: 10.1161/01.hyp.36.6.1079

Hughes, T. M., Kuller, L. H., Barinas-Mitchell, E. J. M., McDade, E. M., Klunk, W. E., Cohen, A. D., et al. (2014). Arterial stiffness and β-amyloid progression in nondemented elderly adults. *JAMA Neurol.* 71, 562–568. doi: 10.1001/jamaneurol.2014.186

Iadecola, C. (2010). The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol.* 120, 287–296. doi: 10.1007/s00401-010-0718-6

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron* 80, 844–866. doi: 10.1016/j.neuron.2013.10.008

Iadecola, C. (2014). Hypertension and dementia. *Hypertension* 64, 3–5.

Jack, C. R. Jr., Wiste, H. J., Weigand, S. D., Therneau, T. M., Lowe, V. J., Knopman, D. S., et al. (2017). Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement.* 13, 205–216. doi: 10.1016/j.jalz.2016.08.005

Johansen, A., Holmen, J., Stewart, R., and Bjerkeset, O. (2012). Anxiety and depression symptoms in arterial hypertension: the influence of antihypertensive treatment. the HUNT study, Norway. *Eur. J. Epidemiol.* 27, 63–72. doi: 10.1007/s10654-011-9641-y

Joutel, A., and Chabriat, H. (2017). Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin. Sci.* 131, 635–651. doi: 10.1042/CS20160380

Khachaturian, A. S., Zandi, P. P., Lyketsos, C. G., Hayden, K. M., Skoog, I., Norton, M. C., et al. (2006). Antihypertensive medication use and incident Alzheimer disease: the Cache County study. *Arch. Neurol.* 63, 686–692. doi: 10.1001/archneur.63.5.noc60013

Kombate, D., Guinhouya, K. M., Kumako, V., Assogba, K., Apetse, K., Kevi, S., et al. (2012). Facteurs de risque vasculaire predisposant aux lacunes cerebrales au CHU de Lome (Togo). *J. Rech. Sci. Univ. Lomé* 14, 191–195.

Korf, E. S. C., White, L. R., Scheltens, P., and Launer, L. J. (2004). Midlife blood pressure and the risk of hippocampal atrophy. *Hypertension* 44, 29–34. doi: 10.1161/01.hyp.0000132475.32317.bb

Kuller, L. H., Margolis, K. L., Gaussoin, S. A., Bryan, N. R., Kerwin, D., Limacher, M., et al. (2010). Relationship of hypertension, blood pressure, and blood pressure control with white matter abnormalities in the women's health initiative memory study (WHIMS)-MRI trial. *J. Clin. Hypertens.* 12, 203–212. doi: 10.1111/j.1751-7176.2009.00234.x

Lane, C. A., Barnes, J., Nicholas, J. M., Sudre, C. H., Cash, D. M., Parker, T. D., et al. (2019). Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol.* 18, 942–952. doi: 10.1016/S1474-4422(19)30228-5

Longstreth, W. T., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. *Stroke* 27, 1274–1282. doi: 10.1161/01.str.27.8.1274

Maclullich, A. M. J., Ferguson, K. J., Reid, L. M., Deary, I. J., Starr, J. M., Seckl, J. R., et al. (2009). Higher systolic blood pressure is associated with increased water diffusivity in normal-appearing white matter. *Stroke* 40, 3869–3871. doi: 10.1161/STROKEAHA.109.547877

MacLullich, A. M. J., Wardlaw, J. M., Ferguson, K. J., Starr, J. M., Seckl, J. R., and Deary, I. J. (2004). Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J. Neurol. Neurosurg. Psychiatry* 75, 1519–1523. doi: 10.1136/jnnp.2003.030858

Maillard, P., Fletcher, E., Lockhart, S. N., Roach, A. E., Reed, B., Mungas, D., et al. (2014). White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. *Stroke* 45, 1721–1726. doi: 10.1161/STROKEAHA.113.004084

Maillard, P., Seshadri, S., Beiser, A., Himali, J. J., Au, R., Fletcher, E., et al. (2012). Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham heart study: a cross-sectional study. *Lancet Neurol.* 11, 1039–1047. doi: 10.1016/S1474-4422(12)70241-7

Martí-Vilalta, J. L., Arboix, A., and Mohr, J. P. (2011). "Microangiopathies (lacunes)," in *Stroke*, eds G. du Boulay, A. Molyneux, and I. Moseley (Amsterdam: Elsevier), 485–515. doi: 10.1016/b978-1-4160-5478-8.10027-2

McEvoy, L. K., Fennema-Notestine, C., Eyler, L. T., Franz, C. E., Hagler, D. J. Jr., Lyons, M. J., et al. (2015). Hypertension-related alterations in white matter microstructure detectable in middle age. *Hypertension* 66, 317–323. doi: 10.1161/HYPERTENSIONAHA.115.05336

Mitchell, G. F. (2014). Arterial stiffness and hypertension: chicken or egg? *Hypertension* 64, 210–214. doi: 10.1161/hypertensionaha.114.03449

Mito, R., Dhollander, T., Xia, Y., Raffelt, D., and Salvado, O. (2019). In vivo microstructural heterogeneity of white matter lesions in Alzheimer's disease using tissue compositional analysis of diffusion MRI data. *bioRxiv* [Preprint]. doi: 10.1101/623124

Moonen, J. E. F., Foster-Dingley, J. C., de Ruijter, W., van der Grond, J., de Craen, A. J. M., and van der Mast, R. C. (2016). Effect of discontinuation of antihypertensive medication on orthostatic hypotension in older persons with mild cognitive impairment: the DANTE study Leiden. *Age Ageing* 45, 249–255. doi: 10.1093/ageing/afv199

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., et al. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an

ICBM template. *Neuroimage* 40, 570–582. doi: 10.1016/j.neuroimage.2007.12.035

Muehlboeck, J.-S., Westman, E., and Simmons, A. (2014). TheHiveDB image data management and analysis framework. *Front. Neuroinform.* 7:49. doi: 10.3389/fninf.2013.00049

Najar, J., van der Lee, S. J., Joas, E., Wetterberg, H., Hardy, J., Guerreiro, R., et al. (2021). Polygenic risk scores for Alzheimer's disease are related to dementia risk in APOE ε4 negatives. *Alzheimers Dement.* 13:e12142. doi: 10.1002/dad2.12142

Noriega de la Colina, A., Wu, R., Desjardins-Crépeau, L., Badji, A., Lamarre-Cliche, M., Doyon, J., et al. (2019). Diurnal blood pressure loads are associated with lower cognitive performances in controlled-hypertensive elderly individuals. *J. Hypertens.* 37:2168. doi: 10.1097/HJH.0000000000002155

Pantoni, L., and Garcia, J. H. (1995). The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. *Stroke* 26, 1293–1301. doi: 10.1161/01.str.26.7.1293

Pires, P. W., Dams Ramos, C. M., Matin, N., and Dorrance, A. M. (2013). The effects of hypertension on the cerebral circulation. *Am. J. Physiol. Heart Circ. Physiol.* 304, H1598–H1614. doi: 10.1152/ajpheart.00490.2012

Potter, G. M., Chappell, F. M., Morris, Z., and Wardlaw, J. M. (2015). Cerebral perivascular spaces visible on magnetic resonance imaging: development of a qualitative rating scale and its observer reliability. *Cerebrovasc. Dis.* 39, 224–231. doi: 10.1159/000375153

Reckelhoff, J. F. (2001). Gender differences in the regulation of blood pressure. *Hypertension* 37, 1199–1208. doi: 10.1161/01.hyp.37.5.1199

Roberts, R. O., Geda, Y. E., Knopman, D. S., Cha, R. H., Pankratz, V. S., Boeve, B. F., et al. (2008). The Mayo clinic study of aging: design and sampling, participation, baseline measures and sample characteristics. *Neuroepidemiology* 30, 58–69. doi: 10.1159/000115751

Rosano, C., Abebe, K. Z., Aizenstein, H. J., Boudreau, R., Jennings, J. R., Venkatraman, V., et al. (2015). Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. *Am. J. Hypertens.* 28, 326–334. doi: 10.1093/ajh/hpu134

Rydberg Sterner, T., Ahlner, F., Blennow, K., Dahlin-Ivanoff, S., Falk, H., Havstam Johansson, L., et al. (2019). The Gothenburg H70 birth cohort study 2014-16: design, methods and study population. *Eur. J. Epidemiol.* 34, 191–209. doi: 10.1007/s10654-018-0459-8

Shah, N. S., Vidal, J.-S., Masaki, K., Petrovitch, H., Ross, G. W., Tilley, C., et al. (2012). Midlife blood pressure, plasma β-amyloid, and the risk for Alzheimer disease: the Honolulu Asia aging study. *Hypertension* 59, 780–786.

Sjögren, M., Rosengren, L., Minthon, L., Davidsson, P., Blennow, K., and Wallin, A. (2000). Cytoskeleton proteins in CSF distinguish frontotemporal dementia from AD. *Neurology* 54, 1960–1964. doi: 10.1212/wnl.54.10.1960

Skoog, I. (1998). A review on blood pressure and ischaemic white matter lesions. *Dement. Geriatr. Cogn. Disord.* 9(Suppl. 1), 13–19. doi: 10.1159/000051184

Skoog, I., and Gustafson, D. (2006). Update on hypertension and Alzheimer's disease. *Neurol. Res.* 28, 605–611. doi: 10.1179/016164106X130506

Skoog, I., Landahl, S., and Lernfelt, B. (1996). High blood pressure and dementia. *Lancet* 348, 65–66. doi: 10.1016/s0140-6736(05)64398-x

Smith, S. M., Johansen-Berg, H., Jenkinson, M., Rueckert, D., Nichols, T. E., Miller, K. L., et al. (2007). Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nat. Protoc.* 2, 499–503. doi: 10.1038/nprot.2007.45

Sörös, P., Whitehead, S., David Spence, J., and Hachinski, V. (2013). Antihypertensive treatment can prevent stroke and cognitive decline. *Nat. Rev. Neurol.* 9, 174–178. doi: 10.1038/nrneurol.2012.255

Spinelli, C., De Caro, M. F., Schirosi, G., Mezzapesa, D., De Benedittis, L., Chiapparino, C., et al. (2014). Impaired cognitive executive dysfunction in adult treated hypertensives with a confirmed diagnosis of poorly controlled blood pressure. *Int. J. Med. Sci.* 11, 771–778. doi: 10.7150/ijms.8147

Sprint Mind Investigators for the Sprint Research Group, Williamson, J. D., Pajewski, N. M., Auchus, A. P., Bryan, R. N., Chelune, G., et al. (2019). Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA* 321, 553–561. doi: 10.1001/jama.2018.21442

Swan, G. E., Carmelli, D., and Larue, A. (1998). Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. *Stroke* 29, 2334–2340. doi: 10.1161/01.str.29.11.2334

Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., et al. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's coordinating centre. *Brain* 136, 2697–2706. doi: 10.1093/brain/awt188

Vanmechelen, E., Vanderstichele, H., Davidsson, P., Van Kerschaver, E., Van Der Perre, B., Sjögren, M., et al. (2000). Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. *Neurosci. Lett.* 285, 49–52. doi: 10.1016/s0304-3940(00)01036-3

Veglio, F., Paglieri, C., Rabbia, F., Bisbocci, D., Bergui, M., and Cerrato, P. (2009). Hypertension and cerebrovascular damage. *Atherosclerosis* 205, 331–341. doi: 10.1016/j.atherosclerosis.2008.10.028

Voevodskaya, O., Simmons, A., Nordenskjöld, R., Kullberg, J., Ahlström, H., Lind, L., et al. (2014). The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. *Front. Aging Neurosci.* 6:264. doi: 10.3389/fnagi.2014.00264

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneraton. *Lancet Neurol.* 12, 822–838. doi: 10.1016/S1474-4422(13)70124-8

Wiseman, R. M., Saxby, B. K., Burton, E. J., Barber, R., Ford, G. A., and O'Brien, J. T. (2004). Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology* 63, 1892–1897. doi: 10.1212/01.wnl.0000144280.59178.78

Wysocki, M., Luo, X., Schmeidler, J., Dahlman, K., Lesser, G. T., Grossman, H., et al. (2012). Hypertension is associated with cognitive decline in elderly people at high risk for dementia. *Am. J. Geriatr. Psychiatry* 20, 179–187. doi: 10.1097/jgp.0b013e31820ee833

Conflict of Interest: KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the present study. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). SK has served at scientific advisory boards for Biogen and Geras Solutions.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Aging Neuroscience

MINI REVIEW
published: 26 May 2022
doi: 10.3389/fnagi.2022.885226

Long Term Cognitive Function After Cardiac Arrest: A Mini-Review

Guri Hagberg[1,2], Håkon Ihle-Hansen[1,3], Else Charlotte Sandset[2], Dag Jacobsen[4], Henning Wimmer[4] and Hege Ihle-Hansen[1,2]*

[1] Department of Medical Research, Baerum Hospital Vestre Viken Hospital Trust, Drammen, Norway, [2] Oslo Stroke Unit, Department of Neurology, Oslo University Hospital, Ullevål, Norway, [3] Department of Medicine, Baerum Hospital Vestre Viken Hospital Trust, Drammen, Norway, [4] Department of Acute Medicine, Oslo University Hospital, Ullevål, Norway

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide. With better pre- and inhospital treatment, including cardiopulmonary resuscitation (CPR) as an integrated part of public education and more public-access defibrillators available, OHCA survival has increased over the last decade. There are concerns, after successful resuscitation, of cerebral hypoxia and degrees of potential acquired brain injury with resulting poor cognitive functioning. Cognitive function is not routinely assessed in OHCA survivors, and there is a lack of consensus on screening methods for cognitive changes. This narrative mini-review, explores available evidence on hypoxic brain injury and long-term cognitive function in cardiac arrest survivors and highlights remaining knowledge deficits.

Keywords: cardiac arrest, cognition, dementia, hypoxic brain injury, cognitive impaiment

OPEN ACCESS

Edited by:
Knut Asbjorn Hestad, Hedmark University of Applied Sciences, Norway

Reviewed by:
Frederick Wilburn Bylsma, Neuropsychological Services PC, United States

****Correspondence:***
Guri Hagberg
guri.hagberg@gmail.com

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *27 February 2022*
Accepted: *09 May 2022*
Published: *26 May 2022*

Citation:
Hagberg G, Ihle-Hansen H, Sandset EC, Jacobsen D, Wimmer H and Ihle-Hansen H (2022) Long Term Cognitive Function After Cardiac Arrest: A Mini-Review. Front. Aging Neurosci. 14:885226. doi: 10.3389/fnagi.2022.885226

INTRODUCTION

Cardiac arrest, defined as sudden cessation of cardiac activity with loss of consciousness, breathing, and no signs of circulation, is a leading cause of mortality worldwide. The condition rapidly progresses to sudden death if untreated with immediate cardiopulmonary resuscitation (CPR) and defibrillation (if indicated) (Kuller, 1980). The exact global burden, meaning mortality and morbidity, of out-of-hospital cardiac arrest (OHCA) to public health is unclear, due to the variability of emergency medical services (EMS) presentations, and regional variations in both systems and survival (Myat et al., 2018; Dyson et al., 2019). The estimated incidence is 275 000 people in Europe and 356 000 in the United States, with approximately 10% surviving to hospital discharge. Incidence increases with age and more commonly occurs in men. The etiology is predominantly cardiovascular in nature, with ischemic heart disease accounting for 60–80% of cases (Benjamin et al., 2018).

Scandinavian registry data including data from 2001 to 2010, show an increased survival in patients with OHCA from 10 to 30%, especially in patients with diagnosis suitable for defibrillation, such as ventricular fibrillation and pulseless ventricular tachycardia. Improvement in survival rates is likely attributable to the application of widespread CPR training and public-access defibrillators (Wissenberg et al., 2013). Additionally, the adoption of standardized post-resuscitation care, including goal-directed therapy with therapeutic hypothermia and increasing access to percutaneous coronary intervention for OCHA presentations of acute coronary syndromes, has also been shown to improve overall survival (Lund-Kordahl et al., 2010). The Norwegian Cardiac Arrest Registry (NorCAR) was established in 2002 and received status as a mandatory national health registry in 2013 (Tjelmeland et al., 2020), as the world's first

mandatory population-based cardiac arrest registry. According to this register, of the 3,405 attempted resuscitations in 2018, 1018 were brought to the hospital, and 405 survived (12%) more than 30 days.

Hypoxic brain injury is the major cause of death and disability in admitted patients post-OHCA after successful resuscitation (Dragancea et al., 2013). To improve the neurological prognosis, guidelines recommend targeted temperature management (TTM) after return of spontaneous circulation (Nolan et al., 2021). The Cerebral performance category (CPC) (Mak et al., 2016), adapted from the Glasgow coma Scale, is the predominantly employed score to assess neurological outcomes in OHCA survivors. The score consists of a five-point scale describing different functional statuses, where a score of 1 or 2 is considered a good outcome, indicating independence in activities of daily living. In 2018, 80% of the survivors in NorCAR had a good neurological outcome (CPC score 1-2) (Tjelmeland et al., 2020). However, the CPC score does not assess cognitive function, a relevant domain form a patient's perspective. In parallel, functional disability after stroke are evaluated with the modified Rankin scale (mRS) (Wilson et al., 2005), and in cases with excellent clinical recovery at 3 months (mRS = 0-1, no disability), the occurrence of cognitive impairment is prevalent (Jokinen et al., 2015). Eemphasizing the importance of long-term outcomes after OHCA, there is a need for good prediction models including cognition.

The majority of patient prognostication takes place in intensive care units, especially regarding the decision to withdraw from life-sustaining treatment in unconscious patients. Prognostication strategy algorithms exist; however, their utility in predicting poor outcome in patients suffering OHCA is uncertain (Cronberg et al., 2020; Nakstad et al., 2020). In the Norwegian Cardio-Respiratory Arrest Study (NORCAST) study, 54% out of the 259 comatose patients survived to discharge. Only 3 (absence of pupillary reflexex, bilateral absent N20 somato-sensory evoked potentials and increased neuron-specific enolase later than 24 h to >80 μg/L) out of 15 clinical, neurological, and biochemical predictors predicted poor outcomes with no false-positive rates (Nakstad et al., 2020).

The brain is vulnerable to hypoxic injury, and neuronal cell areas are more susceptible (Cronberg et al., 2020). The total burden of brain lesions after OHCA is unclear, largely due to the technical challenges in performing diagnostic neuroradiology in critically ill patients and hence, these are often limited to patients without neurological recovery after sedation. In small imaging and autopsy studies, the severity of findings is highly individual and depends on several factors, including the time to reperfusion and imaging. Magnetic resonance imaging (MRI) assessment on recovery has historically been limited due to pacemakers as a contraindication to an MRI scan (Muttikkal and Wintermark, 2013). Most registries, including NorCAR, do not routinely register neuroimaging findings or standardized cognitive assessments. Recent guidelines suggest using brain imaging for prognostication only in centers where specific experience is available (Nolan et al., 2021).

As survival rates from OHCA improve, there are increasing concerns regarding the impact on cognitive function following successful cardiopulmonary resuscitation and more data are needed. To "save the heart but lose the brain," a patient's ability to learn, think and reflect, can have significant consequences longer term. We aim to explore the currently available evidence on the long-term cognitive function and hypoxic brain injury in survivors after cardiac arrest and further identify the remaining knowledge gaps. This narrative mini review will focus on OHCA and long-term cognitive outcomes defined as longer than three months post-arrest.

COGNITIVE FUNCTION AFTER CARDIAC ARREST

Global or domain-specific cognitive test can be used when assessing cognition. There are numerous tests and test batteries, some generic other disease-specific. The most sensitive areas to hypoxic injury are the cortex and basal ganglia, followed by the hippocampus, thalamus, and brainstem. These areas are linked to cognitive domains, shown in **Figure 1**. Cognitive functions are dependent on complex interactions between cortical and subcortical sites across different brain networks. These networks are widely distributed across the brain, frequently intersecting, and overlapping, so that one lesion could affect multiple networks (Nakstad et al., 2020). By that, a global screening tool, including most cognitive domains, might be feasible.

Current evidence available on cognitive function after cardiac arrest is summarized in **Table 1**.

We identified only one systematic review from 2009 based on 28 papers from 1980 to 2006, describing the current evidence on the measured frequency and nature of cognitive impairments in OHCA survivors. Both design, participant, quality, and cognitive measures varied considerably in the studies included in the review. Only three studies with a small sample size (range 45–58) assessed cognitive function using a neuropsychological test battery. Cognitive problems were common and present in 42–50% of the participants (Moulaert et al., 2009).

Two substudies (Cronberg et al., 2015; Lilja et al., 2015) based on a large randomized controlled trial (RCT) (Nielsen et al., 2013), with prespecified secondary outcomes on cognition, randomized OHCA survivors to different temperature regimes (33 vs. 36°C), during the first 36 hours, with six months follow-up. Cognitive function did not differ in the two temperature management groups. In the first study, both OHCA groups performed worse than the age-matched control group, with known cardiovascular disease on tests for attention and mental speed (Lilja et al., 2015). In the other study (Cronberg et al., 2015), relatives reported a minor reduction from previous level in cognition using a modified version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm et al., 1991).

In another RCT comparing 48 h of hypothermia with 24 h of hypothermia in patients post cardiac arrest, the subgroup of patients with CPC score $\leq$2 at 6 months, demonstrated a longer duration of hypothermia (48 h) was associated with a lower risk of cognitive impairment (Evald et al., 2019).

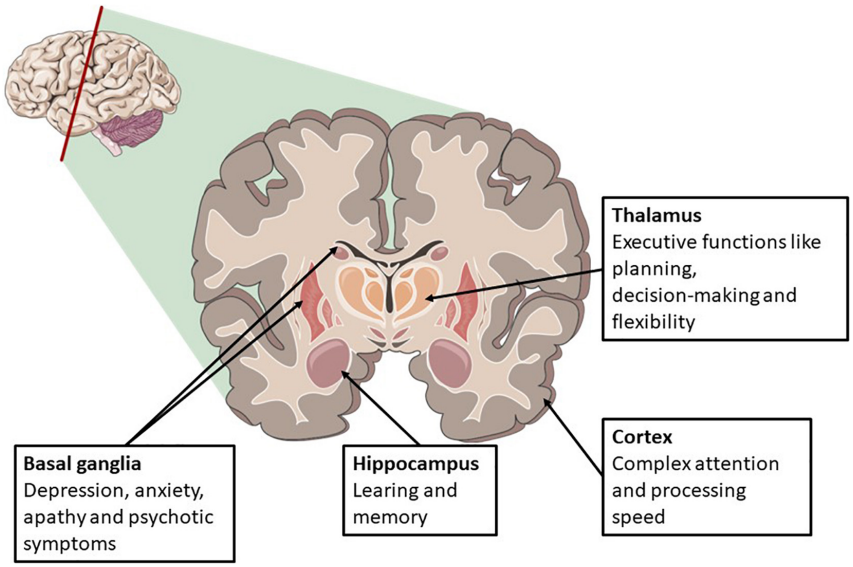


FIGURE 1 | Areas susceptible for global anoxic-ischemic brain injury and related cognitive symptoms. Illustration adapted from servier medial art.

Five small cohort studies with 79, 30, 33, 79, and 139 participants respectively, ranging from one to four years of follow-up, and using different global cognitive screening tools, reported some degree of cognitive impairment in 25–55% of the OHCA survivors (Ørbo et al., 2014; Buanes et al., 2015; Caro-Codón et al., 2018; Byron-Alhassan et al., 2021; Peskine et al., 2021). Caro-Codón et al. (2018) used a set of outcome measures often used in dementia diagnostic workup and compared their findings with the functional score CPC and mRS. Half of the patients scored below the usual limit for the diagnosis of mild cognitive impairment (MCI) and mRS did not detect these impairments (Caro-Codón et al., 2018). Ørbo et al. (2014) identified memory impairments as the most common symptom, and the impairments were stable from three to 12 months. Buanes et al. (2015) reported that more than one-quarter of the patients had cognitive impairment with short-term memory predominantly affected during a four-year follow-up. Byron-Alhassan et al. (2021) compared OHCA survivors to patients who had experienced a myocardial infarction and found a six times higher rate of cognitive impairment in the OHCA group. Peskine et al. (2021) report that 20% of OHCA survivors (with GCS > 12 in the 2 weeks post arrest) had cognitive impairment at 18 months, but observed in general improvement from 3 to 18 months.

Most studies highlight the lack of guideline recommendations on how to perform cognitive screening post-resuscitation.

BRAIN PATHOLOGY ON IMAGING AFTER CARDIAC ARREST

Neuroradiology is so far not an established part of the diagnostic assessment after cardiac arrest. Different patterns of injury have been reported in advanced imaging, depending on modality and timing of the assessment. Computed Tomography (CT) scan showing signs of edema; diffuse graying of the cerebral hemispheres, and loss of gray-white matter differentiation, are known predictors of poor outcomes after cardiac arrest (Nolan et al., 2021). Isolated cerebral edema, however, may not be a bad prognostic sign even if accompanied by late status epilepticus (Sunde et al., 2006). Ischemic lesions in the border zones between two major arterial territories are usually associated with hypoperfusion and described as watershed infarction on MR and CT. Diffuse hypoxic-ischemic changes involving gray matter in both cerebral hemispheres are a frequent finding after cardiac arrest of unknown duration (Keijzer et al., 2018).

A small case-control study (n = 12) on cardiac arrest survivors showed an extensive reduction of gray matter volumes on MRI compared to age- and sex-matched controls (Horstmann et al., 2010). A retrospective study including 50 cases with cardiac arrest, reviewed imaging findings of MRI reports concluding hypoxic-ischemic brain injury, and identified diffuse cortical and deep gray matter pattern of injury as the most common radiologic finding in those with poor outcomes. Lesions in the cerebellum and brainstem were seen in 30 and 7% of cases, respectively. In general, most patients had a poor clinical outcome (mRS 4-6) regardless of the observed pattern of injury, however a basal ganglia pattern without cortical involvement and watershed pattern could be an exception (Muttikkal and Wintermark, 2013).

A review published in Resuscitation 2018 aiming to value CT, MRI, and Positron Emission Tomography (PET) as an early prediction method of neurological outcome of comatose cardiac arrest survivors, identified 51 articles, 21 using CT, 27 MRI, one with both CT and MRI and two with PET imaging. CT or MRI with diffusion weighted imaging (DWI) within 1–3 days of cardiac arrest, demonstrating involvement of more than 10% of the brain with cytotoxic edema, may offer early prediction

TABLE 1 | Excerpts from relevant studies according to level of evidence.

Systematic Reviews			
References	**Population size**	**Measurement and outcome**	**Conclusion/interpretation**
Resuscitation (Moulaert et al., 2009)	3 studies n = 45, 57 and 58	Different battery of neuropsychological tests. Cognitive problems were found in 42, 48, and 50% of participants.	There are few good studies. Cognitive problems, in particular memory problems, seem common in survivors of out-of-hospital cardiac arrest.
Randomized control trials and their substudies			
Circulation (Lilja et al., 2015)	n = 652 The study also included an age-matched control group, with known cardiovascular disease. 50% were alive at follow-up, 90% attended in the structured examination at 6 months.	6 months—follow-up, domain-specific cognitive tests. 50% of the OHCA obtained a normal score at the memory assessment. Both OHCA groups performed worse than the control group on test for attention and mental speed.	No gold standard tests, or combination of tests currently exists. Cognitive function was comparable in the two temperature management groups. Cognitive impairment detected in cardiac arrest survivors was also common in matched control subjects with known cardiovascular disease.
JAMA (Cronberg et al., 2015)	*n* = 950 50% were alive at follow-up, 90% attended in the structured examination at 6 months.	6 months—follow-up. MMSE, IQCODE. Mean MMSE score was 28, which is considered normal compared to an age matched control group. Relatives report a minor reduction from previous level in cognition using the IQCODE.	Need of tests and scales that can improve the discrimination of the degree of neurologic recovery. Cognitive function was similar in both intervention groups, but many patients and observers reported impairment not detected previously by standard outcome scales.
Resuscitation (Evald et al., 2019)	*n* = 79	6 months follow-up. Rey Auditory-Verbal Learning Test (RAVLT) and Rey–Osterreith Complex Figure Test (ROCFT) for learning and memory; WAISIV Digit Span17 and Trail Making Test A & B (TMT-A & B) for attention; and D-KEFS Verbal Fluency for executive functions. TTM48 was associated with a significant better performance on three of 13 cognitive tests specific to memory, namely the RAVALT and immediate and delayed ROCFT tests.	TTM48 was associated with reduced memory retrieval deficits and lower relative risk of cognitive impairment six months after OHCA compared to standard TTM24.
Cohort Studies			
Resuscitation (Caro-Codón et al., 2018)	n = 79	1-year follow-up. MoCA, TMT-B, modified IQCODE, Zarit Caregigiven Burden interview, CPC, mRS. 54.4% scored below the usual cut-off for the diagnosis of MCI.	There is a high prevalence of long-term cognitive deficits and functional limitations in OHCA survivors. CPC or mRS, are crude and lack sensitivity to detect most of these deficits.
Resuscitation (Ørbo et al., 2014)	n = 30	3 months and 1 year follow-up. Neuropsychological tests for memory, executive function, and psychomotor speed. Memory impairments were the most common symptom, and stable from 3 to 12 months.	While systematic, early screening of cognitive performance has been recommended in recent p ost-resuscitation guideline, these concepts are not implemented in most places.
Resuscitation (Buanes et al., 2015)	n = 33	4-year follow-up. Cambridge Neuropsychological Test Automated Battery. 25% had cognitive impairment. Short-term memory was predominantly affected.	Cognitive impairment four years after cardiac arrest affected more than one-quarter of the patients.
Resusitation (Byron-Alhassan et al., 2021)	n = 79	Neuropsychological Assessment Battery (NAB). 43% s were Cognitively impaired (in the lowest decile on a global measure of cognitive functioning). Attention, memory, language and executive function were affected.	OHCA survivors - even those with seemingly good neurological recovery are at risk for cognitive impairment. Cognitive rehabilitation may be an important consideration post-OHCA.
Chest (Peskine et al., 2021)	n = 139	3-, 6-, 12- and 18-month follow-up. MMSE, Repeatable Battery for the assessment of Neuropsychological Status (RBANS) and the Frontal Assessment Battery. At 18 moths 20% had cognitive disabilities (MMSE < 25).	OCHA have good long-term prognosis, some patients improved until 18 moths post OHCA. Whether specific rehabilitation programs for these patients could improve outcome remains to be determined.

MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; TMT-B, Trail-making test-B; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; CPC, Cerebral Performance Category; mRS, modified Rankin Scale.

TABLE 2 | Ongoing trials registered at clinicaltrials.gov.

Study and design NCT number	Planned population size	Primary aim	Cognitive tests	Neuroimaging	Follow-up
Brain Function After Cardiac Arrest (Measured With FMRI and Cognitive Tests) BRAINnHEART, cohort study, NCT03579498	60	Whether cognitive function is affected after cardiac arrest and whether it changes over time	CANTAB MoCa	functional MRI (fMRI)	12 months
Cracking Coma, cohort study, NCT03308305	100	To estimate the additional value of early MRI monitoring for the prediction of neurological outcome of comatose patients after cardiac arrest	Cognitive functioning as defined by professional Neuropsychological examination at 12 months	MRI of the brain at day 3, 7, and three months after cardiac arrest	12 months
The MOCHA Study: Multimodal Outcome CHAracterization in Comatose Cardiac Arrest Patients Data Registry and Tissue Repository, NCT03261089	2500	Develop an accurate and reliable assessment algorithm for determining neurologic prognosis in patients initially unconscious post-cardiac arrest, using multiple prognostic modalities at standardized time points	Cerebral Performance Category- Extended (CPC-E) MoCA	Neuroimaging at standardized time points – not specified	5 years
Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP), RCT, NCT04217551	1800	Determine if increasing durations of induced hypothermia are associated with an increasing rate of good neurological outcomes	NIH Toolbox Crystallized Cognition Composite NIH Toolbox Fluid Cognition Composite Score processing in novel situations	unknown	90 d

for adverse outcomes (Keijzer et al., 2018). Similarly, a more recent meta-analysis (Lopez Soto et al., 2020) and retrospective single center observational study (Schick et al., 2022) have demonstrated the utility of both CT findings of loss of gray-white matter differentiation and MRI with DWI and fluid attenuated inversion recovery (FLAIR) sequencing in neuro-prognostication post-cardiac arrest. No long-term prediction data are included in either study.

Small cohort studies have examined the association between brain atrophy and cognition in OHCA survivors. The hippocampus and cortical volume were smaller in OHCA survivors than in healthy controls at three months, corresponding to observed cognitive impairments, mostly memory deficits. They conclude that neuroimaging studies of long-term OHCA survivors are warranted to guide the development of diagnostic and treatment options (Ørbo et al., 2018, 2019).

DISCUSSION

Up to 50% of OHCA survivors have cognitive impairments, often mild, but largely undetected by contemporary functional outcome measurements, notably the Cerebral Performance Category. Understanding of neuroradiologic findings after cardiac arrest and their relationship to longer term neurological outcomes still in its infancy. Observed patterns of injury, such as diffuse cortical and deep gray matter injury are noted and may related to later clinical findings in cognitive domains involved in executive functions, memory, and processing speed.

Cardiac arrest trials have traditionally reported outcomes that focus on survival and crude functional impairments. In addition, there is lack of consistency in outcome reporting. Recommended primary outcomes for resuscitation science studies, published in a consensus statement from the American Heart Association (AHA) 2011 (Becker et al., 2011), include global and domain-specific cognitive tests. Mini-mental state examination (MMSE) (Folstein et al., 1975) at discharge and follow-up is recommended as standard in clinical practice. MMSE is a global screening tool and has shown limited value in mild cognitive impairment (MCI) and does not assess executive function or complex attention, including processing speed and may not be the test of choice in patients with hypoxic brain injury (Dong et al., 2010). Further, AHA recommends TMT-A and B (Rm, 1958), and specific testing for memory (Rey Auditory Verbal Learning Test (RAVLT)(Ryan and Geisser, 1986) and attention (Digit Symbol Substitution Test (DSST) (Bettcher et al., 2011). The European Resuscitation Council and the European Society of Intensive Care Medicine have collaborated to produce post-resuscitation care guidelines (Nolan et al., 2021). The specific recommendations are screening for cognitive impairments using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) test and screening for emotional problems using the Hospital Anxiety and Depression Scale (HADS) (Snaith and Zigmond, 1986). Referral to a neuropsychological assessment or psychologist or psychiatrist if necessary are also recommended. The guidelines reflect the heterogeneity of the evidence.

Diagnostic criteria can be used to define the severity of cognitive symptoms and identify patients in need of cognitive rehabilitation. Some general, other disease-specific diagnostic criteria exist, including biomarkers such as MRI to include proposed etiology. As no disease-specific criteria exist after cardiac arrest, general criteria could be used, and the Diagnostic and Statistical Manual of Mental Disorders, DSM-5, is often used in clinical settings (Sachdev et al., 2014). No study identified used diagnostic criteria, making comparison

difficult and prevalence estimates uncertain. According to DSM-5, there must be evidence of modest cognitive decline from a previous level in one or more domains, preferably documented by standardized neuropsychological testing. The distinction between mild and major neurocognitive disorder is the interference with independence in everyday activities. No specific tests are recommended in the DSM criteria, but test performance in mild neurocognitive disorder should fall in the range of 1–2 SD below the normative mean and below 2 SD for major. The symptoms must also be present for longer than six months.

In general, there is no linear relationship between changes on imaging and cognitive function. However, chronic changes like periventricular white matter changes, caused by small vessel disease, and atrophy or neurodegeneration, are associated with cognitive decline (Barber et al., 1999; Wardlaw et al., 2013). Cognitive decline and dementia are also common after stroke. A proposed model of mechanisms in post-stroke dementia includes the severity of the vascular insult itself and the patient's total burden of brain pathology and cognitive reserve, together called resilience, prior to the insult. A patient's cognitive reserve is highly dependent on age, education, and lifestyle factors. The total burden of pathological brain changes includes chronic vascular changes, atrophy, and prior stroke. A patient with high brain resilience, suffering stroke will only result in a diagnosis of dementia if the infarct is strategic (Mok et al., 2017). A similar model could be applied to cardiac arrest survivors; patients with cardiac arrest and high brain resilience will probably only develop dementia if global ischemia is severe. The median age in OHCA is 65 years, with ischemic heart disease accounting for 60–80%, implying a high vascular risk factor burden and chronic brain changes are also likely to be prevalent in a cardiac arrest population (Myat et al., 2018). As seen in the RCT from Lilja et al. (2015), cognitive impairment is as prevalent in an age-matched control group as in cardiac arrest survivors, but the OHCA survivors do worse on specific tests for attention and mental speed. This is in line with our knowledge that the most common pattern on MRI after hypoxic-ischemic include diffuse cortical and deep gray matter lesions, areas linked to different cognitive domains like executive functions and attention and processing speed (**Figure 1**).

Long-term data on cognition is needed to make good prediction models, and incorporate pre-arrest factors likely to influence cognition (such as cognitive impairments, genetics, education, comorbidities, or prior brain pathology). Imaging and cognitive assessment data are scarce and not included in national registries, and currently, data beyond six months is limited to small cohort studies.

FUTURE PERSPECTIVES

National Cardiac Arrest Registries need to include cognitive assessments and long-term follow-up. The cognitive test battery needs a domain-specific test, including attention, processing speed, learning, and memory. MoCA is a brief screening tool covering all these domains, and by adding a well-known screening tool for anxiety and depression, the most likely cognitive impairments after cardiac arrest will be covered. This screening could be done during the initial stay if possible, and if deficits are revealed repeated in a follow-up visit. In younger patients planning to return to work, more extensive neuropsychological testing might be necessary even if the initial screening is normal. Neuroimaging is a promising marker for long-term cognitive prognostics and should be a part of a throughout evaluation. Several ongoing trials with cognitive measurements, neuroimaging, and planned at least 3 months follow-up are registered at clinicaltrials.gov (**Table 2**). A dedicated multidisciplinary team offering OHCA survivors and their caregivers systematic psychological, cognitive, and specialized medical support for the first six months has shown promising results (Ørbo et al., 2018). Including follow-up of patients in National Cardiac Arrest Registry, will identify the actual burden of long-term cognitive deficits and subsequently identify patients who may benefit from long-term cognitive rehabilitation.

CONCLUSION

Cognitive impairments after OHCA are common and affect up to 50%. CPC is crude and lacks sensitivity to detect most of these deficits. As diffuse cortical and deep gray matter lesions were the most common findings on neuroimaging, cognitive domains involved in executive functions, memory, and processing speed needs to be addressed. More long-term data is required to develop good prognostic models, which could be in cohort studies or the registries. As of today, no standardized follow-up exists for the OHCA survivors, but recent guidelines recommends both cognitive screening and follow-up.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

REFERENCES

Barber, R., Gholkar, A., Scheltens, P., Ballard, C., McKeith, I. G., and O'Brien, J. T. (1999). Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology* 52, 1153–1158.

Becker, L. B., Aufderheide, T. P., Geocadin, R. G., Callaway, C. W., Lazar, R. M., Donnino, M. W., et al. (2011). Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. *Circulation* 124, 2158–2177. doi: 10.1161/CIR.0b013e3182340239

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., et al. (2018). Heart Disease and Stroke Statistics-2018 Update: a Report From the American Heart Association. *Circulation* 137, e67–e492.

Bettcher, B. M., Libon, D. J., Kaplan, E., Swenson, R., and Penney, D. L. (2011). "Digit Symbol Substitution Test," in *Encyclopedia of Clinical Neuropsychology*, eds J. S. Kreutzer, J. DeLuca, and B. Caplan (New York, NY: Springer), 849–853.

Buanes, E. A., Gramstad, A., Søvig, K. K., Hufthammer, K. O., Flaatten, H., Husby, T., et al. (2015). Cognitive function and health-related quality of life four years

after cardiac arrest. *Resuscitation* 89, 13–18. doi: 10.1016/j.resuscitation.2014.12.021

Byron-Alhassan, A., Collins, B., Bedard, M., Quinlan, B., Le May, M., Duchesne, L., et al. (2021). Cognitive dysfunction after out-of-hospital cardiac arrest: rate of impairment and clinical predictors. *Resuscitation* 165, 154–160. doi: 10.1016/j.resuscitation.2021.05.002

Caro-Codón, J., Rey, J. R., Lopez-de-Sa, E., González Fernández, Ó, Rosillo, S. O., Armada, E., et al. (2018). Long-term neurological outcomes in out-of-hospital cardiac arrest patients treated with targeted-temperature management. *Resuscitation* 133, 33–39.

Cronberg, T., Greer, D. M., Lilja, G., Moulaert, V., Swindell, P., and Rossetti, A. O. (2020). Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. *Lancet Neurol.* 19, 611–622. doi: 10.1016/S1474-4422(20)30117-4

Cronberg, T., Lilja, G., Horn, J., Kjaergaard, J., Wise, M. P., Pellis, T., et al. (2015). Neurologic Function and Health-Related Quality of Life in Patients Following Targeted Temperature Management at 33°C vs 36°C After Out-of-Hospital Cardiac Arrest: a Randomized Clinical Trial. *JAMA Neurol.* 72, 634–641. doi: 10.1001/jamaneurol.2015.0169

Dong, Y., Sharma, V. K., Chan, B. P., Venketasubramanian, N., Teoh, H. L., Seet, R. C., et al. (2010). The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J. Neurol. Sci.* 299, 15–18. doi: 10.1016/j.jns.2010.08.051

Dragancea, I., Rundgren, M., Englund, E., Friberg, H., and Cronberg, T. (2013). The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. *Resuscitation* 84, 337–342. doi: 10.1016/j.resuscitation.2012.09.015

Dyson, K., Brown, S. P., May, S., Smith, K., Koster, R. W., Beesems, S. G., et al. (2019). International variation in survival after out-of-hospital cardiac arrest: a validation study of the Utstein template. *Resuscitation* 138, 168–181. doi: 10.1016/j.resuscitation.2019.03.018

Evald, L., Brønnick, K., Duez, C. H. V., Grejs, A. M., Jeppesen, A. N., Søreide, E., et al. (2019). Prolonged targeted temperature management reduces memory retrieval deficits six months post-cardiac arrest: a randomised controlled trial. *Resuscitation* 134, 1–9. doi: 10.1016/j.resuscitation.2018.12.002

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198.

Horstmann, A., Frisch, S., Jentzsch, R. T., Müller, K., Villringer, A., and Schroeter, M. L. (2010). Resuscitating the heart but losing the brain: brain atrophy in the aftermath of cardiac arrest. *Neurology* 74, 306–312. doi: 10.1212/WNL.0b013e3181cbcd6f

Jokinen, H., Melkas, S., Ylikoski, R., Pohjasvaara, T., Kaste, M., Erkinjuntti, T., et al. (2015). Post-stroke cognitive impairment is common even after successful clinical recovery. *Eur. J. Neurol.* 22, 1288–1294. doi: 10.1111/ene.12743

Jorm, A. F., Scott, R., Cullen, J. S., and MacKinnon, A. J. (1991). Performance of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) as a screening test for dementia. *Psychol. Med.* 21, 785–790. doi: 10.1017/s0033291700022418

Keijzer, H. M., Hoedemaekers, C. W. E., Meijer, F. J. A., Tonino, B. A. R., Klijn, C. J. M., and Hofmeijer, J. (2018). Brain imaging in comatose survivors of cardiac arrest: pathophysiological correlates and prognostic properties. *Resuscitation* 133, 124–136. doi: 10.1016/j.resuscitation.2018.09.012

Kuller, L. H. (1980). Sudden death–definition and epidemiologic considerations. *Prog. Cardiovasc. Dis.* 23, 1–12. doi: 10.1016/0033-0620(80)90002-x

Lilja, G., Nielsen, N., Friberg, H., Horn, J., Kjaergaard, J., Nilsson, F., et al. (2015). Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. *Circulation* 131, 1340–1349.

Lopez Soto, C., Dragoi, L., Heyn, C. C., Kramer, A., Pinto, R., Adhikari, N. K. J., et al. (2020). Imaging for Neuroprognostication After Cardiac Arrest: systematic Review and Meta-analysis. *Neurocrit. Care.* 32, 206–216. doi: 10.1007/s12028-019-00842-0

Lund-Kordahl, I., Olasveengen, T. M., Lorem, T., Samdal, M., Wik, L., and Sunde, K. (2010). Improving outcome after out-of-hospital cardiac arrest by strengthening weak links of the local Chain of Survival; quality of advanced life support and post-resuscitation care. *Resuscitation* 81, 422–426. doi: 10.1016/j.resuscitation.2009.12.020

Mak, M., Moulaert, V. R., Pijls, R. W., and Verbunt, J. A. (2016). Measuring outcome after cardiac arrest: construct validity of Cerebral Performance Category. *Resuscitation* 100, 6–10. doi: 10.1016/j.resuscitation.2015.12.005

Mok, V. C., Lam, B. Y., Wong, A., Ko, H., Markus, H. S., and Wong, L. K. (2017). Early-onset and delayed-onset poststroke dementia - revisiting the mechanisms. *Nat. Rev. Neurol.* 13, 148–159. doi: 10.1038/nrneurol.2017.16

Moulaert, V. R., Verbunt, J. A., van Heugten, C. M., and Wade, D. T. (2009). Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. *Resuscitation* 80, 297–305. doi: 10.1016/j.resuscitation.2008.10.034

Muttikkal, T. J., and Wintermark, M. (2013). MRI patterns of global hypoxic-ischemic injury in adults. *J. Neuroradiol.* 40, 164–171. doi: 10.1016/j.neurad.2012.08.002

Myat, A., Song, K. J., and Rea, T. (2018). Out-of-hospital cardiac arrest: current concepts. *Lancet* 391, 970–979.

Nakstad, E. R., Stær-Jensen, H., Wimmer, H., Henriksen, J., Alteheld, L. H., Reichenbach, A., et al. (2020). Late awakening, prognostic factors and long-term outcome in out-of-hospital cardiac arrest - results of the prospective Norwegian Cardio-Respiratory Arrest Study (NORCAST). *Resuscitation* 149, 170–179. doi: 10.1016/j.resuscitation.2019.12.031

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Nielsen, N., Wetterslev, J., Cronberg, T., Erlinge, D., Gasche, Y., Hassager, C., et al. (2013). Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N. Engl. J. Med.* 369, 2197–2206.

Nolan, J. P., Sandroni, C., Böttiger, B. W., Cariou, A., Cronberg, T., Friberg, H., et al. (2021). European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. *Intens. Care Med.* 47, 369–421.

Ørbo, M., Aslaksen, P. M., Larsby, K., Norli, L., Schäfer, C., Tande, P. M., et al. (2014). Determinants of cognitive outcome in survivors of out-of-hospital cardiac arrest. *Resuscitation* 85, 1462–1468. doi: 10.1016/j.resuscitation.2014.08.010

Ørbo, M. C., Aslaksen, P. M., Anke, A., Tande, P. M., and Vangberg, T. R. (2019). Cortical Thickness and Cognitive Performance After Out-of-Hospital Cardiac Arrest. *Neurorehab. Neural Repair.* 33, 296–306. doi: 10.1177/1545968319834904

Ørbo, M. C., Vangberg, T. R., Tande, P. M., Anke, A., and Aslaksen, P. M. (2018). Memory performance, global cerebral volumes and hippocampal subfield volumes in long-term survivors of Out-of-Hospital Cardiac Arrest. *Resuscitation* 126, 21–28. doi: 10.1016/j.resuscitation.2018.02.011

Peskine, A., Cariou, A., Hajage, D., Deye, N., Guérot, E., Dres, M., et al. (2021). Long-Term Disabilities of Survivors of Out-of-Hospital Cardiac Arrest: the Hanox Study. *Chest* 159, 699–711. doi: 10.1016/j.chest.2020.07.022

Rm, R. (1958). Validity of the trail making test as an indicator of organic brain damage. *Percept. Mot. Skills* 8, 271–276.

Ryan, J. J., and Geisser, M. E. (1986). Validity and diagnostic accuracy of an alternate form of the Rey Auditory Verbal Learning Test. *Arch. Clin. Neuropsychol.* 1, 209–217.

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., et al. (2014). Classifying neurocognitive disorders: the DSM-5 approach. *Nat. Rev. Neurol.* 10, 634–642. doi: 10.1038/nrneurol.2014.181

Schick, A., Prekker, M. E., Kempainen, R. R., Mulder, M., Moore, J., Evans, D., et al. (2022). Association of hypoxic ischemic brain injury on early CT after out of hospital cardiac arrest with neurologic outcome. *Am. J. Emerg. Med.* 54, 257–262. doi: 10.1016/j.ajem.2022.02.003

Snaith, R. P., and Zigmond, A. S. (1986). The hospital anxiety and depression scale. *Brit. Med. J.* 292:344.

Sunde, K., Dunlop, O., Rostrup, M., Sandberg, M., Sjøholm, H., and Jacobsen, D. (2006). Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia. *Resuscitation* 69, 29–32. doi: 10.1016/j.resuscitation.2005.12.003

Tjelmeland, I. B. M., Alm-Kruse, K., Andersson, L. J., Bratland, S., Hafstad, A. K., Haug, B., et al. (2020). Cardiac arrest as a reportable condition:

a cohort study of the first 6 years of the Norwegian out-of-hospital cardiac arrest registry. *BMJ open.* 10:e038133. doi: 10.1136/bmjopen-2020-038133

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., et al. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 12, 822–838. doi: 10.1016/S1474-4422(13)70124-8

Wilson, J. T., Hareendran, A., Hendry, A., Potter, J., Bone, I., and Muir, K. W. (2005). Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview. *StrokeJ. Cerebr. Circul.* 36, 777–781. doi: 10.1161/01.STR.0000157596.13234.95

Wissenberg, M., Lippert, F. K., Folke, F., Weeke, P., Hansen, C. M., Christensen, E. F., et al. (2013). Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *Jama* 310, 1377–1384. doi: 10.1001/jama.2013.278483

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Neuroscience

REVIEW
published: 16 June 2022
doi: 10.3389/fnins.2022.897303

"The Wandering Nerve Linking Heart and Mind" – The Complementary Role of Transcutaneous Vagus Nerve Stimulation in Modulating Neuro-Cardiovascular and Cognitive Performance

Helena Dolphin[1,2], Tim Dukelow[1], Ciaran Finucane[3], Sean Commins[4], Paul McElwaine[1,2] and Sean P. Kennelly[1,2]*

[1] Department of Age-Related Healthcare, Tallaght University Hospital, Dublin, Ireland, [2] Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland, [3] Department of Medical Physics, St James's Hospital, Dublin, Ireland, [4] Department of Psychology, Maynooth University, Maynooth, Ireland

OPEN ACCESS

Edited by:
Knut Asbjorn Hestad, Hedmark University of Applied Sciences, Norway

Reviewed by:
Lin Sørensen, University of Bergen, Norway
Guillaume T. Vallet, UMR 6024 Laboratoire de Psychologie Sociale et Cognitive (LAPSCO), France

***Correspondence:**
Helena Dolphin
helenadolphin@gmail.com

Specialty section:
This article was submitted to Autonomic Neuroscience, a section of the journal Frontiers in Neuroscience

Received: *17 March 2022*
Accepted: *30 May 2022*
Published: *16 June 2022*

Citation:
Dolphin H, Dukelow T, Finucane C, Commins S, McElwaine P and Kennelly SP (2022) "The Wandering Nerve Linking Heart and Mind" – The Complementary Role of Transcutaneous Vagus Nerve Stimulation in Modulating Neuro-Cardiovascular and Cognitive Performance. Front. Neurosci. 16:897303. doi: 10.3389/fnins.2022.897303

The vagus nerve is the longest nerve in the human body, providing afferent information about visceral sensation, integrity and somatic sensations to the CNS *via* brainstem nuclei to subcortical and cortical structures. Its efferent arm influences GI motility and secretion, cardiac ionotropy, chonotropy and heart rate variability, blood pressure responses, bronchoconstriction and modulates gag and cough responses *via* palatine and pharyngeal innervation. Vagus nerve stimulation has been utilized as a successful treatment for intractable epilepsy and treatment-resistant depression, and new non-invasive transcutaneous (t-VNS) devices offer equivalent therapeutic potential as invasive devices without the surgical risks. t-VNS offers exciting potential as a therapeutic intervention in cognitive decline and aging populations, classically affected by reduced cerebral perfusion by modulating both limbic and frontal cortical structures, regulating cerebral perfusion and improving parasympathetic modulation of the cardiovascular system. In this narrative review we summarize the research to date investigating the cognitive effects of VNS therapy, and its effects on neurocardiovascular stability.

Keywords: vagus nerve stimulation, cognition, neurocardiovascular control, cerebral blood flow, LC-NE system, inhibitory control, executive function

INTRODUCTION

Vagus nerve stimulation (VNS) as a neurostimulation technique and has received renewed attention in recent years. Traditionally invasive VNS (iVNS) devices were sutured under the skin of the chest with a lateral left neck dissection undertaken to expose the left cervical vagus nerve and wrap a stimulating electrode around it. Each iVNS device is costly and up to 30% of patients have side effects post implantation (Morris and Mueller, 1999). Since the development in the early 2000s of peripheral stimulating devices that harness the vagus nerve's innervation of the skin of the

external ear demonstrating efficacy in treating epilepsy, depression and headaches, interest in wider therapeutic potentials of this treatment have grown (Yap et al., 2020).

Declining cognition associated with aging is a burgeoning global health crisis, with at least 152.8 million persons projected to have dementia worldwide by the year 2050 (Nichols et al., 2022). There are few effective treatments for cognitive decline and dementia, with no current cure (Cummings et al., 2021) and although the first disease modifying anti-amyloid agent has been licensed by the FDA (Steinbrook, 2021), more therapies are urgently needed to help alleviate the personal, societal and economic cost of increasing dementia diagnoses (Xu et al., 2017). Impaired cognition is associated with impaired autonomic function, specifically impaired parasympathetic measures of heart rate variability (HRV) (Forte et al., 2019; Cheng et al., 2022; Liu et al., 2022) likely reflective of the complex interplay between cognition and cardiac modulation, *via* the central autonomic network.

Studies of patients with intractable epilepsy and treatment -resistant depression treated with iVNS devices showed signals indicating increased alertness and potentially cognitive improvements (Ghacibeh et al., 2006a; McGlone et al., 2008; Schevernels et al., 2016; Sun et al., 2017; van Bochove et al., 2018) and a small pilot study investigated iVNS devices in patients with Alzheimer's Disease with overall positive results (Sjögren et al., 2002; Merrill et al., 2006). Recent meta-analysis of t-VNS in young healthy adults has found an overall moderate effect especially for improved cognitive performance especially executive function (Ridgewell et al., 2021). However the neuroanatomical substrates of persons with treatment-resistant depression or epilepsy are likely both widely variable, and grossly different to both a young cognitively healthy adult and a person with mild cognitive impairment (MCI) or dementia and dedicated larger studies are required to investigate if t-VNS has therapeutic potential in this population.

The purpose of this narrative review will be to outline the research to date investigating both cognitive outcomes of VNS in healthy and clinical populations, and the effect VNS has on HRV as a measure of autonomic tone. The mechanisms of action of VNS including neurotransmitter release, local increased cerebral blood flow and modulation of peripheral hemodynamics are discussed and future research recommendations outlined.

ANATOMY AND PHYSIOLOGY OF THE VAGUS NERVE

The longest nerve in the body, the vagus nerve derives its name from the Latin for 'straying' or 'wandering.' Aptly named, the nerve has an extensive course, traveling from the medulla to the gut. The vagus nerve's function is to transmit information to and from the central nervous system (CNS) regarding control of the gastrointestinal, cardiovascular, and respiratory systems. It is comprised of approximately 80% afferent and 20% efferent fibers (Foley and Dubois, 1937; Agostini et al., 1957) including A, B and C fibers classified by conduction velocity (Erlanger and Gasser, 1937). Vagus neurons may involve visceral (cardiac, bronchopulmonary, gastrointestinal) or somatic (soft tissues, muscles of palate, pharynx) modulation. Afferent fibers are further sub classified as general visceral afferent, general somatic afferent, or special visceral afferent. Two efferent fiber types are recognized, namely special visceral efferent and general visceral efferent (see **Table 1**). Fibers connect centrally to four vagal nuclei; the nucleus of the solitary tract (NTS) and spinal trigeminal nucleus which contain vagal afferent fibers and the nucleus ambiguous and dorsal motor nucleus of the vagus (DMN) from where vagal efferent fibers leave (Rutecki, 1990; Berthoud and Neuhuber, 2000).

Afferent vagus fibers enter the medulla at the level of the olive, and terminate primarily in the NTS (Beckstead and Norgren, 1979; Kalia and Sullivan, 1982). Each vagus nerve (VN) synapses bilaterally in the NTS; so vagal afferent information is processed bilaterally in the CNS (Henry, 2002). Second order afferent fibers from the NTS project most densely to the parabrachial nucleus of the pons (PBN) with the NTS also projecting to noradrenergic (locus coeruleus) and serotonergic (raphe nuclei) neuromodulatory systems (Rutecki, 1990; Saper, 2000). From here vagal information is relayed to a number of mostly subcortical structures, including the hypothalamus, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the intralaminar thalamic nucleus. Vagal afferent information is also sent to the anterior insular cortex which communicates with more rostral regions of the cortex (orbital and ventrolateral prefrontal cortex) and also indirectly with the medial prefrontal cortex (Öngür and Price, 2000; Saleem et al., 2008).

These central structures are part of the central autonomic network (CAN) which is thought to be the origin of autonomic, behavioral, cognitive, and endocrine responses, capable of modulating the functioning of the autonomic nervous system (ANS) *via* descending pathways projecting onto sympathetic pre-ganglionic neurons in the spinal cord and onto the DMN at the origin of vagal efferents (Benarroch, 1993). The central connections of the DMN are considerable, with afferent projections arising from sites including the NST, magnocellular paraventricular nuclei and several medullary nuclei (Roges et al., 1980; Hansen, 2019). Whilst a minority of efferent fibers connect centrally, most DMN fibers project to GI organs *via* parasympathetic ganglia located close to or in the walls of viscera. Further efferent fibers originate from the nucleus ambiguous (NA), a motor nucleus located in the reticular formation of the medulla which gives rise to preganglionic neurons innervating the heart and lungs (Llewellyn-Smith and Verberne, 2011) which exert a cardio-inhibitory effect mediated *via* the sinoatrial and atrioventricular ganglia (Massari et al., 1995; Gatti et al., 1996). The right vagus nerve mostly innervates the sinoatrial node (involved in the pacemaker function of the heart) whereas the left vagus is mostly thought to innervate the atrioventricular node (regulating the force of contraction of the cardiac myocytes with less influence over heart rate) however comprehensive human studies confirming this precise delineation are needed (Coote, 2013). The dorsal branchiomotor division of the NA is the site of origin of efferent fibers innervating striated muscle of the palate, pharynx, larynx and upper esophagus.

TABLE 1 | The constituent fibers of the vagus nerve.

	FIBER				
	Aα	**Aβ**	**Aδ**	**B**	**C**
Fiber diameter	13–20 mm	6–12 mm	1–5 mm	1–5 mm	0.4–2 mm
Gross anatomical structure	Large	Large	Large	Small	Small
Main function afferent	Somatic touch pain temperature	Somatic touch	Visceral: pain stretch chemical, temperature	Visceral	Visceral: pain stretch chemical, temperature
Main function efferent	Muscle tone	Muscle preganglionic	preganglionic	preganglionic	preganglionic
Myelin	+	+	+	+	−
Threshold mA	0.02–0.2 mA	0.02–0.2 mA	0.02–0.2 mA	0.04–0.6 mA	0.3–6 mA
Conduction velocity ms	8–120 ms	35–75 ms	3–30 ms	3–15 ms	0.5–2 ms
Purported effect of VNS on EEG	Synchronization	Synchronization	Synchronization	Synchronization	Desynchronization

Adapted from Groves et al. (2005).

See **Figure 1** for a schematic representation of the VN fibers and central projections.

HISTORY OF VAGUS NERVE STIMULATION

Vagus nerve stimulation was initially proposed as a therapeutic intervention in 1871 (Neftel, 1871) and a device was designed to stimulate bilateral vagus nerves in the late 19th century (Lanska, 2002). Preclinical studies in the 1930–1950s demonstrated *via* EEG signaling that VNS had cortical stimulating activity (Bailey and Bremer, 1938; Zanchetti et al., 1952), and could terminate canine seizures (Zabara, 1985, 1992).

Invasive VNS (iVNS) received United States regulatory approval for the adjunctive treatment of refractory seizures in 1997 and for use in treatment resistant depression in 2005 (O'Reardon et al., 2006). However, given the invasive nature of iVNS (requiring general anesthesia, thoracic implantation of a battery generator, and neck dissection to attach stimulating electrodes to the left cervical vagus nerve), the concept of non-invasive VNS was proposed in 2000 whereby, drawing on evidence from studies of auricular acupuncture, it was postulated that transcutaneous vagal stimulation could represent a valuable tool in epilepsy treatment (Ventureyra, 2000). Non-invasive VNS involves using stimulating electrodes on the skin to excite afferent vagal fibers and can be performed *via* the ear (transcutaneous auricular VNS: t-VNS) or the neck (transcutaneous cervical VNS: tcVNS). For the purposes of this narrative review non-invasive VNS will refer to auricular t-VNS.

The technique of t-VNS exploits the peripheral anatomy of the vagus nerve, activating vagal afferent projections through stimulation of the auricular branch of vagus nerve (ABVN) at the ear (Peuker and Filler, 2002; Mercante et al., 2018) see **Figure 2** for a schematic representation of the anatomy of the ABVN and central structures it modulates. Anti-seizure efficacy equivalent to iVNS was demonstrated in preclinical studies before the feasibility and therapeutic significance of this technique in humans were demonstrated (Stefan et al., 2012) and evidence from multiple functional brain imaging studies confirms significant activation of central vagal projections *via* this non-invasive method (Kraus et al., 2013; Frangos et al., 2015; Yakunina et al., 2017; Badran et al., 2018a).

Transcutaneous auricular vagus nerve stimulation waveforms can be delivered at a variety of different parameter settings which vary frequency (Hz), amplitude (mA), pulse width (μs-msec) and duration of stimulation. It is currently being investigated as a therapeutic intervention for a variety of medical disorders including epilepsy, migraine and cluster headaches, tinnitus, atrial fibrillation, Parkinson's disease, schizophrenia, impaired glucose tolerance, obesity, and pain (Goadsby et al., 2014; Huang et al., 2014; Laqua et al., 2014; Hasan et al., 2015; Hyvarinen et al., 2015; Nesbitt et al., 2015; Stavrakis et al., 2015; Cakmak et al., 2017; Obst et al., 2020). There is particular interest in the evolving literature reporting the use of t-VNS in cognitive disorders (Broncel et al., 2020; Lam et al., 2021). Potential mechanisms of action include modulation of HRV, impacts on cerebral perfusion, and noradrenergic neuromodulation. The complementary role of vagus nerve stimulation in modulating neuro-cardiovascular and cognitive performance is explored in detail below.

See **Figure 2** for a schematic diagram of the area of innervation of the ABVN and its central projections.

COGNITIVE PERFORMANCE AND VAGUS NERVE STIMULATION

Brain imaging during t-VNS demonstrates strong activation of vagal projections to subcortical nuclei and frontal brain regions, i.e., superior frontal gyrus and medial frontal gyrus during stimulation (Kraus et al., 2013) (See below in "Mechanisms of Action" for further detailed discussion regarding the neuroanatomical structures modulated during VNS). Cognitive effects of both iVNS and t-VNS in both clinical populations and healthy volunteers will be examined under the following themes: Cognitive control, i.e., the non-automatic regulation of behavior to achieve a goal (Gonthier, 2014) a primarily

executive function that involves suppression of goal-irrelevant stimuli *via* response and attention-inhibition (Tiego et al., 2018) and it primarily involves the lateral prefrontal cortex (Dixon, 2015); Language, both assessing categorical fluency a semantic memory language task involving the temporal lobe, and word recognition and retrieval which mostly involves episodic working memory, involving prefrontal cortex and medial temporal structures (Squire and Zola, 1998; Camina and Güell, 2017); Associative memory, a subcategory of declarative episodic memory and involves the ability to link disparate novel stimuli (Naveh-Benjamin, 2000); Emotion recognition as a subtype of cognition involves areas of the brain involved in perceiving social information including the medial prefrontal cortex and the orbitofrontal cortex (Bachmann et al., 2018) and regions implicated in emotional processing, including the cortical orbitofrontal cortex and the anterior cingulate cortex but also subcortical structures including the amygdala, hypothalamus, basal ganglia and the periaqueductal gray matter (van den Stock et al., 2011).

Interest in the potential role of VNS as a cognitive enhancer started following a preclinical rodent study of an inhibitory-avoidance task. Subjects received a single exposure to a foot shock followed immediately by VNS or sham. Those undergoing true VNS stimulation had longer step times demonstrating enhanced avoidance and this effect was modulated by the intensity of the stimulus, with 0.4 mA being an effective level of stimulation and 0.2 and 0.8 mA having no significant effect (Clark et al., 1995). Subsequent in-human trials tested word recognition in patients with intractable epilepsy who had iVNS devices implanted 2–24 weeks prior to testing. The stimulation parameters were 30Hz, 0.5 mA at 0.5 ms pulse width compared to an amplitude of 0.75–1 mA, and improved word recognition was only found in the group stimulated at the lower amplitude (Clark et al., 1999). These results paved the way for further investigation in this area as detailed below.

VAGUS NERVE STIMULATION AND COGNITIVE CONTROL, i.e., EXECUTIVE FUNCTION IN HEALTHY VOLUNTEERS

Inhibitory control is commonly measured using performance on tasks such as the Stroop, Eriksen Flanker (Flanker), and Simon tasks, i.e., forced-choice reaction time tasks that require participants to selectively attend and respond to target stimuli whilst ignoring goal-irrelevant distracting stimuli (Kornblum et al., 1990; MacLeod, 1991; Eriksen, 1995).

Enhanced response times, as reflected by participants' ability to stop a process and change to another response simultaneously and sequentially, and increased post error slowing were demonstrated during t-VNS (Sellaro et al., 2015; Steenbergen et al., 2015). Post error slowing refers to appropriate slowing after negative feedback or unforeseen errors and is linked to the activity of the locus coeruleus–norepinephrine (LC–NE) system and therefore postulated to be enhanced by VNS. As with the above trials, there were fewer false alarms during a more challenging paradigm with t-VNS when working memory processes were simultaneously engaged (Beste et al., 2016) and improved response selection and control performance was demonstrated with t-VNS in a serial reaction time test in young volunteers (Jongkees et al., 2018). In a sequence learning paradigm, the presentation of so-called reversal trials is associated with longer response latencies as compared to non-reversal trials, a result attributable to the 'inhibition of return' type phenomenon. Inhibition of return refers to an inhibitory after-effect of attention whereby, following exogenous orientation of attention to a stimulus, processing of stimuli at this location is first facilitated and then inhibited (Wang et al., 2018). Jongkees et al. (2018) demonstrated that active t-VNS, as compared to sham stimulation in the context of a serial reaction time test, reduced reaction time for reversal trials, eliminating the inhibition of return like effect described above.

In a similar experimental set up, increased attention, globally enhanced accuracy and reduced performance costs were demonstrated in a Stop-Change paradigm with t-VNS (Keute et al., 2020).

Results in this area have not been uniformly positive. In a testing paradigm in healthy volunteers using higher than average amplitude settings (see **Table 2**) there were no improvements in a Stroop test, Modified Flanker test or a number/letter working memory task with t-VNS. Improved accuracy in a dimensional change card sorting task was however noted (Borges et al., 2020). Similar previous studies failed to show improved behavioral performance with t-VNS (Fischer et al., 2018; Ventura-Bort et al., 2018) however non-performance parameters, namely a frontal EEG signal (P3 amplitude) thought to change with response inhibition and higher salivary amylase levels, were noted in the intervention group (Ventura-Bort et al., 2018). Further studies investigating EEG amplitudes affected by t-VNS and cognitive control paradigms included one involving an acoustic rather than visual oddball paradigm. In this context, t-VNS augmented the P3 amplitude, and with random noise stimulation with t-VNS reaction times were reduced (Rufener et al., 2018). There are myriad potential reasons for replication challenges in this newly expanding area of research and may include stimulation parameter differences including lack of pre-testing active stimulation.

The most recent studies in this area have involved a spatial stimulation and response inhibition multitask, with notable improved results in accuracy with 25 min pre-assessment t-VNS stimulation (Sun et al., 2021) and improved objective attention, arousal and multitasking ability in sleep deprived military personnel (McIntire et al., 2021).

VAGUS NERVE STIMULATION AND LANGUAGE IN HEALTHY VOLUNTEERS

Fluency scores in healthy volunteers during a convergent and divergent thinking task were significantly higher during active t-VNS at the left conchae, and categorical flexibility (i.e., participants' ability to think of more and varied categories of nouns) was also significantly improved (Colzato et al., 2018). However, an experimental design investigating the difference in

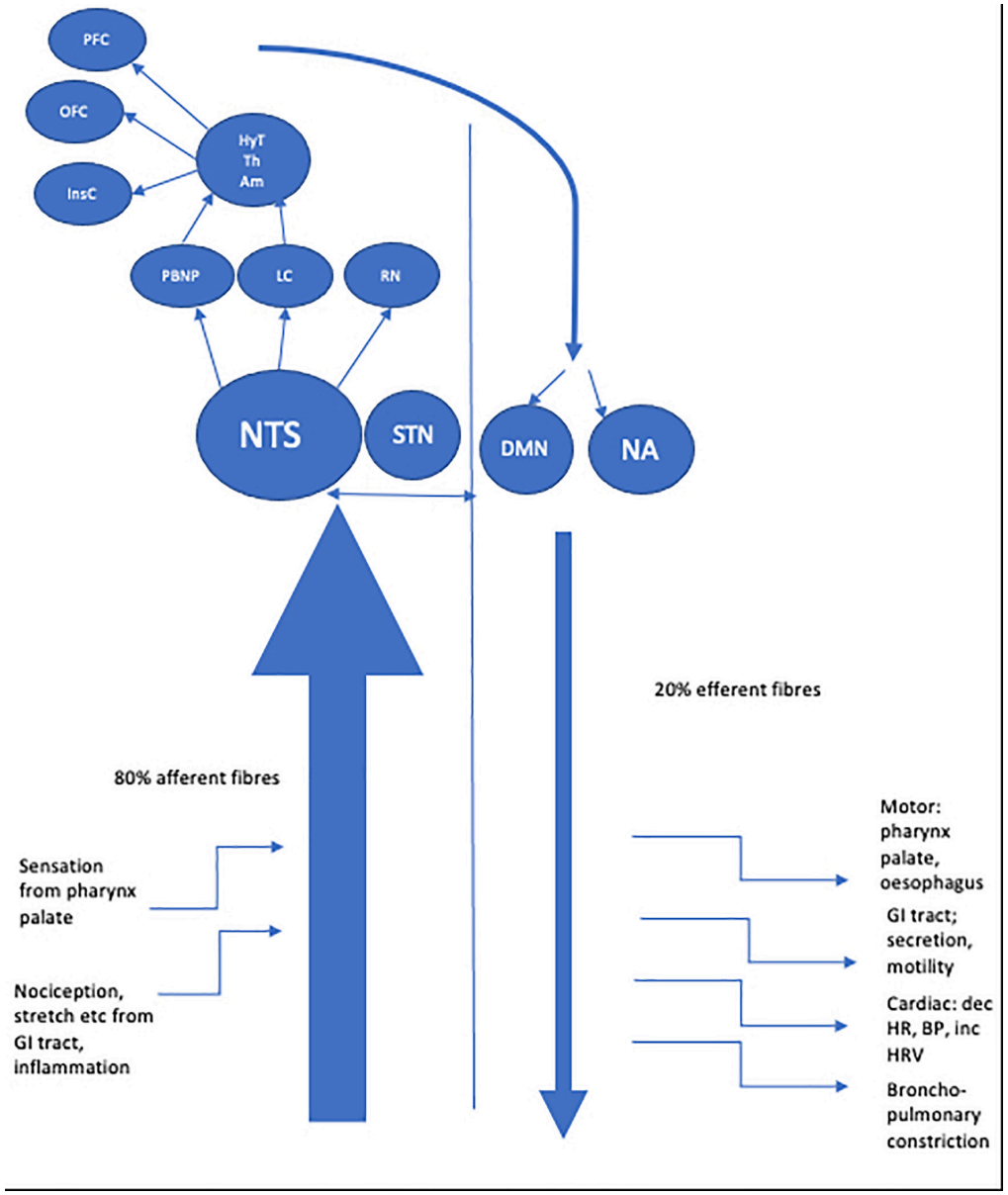


FIGURE 1 | Schematic representation of afferent and efferent fibers of the vagus nerve and central projections.

effect of t-VNS on word recognition memory in young compared to older volunteers (average age 22.2 and 55.1) whereby t-VNS was delivered for 30 s during the consolidation phase of a word recognition memory task showed no improvement in accuracy scores for immediate recall or delayed recognition in both age groups (Mertens et al., 2020). Possible reasons for this may be that 30 s of t-VNS may be insufficient for a non-invasive device to effectively stimulate the vagal afferent pathway, that longer and more repetitive stimulation of the vagus nerve might be required to effectively modulate hippocampal processes *via* synaptic plasticity. A recent investigation of word retention, stimulating the left tragus with t-VNS at again similar parameters but wider amplitude found improved accuracy in word retention but only in items that rhymed, i.e., were phonologically similar (Kaan et al., 2021).

VAGUS NERVE STIMULATION AND ASSOCIATIVE MEMORY IN HEALTHY VOLUNTEERS

Transcutaneous auricular vagus nerve stimulation has been tested in a group of healthy older adults to determine the technique's impact on performance in a face-name association task (Jacobs et al., 2015). VNS was employed in the encoding and consolidation phases of the task with active and sham stimulation

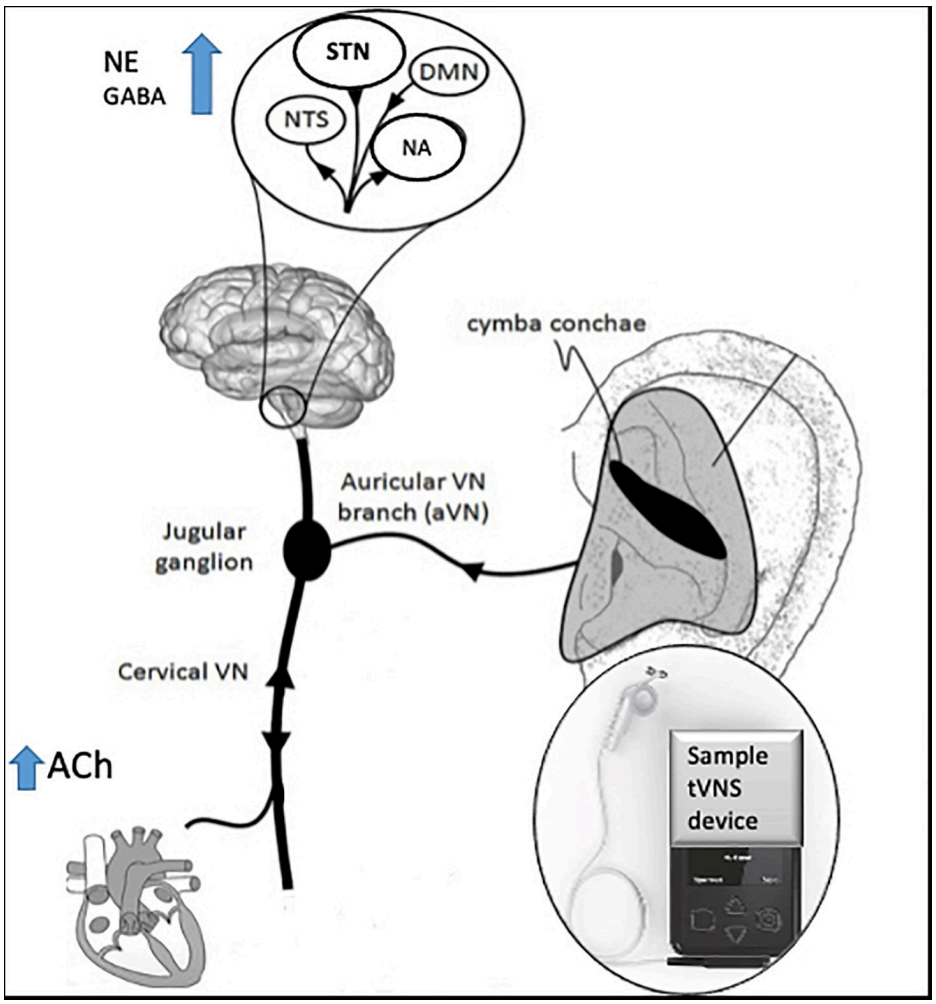


FIGURE 2 | Schematic diagram of innervation of ABVN and central projections, adapted with permission from Kaniusas et al. (2019).

compared in a randomized crossover design. Active t-VNS was demonstrated to increase the number of 'hits' on the memory task. Stimulation parameters employed differed somewhat from those seen in the broader literature concerning the impact of VNS on cognitive function. A stimulation intensity of 5.0 mA, a pulse width of 0.2 ms, and a frequency of 8Hz were utilized, citing previous functional and electrophysiological studies (Kraus et al., 2007; Polak et al., 2009). A stimulation lead in time of 17 min was also utilized, which has been theorized to be beneficial for targeted neuronal plasticity (Hays et al., 2013).

VAGUS NERVE STIMULATION AND EMOTION RECOGNITION IN HEALTHY VOLUNTEERS

This ability to recognize different emotions in others was investigated and found to be enhanced by t-VNS at the left outer auditory canal in young healthy adults but only for objectively easy, not challenging, items *via* the Reading the Mind in the Eyes test (Colzato et al., 2017). Subsequent investigations of fear conditioning and extinction in young volunteers, after previous positive studies, found that t-VNS at the left cymba conchae did not infer any difference in physiological or declarative indices of fear or improve fear extinction (Burger et al., 2019). Further studies are needed in this area to elucidate if t-VNS has a specific beneficial effect, given its ability to modulate both cortical and subcortical structures.

See **Table 2** for parameters settings and outcomes in trials of VNS in healthy volunteers.

VAGUS NERVE STIMULATION AND COGNITION IN CLINICAL POPULATIONS

In this section we highlight the studies to date investigating the cognitive effects of VNS on clinical populations, mostly with treatment-resistant depression or epilepsy. Many studies investigating the role of VNS in clinical populations has involved

TABLE 2 | Cognition and VNS in healthy volunteer populations.

COGNITION AND VNS: Healthy volunteers

		Stimulation Parameters						
Study	**iVNS/tVNS**	**Hz**	**mA**	**Pulse width**	**Time**	**Population**	**Task**	**Outcome**
Steenbergen et al., 2015	tVNS	25Hz	0.5mA	200–300 μs	30 s blocks	Healthy young adult volunteers $n = 30$	Stop change paradigm	Enhanced response selection and faster response times when two actions executed in succession
Sellaro et al., 2015	tVNS left outer auditory canal	25Hz	0.5 mA	200–300 μs	30 s blocks	Healthy young adult volunteers $n = 40$	Modified Flanker test	Increased post error slowing during active tVNS
Jacobs et al., 2015	tVNS left external acoustic meatus	8Hz	5.0 mA	200 μs	17 min	Healthy older adults avg age 60.5 $n = 30$	-Face name recognition task −15 word learning test -Digit span forward/backward -Verbal fluency test -Concept shifting task -Letter digit subtraction -Stroop color word test	Higher number of accurate "hits" during tVNS for face name recognition
Beste et al., 2016	tVNS left inner ear	25Hz	0.5 mA	200–300 μs	30 s on/30 s off	Healthy young volunteers $n = 51$	Inhibitory control (go-no-go task)	Fewer false alarms in the more challenging paradigm, i.e., when working memory processes also engaged
Colzato et al., 2017	tVNS Left outer auditory canal	25Hz	0.5 mA	200–300 μs	30 s on/30 s off	Healthy young volunteers $n = 38$	Emotion recognition Reading the mind in the Eyes test	Enhanced emotion recognition for easy (not challenging) items suggesting it promoted the ability to decode salient social cues
Fischer et al., 2018	tVNS	25Hz	Avg 1.3 mA (0.4–3.3)	200–300 μs	Continuous	Healthy adult volunteers $n = 21$	-Adapted response conflict Simon task -Novelty oddball task	No behavioral change noted Down-regulated N2 potential EEG reading
Ventura-Bort et al., 2018	tVNS Left cymba conchae	25 Hz	−1.3 mA (0.4–3.3) active −1.49 mA (0.6–4.8) sham	200–300 μs	28 min task 1 7 min task 2	Healthy young volunteers $n = 21$	-Novelty oddball task -number version of the Simon task	-No difference with tVNS with difficult targets or novel stimuli -Difference between tVNS and sham stimulation (P3 amplitude) in EEG parameters for easy targets associated with larger increase in sAA levels after tVNS
Rufener et al., 2018	tVNS Left cymba conchae	25Hz	0.5 mA	250 μs	30 s on/30 s off Started 90 min prior to task	Healthy young volunteers $n = 20$ avg age 24.8	-Acoustic oddball paradigm (respond as quickly as possible whenever a target tone was detected)	- tVNS increased EEG parameter P3 amplitude - Random noise stimulation reduced the reaction time
Maharjan et al., 2018	tVNS at left ear both anterior (cymba conchae) and posterior of ear	−80Hz −10Hz -No stim	10–15 mA	180 μs in square waveform	25–35 min lead in time	Healthy adult males $n = 18$	Two olfactory tests (odor threshold test (OTT) and supra-threshold test (STT)	High frequency (80Hz) VNS positively modulated olfactory performance in healthy participants and showed significant increase in NIRS recordings of the right hemispheric orbitofrontal cortex
Colzato et al., 2018	tVNS left concha $n = 40$ sham left earlobe $n = 40$	25Hz	0.5 mA	200–300 μs	15 min lead in time	Healthy young volunteers $n = 80$ (50 females, 30 males, mean age 20.96)	Convergent and divergent thinking tasks	-Fluency scores were significantly higher in the active tVNS group (able to generate more answers) -tVNS affected cognitive flexibility, i.e., participants could think of more different categories than sham
Jongkees et al., 2018	tVNS left medial acoustic meatus	25Hz	0.5 mA	200–300 μs	30 s blocks 15 min lead in time	Healthy young adult volunteers $n = 40$	Serial reaction time test	Enhanced response selection process and action control performance

(Continued)

TABLE 2 | (Continued)

COGNITION AND VNS: Healthy volunteers

		Stimulation Parameters						
Study	**iVNS/tVNS**	**Hz**	**mA**	**Pulse width**	**Time**	**Population**	**Task**	**Outcome**
Burger et al., 2019	tVNS Left cymba conchae	25Hz	0.5 mA	250 μs	30 s on/30 s off 10 min lead in time	Healthy young volunteers $n = 61$	Computerized fear conditioning, fear generalization, and fear extinction paradigm	No difference in physiological and declarative indices of fear between tVNS and sham conditions
Mertens et al., 2020	tVNS cymba conchae	25Hz	0.5 mA for 16 0.54–0.57 mA for rest	250 μs	30 s during consolidation	Healthy volunteers $-n = 41$ age avg 22.2 $-n = 24$ age avg 55.1	Word recognition task	No effect on verbal word memory
Giraudier et al., 2020	tVNS left cymba conchae (active) or left earlobe (sham)	25Hz	Active 1.48 mA ± 0.59 sham 1.31 mA ± 0.5	200–300 μs	30 s on/30 s off Stimulated for 23 min 5 min before 13 min during and 5 in after lexical decision task	Healthy volunteers $-n = 60$ $-46 =$ female -avg age 23.45	Lexical decision task and recognition memory task of selected German words (either emotionally charged or neutral) Also – BP, HR and sAA	Overall no effect of tVNS on task performance or word recognition memory – however higher recollection based memory performance was observed during tVNS than sham
Borges et al., 2020	tVNS	25Hz	2.19 mA (±0.93)	200–300 μs	30 s on/30 s off 4 min lead in time	Healthy adult volunteers $n = 35$	-Modified Flanker test -Spatial Stroop task -Number/Letter task -Dimensional change card sorting task	Only the DCCS shows improvement with tVNS
Keute et al., 2020	tVNS left cymba conchae	25Hz	2.37 mA (±0.16)	200 μs	30 s on/30 s off 30 min lead in time	Healthy adult volunteers $n = 22$	Stop Change paradigm (go-no-go task)	Globally enhanced accuracy across conditions -Reduced the performance costs of go/change response conflicts -increased attention
Sun et al., 2021 Study 1	tVNS Left cymba conchae Sham: no stimulation	25Hz	Online 0.7 ± 0.36 mA Offline 0.69 ± 0.38 mA Sham 0.73 ± 0.27 mA	500 μs	30 s on and 30 s off 25 min pre task (offline) or 15 min during task (online)	Healthy young volunteer $n = 46$ (25 female, average age 20.39 ± 1.96)	Spatial stimuli task Four blocks with 72 experiment trials in each block	Offline (pre-task stim for 25 min) tVNS significantly increased hits in spatial 3-back task but not rejections or reaction times
Sun et al., 2021 Study 2	tVNS left cymba conchae sham; active stimulation of earlobe	25 Hz	Active: 0.74 mA ± 0.37 Sham: 0.84 mA ± 0.39	500 μs	30 s on and 30 s off Both 25 min stimulation	Healthy young volunteers $n = 58$ (24 female, average age 19.9 ± 1.49)	Spatial stimuli task Four blocks with 72 experiment trials in each block	Offline (pre- task stimulation for 25 min) tVNS improved hits but not correct rejections or reaction time of accurate trials in spatial WM performance
Kaan et al., 2021	tVNS Left tragus	25Hz	1–6 mA	250 μs		Healthy young volunteers $n = 33$ control $n = 29$ experiment	-Word retention: – non-rhyming, easily separable words -rhyming words	tVNS was associated with higher accuracy but only when the items are phonologically similar
McIntire et al., 2021	Cervical VNS *via* gammaCore device cVNS vs. sham ($n = 20$ both groups)	25Hz	Not available	Not available	2 min cycles	Healthy young military recruits $n = 40$ (M:F 33:7) avg age 28 ± 6 years	34 h of continuous sleep deprivation Air Force–Multi-Attribute Task Battery (AF-MATB); simultaneously monitor and respond to four separate cognitive process tasks: a visual system alert monitoring task, a visual–motor tracking task, an auditory communication monitoring task and a management task	cVNS significantly improved objective arousal and multitasking for as long as 24-h post-stimulation Subjective ratings of fatigue also improved

invasive VNS (iVNS). A further potential confounder is the impact some of these underlying pathologies have on cognition, the altered medial temporal anatomy especially in cases of epilepsy and the medications used to manage these conditions can also have deleterious effects on cognition.

VAGUS NERVE STIMULATION AND COGNITIVE CONTROL, i.e., EXECUTIVE FUNCTION IN CLINICAL POPULATIONS

Vagus nerve stimulation has been shown experimentally to have mixed results when examining the subdomain of decision making, specifically on the Iowa Gambling Task (IGT). In one paradigm eleven patients with refractory epilepsy and iVNS devices completed a gambling task involving control and experimental trials with active VNS synchronized to stimulate in the latter. Whilst improved performance was demonstrated in the earlier part of the task, this trend was reversed later in the experimental trial with active stimulation trending toward being detrimental to performance (Martin et al., 2004). Technical failure and a cumulative stimulation-dose effect were amongst the potential explanations proposed by the authors to explain this phenomenon. Decision-making may depend on intact working memory (Bechara and Martin, 2004) and several studies have demonstrated working memory involvement in the IGT (Bagneux et al., 2013) which may have affected results in this study.

Working memory refers to a cognitive process that provides temporary storage and manipulation of the information necessary for complex cognitive tasks (Baddeley, 2010). Literature concerning the impact of acutely administered VNS on working memory is promising but limited to a small number of studies. In one experimental paradigm, twenty participants with poorly controlled epilepsy were required to perform a computer-based Executive-Reaction Time (Executive RT) Test, wherein ability to memorize and store the orientation of a triangle and indicate its position in response to a go signal were assessed whilst VNS was delivered in a cyclic fashion. Active iVNS stimulation was associated with fewer errors in the subtask relying on working memory (Sun et al., 2017).

The effect of active iVNS on response inhibition was also assessed by employing a classic stop-signal task in participants with refractory epilepsy (Schevernels et al., 2016). Quicker response inhibition has been demonstrated during active stimulation in patients who had previously shown a larger therapeutic effect of VNS. The beneficial effects of VNS on cognitive control may be maximally demonstrated in so-called 'VNS responders' (for the primary clinical indication) as demonstrated by patients with iVNS devices who undertook the Eriksen Flanker task during both VNS 'on' and 'off' stimulation. Only those deemed VNS responders (i.e., those whose seizure frequency had decreased by >50% post-device implantation) had demonstrable improved reaction times and reduced distractor interference during active stimulation (van Bochove et al., 2018). There is a subcategory of patients with refractory epilepsy who do not respond to iVNS therapy, i.e., do not have seizure reduction of 50%, and deemed "non-responders." It is notable that a current output of 2.28 mA was utilized in the VNS "responder" group and it's possible that, in keeping with previous studies examining optimal amplitude for stimulation, that the higher amplitudes employed exceeded that at which cognitive control is optimized for the iVNS "non-responders." Further research is needed in this area in particular regarding stimulation parameters and iVNS responders.

VAGUS NERVE STIMULATION AND LANGUAGE IN CLINICAL POPULATIONS

In the first study of its kind, building on previous preclinical research, the impact of iVNS on word retrieval memory was assessed *via* an experimental protocol whereby participants with iVNS devices inserted for epilepsy control, were required to read a series of paragraphs, and subsequently identify words that were highlighted in the text. The study population comprised two groups of patients who were administered active (0.5–1.5 mA) or sham VNS, delivered 2-min after learning in the memory consolidation phase. An inverted U-shaped relationship was demonstrated regarding stimulus intensity and modulation of cognitive performance, with memory enhancing effects demonstrated only at moderate intensities, namely 0.5 mA (Clark et al., 1999). These results were in part corroborated by a subsequent study which employed higher stimulation intensities (>1.0 mA) and failed to demonstrate enhancement of verbal recognition memory, in fact demonstrating a reversible deterioration in figural memory (Helmstaedter et al., 2001). However, study design may have impacted cognitive outcomes here as delivery of stimulation was not restricted to the consolidation period. The propensity for iVNS to positively impact word retrieval memory in a population of patients being treated with iVNS for intractable epilepsy was highlighted again in 2006 whereby the impact of iVNS on performance in the Hopkins Verbal Learning Test was assessed, demonstrating a significant improvement in word retention when active (amplitude 0.5 mA) as opposed to sham stimulation was applied during memory consolidation (Ghacibeh et al., 2006b).

VAGUS NERVE STIMULATION AND EMOTIONAL RECOGNITION IN CLINICAL POPULATIONS

The effect of t-VNS on participants' ability to recognize facial emotions in three experimental paradigms (graded presentation, static images and in a go-no-go task) was assessed in a group of adolescents diagnosed with major depressive disorder (MDD). In non-depressed controls t-VNS delivered at 1Hz, 0.5 mA 30 s block with 15 min lead in time, demonstrated enhanced recognition of emotions but notably led to a significant decrease in the ability of those with MDD to recognize sad emotions (Koenig et al., 2021).

TABLE 3 | VNS and cognition in clinical populations.

COGNITION AND VNS: Clinical Populations								
		Stimulation Parameters						
Study	**iVNS/tVNS**	**Hz**	**mA**	**Pulse width**	**Time**	**Population**	**Task**	**Outcome**
Clark et al., 1999	iVNS 2–24/52 post implantation	30Hz	−0.5 mA −0.75–1.5 mA	0.5 ms	30 s	Intractable epilepsy $n = 10$	Word recognition task	Improved word recognition memory only when 0.5 mA delivered post reading
Sjögren et al., 2002	iVNS Assessed at 3 and 6 months	20Hz	0.25 mA, increased 0.25 mA increments over 2 weeks then fixed	500 μs	30 s followed by 5 min pause	Probable Alzheimer's $n = 10$ age 67 ± 7.6 8 women 2 men	Median change in ADAS-cog Median change in MMSE after 3 and 6/12 Depression, behavior and QOL variables	After 6/12 8 of 10 patients showed improvement from 3/12 ADAS-cog scores After 6/12 7 of 10 patients improved MMSE score by average 2.5 points No change in other variables
Martin et al., 2004	iVNS	30Hz	0.5 mA	500 μs	60 s	Intractable epilepsy $n = 11$	Iowa Gambling Task	Conflicting results, deleterious at higher doses
Merrill et al., 2006	iVNS At least 1 year of VNS treatment	20Hz	0.25 mA, increased in 0.25 mA increments over 2 weeks then fixed	500 μs	30 s followed by 5 min pause	Probable Alzheimer's $n = 17$ (age 63 range 57–81) 11 women 6 men	Median change in ADAS-cog Median change in MMSE after 1 year Depression, behavior and QOL variables	At 1 year, 41% had improvement or no decline from baseline on ADAS-cog 70% had improvement or no decline on MMSE No change in other variables
Helmstaedter et al., 2001	iVNS 5–7/12 post implantation	30Hz	Mean 1.75 mA (range 1–2.5)	500 μs	30 s–4.5 min	Intractable Epilepsy $n = 11$	Word recognition task Design recognition task	Deterioration in figural recognition memory
Dodrill and Morris, 2001	iVNS 12–16/52 after implantation	30 Hz in high stim group 1 Hz in low stim group	Avg 1.3 mA in high simulation group Avg 1.2 mA in low stimulation group	500 μs 130 μs	30 s on every 5 min 30 s on every 3 h	Intractable Epilepsy $n = 160$	Wonderlic personell test, Stroop test, Digit cancelation, Symbol Digit Modalities	No significant changes were noted in the cognitive tests in low or high stimulation
Ghacibeh et al., 2006b	iVNS >3/12 post implantation	X	0.5 mA	x	30 s	Intractable Epilepsy $n = 10$	Hopkins verbal learning test	Improved retention index
McGlone et al., 2008	iVNS 12/12 post implantation	30 Hz	0.5–3 mA avg 1.72 ± 0.53	500 μs	30 s every 5 min	Intractable epilepsy $n = 16$	Memory Observation Questionnaire	Improved subjective and objective memory scores compared to baseline, but similar to medical management
Schevernels et al., 2016	iVNS >18/12 post implantation	Avg 25 (20–30)	Avg 2.3 mA (0.75–3.0)	Avg 431 μs (130–500 μs)	7 s on/ 18 s off	Intractable epilepsy $n = 20$	Stop signal task	VNS responders demonstrated quicker response inhibition
Sun et al., 2017	iVNS 2–130 months post implantation	30Hz	1.5–1.75 mA	250 μs	30 s on/48 s off	Intractable epilepsy $n = 20$	Executive reaction time test (go-no-go task)	Improved working memory (only when 3 participants with cognitive impairment removed)
van Bochove et al., 2018	iVNS	20 or 30 Hz	Avg 2.28 mA (0.75–3.0)	250 μs or 500 μs	7 s on/ 18 s off	Intractable epilepsy $n = 17$	Eriksen Flanker task	VNS responders demonstrated improved reaction times and decreased distraction interference
Koenig et al., 2021	tVNS Left conchae	1Hz	0.5 mA	250 μs	30 s on/30 s off 15 min lead in time	-Adolescents with major depressive disorder $n = 33$ control group: adolescents with headache $n = 30$	Facial emotional recognition in three tests 1. As a graded presentation 2. As static images 3. in a go – no -go task	-In non-depressed controls tVNS enhances the general ability to recognize emotions -tVNS specifically led to a decrease in the recognition of sad emotions in patients with MDD

TABLE 4 | VNS and neurocardiovascular assessment.

Neurocardiovascular assessment AND VNS

		VNS Stimulation Parameters						
Study	**iVNS/tVNS/site specific**	**Hz**	**mA**	**Pulse width**	**Time**	**Analysis parameters**	**Population**	**Result**
Kamath et al., 1992	iVNS for refractory epilepsy (left cervical vagus)	2 Hz 30 Hz	0.1 mA 1 mA	130 ms 500 ms	Not specified	Baseline 45 min ECG readings pre implantation and at 2/52 post implant	Refractory epilepsy $n = 8$ High stimulation and low stimulation groups avg age 34 ± 7.8 range 21–47	HiStim group: LF:HF ratio decreased from 2.5 ± 1.5 preimplant to 1.5 ± 0.49 ($P < 0.02$) with iVNS Significantly higher HF power in the HiStim compared to LoStim group
Setty et al., 1998	iVNS for refractory epilepsy (left cervical vagus) implanted for minimum 1/12	30 Hz	Max tolerated threshold	750 μs	30 s on 5 min off	Pre and post stimulation ECG (7 min baseline, 2.5 min of stimulation and a 7 min post-stimulation)	Refractory epilepsy $n = 10$ (avg age 28 range 14–46) 8 men	No significant effect noted on HRV variables
Handforth et al., 1998	iVNS for refractory epilepsy (left cervical vagus)	30Hz in high stimulation group I Hz in low stimulation group	Avg 1.3 mA in high simulation group Avg 1.2 mA in low stimulation group	500 μs 130 μs	30 s on every 5 min 30 s on every 3 h	Study mainly aimed at seizure reduction in two groups (high vs. low stimulation) in refractory epilepsy	Refractory epilepsy High stimulation group $n = 95$ age 32.1 ± 10.8 Low stimulation $n = 103$ age 34.2 ± 10.1	"Autonomic function assessments revealed no significant changes in Holter function measures; mean heart rate, mean lowest or highest heart rate, heart rate variability, occurrences of bradycardia"
Galli et al., 2003	iVNS for refractory epilepsy (left cervical vagus)	30 Hz	0.25 mA adjusted	500 μs	30 s on every 5 min	24-h analysis of RR variability at baseline (t0), 1 month (t1, short-term VNS) and 36 months after VNS initiation (t2, long-term VNS).	Refractory epilepsy $n = 7$ (4 men) age 47 ± 11.2 range 34–63 f	No significant changes in HRV variables, trend to increased HF at night-time
Ronkainen et al., 2006	iVNS for refractory epilepsy (left cervical vagus)	30 Hz	2.9 mA avg	500 ms	30 s on 5 min off	Pre and 1 year post implantation 24 h Holter HRV variables	Refractory epilepsy $n = 14$ (eight male and six female age 34.3 ± 9.3; 20–52) compared to matched controls	VNS had no significant effects on any HRV indices despite a significant reduction in seizure frequency
Barone et al., 2007	iVNS for refractory epilepsy (left cervical vagus)	30 Hz	0.75–1.75 mA	500 μs	30 s on, 5 s off	24 h ECG holter at baseline and after 3/12 implantation	Refractory epilepsy 8 patients (age 32 range 9–65 2 men)	No significant change in HRV parameters after 3/12 iVNS
Sperling et al., 2010	iVNS (left cervical vagus) for treatment resistant depression (post implantation 6–40 months)	15–30Hz	0.25–2.5 mA	500 μs	30 s on 5 min off	ECG testing at baseline, switched on and switched off conditions	Patients with major depressive disorder (ICD-10) $n = 9$ (51.6 years, 5 women, 4 men) Compared to age and sex matched controls	RMSSD increased significantly in switched on conditions during stimulation (30 s) in six patients compared to stimulation-free intervals and baseline
Clancy et al., 2014	tVNS on inner and outer surface of the tragus of the ear Sham – on tragus but disconnected Either active or sham tVNS	30Hz	10–50 mA	200 μs	Continuous 15 min stimulation	HRV frequency and spectral analysis Muscle sympathetic nerve activity (MSNA) recordings	Healthy volunteers $n = 48$ age 20–62 years old (M:F 1:1)	Significant decrease in LF/HF ratio during active tVNS Greater response to tVNS in those who had higher sympathetic predominance at baseline (higher LF/HF ratio)

(Continued)

TABLE 4 | (Continued)

Neurocardiovascular assessment AND VNS								
		VNS Stimulation Parameters						
Study	**iVNS/tVNS/site specific**	**Hz**	**mA**	**Pulse width**	**Time**	**Analysis parameters**	**Population**	**Result**
de Couck et al., 2017 Study 1	tVNS cymba conchae left or right ear vs. sham (earlobe)	25Hz	0.7 mA average	250 μs	30 s on/30 s off 10 min	HRV frequency and spectral analysis	Healthy older volunteer $n = 30$ age 23–58	Right stimulation alone significantly increased SDNN compared to baseline
de Couck et al., 2017 Study 2	tVNS cymba conchae right ear	25Hz	1 mA average	250 μs	30 s on/30 s off 1 h	HRV frequency and spectral analysis	Healthy older volunteer $n = 30$ age range 30–65	SDNN significantly increased after 35 min and after 1 h specifically in female participants LF and LF/HF significantly increased after 35 min of stimulation
Antonino et al., 2017	tVNS active – tragus- inner and outer surface sham ear lobe Electrodes placed bilaterally (1) active tVNS (2) sham- olunteer placed on tragus –no current (3) olunteer placed on the earlobe current applied	30 Hz	45 ± 1 mA	200 μs	Continuous 15 min	HRV, BP variability, cBRS	Healthy young male olunteer $n = 13$ age = 23 ± 1	Active tVNS acutely improved spontaneous cBRS, olunteer LF/HF ratio and evoked slight decrease in HR Nil change with two sham conditions
Lamb et al., 2017	tVNS left tragus/auditory meatus or sham (no current)	20Hz	5.6 mA range 3–11.3 mA	100 μs	unavailable	Postural HRV *via* Tilt Table Test Startle Blink Paradigm	Military veterans with PTSD and mild TBI $n = 12$ or healthy control $n = 10$ age 30 ± 7	Significantly increased RSA (HF HRV) in tilt during tVNS Trend toward reduced reactivity (*via* electrodermal response monitoring) to startle
Badran et al., 2018b Study 1	tVNS to the inner side of the left tragus (anode in the ear canal, cathode on the surface of the tragus) of the left ear for 9 different stimulation rounds sham = left earlobe crossover design	1Hz 10 Hz 25 Hz	At 100 μs: tragus 9.28 ± 2.56 mA earlobe 6.5 ± 1.83 mA At 200 μs tragus 5.32 ± 1.60 mA earlobe 3.64 ± 1.26 mA At 500 μs tragus 3.0 ± 0.93 mA earlobe 1.97 ± 0.70 mA	100 μs 200 μs 500 μs	Stimulation period (60s) recovery period (180s)	Heart rate analysis	Healthy young adult olunteer $n = 15$ (M:F 1:1) age 26.5 ± 4.9	Active stimulation olunteer HR more than control stimulation on with these parameters: 500 μs at 25 Hz 500 μs at 10 Hz
Badran et al., 2018b Study 2	tVNS to the inner side of the left tragus (anode in the ear canal, cathode on the surface of the tragus) of the left ear for 10 stimulation rounds sham = left earlobe crossover design	10 Hz 25 Hz	tragus- 2.09 ± 0.97 mA earlobe 2.04 ± 0.82 mA	500 μs	Stimulation period (60s) recovery period (90s)	Heart rate analysis	Healthy young adult olunteer $n = 20$ (M:F 1:1)	The parameters 500 ms at 10 Hz alone induced a significant decrease in HR
Bretherton et al., 2019 Study 1	tVNS left tragus 1 week later sham (electrodes on tragus but no current)	30Hz	2–4 mA	200 μs	15 min	Baroreceptor sensitivity §	Healthy participants aged ≥55 years $n = 14$ Age 69.11 ± 1.52	Baseline LF/HF ratio power significantly predicted response to tVNS where higher resting LF/HF ratio was associated with greater olunteer during tVNS

(Continued)

TABLE 4 | (Continued)

Neurocardiovascular assessment AND VNS

		VNS Stimulation Parameters						
Study	**iVNS/tVNS/site specific**	**Hz**	**mA**	**Pulse width**	**Time**	**Analysis parameters**	**Population**	**Result**
Bretherton et al., 2019 Study 2	tVNS left tragus no sham	30 Hz	2–4 mA	200 μs	15 min	Baroreceptor sensitivity, HRV frequency and spectral analysis	Healthy participants aged ≥55 years $n = 51$ Age 65.20 ± 0.79	Total power, mean RR interval, Δ RR, SDRR were significantly affected during tVNS A higher LF/HF ratio predicted a greater decrease to tVNS
Bretherton et al., 2019 Study 3	tVNS left tragus daily at home for 15 min for 2 weeks	30Hz	2–4 mA	200 μs	15 min daily for 14 days	HRV frequency and spectral analysis	Healthy participants aged ≥55 years $n = 29$ Age 64.14 ± 0.89	RMSSD, pRR50, SD1 and nSD1, were significantly higher after 2 weeks tVNS
Tobaldini et al., 2019	tVNS left cymba conchae Cross-over design 2-day protocol, 1 day with tVNS and a control day, at least 24 h difference	25Hz	1–6 mA adjusted to sensory threshold	200 μs	10 min supine stimulator on (rest tVNS on), 15 min orthostatic position with tVNS on (tilt tVNS on)	(1) ECG (2) Respiration (3) Non-invasive beat-to-beat arterial blood pressure at rest and during a 75° tilt test	Healthy young olunteer $n = 13$ (5 males, 8 females) age 27 ± 4 years	Clinostasis: tVNS reduced HR, systolic BP variability and cardiac and peripheral sympathetic modulation Responsivity of HR and BP to orthostatic stress during tVNS was significantly higher when compared to control
Borges et al., 2019 Study 1	tVNS to left cymba conchae	25Hz	0.5, 1, and 1.5 mA	200–300 μs	30 s on/off cycling 10 min stimulation	RMSSD	Healthy young olunteer $n = 61$ (16 female) avg age 23.32	Increase in RMSSD during stimulation compared to the resting phases for all mA settings
Borges et al., 2019 Study 2	tVNS to left cymba conchae	25Hz	1 mA Compared to 1.78 mA ± 1.13	200–300 μs	30 s on/off cycling 10 min stimulation	RMSSD	Healthy young olunteer $n = 62$ (26 females avg age 24.77)	RMSSD values showed a significant overall increase during the stimulation phase none of the different stimulation conditions significantly differed from each other regarding RMSSD values
Borges et al., 2019 Study 3	tVNS to left cymba conchae vs. sham (earlobe)	25 Hz	Active 2.5 mA ± 0.93) Sham 2.76 mA ± 1.01	200–300 μs	30 s on/off cycling 10 min stimulation each	RMSSD	Healthy young volunteers $n = 60$ (31 females, age avg 23.62)	No difference between active and sham stimulation
Sclocco et al., 2019	tVNS (1) to cymba conchae no current (2) to cymba conchae active during exhalation (3) to cymba conchae active during inhalation (4) sham to earlobe	25 Hz	(1) 1.6 mA ± 2.3 (2) 1.7 mA ± 2.4 (3) 1.4 mA ± 1.1	450 ms pulse width duration of 1 s	32 min	-Instantaneous HF-HRV index -four 8-min duration fMRI scans (1) passive control (2) active stimulation exhalation (3) active stimulation inhalation (4) active control	Healthy adult participants $n = 16$ (9 female, age 27.0 ± 6.6)	Exhalation tVNS but not inhalation enhanced cardiovagal modulation, i.e., increased instantaneous HF hRV index Exhalation found significantly signal at MRI site of LC/NTS
Gauthey et al., 2020	tVNS Cymba Crossover design	5Hz 20Hz active 5Hz sham	1.5 ± 0. mA 1.2 ± 0. mA 5.5 ± 1. mA	0.2 ms	10 min stimulation 10 min washout	Muscle sympathetic nerve activity (MSNA) recorded by microneurography at rest, during apnoea and tVNS HRV power and spectral analysis	Healthy, young male volunteers $n = 28$ (age 27 ± 4)	Acute right cymba tVNS did not induce any effects on HRV nor MSNA variables when compared to active control

(Continued)

TABLE 4 | (Continued)

Neurocardiovascular assessment AND VNS								
		VNS Stimulation Parameters						
Study	**iVNS/tVNS/site specific**	**Hz**	**mA**	**Pulse width**	**Time**	**Analysis parameters**	**Population**	**Result**
Machetanz et al., 2021	tVNS right $n = 7$ left $n = 6$ -cymba conchae -cavum conchae -outer tragus -inner tragus -crus helicis -fossa triangularis	25 Hz at a periodicity of 1 Hz	0.2–2 mA 0.096–0.769 mA 0.05–0.4 mA	100 μs 260 μs 260 μs	90 s (i.e., 3 s × 30 s) at each stimulation site 144 parameter combinations	HRV power and spectral analysis	Healthy adults $n = 13$ (age 24 ± 3, 8 female)	Significant differences between right- and left-sided stimulation for the SDNN and RMSSD analysis only (increasing with right ear stimulation) HRV increases were highest at cymba conchae and fossa triangularis, to a lesser extent to stimulation at the inner tragus
Sinkovec et al., 2021	tVNS to right tragus during rest (60 min) and autonomic nervous system testing (15 min) (Valsalva, wet cold face, etc.) sham = no stimulation, preceded stimulation	20Hz	Adjusted individually to barely perceptible <150 μA	1 ms rectangular pulse width	1 h resting tVNS vs. sham 15 min ANST vs. sham	Continuous cardiac measurements with impedance cardiography Non-invasive arterial BP monitor ECG for HRV analysis	Healthy male volunteers $n = 15$ (age 23 range 20–25)	Indices of LV contractility, LV output, and LV work significantly decreased SBP and TPR significantly increased No difference HRV or ANST parameters

See **Table 3** for parameters settings and outcomes in trials of VNS in clinical populations and please see below "VNS, cognition and HRV" for a discussion of VNS in Alzheimer's disease.

LINKING BRAIN AND HEART: POTENTIAL MECHANISMS OF ACTION OF VAGUS NERVE STIMULATION-MEDIATED COGNITIVE ENHANCEMENT

There are many potential mechanisms through which VNS may exert its cognitive enhancing effects, including direct neurotransmitter release, increased cerebral perfusion to discreet neuroanatomical structures, reduced neuro-inflammation and *via* modulation of peripheral hemodynamics. For the purposes of this narrative review, we will analyze the link between cerebral blood flow, cerebral autoregulation and cardiac modulation. Beyond the scope of this review is how t-VNS may therapeutically affect the inflammatory cascade *via* activating the cholinergic anti-inflammatory pathway and the beneficial effects this may have in aging populations.

MECHANISM OF ACTION: VAGUS NERVE STIMULATION AND LOCAL NEUROTRANSMITTER RELEASE

The main neurotransmitters centrally released *via* the afferent projections of the vagus nerve are thought to be GABA and Norepinephrine (NE). For a comprehensive review of the preclinical and clinical studies detailing the evidence supporting the modulation of these neurotransmitters during iVNS and t-VNS see (Colzato and Beste, 2020).

As the primary inhibitory neurotransmitter in the brain, higher levels of GABA decrease cortical excitability, and is the accepted proposed method for VNS' anti-seizure efficacy. It has been suggested that increased cortical inhibition due to high GABA levels can sharpen task-relevant representations in the cortex and inhibit competing responses, thereby facilitating response selection and inhibition processes (Munakata et al., 2011; de la Vega et al., 2014).

Norepinephrine is a crucial neurotransmitter modulating arousal and attention, and is primarily released *via* the locus coeruleus (LC). There are two distinct modes of LC firing that are associated with equally distinct modes of attentional strategy. Connections with the orbitofrontal cortex and anterior cingulate cortex are thought to drive the LC-NE system into one of these two stable states of activity, a high tonic (sustained) mode or a phasic (bursting) mode accompanied by moderate tonic activity (Aston-Jones and Cohen, 2005). This switching of attentional state *via* tonic LC activity is thought to result in a flexible attentional system that allows cycling between behaviors to find and meet task demands in one's environment, i.e., the adaptive gain theory (Aston-Jones and Cohen, 2005).

Interestingly, and similar to the effects noted with iVNS stimulation levels and responses by Clark et al. (1995), moderate levels of NE augment prefrontal cortex function, whereas high and low concentrations of NE impair function, i.e., NE exhibits an inverted-U relationship between LC-NE activity and optimal performance on attention tasks (Berridge and Waterhouse, 2003). However, in general as NE levels rise executive function improves, likely *via* enhanced activation of the prefrontal cortex and frontoparietal control network (Xing et al., 2016; Unsworth and Robison, 2017). Inhibitory control for action cancelation is specifically enhanced with noradrenergic modulation, likely *via* this prefrontal cortical network (Chambers et al., 2009; Duann et al., 2009).

Older adults with more dense LC innervation (i.e., higher neuromelanin MRI contrast) had overall better performance on a reversal memory tasks (Hämmerer et al., 2018) and had improved cognitive reserve (Clewett et al., 2016). Similarly in a post-mortem study of patients with Alzheimer's disease, lower LC cell integrity and greater cortical tangle density was associated with greater tau burden beyond the medial temporal lobes and worsening memory decline, identifying LC integrity as a promising indicator of initial AD-related processes (Jacobs et al., 2021).

Studies have also demonstrated a decline in GABA concentration in frontal and parietal regions in aging populations, areas crucial for cognitive control (Gao et al., 2013; Porges et al., 2017). NE and GABA may in fact work synergistically to facilitate executive functioning; GABA by encouraging response inhibition of task irrelevant stimuli and NE *via* the LC-NE system increasing frontal NE release and thus executive functioning (Ridgewell et al., 2021).

MECHANISM OF ACTION: VAGUS NERVE STIMULATION INCREASES CEREBRAL PERFUSION

Cerebral autoregulation is the phenomenon by which the brain receives the same cerebral blood flow (CBF) despite variations in perfusion pressure. The aim of autoregulation is to protect the brain against hypoxia and edema as a result of decreased or critically high arterial blood pressures respectively. Multiple factors physiologically modify autoregulation including blood CO2 levels, hypoxia etc. While still controversial, the ANS may play a prominent role in cerebral autoregulation in response to such stimuli, inducing vasodilation or constriction, and parasympathetic and sympathetic nerves are anatomically located in the same perineural sheath innervating cerebral arteries (Tamayo and Siepmann, 2021). The means by which VNS exerts its cognitive enhancing effect is probably multimodal, however modulating CBF is likely a crucial factor.

Multiple modalities have been utilized to assess for CBF changes due to vagus nerve stimulation, including position emission tomography (PET), functional magnetic resonance imaging (fMRI) and single photon emission computed tomography (SPECT) studies and trials of patients with iVNS treatment for epilepsy and depression have demonstrated a variety of CBF modulatory effects at specific cortical and subcortical areas. Increased CBF at the orbitofrontal cortex (Henry et al., 1998; Bohning et al., 2001; Lomarev et al., 2002; Mu et al., 2004; Vonck et al., 2008), temporal lobe (Ko et al., 1996; Lomarev et al., 2002; Liu et al., 2003; Vonck et al., 2008; Conway et al., 2012), insular cortex (Liu and Hu, 1988; Henry et al., 1998, 2004), bilateral frontal lobes (Sucholeiki et al., 2002), left dorsolateral prefrontal cortex (Kosel et al., 2011) and subcortical structures including thalamus, hypothalamus, basal ganglia and other nuclei (Narayanan et al., 2002; Sucholeiki et al., 2002; Conway et al., 2012) has been observed. For a comprehensive review see Chae et al. (2003).

Notably analysis undertaken during acute iVNS has noted bilateral decreased hippocampal CBF (Henry et al., 1998; Mu et al., 2004; Vonck et al., 2008). This has been replicated in t-VNS functional imaging studies which have confirmed stimulation and increased CBF at vagally innervated brain regions during auricular t-VNS and notably decreased perfusion at hippocampal regions (Kraus et al., 2007, 2013; Frangos and Komisaruk, 2017). T-VNS has also demonstrated efficacy in increasing arousal in comatose patients who respond to auditory signaling and again the brain regions noted on fMRI to be activated were similar to previous iVNS studies, including left superior temporal gyrus, left prefrontal cortex, left insular cortex, left middle frontal gyrus among other cortical and subcortical structures (Yu et al., 2021).

It is worth considering that intermittently stimulating neurons at different frequencies produces drastically different changes in neuronal behavior with low frequency stimulation inducing long term depression (LTD) and less connectivity while intermittent high frequency stimulation produces long term potentiation (LTP) and increased signaling (Lomarev et al., 2002; Kealy and Commins, 2010). Therefore acute VNS stimulates brain regions mostly involved in alertness and frontal processing, whereas chronic stimulation may improve LTP in classic memory-associated regions, including the hippocampus. Evidence for this can be seen in preclinical studies (Zuo et al., 2007) but also significant increases in hippocampal gray matter volume over time has been observed in patients with iVNS devices inserted for treatment-resistant depression (Perini et al., 2017). More recently, Near Infrared Spectroscopy (NIRS) has been utilized to monitor cerebral blood flow and increased frontal perfusion in patients with epilepsy was noted during iVNS when paired with a cognitive task (Kunii et al., 2021).

Both dementia and even its prodromal stage, MCI, are characterized by a reduction in cerebral blood flow (Mazza et al., 2011; Sierra-Marcos, 2017). A meta-analysis of twenty-six studies investigating CBF in MCI found overall reduced tissue oxygenation, CBF and velocity in MCI compared to healthy controls (Beishon et al., 2017) and studies are underway investigating the CBF changes that may occur with cognitive stimulation in MCI and dementia (Beishon et al., 2019). Similar findings have been noted in patients with Alzheimer's disease, with reduced CBF in many cortical regions including temporal (Sandson et al., 1996; Alsop et al., 2000; Asllani et al., 2008; Yoshiura et al., 2009; Ding et al., 2014) parietal (Alsop et al., 2000; Johnson et al., 2005) and other regions including precuneus,

frontal and posterior cingulate cortex (Alsop et al., 2008; Yoshiura et al., 2009).

MECHANISM OF ACTION: VAGUS NERVE STIMULATION MODULATES PERIPHERAL HEMODYNAMICS

As well as modulating central neurotransmitter release and cerebral blood flow, VNS has been shown to have positive peripheral modulatory effects in pathological states characterized by impaired autonomic regulation including postural orthostatic tachycardia syndrome (POTS) (Petelin Gadze et al., 2018) specifically patients with POTS and impaired vagal cardiac control, as defined by reduced HRV (Jacob et al., 2019). T-VNS has also shown benefits in modulating blood pressure in induced orthostatic hypotension (Tobaldini et al., 2019). These studies suggest VNS may have a role in positively manipulating the peripheral baroreceptor-reflex and thus cerebral autoregulation, and potentially may improve cortical perfusion *via* this route, however further dedicated studies are required to precisely delineate this relationship.

VAGUS NERVE STIMULATION AND HEART RATE VARIABILITY

Heart rate variability analysis can be performed *via* a variety of approaches and is based on the extrapolation of time intervals between each R wave peak (Shaffer and Ginsberg, 2017), discounting any ectopic beats or arrhythmias, e.g., atrial fibrillation. The most commonly applied methods to determine HRV are time-domain analysis and frequency/spectral analysis. Indices deriving from the time domain analysis quantify the amount of variance in the selected inter-beat interval employing statistical measures, such as the standard deviation of the normal beat intervals (SDNN) and the root mean square of successive differences between normal beats (RMSSD) (Shaffer et al., 2014). The spectral analysis of HRV identifies oscillatory rhythms that occur in specific frequency ranges. Three main components of the spectrums can be identified as: the very low frequency band (VLF), below 0.04 Hz, likely influenced by thermoregulatory mechanisms and circadian rhythms; the low-frequency band (LF) between 0.04 and 0.15 Hz in humans, a marker influenced by baroreflex (Furlan et al., 2019) sympathetic and parasympathetic modulation; the high-frequency band (HF) in the range from 0.15 to 0.4 Hz, a marker of vagal modulation that is influenced by respiratory activity (Montano et al., 2009; Shaffer et al., 2014). One of the limitations of HRV analysis is high within and between individual variability, which may be reduced by longer measurement intervals, i.e., 24 h but which is resultantly harder to process. For a comprehensive review on the various indices please see Merrick et al. (2017).

The ANS influences cardiac beat-to-beat interval length in response to several factors. The sympathetic and parasympathetic systems are the principal rapidly reacting systems that control heart rate. The two systems have different latency periods with sympathetic effects on heart rate slower than parasympathetic (Warner and Cox, 1962; Pickering and Davies, 1973; Koizumi et al., 1983) i.e., the parasympathetic system has the ability to alter heart rate within 1–2 beats, while sympathetic effects take up to 10 s to take effect.

Low HRV has been associated with poorer prognosis in cardiovascular diseases, cancer, Metabolic Syndrome and Alzheimer's disease and it has been postulated that related pathophysiological mechanisms often contribute to their occurrence and progression, namely inflammatory responses, sympathetic overactivity, and oxidative stress (Entschladen et al., 2004; Thayer and Lane, 2007; de Couck et al., 2012). Lower vagal nerve activity has been found to be significantly correlated with oxidative stress (Tsutsumi et al., 2008), with inflammatory markers in healthy individuals as well as in those with cardiovascular diseases (Haensel et al., 2008) and anxiety disorders have also been characterized by low HRV (Chalmers et al., 2014). Experimental studies have long demonstrated the success of behavioral (Stein and Kleiger, 2003) and pharmacological (Sandrone et al., 1994) interventions in manipulating HRV. Increases in HRV seen with physical fitness training are associated with improvements in executive function (Hansen et al., 2004). The links between executive function and cardiac autonomic regulation were further highlighted by a recent study examining the impact of cognitive and motor training on HRV indices. Physical training alone failed to impact HRV in older adults whereas dual cognitive and motor training significantly improved global and parasympathetic autonomic nervous system activity (Eggenberger et al., 2020). These studies point toward a duality; the vagal communications between heart and mind can be bidirectionally manipulated to improve both parasympathetic control of HRV and, synergistically, executive cognitive function.

Preclinical research has noted that VNS, particularly to the right vagus nerve, increases vagally mediated (vm-) HRV measures (Huang et al., 2010; Sun et al., 2013). In a canine study, VNS treatment enhanced HRV at 4 and 8 weeks and reduced heart failure development (Zhang et al., 2009) and a Japanese study in rabbits founds that intermittent VNS, but not constant VNS, increased the HF (vagal) component of HRV (Iwao et al., 2000). Discrepancies in this preclinical work may be due to different species, devices and parameters but indicate that manipulating the vagus nerve electrically can have positive impacts on cardiac function and HRV.

VAGUS NERVE STIMULATION AND HEART RATE VARIABILITY IN HEALTHY VOLUNTEERS

Transcutaneous auricular vagus nerve stimulation devices and their stimulation effect on HRV have been examined in several experimental paradigms involving multiple auricular positions, left vs. right ear stimulation, and different stimulation settings. There is a trend toward positive findings, i.e., improved HRV indices, with t-VNS in healthy volunteer populations when the right auricular branch of the vagus is stimulated

(de Couck et al., 2017; Machetanz et al., 2021). It is notable that greater responses to t-VNS (i.e., improved vagally medicated HRV signals) have been demonstrated in those with higher sympathetic balance at baseline in both younger and older volunteers, both acutely and with 2 weeks t-VNS at home for 15 min daily (Clancy et al., 2014; Bretherton et al., 2019). An experimental design comparing left and right t-VNS at multiple stimulation targets found that SDNN and RMSSD both were most significantly improved when the right cymba conchae and fossa triangularis were stimulated (Machetanz et al., 2021).

When specific parameters of stimulation at the left tragus were sequentially analyzed, the settings that had the most significant impact on heart rate analysis in young volunteers were 500 μs at 10 Hz (Badran et al., 2018b). Studies investigating the effect of t-VNS and 70-degree tilt table testing on HRV at the left tragus found that the RSA measure of HRV (HF domain) was also significantly increased during an orthostatic maneuver (Lamb et al., 2017) and similarly stimulation at the left cymba conchae during 75-degree tilt found that responsivity, i.e., degree of change of heart rate and systolic blood pressure during t-VNS were significantly higher during orthostasis compared to control (Tobaldini et al., 2019).

Research in this area has not been consistent. Some initial findings indicated improved HRV measures with t-VNS to the left cymba conchae but ultimately no difference compared to sham and at multiple intensities (Borges et al., 2019). In an experimental crossover design employing a variety of amplitudes at the right cymba, there was no positive signal in affecting HRV measures (Gauthey et al., 2020) and similarly t-VNS to the right tragus during rest and autonomic nervous system testing, with appreciably different stimulation parameters to what was previously cited in the literature, also did not have any effect on HRV (Sinkovec et al., 2021). Inconsistent results are likely due to the use of different anatomical sites and stimulation parameters being utilized, some with "lead in" times and some without, and reporting on this area has been of variable quality, and recent international consensus has called for standardized reporting of this research (Farmer et al., 2021).

VAGUS NERVE STIMULATION AND HEART RATE VARIABILITY IN CLINICAL POPULATIONS

Initial studies in clinical populations involved patients with iVNS devices inserted for control of refractory epilepsy. The earliest study demonstrated a reduction in LF:HF ratio and significantly higher HF power was noted in the higher stimulation group than lower stimulation (see **Table 4**; Kamath et al., 1992). These results were not however replicated in further studies of similar populations with comparable stimulation settings at timeframes ranging from minutes to 1 year of stimulation (Handforth et al., 1998; Setty et al., 1998; Galli et al., 2003; Ronkainen et al., 2006; Barone et al., 2007). A small study analyzing HRV in patients with iVNS devices implanted for management of treatment-resistant depression noted an increase in the RMSSD (increased vagal predominance) during stimulation compared to baseline and healthy controls (Sperling et al., 2010). It is notable that iVNS devices are for the most part inserted to activate the vagus *via* its left cervical branch, thereby appropriately reducing adverse cardiac effects but also not demonstrably influencing HRV measures in these populations.

Please see **Table 4** for further analysis of the specific neurocardiovascular assessments, specific t-VNS parameters and outcomes measures in discreet populations in this area.

VAGUS NERVE STIMULATION, COGNITION AND HEART RATE VARIABILITY

Heart rate variability can be conceptualized as a biomarker of parasympathetic modulation, and it is associated with a network of brain regions involved in autonomic nervous system regulation, known as the central autonomic network (Benarroch, 1993; Thayer et al., 2009). This network, which comprises prefrontal cortical (anterior cingulate, insula, orbitofrontal, and ventromedial cortices), limbic (central nucleus of the amygdala, hypothalamus), and brainstem regions, areas of the brain intimately involved in emotional regulation and executive functioning, leading to the proposal that vagally mediated HRV may index these aspects of prefrontal cortical function (Thayer and Lane, 2007; Thayer et al., 2009). Higher HRV has been linked to better cognitive function in healthy adults including healthy older individuals (Frewen et al., 2013; Grässler et al., 2020) and a meta-analysis found a positive overall correlation ($r = 0.09$) between vagally mediated HRV indices and emotional regulation processes (including executive functioning, emotion regulation, and effortful or self-control) in mostly healthy participants across a number of age groups (Holzman and Bridgett, 2017).

Autonomic system dysfunction is common in patients with MCI, with studies suggesting MCI participants are 5.6 times more likely than controls to have autonomic dysfunction, specifically on assessment of HRV and cardiac reflexes (Collins et al., 2012). A meta-analysis of MCI with dementia also found autonomic dysfunction, as defined by reduced HRV, was significantly associated with cognitive impairment (da Silva et al., 2017). Reduced HRV is associated with worse performance on tests of global cognitive function, more than cardiovascular risk factors (Zeki Al Hazzouri et al., 2014).

Recent meta-analyses of HRV in patients with neurodegenerative conditions including MCI, Alzheimer's disease, Lewy Body dementia (DLB), vascular dementia, Parkinson's disease and multiple sclerosis found a significant, moderate effect ($r = 0.25$) indicating that higher HRV was related to better cognitive and behavioral scores, which was not influenced by mean age or cognitive status (Liu et al., 2022). These results were mirrored in a similar recent meta-analysis of patients with dementia compared to healthy controls, which found significantly lower resting HRV for parasympathetic function and total variability in those with dementia. On subgroup analysis then most striking differences, i.e., worse HRV analysis was found in those with MCI or DLB (Cheng et al., 2022).

Heart rate variability and CBF are linked *via* vagal afferents, and a meta-analysis revealed that HRV was significantly associated with regional cerebral blood flow in the ventromedial prefrontal cortex (including anterior cingulate regions) and the amygdala (Thayer et al., 2012). In both younger and older adults scanned while at rest, higher HRV is associated with higher medial prefrontal cortex and amygdala functional connectivity (Sakaki et al., 2016). The Neurovisceral Integration Model holds that HRV, executive cognitive function, and prefrontal neural function are integrally associated (Thayer et al., 2009).

In an interesting Swedish clinical trial in 2002, iVNS devices were implanted in a small group of patients with likely Alzheimer's Dementia (AD) as defined by the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), with a view to assessing its impact on cognition *via* memory test scores. In the primary trial, 10 patients with average Mini Mental State Exam (MMSE) scores of 21 (range 16–24) had iVNS devices implanted and the median change in MMSE and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores among a battery of tests was assessed at 3 and 6 months, with improvements in both assessments noted in the majority (6 out of 10) of cases (Sjögren et al., 2002). The follow up trial by the same research group involved 17 patients with likely AD, who had iVNS devices implanted and had outcomes measured and available at 1 year post implantation. At 1 year, 7 of 17 (41%) had improvement or no decline from baseline in ADAS-cog scores and 12 of 17 (70%) had improvement or no decline in MMSE scores. There was no change in noted in other outcomes including depressive symptoms (Merrill et al., 2006). There are a small number of trials registered investigating the therapeutic potential of t-VNS in older populations, both healthy and with cognitive impairment (for a recent review see (Vargas-Caballero et al., 2022)) however there are no known published studies to date investigating t-VNS in populations with dementia or MCI, and the associated effect on HRV.

SUMMARY

There is mounting evidence of the potential benefits of VNS in myriad disease states, with notable promise in the area of cognition. VNS shows promise as a neuromodulatory technique in cognitive decline and this may be *via* its ability to regulate both cardiac autonomic function and increase cerebral perfusion. Dementia is a multifactorial process and together with reduced cerebral perfusion is associated with neuroinflammation and altered synaptic plasticity, both of which may also be favorably modulated by VNS. It has been noted that perfusion to cortical and subcortical areas increases with VNS, specifically to areas that modulate executive function and attention, i.e., insular, orbitofrontal and prefrontal cortex. These areas are hypothesized by the neurovisceral integration model to be crucial areas in modulating the ANS (Thayer et al., 2009). Given that the LC-NE system is intimately involved in the therapeutic effects of VNS, and likely improves cognition *via* norepinephrine release and improved executive performance, it is notable that the earliest stages of pathological tau accumulation in Alzheimer's disease are seen in the LC. Whether this small midbrain nucleus will prove to be pivotal in our understanding of how to modulate the vagus nerve and harness its benefits cognitively remains to be elucidated. VNS can now be delivered safely and non-invasively *via* t-VNS devices with equivalent neuromodulatory effects on brain imaging as invasive devices, which broadens its therapeutic applicability considerably, especially to an older population with cognitive complaints for whom device implantation may not be feasible. Globally, the need for effective therapies to both treat the cause and symptoms of cognitive decline are needed urgently as rates of dementia increase due to population expansion. Dedicated studies into the potential therapeutic effects of t-VNS in early cognitive decline and dementia are needed. Research to date has been limited by myriad issues, including studies on cognition in clinical populations with altered neuroanatomy, lack of standardization in device usage, parameter settings, frequency of use, duration of stimulation. Minimum reporting standards have recently been published to help ameliorate some of these issues. Further rigorous studies of the therapeutic benefit of VNS are required, especially in populations with autonomic instability and cognitive decline.

AUTHOR CONTRIBUTIONS

HD did most of the research, writing, and editing of the article. Significant contributions were made by each author, specifically TD with manuscript reading, editing, and direction, SC with direction RE psychological assessments and plasticity, CF with neurocardiovascular assessments, ANS testing. PM and SK assisted significantly with overall editorial support and guidance. All authors contributed to the article and approved the submitted version.

FUNDING

This study is part of a research study generously funded by the Meath Foundation, Tallaght University Hospital.

REFERENCES

Agostini, E., Chinnock, J., de Daly, M., and Murray, J. (1957). Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera in the cat. *J. Physiol.* 135, 182–205. doi: 10.1113/JPHYSIOL.1957.SP005703

Alsop, D., Detre, J., and Grossman, M. (2000). Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. *Ann. Neurol.* 47, 93–100. doi: 10.1002/1531-8249(200001)47:1<93::AID-ANA15<3.0.CO;2-8

Alsop, D. C., Casement, M., de Bazelaire, C., Fong, T., and Press, D. Z. (2008). Hippocampal hyperperfusion in Alzheimer's disease. *NeuroImage* 42, 1267–1274. doi: 10.1016/J.NEUROIMAGE.2008.06.006

Antonino, D., Teixeira, A. L., Maia-Lopes, P. M., Souza, M. C., Sabino-Carvalho, J. L., Murray, A. R., et al. (2017). Non-invasive vagus nerve stimulation acutely improves spontaneous cardiac baroreflex sensitivity in healthy young men: a

randomized placebo-controlled trial. *Brain Stimul.* 10, 875–881. doi: 10.1016/j.brs.2017.05.006

Asllani, I., Habeck, C., Scarmeas, N., Borogovac, A., Brown, T. R., and Stern, Y. (2008). Multivariate and univariate analysis of continuous arterial spin labeling perfusion MRI in Alzheimer's disease. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* 28, 725–736. doi: 10.1038/SJ.JCBFM.9600570

Aston-Jones, G., and Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu. Rev. Neurosci.* 28, 403–450. doi: 10.1146/ANNUREV.NEURO.28.061604.135709

Bachmann, J., Munzert, J., and Krüger, B. (2018). Neural underpinnings of the perception of emotional states derived from biological human motion: a review of neuroimaging research. *Front. Psychol.* 9:1763. doi: 10.3389/FPSYG.2018.01763

Baddeley, A. (2010). Working memory. *Curr. Biol.* 20, R136–R140. doi: 10.1016/J.CUB.2009.12.014

Badran, B. W., Dowdle, L. T., Mithoefer, O. J., LaBate, N. T., Coatsworth, J., Brown, J. C., et al. (2018a). Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: a concurrent taVNS/fMRI study and review. *Brain Stimul.* 11, 492–500. doi: 10.1016/J.BRS.2017.12.009

Badran, B. W., Mithoefer, O. J., Summer, C. E., LaBate, N. T., Glusman, C. E., Badran, A. W., et al. (2018b). Short trains of transcutaneous auricular vagus nerve stimulation (taVNS) have parameter-specific effects on heart rate. *Brain Stimul. Basic Transl. Clin. Res. Neuromodul.* 11, 699–708. doi: 10.1016/J.BRS.2018.04.004

Bagneux, V., Thomassin, N., Gonthier, C., and Roulin, J. L. (2013). Working memory in the processing of the iowa gambling task: an individual differences approach. *PLoS One* 8:e81498. doi: 10.1371/JOURNAL.PONE.0081498

Bailey, P., and Bremer, F. (1938). A sensory cortical representation of the vagus nerve: with a note on the effects of low blood pressure on the cortical electrogram. *J. Neurophysiol.* 1, 405–412. doi: 10.1152/JN.1938.1.5.405

Barone, L., Colicchio, G., Policicchio, D., di Clemente, F., di Monaco, A., Meglio, M., et al. (2007). Effect of vagal nerve stimulation on systemic inflammation and cardiac autonomic function in patients with refractory epilepsy. *Neuroimmunomodulation* 14, 331–336. doi: 10.1159/000127360

Bechara, A., and Martin, E. M. (2004). Impaired decision making related to working memory deficits in individuals with substance addictions. *Neuropsychology* 18, 152–162. doi: 10.1037/0894-4105.18.1.152

Beckstead, R. M., and Norgren, R. (1979). An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagal nerves in the monkey. *J. Comparat. Neurol.* 184, 455–472. doi: 10.1002/CNE.901840303

Beishon, L., Evley, R., Panerai, R. B., Subramaniam, H., Mukaetova-Ladinska, E., Robinson, T., et al. (2019). Effects of brain training on brain blood flow (The Cognition and Flow Study-CogFlowS): protocol for a feasibility randomised controlled trial of cognitive training in dementia. *BMJ Open* 9:27817. doi: 10.1136/bmjopen-2018-027817

Beishon, L., Haunton, V. J., Panerai, R. B., and Robinson, T. G. (2017). Cerebral hemodynamics in mild cognitive impairment: a systematic review. *J. Alzheimer's Dis.* 59, 369–385. doi: 10.3233/JAD-170181

Benarroch, E. E. (1993). The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin. Proc.* 68, 988–1001. doi: 10.1016/S0025-6196(12)62272-1

Berridge, C. W., and Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res. Rev.* 42, 33–84. doi: 10.1016/S0165-0173(03)00143-7

Berthoud, H. R., and Neuhuber, W. L. (2000). Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.* 85, 1–17. doi: 10.1016/S1566-0702(00)00215-0

Beste, C., Steenbergen, L., Sellaro, R., Grigoriadou, S., Zhang, R., Chmielewski, W., et al. (2016). Effects of concomitant stimulation of the GABAergic and norepinephrine system on inhibitory control – a study using transcutaneous vagus nerve stimulation. *Brain Stimul.* 9, 811–818. doi: 10.1016/J.BRS.2016.07.004

Bohning, D. E., Lomarev, M. P., Denslow, S., Nahas, Z., Shastri, A., and George, M. S. (2001). Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. *Invest. Radiol.* 36, 470–479. doi: 10.1097/00004424-200108000-00006

Borges, U., Knops, L., Laborde, S., Klatt, S., and Raab, M. (2020). Transcutaneous vagus nerve stimulation may enhance only specific aspects of the core executive functions. A randomized crossover trial. *Front. Neurosci.* 14:523. doi: 10.3389/FNINS.2020.00523

Borges, U., Laborde, S., and Raab, M. (2019). Influence of transcutaneous vagus nerve stimulation on cardiac vagal activity: not different from sham stimulation and no effect of stimulation intensity. *PLoS One* 14:e0223848. doi: 10.1371/JOURNAL.PONE.0223848

Bretherton, B., Atkinson, L., Murray, A., Clancy, J., Deuchars, S., and Deuchars, J. (2019). Effects of transcutaneous vagus nerve stimulation in individuals aged 55 years or above: potential benefits of daily stimulation. *Aging* 11, 4836–4857. doi: 10.18632/aging.102074

Broncel, A., Bocian, R., Kłos-Wojtczak, P., Kulbat-Warycha, K., and Konopacki, J. (2020). Vagal nerve stimulation as a promising tool in the improvement of cognitive disorders. *Brain Res. Bull.* 155, 37–47. doi: 10.1016/j.brainresbull.2019.11.011

Burger, A. M., Van Diest, I., Van der Does, W., Korbee, J. N., Waziri, N., Brosschot, J. F., et al. (2019). The effect of transcutaneous vagus nerve stimulation on fear generalization and subsequent fear extinction. *Neurobiol. Learn. Mem.* 161, 192–201. doi: 10.1016/J.NLM.2019.04.006

Cakmak, Y. O., Apaydin, H., Kiziltan, G., Gündüz, A., Ozsoy, B., Olcer, S., et al. (2017). Rapid alleviation of parkinson's disease symptoms via electrostimulation of intrinsic auricular muscle zones. *Front. Hum. Neurosci.* 11:338. doi: 10.3389/FNHUM.2017.00338

Camina, E., and Güell, F. (2017). The neuroanatomical, neurophysiological and psychological basis of memory: current models and their origins. *Front. Pharmacol.* 8:438. doi: 10.3389/FPHAR.2017.00438

Chae, J. H., Nahas, Z., Lomarev, M., Denslow, S., Lorberbaum, J. P., Bohning, D. E., et al. (2003). A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J. Psychiatric Res.* 37, 443–455. doi: 10.1016/S0022-3956(03)00074-8

Chalmers, J. A., Quintana, D. S., Abbott, M. J. A., and Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front. Psychiatry* 5:80. doi: 10.3389/FPSYT.2014.00080

Chambers, C. D., Garavan, H., and Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci. Biobehav. Rev.* 33, 631–646. doi: 10.1016/J.NEUBIOREV.2008.08.016

Cheng, Y. C., Huang, Y. C., and Huang, W. L. (2022). Heart rate variability in patients with dementia or neurocognitive disorders: a systematic review and meta-analysis. *Aust. N. Z. J. Psychiatry* 56, 16–27. doi: 10.1177/0004867420976853

Clancy, J. A., Mary, D. A., Witte, K. K., Greenwood, J. P., Deuchars, S. A., and Deuchars, J. (2014). Non-invasive Vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul.* 7, 871–877.

Clark, K. B., Krahl, S. E., Smith, D. C., and Jensen, R. A. (1995). Post-training unilateral vagal stimulation enhances retention performance in the rat. *Neurobiol. Learn. Mem.* 63, 213–216. doi: 10.1006/NLME.1995.1024

Clark, K. B., Naritoku, D. K., Smith, D. C., Browning, R. A., and Jensen, R. A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nat. Neurosci.* 2, 94–98. doi: 10.1038/4600

Clewett, D. V., Lee, T. H., Greening, S., Ponzio, A., Margalit, E., and Mather, M. (2016). Neuromelanin marks the spot: identifying a locus coeruleus biomarker of cognitive reserve in healthy aging. *Neurobiol. Aging* 37:117. doi: 10.1016/J.NEUROBIOLAGING.2015.09.019

Collins, O., Dillon, S., Finucane, C., Lawlor, B., and Kenny, R. A. (2012). Parasympathetic autonomic dysfunction is common in mild cognitive impairment. *Neurobiol. Aging* 33, 2324–2333. doi: 10.1016/J.NEUROBIOLAGING.2011.11.017

Colzato, L., and Beste, C. (2020). A literature review on the neurophysiological underpinnings and cognitive effects of transcutaneous vagus nerve stimulation: challenges and future directions. *J. Neurophysiol.* 123, 1739–1755. doi: 10.1152/jn.00057.2020.-Brain

Colzato, L. S., Ritter, S. M., and Steenbergen, L. (2018). Transcutaneous vagus nerve stimulation (tVNS) enhances divergent thinking. *Neuropsychologia* 111, 72–76. doi: 10.1016/J.NEUROPSYCHOLOGIA.2018.01.003

Colzato, L. S., Sellaro, R., and Beste, C. (2017). Darwin revisited: the vagus nerve is a causal element in controlling recognition of other's emotions. *Cortex* 92, 95–102. doi: 10.1016/J.CORTEX.2017.03.017

Conway, C. R., Sheline, Y. I., Chibnall, J. T., Bucholz, R. D., Price, J. L., Gangwani, S., et al. (2012). Brain blood-flow change with acute vagus nerve stimulation in treatment-refractory major depressive disorder. *Brain Stimul.* 5, 163–171. doi: 10.1016/J.BRS.2011.03.001

Coote, J. H. (2013). Myths and realities of the cardiac vagus. *J. Physiol.* 591, 4073–4085. doi: 10.1113/JPHYSIOL.2013.257758

Cummings, J., Lee, G., Zhong, K., Fonseca, J., and Taghva, K. (2021). Alzheimer's disease drug development pipeline: 2021. *Alzheimer's Dementia Transl. Res. Clin. Intervent.* 7:e12179. doi: 10.1002/TRC2.12179

da Silva, V. P., Ramalho Oliveira, B. R., Tavares Mello, R. G., Moraes, H., Deslandes, A. C., and Laks, J. (2017). Heart rate variability indexes in dementia: a systematic review with a quantitative analysis. *Curr. Alzheimer Res.* 15, 80–88. doi: 10.2174/1567205014666170531082352

de Couck, M., Cserjesi, R., Caers, R., Zijlstra, W. P., Widjaja, D., Wolf, N., et al. (2017). Effects of short and prolonged transcutaneous vagus nerve stimulation on heart rate variability in healthy subjects. *Autonomic Neurosci. Basic Clin.* 203, 88–96. doi: 10.1016/j.autneu.2016.11.003

de Couck, M., Mravec, B., and Gidron, Y. (2012). You may need the vagus nerve to understand pathophysiology and to treat diseases. *Clin. Sci.* 122, 323–328. doi: 10.1042/CS20110299

de la Vega, A., Brown, M. S., Snyder, H. R., Singel, D., Munakata, Y., and Banich, M. T. (2014). Individual differences in the balance of GABA to glutamate in pFC predict the ability to select among competing options. *J. Cogn. Neurosci.* 26, 2490–2502. doi: 10.1162/JOCN_A_00655

Ding, B., Ling, H. W., Zhang, Y., Huang, J., Zhang, H., Wang, T., et al. (2014). Pattern of cerebral hyperperfusion in Alzheimer's disease and amnestic mild cognitive impairment using voxel-based analysis of 3D arterial spin-labeling imaging: initial experience. *Clin. Intervent. Aging* 9, 493–500. doi: 10.2147/CIA.S58879

Dixon, M. L. (2015). Cognitive control, emotional value, and the lateral prefrontal cortex. *Front. Psychol.* 6:758. doi: 10.3389/FPSYG.2015.00758

Dodrill, C. B., and Morris, G. L. (2001). Effects of vagal nerve stimulation on cognition and quality of life in epilepsy. *Epilepsy Behav.* 2, 46–53. doi: 10.1006/EBEH.2000.0148

Duann, J. R., Ide, J. S., Luo, X., and Li, C. S. R. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *J. Neurosci.* 29, 10171–10179. doi: 10.1523/JNEUROSCI.1300-09.2009

Eggenberger, P., Annaheim, S., Kündig, K. A., Rossi, R. M., Münzer, T., and de Bruin, E. D. (2020). Heart rate variability mainly relates to cognitive executive functions and improves through exergame training in older adults: a secondary analysis of a 6-month randomized controlled trial. *Front. Aging Neurosci.* 12:197. doi: 10.3389/FNAGI.2020.00197

Entschladen, F., Drell, T. L., Lang, K., Joseph, J., and Zaenker, K. S. (2004). Tumour-cell migration, invasion, and metastasis: navigation by neurotransmitters. *Lancet Oncol.* 5, 254–258. doi: 10.1016/S1470-2045(04)01431-7

Eriksen, C. W. (1995). The flankers task and response competition: a useful tool for investigating a variety of cognitive problems. *Visual Cogn.* 2, 101–118. doi: 10.1080/13506289508401726

Erlanger, J., and Gasser, H. (1937). Electrical signs of nervous activity. *Am. J. Psychiatry* 93, 1472–a–1473. doi: 10.1176/AJP.93.6.1472-A

Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., et al. (2021). International consensus based review and recommendations for minimum reporting standards in research on transcutaneous vagus nerve stimulation (Version 2020). *Front. Hum. Neurosci.* 14:568051. doi: 10.3389/FNHUM.2020.568051

Fischer, R., Ventura-Bort, C., Hamm, A., and Weymar, M. (2018). Transcutaneous vagus nerve stimulation (tVNS) enhances conflict-triggered adjustment of cognitive control. *Cogn. Affect. Behav. Neurosci.* 18, 680–693. doi: 10.3758/s13415-018-0596-2

Foley, J., and Dubois, F. S. (1937). Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory to motor fibres. *J. Comp. Neurol.* 67, 49–64.

Forte, G., Favieri, F., and Casagrande, M. (2019). Heart rate variability and cognitive function: a systematic review. *Front. Neurosci.* 13:710. doi: 10.3389/FNINS.2019.00710

Frangos, E., Ellrich, J., and Komisaruk, B. R. (2015). Non-invasive access to the vagus nerve central projections via electrical stimulation of the external ear: fMRI evidence in humans. *Brain Stimul.* 8, 624–636. doi: 10.1016/J.BRS.2014.11.018

Frangos, E., and Komisaruk, B. R. (2017). Access to vagal projections via cutaneous electrical stimulation of the neck: fMRI evidence in healthy humans. *Brain Stimul.* 10, 19–27. doi: 10.1016/J.BRS.2016.10.008

Frewen, J., Finucane, C., Savva, G. M., Boyle, G., Coen, R. F., and Kenny, R. A. (2013). Cognitive function is associated with impaired heart rate variability in ageing adults: the Irish longitudinal study on ageing wave one results. *Clin. Autonomic Res.* 23, 313–323. doi: 10.1007/S10286-013-0214-X

Furlan, R., Heusser, K., Minonzio, M., Shiffer, D., Cairo, B., Tank, J., et al. (2019). Cardiac and vascular sympathetic baroreflex control during orthostatic pre-syncope. *J. Clin. Med.* 8:1434. doi: 10.3390/JCM8091434

Galli, R., Limbruno, U., Pizzanelli, C., Giorgi, F. S., Lutzemberger, L., Strata, G., et al. (2003). Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. *Autonomic Neurosci. Basic Clin.* 107, 52–59. doi: 10.1016/S1566-0702(03)00081-X

Gao, F., Edden, R. A. E., Li, M., Puts, N. A. J., Wang, G., Liu, C., et al. (2013). Edited magnetic resonance spectroscopy detects an age-related decline in brain GABA levels. *Neuroimage* 78, 75–82. doi: 10.1016/j.neuroimage.2013.04.012

Gatti, P. J., Johnson, T. A., and Massari, V. J. (1996). Can neurons in the nucleus ambiguus selectively regulate cardiac rate and atrio-ventricular conduction? *J. Autonomic Nerv. Syst.* 57, 123–127. doi: 10.1016/0165-1838(95)00104-2

Gauthey, A., Morra, S., van de Borne, P., Deriaz, D., Maes, N., and le Polain de Waroux, J. B. (2020). Sympathetic effect of auricular transcutaneous vagus nerve stimulation on healthy subjects: a crossover controlled clinical trial comparing vagally mediated and active control stimulation using microneurography. *Front. Physiol.* 11:599896. doi: 10.3389/FPHYS.2020.599896

Ghacibeh, G. A., Shenker, J. I., Shenal, B., Uthman, B. M., and Heilman, K. M. (2006a). Effect of vagus nerve stimulation on creativity and cognitive flexibility. *Epilepsy Behav.* 8, 720–725. doi: 10.1016/j.yebeh.2006.03.008

Ghacibeh, G. A., Shenker, J. I., Shenal, B., Uthman, B. M., and Heilman, K. M. (2006b). The influence of vagus nerve stimulation on memory. *Cogn. Behav. Neurol. Off. J. Soc. Behav. Cogn. Neurol.* 19, 119–122. doi: 10.1097/01.WNN.0000213908.34278.7D

Giraudier, M., Ventura-Bort, C., and Weymar, M. (2020). Transcutaneous Vagus Nerve Stimulation (tVNS) improves high-confidence recognition memory but not emotional word processing. *Front. Psychol.* 11:1276. doi: 10.3389/FPSYG.2020.01276

Goadsby, P. J., Grosberg, B. M., Mauskop, A., Cady, R., and Simmons, K. A. (2014). Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. *Cephalalgia* 34, 986–993. doi: 10.1177/0333102414524494

Gonthier, C. (2014). *Cognitive Control in Working Memory: an Individual Differences Approach Based on the Dual Mechanisms of Control Framework*. Saint-Martin-d'Hères: University of Grenoble.

Grässler, B., Hökelmann, A., and Cabral, R. H. (2020). Resting heart rate variability as a possibly marker of cognitive decline. *Kinesiology* 52, 72–84. doi: 10.26582/k.52.1.9

Groves, D. A., Bowman, E. M., and Brown, V. J. (2005). Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. *Neurosci. Lett.* 379, 174–179. doi: 10.1016/j.neulet.2004.12.055

Haensel, A., Mills, P. J., Nelesen, R. A., Ziegler, M. G., and Dimsdale, J. E. (2008). The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. *Psychoneuroendocrinology* 33, 1305–1312. doi: 10.1016/J.PSYNEUEN.2008.08.007

Hämmerer, D., Callaghan, M. F., Hopkins, A., Kosciessa, J., Betts, M., Cardenas-Blanco, A., et al. (2018). Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events. *Proc. Natl. Acad. Sci. U.S.A.* 115, 2228–2233. doi: 10.1073/PNAS.1712268115

Handforth, A., DeGiorgio, C. M., Schachter, S. C., Uthman, B. M., Naritoku, D. K., Tecoma, E. S., et al. (1998). Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology* 51, 48–55. doi: 10.1212/WNL.51.1.48

Hansen, A. L., Johnsen, B. H., Sollers, J. J., Stenvik, K., and Thayer, J. F. (2004). Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. *Eur. J. Appl. Physiol.* 93, 263–272. doi: 10.1007/S00421-004-1208-0

Hansen, N. (2019). Memory reinforcement and attenuation by activating the human locus coeruleus via transcutaneous vagus nerve stimulation. *Front. Neurosci.* 13:955. doi: 10.3389/FNINS.2018.00955

Hasan, A., Wolff-Menzler, C., Pfeiffer, S., Falkai, P., Weidinger, E., Jobst, A., et al. (2015). Transcutaneous noninvasive vagus nerve stimulation (tVNS) in the treatment of schizophrenia: a bicentric randomized controlled pilot study. *Eur. Arch. Psychiatry Clin. Neurosci.* 265, 589–600. doi: 10.1007/S00406-015-0618-9

Hays, S. A., Rennaker, R. L., and Kilgard, M. P. (2013). Targeting plasticity with vagus nerve stimulation to treat neurological disease. *Progr. Brain Res.* 207, 275–299. doi: 10.1016/B978-0-444-63327-9.00010-2

Helmstaedter, C., Hoppe, C., and Elger, C. E. (2001). Memory alterations during acute high-intensity vagus nerve stimulation. *Epilepsy Res.* 47, 37–42. doi: 10.1016/S0920-1211(01)00291-1

Henry, T. R. (2002). Therapeutic mechanisms of vagus nerve stimulation. *Neurology* 59(Suppl. 4), S3–S14. doi: 10.1212/WNL.59.6_SUPPL_4.S3

Henry, T. R., Bakay, R. A. E., Pennell, P. B., Epstein, C. M., and Votaw, J. R. (2004). Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. Prolonged effects at high and low levels of stimulation. *Epilepsia* 45, 1064–1070. doi: 10.1111/J.0013-9580.2004.03104.X

Henry, T. R., Bakay, R. A. E., Votaw, J. R., Pennell, P. B., Epstein, C. M., Faber, T. L., et al. (1998). Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. *Epilepsia* 39, 983–990. doi: 10.1111/J.1528-1157.1998.TB01448.X

Holzman, J. B., and Bridgett, D. J. (2017). Heart rate variability indices as bio-markers of top-down self-regulatory mechanisms: a meta-analytic review. *Neurosci. Biobehav. Rev.* 74, 233–255. doi: 10.1016/J.NEUBIOREV.2016.12.032

Huang, F., Dong, J., Kong, J., Wang, H., Meng, H., Spaeth, R. B., et al. (2014). Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. *BMC Complement. Alternat. Med.* 14:203. doi: 10.1186/1472-6882-14-203

Huang, J., Wang, Y., Jiang, D., Zhou, J., and Huang, X. (2010). The sympathetic-vagal balance against endotoxemia. *J. Neural Transm.* 117, 729–735. doi: 10.1007/S00702-010-0407-6

Hyvarinen, P., Yrttiaho, S., Lehtimaki, J., Ilmoniemi, R. J., Makitie, A., Ylikoski, J., et al. (2015). Transcutaneous vagus nerve stimulation modulates tinnitus-related beta-and gamma-band activity. *Ear Hear.* 36, e76–e85. doi: 10.1097/AUD.0000000000000123

Iwao, T., Yonemochi, H., Nakagawa, M., Takahashi, N., Saikawa, T., and Ito, M. (2000). Effect of constant and intermittent vagal stimulation on the heart rate and heart rate variability in rabbits. *Jpn. J. Physiol.* 50, 33–39. doi: 10.2170/JJPHYSIOL.50.33

Jacob, G., Diedrich, L., Sato, K., Brychta, R. J., Raj, S. R., Robertson, D., et al. (2019). Vagal and sympathetic function in neuropathic postural tachycardia syndrome. *Hypertension* 73, 1087–1096. doi: 10.1161/HYPERTENSIONAHA.118.11803/FORMAT/EPUB

Jacobs, H. I. L., Becker, J. A., Kwong, K., Engels-Domínguez, N., Prokopiou, P. C., Papp, K. V., et al. (2021). In vivo and neuropathology data support locus coeruleus integrity as indicator of Alzheimer's disease pathology and cognitive decline. *Sci. Transl. Med.* 13:eabj2511. doi: 10.1126/scitranslmed.abj2511

Jacobs, H. I. L., Riphagen, J. M., Razat, C. M., Wiese, S., and Sack, A. T. (2015). Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. *Neurobiol. Aging* 36, 1860–1867. doi: 10.1016/j.neurobiolaging.2015.02.023

Johnson, N. A., Jahng, G. H., Weiner, M. W., Miller, B. L., Chui, H. C., Jagust, W. J., et al. (2005). Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: initial experience. *Radiology* 234, 851–859. doi: 10.1148/RADIOL.2343040197

Jongkees, B. J., Immink, M. A., Finisguerra, A., and Colzato, L. S. (2018). Transcutaneous vagus nerve stimulation (tVNS) Enhances response selection during sequential action. *Front. Psychol.* 9:1159. doi: 10.3389/FPSYG.2018.01159

Kaan, E., De Aguiar, I., Clarke, C., Lamb, D. G., Williamson, J. B., and Porges, E. C. (2021). A transcutaneous vagus nerve stimulation study on verbal order memory. *J. Neurolinguist.* 59:100990. doi: 10.1016/j.jneuroling.2021.100990

Kalia, M., and Sullivan, J. M. (1982). Brainstem projections of sensory and motor components of the vagus nerve in the rat. *J. Comparat. Neurol.* 211, 248–264. doi: 10.1002/CNE.902110304

Kamath, M., Upton, A., Talalla, A., and Fallen, E. (1992). Neurocardiac responses to vagoafferent electrostimulation in humans. *Pacing Clin. Electrophysiol. PACE* 15(Pt 2), 1581–1587. doi: 10.1111/J.1540-8159.1992.TB02937.X

Kaniusas, E., Kampusch, S., Tittgemeyer, M., Panetsos, F., Gines, R. F., Papa, M., et al. (2019). Current directions in the auricular vagus nerve stimulation II - An engineering perspective. *Front. Neurosci.* 13:772. doi: 10.3389/FNINS.2019.00772

Kealy, J., and Commins, S. (2010). Frequency-dependent changes in synaptic plasticity and brain-derived neurotrophic factor (BDNF) expression in the CA1 to perirhinal cortex projection. *Brain Res.* 1326, 51–61. doi: 10.1016/j.brainres.2010.02.065

Keute, M., Barth, D., Liebrand, M., Heinze, H.-J., Kraemer, U., and Zaehle, T. (2020). Effects of Transcutaneous Vagus Nerve Stimulation (tVNS) on conflict-related behavioral performance and frontal midline theta activity. *J. Cogn. Enhanc.* 4, 121–130. doi: 10.1007/S41465-019-00152-5

Ko, D., Heck, C., Grafton, S., Apuzzo, M. L. J., Couldwell, W. T., Chen, T., et al. (1996). Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H215O blood flow imaging. *Neurosurgery* 39, 426–431. doi: 10.1097/00006123-199608000-00061

Koenig, J., Parzer, P., Haigis, N., Liebemann, J., Jung, T., Resch, F., et al. (2021). Effects of acute transcutaneous vagus nerve stimulation on emotion recognition in adolescent depression. *Psychol. Med.* 51, 511–520. doi: 10.1017/S0033291719003490

Koizumi, K., Terui, N., and Kollai, M. (1983). Neural control of the heart: significance of double innervation re-examined. *J. Autonomic Nerv. Syst.* 7, 279–294. doi: 10.1016/0165-1838(83)90081-4

Kornblum, S., Hasbroucq, T., and Osman, A. (1990). Dimensional overlap: cognitive basis for stimulus-response compatibility-a model and taxonomy. *Psychol. Rev.* 97, 253–270. doi: 10.1037/0033-295X.97.2.253

Kosel, M., Brockmann, H., Frick, C., Zobel, A., and Schlaepfer, T. E. (2011). Chronic vagus nerve stimulation for treatment-resistant depression increases regional cerebral blood flow in the dorsolateral prefrontal cortex. *Psychiatry Res. Neuroimaging* 191, 153–159. doi: 10.1016/J.PSCYCHRESNS.2010.11.004

Kraus, T., Hösl, K., Kiess, O., Schanze, A., Kornhuber, J., and Forster, C. (2007). BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. *J. Neural Transm.* 114, 1485–1493. doi: 10.1007/S00702-007-0755-Z

Kraus, T., Kiess, O., Hösl, K., Terekhin, P., Kornhuber, J., and Forster, C. (2013). CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal - A pilot study. *Brain Stimul.* 6, 798–804. doi: 10.1016/j.brs.2013.01.011

Kunii, N., Koizumi, T., Kawai, K., Shimada, S., and Saito, N. (2021). Vagus nerve stimulation amplifies task-induced cerebral blood flow increase. *Front. Hum. Neurosci.* 15:726087. doi: 10.3389/FNHUM.2021.726087

Lam, J., Williams, M., Ashla, M., and Lee, D. J. (2021). Cognitive outcomes following vagus nerve stimulation, responsive neurostimulation and deep brain stimulation for epilepsy: a systematic review. *Epilepsy Res.* 172:106591. doi: 10.1016/J.EPLEPSYRES.2021.106591

Lamb, D. G., Porges, E. C., Lewis, G. F., and Williamson, J. B. (2017). Non-invasive vagal nerve stimulation effects on hyperarousal and autonomic state in patients with Posttraumatic Stress Disorder and history of mild traumatic brain injury: preliminary evidence. *Front. Med.* 4:124. doi: 10.3389/FMED.2017.00124

Lanska, D. J. (2002). J.L. Corning and vagal nerve stimulation for seizures in the 1880s. *Neurology* 58, 452–459. doi: 10.1212/WNL.58.3.452

Laqua, R., Leutzow, B., Wendt, M., and Usichenko, T. (2014). Transcutaneous vagal nerve stimulation may elicit anti- and pro-nociceptive effects under experimentally-induced pain - a crossover placebo-controlled investigation. *Autonomic Neurosci. Basic Clin.* 185, 120–122. doi: 10.1016/J.AUTNEU.2014.07.008

Liu, D., and Hu, Y. (1988). The central projections of the great auricular nerve primary afferent fibers - an HRP transganglionic tracing method. *Brain Res.* 445, 205–210. doi: 10.1016/0006-8993(88)91179-1

Liu, K. Y., Elliott, T., Knowles, M., and Howard, R. (2022). Heart rate variability in relation to cognition and behavior in neurodegenerative diseases: a systematic review and meta-analysis. *Ageing Res. Rev.* 73:101539. doi: 10.1016/J.ARR.2021.101539

Liu, W. C., Mosier, K., Kalnin, A. J., and Marks, D. (2003). BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. *J. Neurol. Neurosurg. Psychiatry* 74, 811–813. doi: 10.1136/JNNP.74.6.811

Llewellyn-Smith, I. J., and Verberne, A. J. M. (2011). *Central Regulation of Autonomic Functions*. Oxford: Oxford University, 1–400.

Lomarev, M., Denslow, S., Nahas, Z., Chae, J. H., George, M. S., and Bohning, D. E. (2002). Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. *J. Psychiatric Res.* 36, 219–227. doi: 10.1016/S0022-3956(02)00013-4

Machetanz, K., Berelidze, L., Guggenberger, R., and Gharabaghi, A. (2021). Transcutaneous auricular vagus nerve stimulation and heart rate variability: analysis of parameters and targets. *Autonomic Neurosci. Basic Clin.* 236:102894. doi: 10.1016/j.autneu.2021.102894

MacLeod, C. M. (1991). Half a century of reseach on the stroop effect: an integrative review. *Psychol. Bull.* 109, 163–203. doi: 10.1037/0033-2909.109.2.163

Maharjan, A., Wang, E., Peng, M., and Cakmak, Y. O. (2018). Improvement of olfactory function with high frequency non-invasive auricular electrostimulation in healthy humans. *Front. Neurosci.* 12:225. doi: 10.3389/FNINS.2018.00225

Martin, C. O., Denburg, N. L., Tranel, D., Granner, M. A., and Bechara, A. (2004). The effects of vagus nerve stimulation on decision-making. *Cortex* 40, 605–612. doi: 10.1016/S0010-9452(08)70156-4

Massari, V. J., Johnson, T. A., and Gatti, P. J. (1995). Cardiotopic organization of the nucleus ambiguus? An anatomical and physiological analysis of neurons regulating atrioventricular conduction. *Brain Res.* 679, 227–240. doi: 10.1016/0006-8993(95)00227-H

Mazza, M., Marano, G., Traversi, G., Bria, P., and Mazza, S. (2011). Primary cerebral blood flow deficiency and Alzheimer's disease: shadows and lights. *J. Alzheimer's Dis.* 23, 375–389. doi: 10.3233/JAD-2010-090700

McGlone, J., Valdivia, I., Penner, M., Williams, J., Sadler, R. M., and Clarke, D. B. (2008). Quality of life and memory after vagus nerve stimulator implantation for epilepsy. *Can. J. Neurol. Sci. J. Can. Sci. Neurol.* 35, 287–296. doi: 10.1017/S0317167100008854

McIntire, L. K., McKinley, R. A., Goodyear, C., McIntire, J. P., and Brown, R. D. (2021). Cervical transcutaneous vagal nerve stimulation (ctVNS) improves human cognitive performance under sleep deprivation stress. *Commun. Biol.* 4:634. doi: 10.1038/s42003-021-02145-7

Mercante, B., Deriu, F., and Rangon, C.-M. (2018). Auricular neuromodulation: the emerging concept beyond the stimulation of vagus and trigeminal nerves. *Medicines* 5:10. doi: 10.3390/medicines5010010

Merrick, J., Grippo, A. J., Bartlett, G., Shaffer, F., and Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Front. Public Health* 5:258. doi: 10.3389/fpubh.2017.00258

Merrill, C. A., Jonsson, M. A. G., Minthon, L., Ejnell, H., Silander, H. C. S., Blennow, K., et al. (2006). Vagus nerve stimulation in patients with Alzheimer's disease: additional follow-up results of a pilot study through 1 year. *J. Clin. Psychiatry* 67, 1171–1178. doi: 10.4088/JCP.V67N0801

Mertens, A., Naert, L., Miatton, M., Poppa, T., Carrette, E., Gadeyne, S., et al. (2020). Transcutaneous vagus nerve stimulation does not affect verbal memory performance in healthy volunteers. *Front. Psychol.* 11:551. doi: 10.3389/FPSYG.2020.00551

Montano, N., Porta, A., Cogliati, C., Costantino, G., Tobaldini, E., Casali, K. R., et al. (2009). Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. *Neurosci. Biobehav. Rev.* 33, 71–80. doi: 10.1016/J.NEUBIOREV.2008.07.006

Morris, G. L., and Mueller, W. M. (1999). Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The vagus nerve stimulation study group E01-E05. *Neurology* 53, 1731–1735. doi: 10.1212/WNL.53.8.1731

Mu, Q., Bohning, D. E., Nahas, Z., Walker, J., Anderson, B., Johnson, K. A., et al. (2004). Acute vagus nerve stimulation using different pulse widths produces varying brain effects. *Biol. Psychiatry* 55, 816–825. doi: 10.1016/J.BIOPSYCH.2003.12.004

Munakata, Y., Herd, S. A., Chatham, C. H., Depue, B. E., Banich, M. T., and O'Reilly, R. C. (2011). A unified framework for inhibitory control. *Trends Cogn. Sci.* 15:453. doi: 10.1016/J.TICS.2011.07.011

Narayanan, J. T., Watts, R., Haddad, N., Labar, D. R., Li, P. M., and Filippi, C. G. (2002). Cerebral activation during vagus nerve stimulation: a functional MR study. *Epilepsia* 43, 1509–1514. doi: 10.1046/J.1528-1157.2002.16102.X

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: tests of an associative deficit hypothesis. *J. Exp. Psychol. Learn. Mem. Cogn.* 26, 1170–1187. doi: 10.1037/0278-7393.26.5.1170

Neftel, W. B. (1871). *Galvano-Therapeutics. The Physiological and Therapeutical Action of the Galvanic Current Upon the Acoustic, Optic, Sympathetic, and Pneumogastric Nerves*. New York, NY: D Appleton & Company.

Nesbitt, A. D., Marin, J. C. A., Tompkins, E., Ruttledge, M. H., and Goadsby, P. J. (2015). Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. *Neurology* 84, 1249–1253. doi: 10.1212/WNL.0000000000001394

Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., et al. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 7, e105–e125. doi: 10.1016/S2468-2667(21)00249-8/ATTACHMENT/60E03FD1-38B2-4B40-A91D-9AFDDA22B45E/MMC1.PDF

Obst, M. A., Heldmann, M., Alicart, H., Tittgemeyer, M., and Münte, T. F. (2020). Effect of Short-Term Transcutaneous Vagus Nerve Stimulation (tVNS) on brain processing of food cues: an electrophysiological study. *Front. Hum. Neurosci.* 14:206. doi: 10.3389/FNHUM.2020.00206

Öngür, D., and Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex (New York, N.Y.: 1991)* 10, 206–219. doi: 10.1093/CERCOR/10.3.206

O'Reardon, J. P., Cristancho, P., and Peshek, A. D. (2006). Vagus Nerve Stimulation (VNS) and treatment of depression: to the brainstem and beyond. *Psychiatry (Edgmont)* 3:54.

Perini, G. I., Toffanin, T., Pigato, G., Ferri, G., Follador, H., Zonta, F., et al. (2017). Hippocampal gray volumes increase in treatment-resistant depression responding to vagus nerve stimulation. *J. ECT* 33, 160–166. doi: 10.1097/YCT.0000000000000424

Petelin Gadze, Z., Bujan Kovac, A., Adamec, I., Milekic, N., and Sulentic, V. (2018). Vagal nerve stimulation is beneficial in postural orthostatic tachycardia syndrome and epilepsy. *Seizure* 57, 11–13. doi: 10.1016/J.SEIZURE.2018.03.001

Peuker, E. T., and Filler, T. J. (2002). The nerve supply of the human auricle. *Clin. Anatomy* 15, 35–37. doi: 10.1002/ca.1089

Pickering, T. G., and Davies, J. (1973). Estimation of the conduction time of the baroreceptor-cardiac reflex in man. *Cardiovasc. Res.* 7, 213–219. doi: 10.1093/CVR/7.2.213

Polak, T., Markulin, F., Ehlis, A. C., Langer, J. B. M., Ringel, T. M., and Fallgatter, A. J. (2009). Far field potentials from brain stem after transcutaneous Vagus nerve stimulation: optimization of stimulation and recording parameters. *J. Neural Transm.* 116, 1237–1242. doi: 10.1007/S00702-009-0282-1

Porges, E. C., Woods, A. J., Edden, R. A. E., Puts, N. A. J., Harris, A. D., Chen, H., et al. (2017). Frontal gamma-aminobutyric acid concentrations are associated with cognitive performance in older adults. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 2:38. doi: 10.1016/J.BPSC.2016.06.004

Ridgewell, C., Heaton, K. J., Hildebrandt, A., Couse, J., Leeder, T., and Neumeier, W. H. (2021). The effects of transcutaneous auricular vagal nerve stimulation on cognition in healthy individuals: a meta-analysis. *Neuropsychology* 35, 352–365. doi: 10.1037/NEU0000735

Roges, R. C., Kita, H., Butcher, L. L., and Novin, D. (1980). Afferent projections to the dorsal motor nucleus of the vagus. *Brain Res. Bull.* 5, 365–373. doi: 10.1016/S0361-9230(80)80006-2

Ronkainen, E., Korpelainen, J. T., Heikkinen, E., Myllylä, V. V., Huikuri, H. V., and Isojärvi, J. I. T. (2006). Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. *Epilepsia* 47, 556–562. doi: 10.1111/J.1528-1167.2006.00467.X

Rufener, K. S., Geyer, U., Janitzky, K., Heinze, H. J., and Zaehle, T. (2018). Modulating auditory selective attention by non-invasive brain stimulation: differential effects of transcutaneous vagal nerve stimulation and transcranial random noise stimulation. *Eur. J. Neurosci.* 48, 2301–2309. doi: 10.1111/ejn.14128

Rutecki, P. (1990). Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia* 31(Suppl. 2), S1–S6. doi: 10.1111/J.1528-1157.1990.TB05843.X

Sakaki, M., Yoo, H. J., Nga, L., Lee, T.-H., Thayer, J. F., and Mather, M. (2016). Heart rate variability is associated with amygdala functional connectivity with MPFC across younger and older adults HHS Public Access. *Neuroimage* 139, 44–52. doi: 10.1016/j.neuroimage.2016.05.076

Saleem, K. S., Kondo, H., and Price, J. L. (2008). Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. *J. Comparat. Neurol.* 506, 659–693. doi: 10.1002/CNE.21577

Sandrone, G., Mortara, A., Torzillo, D., la Rovere, M. T., Malliani, A., and Lombardi, F. (1994). Effects of beta blockers (atenolol or metoprolol) on heart rate variability after acute myocardial infarction. *Am. J. Cardiol.* 74, 340–345. doi: 10.1016/0002-9149(94)90400-6

Sandson, T. A., O'Connor, M., Sperling, R. A., Edelman, R. R., and Warach, S. (1996). Noninvasive perfusion MRI in Alzheimer's disease: a preliminary report. *Neurology* 47, 1339–1342. doi: 10.1212/WNL.47.5.1339

Saper, C. B. (2000). Hypothalamic connections with the cerebral cortex. *Progr. Brain Res.* 126, 39–48. doi: 10.1016/S0079-6123(00)26005-6

Schevernels, H., van Bochove, M. E., de Taeye, L., Bombeke, K., Vonck, K., van Roost, D., et al. (2016). The effect of vagus nerve stimulation on response inhibition. *Epilepsy Behav.* 64, 171–179. doi: 10.1016/J.YEBEH.2016.09.014

Sclocco, R., Garcia, R. G., Kettner, N. W., Isenburg, K., Fisher, H. P., Hubbard, C. S., et al. (2019). The influence of respiration on brainstem and cardiovagal response to auricular vagus nerve stimulation: a multimodal ultrahigh-field (7T) fMRI study. *Brain Stimul.* 12, 911–921. doi: 10.1016/J.BRS.2019.02.003

Sellaro, R., van Leusden, J. W. R., Tona, K. D., Verkuil, B., Nieuwenhuis, S., and Colzato, L. S. (2015). Transcutaneous vagus nerve stimulation enhances post-error slowing. *J. Cogn. Neurosci.* 27, 2126–2132. doi: 10.1162/JOCN_A_00851

Setty, A. B., Vaughn, B. V., Quint, S. R., Robertson, K. R., and Messenheimer, J. A. (1998). Heart period variability during vagal nerve stimulation. *Seizure* 7, 213–217. doi: 10.1016/S1059-1311(98)80038-1

Shaffer, F., and Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Front. Public Health* 5:258.

Shaffer, F., McCraty, R., and Zerr, C. L. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front. Psychol.* 5:1040. doi: 10.3389/FPSYG.2014.01040

Sierra-Marcos, A. (2017). Regional cerebral blood flow in mild cognitive impairment and Alzheimer's disease measured with arterial spin labeling magnetic resonance imaging. *Int. J. Alzheimer's Dis.* 2017:5479597. doi: 10.1155/2017/5479597

Sinkovec, M., Trobec, R., and Meglic, B. (2021). Cardiovascular responses to low-level transcutaneous vagus nerve stimulation. *Autonomic Neurosci.* 236:102851. doi: 10.1016/J.AUTNEU.2021.102851

Sjögren, M. J. C., Hellström, P. T. O., Jonsson, M. A. G., Runnerstam, M., Silander, H. C. S., and Ben-Menachem, E. (2002). Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. *J. Clin. Psychiatry* 63, 972–980. doi: 10.4088/jcp.v63n1103

Sperling, W., Reulbach, U., Bleich, S., Padberg, F., Kornhuber, J., and Mueck-Weymann, M. (2010). Cardiac effects of vagus nerve stimulation in patients with major depression. *Pharmacopsychiatry* 43, 7–11. doi: 10.1055/S-0029-1237374

Squire, L., and Zola, S. (1998). Episodic memory, semantic memory, and amnesia. *Hippocampus* 8, 205–211.

Stavrakis, S., Humphrey, M. B., Scherlag, B. J., Hu, Y., Jackman, W. M., Nakagawa, H., et al. (2015). Low-level transcutaneous electrical vagus nerve stimulation suppresses atrial fibrillation. *J. Am. College Cardiol.* 65, 867–875. doi: 10.1016/j.jacc.2014.12.026

Steenbergen, L., Sellaro, R., Stock, A. K., Verkuil, B., Beste, C., and Colzato, L. S. (2015). Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes. *Eur. Neuropsychopharmacol. J. Eur. College Neuropsychopharmacol.* 25, 773–778. doi: 10.1016/J.EURONEURO.2015.03.015

Stefan, H., Kreiselmeyer, G., Kerling, F., Kurzbuch, K., Rauch, C., Heers, M., et al. (2012). Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia* 53, e115–e118. doi: 10.1111/J.1528-1167.2012.03492.X

Stein, P. K., and Kleiger, R. E. (2003). Insights from the study of heart rate variability. *Annu. Rev. Med.* 50, 249–261. doi: 10.1146/ANNUREV.MED.50.1.249

Steinbrook, R. (2021). The accelerated approval of aducanumab for treatment of patients with Alzheimer disease. *JAMA Internal Med.* 181:1281. doi: 10.1001/JAMAINTERNMED.2021.4622

Sucholeiki, R., Alsaadi, T. M., Morris, G. L., Ulmer, J. L., Biswal, B., and Mueller, W. M. (2002). fMRI in patients implanted with a vagal nerve stimulator. *Seizure* 11, 157–162. doi: 10.1053/SEIZ.2001.0601

Sun, J.-B., Cheng, C., Tian, Q.-Q., Yuan, H., Yang, X.-J., Deng, H., et al. (2021). Transcutaneous auricular vagus nerve stimulation improves spatial working memory in healthy young adults. *Front. Neurosci.* 15:790793. doi: 10.3389/FNINS.2021.790793

Sun, L., Peräkylä, J., Holm, K., Haapasalo, J., Lehtimäki, K., Ogawa, K. H., et al. (2017). Vagus nerve stimulation improves working memory performance. *J. Clin. Exp. Neuropsychol.* 39, 954–964. doi: 10.1080/13803395.2017.1285869

Sun, P., Zhou, K., Wang, S., Li, P., Chen, S., Lin, G., et al. (2013). Involvement of MAPK/NF-κB signaling in the activation of the cholinergic anti-inflammatory pathway in experimental colitis by chronic vagus nerve stimulation. *PLoS One* 8:e69424. doi: 10.1371/JOURNAL.PONE.0069424

Tamayo, A., and Siepmann, T. (2021). Regulation of blood flow in the cerebral posterior circulation by parasympathetic nerve fibers: physiological background and possible clinical implications in patients with vertebrobasilar stroke. *Front. Neurol.* 12:660373. doi: 10.3389/FNEUR.2021.660373

Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., and Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci. Biobehav. Rev.* 36, 747–756. doi: 10.1016/J.NEUBIOREV.2011.11.009

Thayer, J. F., Hansen, A. L., Saus-Rose, E., and Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann. Behav. Med.* 37, 141–153. doi: 10.1007/S12160-009-9101-Z

Thayer, J. F., and Lane, R. D. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biol. Psychol.* 74, 224–242. doi: 10.1016/J.BIOPSYCHO.2005.11.013

Tiego, J., Testa, R., Bellgrove, M. A., Pantelis, C., and Whittle, S. (2018). A hierarchical model of inhibitory control. *Front. Psychol.* 9:1339. doi: 10.3389/FPSYG.2018.01339

Tobaldini, E., Toschi-Dias, E., Appratto de Souza, L., Rabello Casali, K., Vicenzi, M., Sandrone, G., et al. (2019). Cardiac and peripheral autonomic responses to orthostatic stress during transcutaneous vagus nerve stimulation in healthy subjects. *J. Clin. Med.* 8:496. doi: 10.3390/jcm8040496

Tsutsumi, T., Ide, T., Yamato, M., Kudou, W., Andou, M., Hirooka, Y., et al. (2008). Modulation of the myocardial redox state by vagal nerve stimulation after experimental myocardial infarction. *Cardiovasc. Res.* 77, 713–721. doi: 10.1093/CVR/CVM092

Unsworth, N., and Robison, M. K. (2017). A locus coeruleus-norepinephrine account of individual differences in working memory capacity and attention control. *Psychonomic Bull. Rev.* 24, 1282–1311. doi: 10.3758/S13423-016-1220-5

van Bochove, M. E., de Taeye, L., Raedt, R., Vonck, K., Meurs, A., Boon, P., et al. (2018). Reduced distractor interference during vagus nerve stimulation. *Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol.* 128, 93–99. doi: 10.1016/J.IJPSYCHO.2018.03.015

van den Stock, J., Tamietto, M., Sorger, B., Pichon, S., Grézes, J., and de Gelder, B. (2011). Cortico-subcortical visual, somatosensory, and motor activations for perceiving dynamic whole-body emotional expressions with and without striate cortex (V1). *Proc. Natl. Acad. Sci. U.S.A.* 108, 16188–16193. doi: 10.1073/PNAS.1107214108/-/DCSUPPLEMENTAL

Vargas-Caballero, M., Warming, H., Walker, R., Holmes, C., Cruickshank, G., and Patel, B. (2022). Vagus nerve stimulation as a potential therapy in Early Alzheimer's disease: a review. *Front. Hum. Neurosci.* 16:866434. doi: 10.3389/FNHUM.2022.866434

Ventura-Bort, C., Wirkner, J., Genheimer, H., Wendt, J., Hamm, A. O., and Weymar, M. (2018). Effects of Transcutaneous Vagus Nerve Stimulation (tVNS) on the P300 and alpha-amylase level: a pilot study. *Front. Hum. Neurosci.* 12:202. doi: 10.3389/fnhum.2018.00202

Ventureyra, E. C. G. (2000). Transcutaneous vagus nerve stimulation for partial onset seizure therapy. A new concept. *Child's Nerv. Syst. ChNS Off. J. Int. Soc. Pediatric Neurosurg.* 16, 101–102. doi: 10.1007/S003810050021

Vonck, K., de Herdt, V., Bosman, T., Dedeurwaerdere, S., van Laere, K., and Boon, P. (2008). Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study. *Seizure* 17, 699–706. doi: 10.1016/J.SEIZURE.2008.05.001

Wang, B., Yan, C., Klein, R. M., and Wang, Z. (2018). Inhibition of return revisited: localized inhibition on top of a pervasive bias. *Psychonomic Bull. Rev.* 25, 1861–1867. doi: 10.3758/S13423-017-1410-9/TABLES/2

Warner, H., and Cox, A. (1962). A mathematical model of heart rate control by sympathetic and vagus efferent information. *J. Appl. Physiol.* 17, 349–355. doi: 10.1152/JAPPL.1962.17.2.349

Xing, B., Li, Y. C., and Gao, W. J. (2016). Norepinephrine versus dopamine and their interaction in modulating synaptic function in the prefrontal cortex. *Brain Res.* 1641(Pt B), 217. doi: 10.1016/J.BRAINRES.2016.01.005

Xu, J., Zhang, Y., Qiu, C., and Cheng, F. (2017). Global and regional economic costs of dementia: a systematic review. *Lancet* 390:S47. doi: 10.1016/S0140-6736(17)33185-9

Yakunina, N., Kim, S. S., and Nam, E. C. (2017). Optimization of transcutaneous vagus nerve stimulation using functional MRI. *Neuromodulation* 20, 290–300. doi: 10.1111/ner.12541

Yap, J. Y. Y., Keatch, C., Lambert, E., Woods, W., Stoddart, P. R., and Kameneva, T. (2020). Critical review of transcutaneous vagus nerve stimulation: challenges for translation to clinical practice. *Front. Neurosci.* 14:284. doi: 10.3389/FNINS.2020.00284

Yoshiura, T., Hiwatashi, A., Yamashita, K., Ohyagi, Y., Monji, A., Takayama, Y., et al. (2009). Simultaneous measurement of arterial transit time, arterial blood volume, and cerebral blood flow using arterial spin-labeling in patients with Alzheimer disease. *AJNR. Am. J. Neuroradiol.* 30, 1388–1393. doi: 10.3174/AJNR.A1562

Yu, Y., Yang, Y., Gan, S., Guo, S., Fang, J., Wang, S., et al. (2021). Cerebral hemodynamic correlates of transcutaneous auricular vagal nerve stimulation in consciousness restoration: an open-label pilot study. *Front. Neurol.* 12:684791. doi: 10.3389/FNEUR.2021.684791

Zabara, J. (1985). Time course of seizure control to breaf repetitive stimuli. *Epilepsia* 26:518.

Zabara, J. (1992). Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia* 33, 1005–1012. doi: 10.1111/J.1528-1157.1992.TB01751.X

Zanchetti, A., Wang, S. C., and Moruzzi, G. (1952). The effect of vagal afferent stimulation on the EEG pattern of the cat. *Electroencephalogr. Clin. Neurophysiol.* 4, 357–361. doi: 10.1016/0013-4694(52)90064-3

Zeki Al Hazzouri, A., Haan, M. N., Deng, Y., Neuhaus, J., and Yaffe, K. (2014). Reduced heart rate variability is associated with worse cognitive performance in elderly mexican americans. *Hypertension* 63, 181–187. doi: 10.1161/HYPERTENSIONAHA.113.01888

Zhang, Y., Popović, Z. B., Bibevski, S., Fakhry, I., Sica, D. A., Van Wagoner, D. R., et al. (2009). Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ. Heart Fail.* 2, 692–699. doi: 10.1161/CIRCHEARTFAILURE.109.873968

Zuo, Y., Smith, D. C., and Jensen, R. A. (2007). Vagus nerve stimulation potentiates hippocampal LTP in freely-moving rats. *Physiol. Behav.* 90, 583–589. doi: 10.1016/j.physbeh.2006.11.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 21 June 2022
doi: 10.3389/fnagi.2022.856782

Relationship Between Arterial Stiffness Index, Pulse Pressure, and Magnetic Resonance Imaging Markers of White Matter Integrity: A UK Biobank Study

Atef Badji[1,2,3], *Julien Cohen-Adad*[1,2,7†] *and Hélène Girouard*[2,4,5,6,8*†]

[1] NeuroPoly Lab, Institute of Biomedical Engineering, Polytechnique Montréal, Montréal, QC, Canada, [2] Functional Neuroimaging Unit, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Université de Montréal, Montréal, QC, Canada, [3] Department of Neurosciences, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [4] Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada, [5] Groupe de Recherche sur le Système Nerveux Central, Montréal, QC, Canada, [6] Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Montréal, QC, Canada, [7] Mila - Quebec AI Institute, Montréal, QC, Canada, [8] Groupe de Recherche Universitaire Sur le Médicament (GRUM), Montréal, QC, Canada

OPEN ACCESS

Edited by:
Anja Soldan,
Johns Hopkins University,
United States

Reviewed by:
Ashley E. Walker,
University of Oregon, United States
Timothy Hughes,
Wake Forest School of Medicine,
United States

***Correspondence:**
Hélène Girouard
helene.girouard@umontreal.ca

[†] *These authors have contributed equally to this work*

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *17 January 2022*
Accepted: *09 May 2022*
Published: *21 June 2022*

Citation:
Badji A, Cohen-Adad J and Girouard H (2022) Relationship Between Arterial Stiffness Index, Pulse Pressure, and Magnetic Resonance Imaging Markers of White Matter Integrity: A UK Biobank Study. Front. Aging Neurosci. 14:856782. doi: 10.3389/fnagi.2022.856782

Background: Alzheimer's disease and dementia in general constitute one of the major public health problems of the 21st century. Research in arterial stiffness and pulse pressure (PP) play an important role in the quest to reduce the risk of developing dementia through controlling modifiable risk factors.

Objective: The aim of the study is to investigate the association between peripheral PP, arterial stiffness index (ASI) and brain integrity, and to discover if ASI is a better predictor of white matter integrity than peripheral PP.

Materials and Methods: 17,984 participants 63.09 ± 7.31 from the UK Biobank were used for this study. ASI was estimated using infrared light (photoplethysmography) and peripheral PP was calculated by subtracting the diastolic from the systolic brachial blood pressure value. Measure of fractional anisotropy (FA) was obtained from diffusion imaging to estimate white matter microstructural integrity. White matter hyperintensities were segmented from the combined T1 and T2-weighted FLAIR images as a measure of irreversible white matter damage.

Results: An important finding is that peripheral PP better predicts white matter integrity when compared to ASI. This finding is consistent until 75 years old. Interestingly, no significant relationship is found between either peripheral PP or ASI and white matter integrity after 75 years old.

Conclusion: These results suggest that ASI from plethysmography should not be used to estimate cerebrovascular integrity in older adults and further question the relationship between arterial stiffness, blood pressure, and white matter damage after the age of 75 years old.

Keywords: arterial stiffness index (ASI), pulse pressure (PP), UK Biobank, white matter, MRI

INTRODUCTION

Alzheimer's disease and dementia in general is one of the major public health problems of the 21st century (Wiesmann et al., 2013; World Health Organization, 2015), yet there is currently no cure nor disease-modifying treatment for it. This stresses the need to find ways to reduce the risk of developing dementia through controlling modifiable factors (Baumgart et al., 2015). Vascular risk factors, such as hypertension and arterial stiffness have been associated with the pathogenesis of dementia, in particular Alzheimer's disease and vascular dementia through their impact on the white matter (Singer et al., 2014; Badji et al., 2019, 2020).

White matter lesions described as white matter hyperintensities by T2-weighted or fluid-attenuated inversion recovery (FLAIR), have consistently been shown to be associated with arterial stiffness of large arteries (Longstreth et al., 1996; Tsao et al., 2013; Maillard et al., 2016). Studies using diffusion imaging highlight that arterial stiffness alters the microstructural integrity of three vulnerable white matter tracts (corpus callosum, internal capsule, and corona radiata) prior to irreversible white matter lesions (Badji et al., 2019).

Arterial stiffness increases with age. Indeed, as we age, our large elastic vessels undergo progressive luminal dilatation, thickening of the arterial wall, increased deposition of collagen, and combined fragmentation and degeneration of elastin which reduce their capacity for dampening blood pulsatility arising from the heart during each contraction (Wiesmann et al., 2013). As a result, arterial stiffness leads to an increase of the pulse wave propagation which escalates systolic blood pressure (SBP) (Laurent et al., 2005; Pase, 2012). During aging, diastolic blood pressure (DBP) is also known to decrease. Arterial stiffness contributes therefore to the increase of pulse pressure (PP) as it reflects the difference between SBP and DBP (Kaess et al., 2012).

Increased PP and arterial stiffness are strongly correlated. However, they are also considered independent measures of vascular aging (Franklin et al., 1999; Mitchell et al., 2010). Indeed, on the one's hand, PP has been shown to be strongly associated with outcomes such as coronary heart disease (CHD), and cardiovascular events in hypertensive patients (Madhavan et al., 1994), elderly (Vaccarino et al., 2000), and the general population (Glasser et al., 2014). On the other hand, arterial stiffness as measured by carotid-femoral pulse wave velocity (cfPWV), which is considered the gold standard measure of arterial stiffness has been shown not only to be related to CHD (Boutouyrie et al., 2002), stroke (Vlachopoulos et al., 2010) but also to risk factors for dementia (Iulita et al., 2018) such as atherosclerosis (Fernandes et al., 2008), hypertension (Laurent et al., 2006), metabolic syndrome (Laurent et al., 2006) and diabetes mellitus (Laurent et al., 2006).

While cfPWV provides excellent prognostic value in adults, it is cumbersome due to the need for specialized equipment and remains mostly utilized in research nowadays (Matsui et al., 2004; Nichols, 2005). Conversely, the arterial stiffness index (ASI) estimates arterial stiffness using infrared light (photoplethysmography) to record the volume waveform of the blood in the finger in 10–15 s (Chowienczyk et al., 1999; Millasseau et al., 2000, 2002). It is therefore a fast, inexpensive, simple-to-use and therefore convenient measure of arterial stiffness that does not require specific expertise (Elgendi, 2012).

Recently, Said et al. (2018) investigated the association between vascular aging as indicated by ASI and peripheral PP with cardiovascular disease (CVD) risk factors, CVD events and mortality in 169,613 participants from the UK Biobank. Said et al. (2018) highlighted in their study that peripheral PP has more added value than ASI to improve the risk classification of incident cardiovascular disease. However, this study did not investigate the association between peripheral PP, ASI and brain integrity. Therefore, several questions remain: Is ASI a predictor of white matter integrity? If so, is it a better predictor of white matter integrity than peripheral PP? In this study we investigated the association of vascular aging as indicated by ASI and peripheral PP with magnetic resonance imaging (MRI) markers of white matter integrity.

MATERIALS AND METHODS

Study Participants

The data from the UK Biobank resource were used for the purpose of this study. The UK Biobank study design and population had previously been detailed (Sudlow et al., 2015). In brief, UK Biobank is a large community-based prospective study in the United Kingdom that recruited 502,299 participants aged 40–85 years old with the aim of improving prevention, diagnosis, and treatment of a plethora of illnesses. The study collected detailed phenotype and genotype data, including sociodemographic, lifestyle, clinical diagnosis, treatment genetic, imaging and physiological parameters. UK Biobank has approval from the institutional review boards, namely, the North West Multi-centre Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and from the Community Health Index Advisory Group for Scotland[1]. All participants gave informed consent for the study via a touch-screen interface that required agreement for all individual statements on the consent form as well as the participant's signature on an electronic pad[2]. The present study is restricted to a subsample of United Kingdom participants with information of ASI, blood pressure, diffusion tensor imaging (DTI) and white matter hyperintensities volumes (WMHV). Those with self-reported conditions listed in SM1 were excluded which led to a total of 20,742 participants included in the study. The research reported here was conducted using the UK Biobank Resource under Application Number 54531.

Cardiovascular Measurements

Arterials Stiffness Index

Pulse wave velocity was measured using the PulseTrace PCA2 (CareFusion, San Diego, CA, United States) which uses finger

[1]https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics
[2]https://www.ukbiobank.ac.uk/media/05ldg1ez/consent-form-uk-biobank.pdf

photoplethysmography to record a 10–15 s pulse waveform on the index finger of the participant's dominant hand (Collins and UK Biobank Steering Committee, 2007). The pulse waveform comprises a systolic peak and second diastolic peak, and the transit time [peak-to-peak time (PPT)] between the 2 peaks is related to the time it takes for the pulse wave to travel through the peripheral arterial tree (Millasseau et al., 2002; Gunarathne et al., 2008). This path length is proportional to a person's height (h), enabling the calculation of an index of large artery stiffness using the formula ASI = h/PPT, expressed in m/s (Gunarathne et al., 2008).

Blood Pressure Measurements and Pulse Pressure

SBP and DBP were measured twice by trained nurses after the participant had been at rest for at least 5 min in the seated position using an automated blood pressure device [Omron 705 IT electronic blood pressure (BP) monitor; OMRON Healthcare Europe B.V. Kruisweg 577 2132 NA, Hoofddorp, Netherlands], or manually using a sphygmomanometer with an inflatable cuff in combination with a stethoscope. For the purpose of the study, we first calculated the mean SBP and DBP from the two available automated BP measures for each participant. Then, since automated devices tend to measure higher SBPs than manual sphygmomanometers, we adjusted both SBP and DBP that were measured using the automated device using algorithms by Stang et al. (2006) as done recently by Said et al. (2018) for the UK Biobank data. The peripheral PP was calculated by subtracting the DBP from the SBP brachial values.

Brain Magnetic Resonance Imaging Analysis

Data Acquisition

All brain MRI data were acquired on a Siemens Skyra 3T scanner using a standard Siemens 32-channel head coil according to a freely available protocol[3].

Diffusion-weighted images were acquired using a spin-echo echo-planar sequence encoded with 5 $b = 0$ s/mm^2 (plus an additional 3 blip-reversed $b = 0$ s/mm^2), 50 $b = 1{,}000$ s/mm^2 and 50 $b = 2{,}000$ s/mm^2 diffusion-weighted volumes, for a total of 100 distinct diffusion-encoding directions. A multiband acceleration factor of 3 was used for acquisitions, spatial resolution = 2.0 mm isotropic, TR = 3,600 ms, TE = 92.00 ms. T2-weighted FLAIR volumes were acquired in sagittal orientation at $1.05 \times 1 \times 1$ mm resolution with the 3D space optimized readout (Mugler, 2014) with the following parameters: TR = 5,000 ms, TE = 395 ms.

Diffusion Weighted imaging Processing

Imaging-derived data generated by an image-processing pipeline developed and run by the UK Biobank team were used in this study (Alfaro-Almagro et al., 2018). Briefly, preprocessing of diffusion data included Eddy current distortion correction, head motion correction, and outlier slices correction using FSL's Eddy tool (Andersson and Sotiropoulos, 2015, 2016), prior to gradient distortion correction. Next, fractional anisotropy (FA) was calculated by fitting a diffusion tensor model to the pre-processed single-shell Diffusion weighted imaging (DWI) ($b = 1{,}000$ s/mm^2) data using FSL's DTIFIT (Nir et al., 2017).

The FA maps were used in FSL's Tract-Based Spatial statistics (TBSS) (Smith et al., 2006) and TBSS-derived measures were computed by averaging the skeletonized image of each FA map within a set of 48 standard-space tract masks defined by the JHU white matter atlas (ICBM-DTI-81) (Mori et al., 2008). For the purpose of the study the mean FA in the corpus callosum (CC), the internal capsule (IC) and the corona radiata (CR) were used.

White matter hyperintensities (WMH) were automatically segmented from the combined T1 and T2-weighted FLAIR images using the Brain Intensity Abnormality Classification Algorithm tool (Griffanti et al., 2016). An automated pipeline was used to delineate white matter hyperintensities from the FLAIR images. The full details of the image processing and QC pipeline are available in an open-access article (Alfaro-Almagro et al., 2018). The WMHs volumes were expressed as the percentage of intracranial volume and then natural log-transformed.

Statistical Analysis

Prior to analysis, we tested the presence of outliers in each variable of interest and removed 2,758 participants in total ASI, WMHV, FA in CC, IC and CR data using the 1.5 interquartile rule. Therefore in this study, we only considered the remaining 17984 participants. The association between vascular risk factors (e.g., increased in peripheral PP or in ASI) and changes in the white matter and cognitive decline is complex, and largely mediated by mixed cerebrovascular and neurodegenerative lesions (Qiu and Fratiglioni, 2015; Wang et al., 2017). These associations have been found to be stronger when multiple vascular risk factors are present in mid-life (40–59 years of age), especially if left untreated (Launer et al., 1995; Kivipelto et al., 2001; Yaffe et al., 2014; Qiu and Fratiglioni, 2015). These associations are in contrast less certain when these vascular risk factors occur in later life (>75 years of age) (Qiu et al., 2005; Novak and Hajjar, 2010; Anstey et al., 2011; Tolppanen et al., 2012). For that reason, we divided our participants into 4 groups based on their age G1 (45–55 years), G2 (55–65 years), G3 (65–75 years), and G4 (≥75 years).

To test the hypothesis that ASI is a better predictor of white matter integrity than peripheral PP, a stepwise linear model was performed. For this analysis, each MRI metric was treated as a dependent variable and all the following variables were considered as independent variables: age, sex, peripheral PP, and ASI (**Table 2**). To better understand the relationship between vascular aging and white matter damage across the age span, we then looked at the relationship between either peripheral PP or ASI with our MRI markers of white matter integrity across different age brackets. Scatter plots between age and peripheral PP, ASI, FA in the CC, and WMHV, respectively, further help to interpret the results (SM2).

All statistical tests and figures except the stepwise linear regression were done with R version 3.5.2. The stepwise linear regression was done with SPSS (IBM SPSS 25, Statistics, Chicago, IL, United States).

[3]https://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf

To promote reproducibility, the data and code to perform all statistical analyses and figures are publicly available at https://github.com/atefbadji/ASI_PP_MRI_UKBiobank.

RESULTS

This study included 17,984 participants, mean age 63.09 ± 7.31 years, of which 9,311 are female. **Table 1** presents the descriptive statistics for the sample as well as for subsample based on age bracket. Differences between groups in demographic and clinical variables were analyzed using an analysis of variance (ANOVA) or Chi-squared (χ^2) tests for continuous or categorical variables, respectively. One can note that all comparisons were significant among groups ($p < 0.001$). We even performed additional groupwise analysis and found almost all pairwise comparisons to be significant for all variables. The only groupwise comparison that were not significant were the following: G1 vs. G2 ($p = 0.82$) and G3 vs. G4 ($p = 0.07$) for BMI, G1 vs. G2 ($p = 0.09$) for DBP, G2 vs. G4 ($p = 0.32$) and G3 vs. G4 ($p = 0.34$) for ASI and finally G3 vs. G4 ($p = 0.36$) for FA IC. However, due to the very large sample size, one can wonder about the statistical relevance from a clinical point of view. These results are in line with the literature but outside the scope of the present study. They are therefore not discussed in the present study.

To answer our hypothesis that ASI is not only a predictor of white matter integrity but also a better one than peripheral PP, we performed a stepwise linear regression (**Table 2**). In **Table 2**, model FA CC_1 revealed that age and sex alone predict FA in the CC ($p < 0.001$). This analysis indicated an R^2 of 0.05, which means that age and sex accounted for about 5% of the total variance of FA CC. Interestingly, model FA CC_2 highlights that peripheral PP is found to be the best predictor of FA CC in comparison with ASI. Indeed, the contribution of peripheral PP on top of age and sex was found to account for significantly more variance than the previous model (F change at $p < 0.001$). The overall model of FA CC_2 (age, sex, and peripheral PP) was also found to be a significant predictor of FA CC_2 ($p < 0.001$). This analysis indicated an R^2 of 0.051 which means that age, sex, and peripheral PP accounted for 5.1% of the total variance of FA CC. Similar results have been found for all DTI metrics of interest (FA IC and FA CR, **Table 2**). In particular, age, sex, and peripheral PP were found to account for 6.9% of the total variance of FA CR. **Table 2** also highlights that age and sex predict WMHV independently ($p < 0.001$). This analysis indicated and R^2 of 0.184 which means that age and sex accounted for about 18.4% of the total variance of WMHV.

Interestingly, model WMHV_2 highlights that peripheral PP is found to be the best predictor of WMHV in comparison to ASI. Indeed, the contribution of peripheral PP on top of age and sex was found to account for significantly more variance than the previous model (F change at $p < 0.001$). The overall model of WMHV (age, sex, and peripheral PP) was also found to be a significant predictor of WMHV ($p < 0.001$). This analysis indicated an R^2 of 0.189 which means that age, sex, and peripheral PP accounted for 18.9% of the total variance of WMHV. Moreover, the contribution of ASI on top of age, sex, and peripheral PP was found to account for significantly more variance than the previous model (F change at $p < 0.001$). The overall model of WMHV (age, sex, peripheral PP, and ASI) was found to be a significant predictor of WMHV ($p < 0.001$). This analysis indicated an R^2 of 0.190 which means that age, sex, peripheral PP, and ASI accounted for 19% of the total variance of WMHV.

A closer look at the association between peripheral PP and ASI with our MRI metrics of interest revealed that peripheral PP was negatively associated with FA in CC ($r = -0.048$, $p = 0.008$)

TABLE 1 | Characteristics of all participants.

	All participants	Between 45 and 55 years	Between 55 and 65 years	Between 65 and 75 years	Over 75 years	*p*-value
Women/men (N)	9,311/8,673 (17,984)	1,652/1,363 (3,015)	3,986/3,320 (7,306)	3,365/3,510 (6,875)	308/480 (788)	**<2.2e-16**
Age (years)	63.09 ± 7.31	52.14 ± 1.94	60.25 ± 2.88	69.34 ± 2.67	76.86 ± 1.47	**<2.0e-16**
BMI (kg/m^2)	26.17 ± 4.12	26.34 ± 4.40	26.30 ± 4.26	26.00 ± 3.91	25.65 ± 3.44	**7.42e-8**
Cardiovascular measures						
SBP (mmHg)	131.53 ± 16.61	124.80 ± 15.36	129.78 ± 16.23	135.54 ± 16.28	138.45 ± 15.89	**<2.0e-16**
DBP (mmHg)	78.93 ± 8.24	79.15 ± 8.42	79.35 ± 8.23	78.54 ± 8.12	77.45 ± 8.26	**<1.92e-16**
PP (mmHg)	52.60 ± 12.36	45.65 ± 9.93	50.43 ± 11.30	55.99 ± 12.20	60.99 ± 12.58	**<2.0e-16**
ASI (m/s)	9.37 ± 2.67	8.96 ± 2.46	9.35 ± 2.62	9.55 ± 2.76	9.45 ± 2.76	**<2.0e-16**
MRI measure						
FA in CC	0.745 ± 0.021	0.751 ± 0.019	0.747 ± 0.020	0.741 ± 0.021	0.734 ± 0.022	**<2.0e-16**
FA in IC	0.630 ± 0.018	0.633 ± 0.017	0.630 ± 0.017	0.628 ± 0.018	0.627 ± 0.018	**<2.0e-16**
FA in CR	0.479 ± 0.019	0.486 ± 0.018	0.482 ± 0.019	0.475 ± 0.019	0.469 ± 0.019	**<2.0e-16**
WMHV	3095.41 ± 2422.66	1693.63 ± 1466.11	2593.85 ± 2043.15	3992.16 ± 2579.82	5285.21 ± 2704.12	**<2.0e-16**

Values are means ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FA in CC and FA in CR are fractional anisotropy of the corpus callosum, internal capsule and corona radiata, respectively; WMHV, white matter hyperintensities volume. Bold values are significant values after correction for multiple comparison.

TABLE 2 | Result of stepwise entry linear model based on a priory hypothesis on the influence of age, sex, and vascular risk factors on white matter integrity.

Dependent variable = FA CC				
Name	Independent variables	R^2	*p*	*F* change *p*
1	Age + Sex	0.050	<0.001	N/A
2	Age + Sex + PP	0.051	<0.001	<0.001
Dependent variable = FA IC				
Name	Independent variables	R^2	*P*	*F* change *p*
1	Age + Sex	0.031	<0.001	N/A
2	Age + Sex + PP	0.032	<0.001	<0.001
Dependent variable = FA CR				
Name	Independent variables	R^2	*p*	*F* change *p*
1	Age + Sex	0.068	<0.001	N/A
2	Age + Sex + PP	0.069	<0.001	<0.001
Dependent variable = WMHV				
Name	Independent variables	R^2	*p*	*F* change *p*
1	Age + Sex	0.184	<0.001	N/A
2	Age + Sex + PP	0.189	<0.001	<0.001
3	Age + Sex + ASI	0.190	<0.001	<0.001

Two cardiovascular risk factors were fed to each stepwise linear model: PP and ASI. These models aimed to find which cardiovascular risk factors among PP and ASI best predict the fractional anisotropy (FA) of the corpus callosum (CC), internal capsule (CI), corona radiata (CR) and the white matter hyperintensity volume (WMHV). Fixed covariates were age and sex. R^2 of the significant models are reported as well as the overall p-value of the model and the significant F changes when comparing with previous model.

and positively WMHV (r = 0.119, p = 5.306e-11) in participants aged 45–55 years old (**Figure 1**). The same relationship was found in participants aged between 55 and 65 (**Figure 2**) and 65 and 75 years old (**Figure 3**). However, ASI was not found to be associated with neither FA in CC nor WMHV in any group of participants (**Figures 1**–**4**) with the exception of a positive association found between ASI and WMHV in participants aged 55–65 years old (r = 0.05, p = 2.42e-06). Interestingly, in participants over 75 years old, we did not find a significant relationship between either peripheral PP or ASI with MRI metrics (**Figure 4**).

DISCUSSION

In this study, we investigated the relationship between ASI and peripheral PP with white matter integrity as assessed by FA metric and WMHV volumes in participants of the UK Biobank. An important finding is that peripheral PP better predicts white matter integrity when compared to ASI measured with plethysmography. We found that an increase in peripheral PP was associated with a lower FA and increased WMHV. This finding was consistent until 75 years old. Interestingly, no significant relationship was found between neither peripheral PP nor ASI and white matter integrity after 75 years old, which may question the nature of the relationship between markers of vascular aging and white matter damage in individuals over 75 years old.

Pulse Pressure Is a Better Predictor of White Matter Integrity Than Arterial Stiffness Index in Participants Aged 45–75 Years Old

Several studies have previously compared different markers of arterial stiffness and vascular aging on the incidence of cardiovascular events, in particular cfPWV and PP. cfPWV has been established as the gold standard measure of arterial stiffness and a stronger predictor of cardiovascular events than peripheral PP, not only in older adults but also in individuals with different

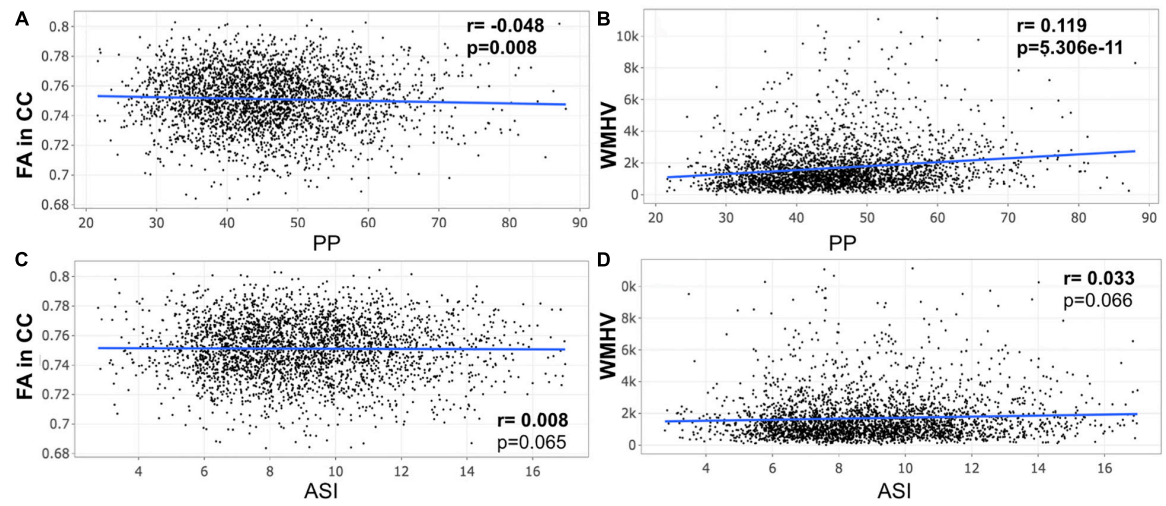


FIGURE 1 | Scatter plot for partial correlation analysis of either pulse pressure (PP) or arterial stiffness index (ASI) with the fractional anisotropy of the corpus callosum (FA in CC) or the white matter hyperintensity volume (WMHV) in 3,015 participants between 45 and 55 years old. Significant *p*-values are in bold (adjusted threshold with FDR was 0.025). Covariates included sex. An additional analysis was performed with both age and sex as covariates showing similar significant results: **(A)** p = 0.012; **(B)** p = 2.65e-09; **(C,D)** p > 0.025.

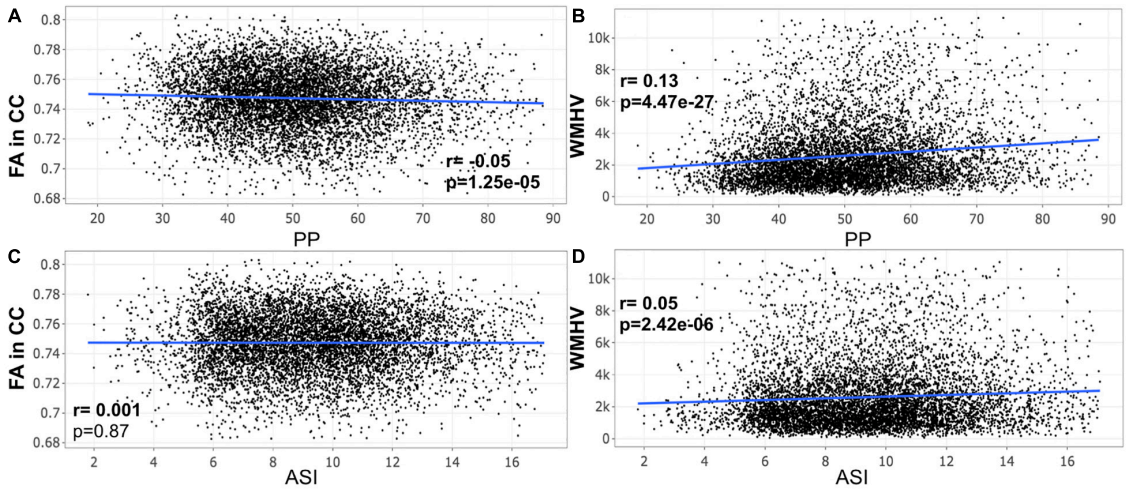


FIGURE 2 | Scatter plot for partial correlation analysis of either pulse pressure (PP) or stiffness Index (ASI) with the fractional anisotropy of the corpus callosum (FA in CC) or the white matter hyperintensity volume (WMHV) in 7,306 participants between 55 and 65 years old. Significant *p*-values are in bold (adjusted threshold with FDR was 0.0375). Covariates included sex. An additional analysis was performed with both age and sex as covariates showing similar significant results: **(A)** p = 5.2e-04; **(B)** p = 7.38e-17; **(C)** $p > 0.0375$; **(D)**, p = 2.75e-05.

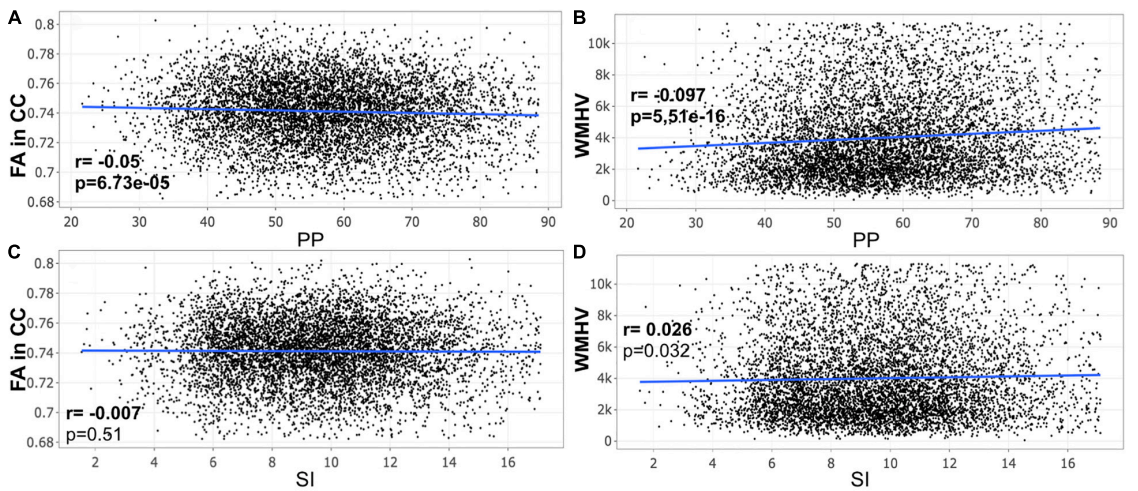


FIGURE 3 | Scatter plot for partial correlation analysis of either pulse pressure (PP) or stiffness Index (ASI) with the fractional anisotropy of the corpus callosum (FA in CC) or the white matter hyperintensity volume (WMHV) in 6,875 participants between 65 and 75 years old. Significant *p*-values are in bold (adjusted threshold with FDR was 0.0375). Covariates included sex. An additional analysis was performed with both age and sex as covariates showing similar significant results: **(A)** p = 2.03e-05; **(B)** p = 6.73e-33; **(C)** $p > 0.0375$; **(D)** p = 1.54e-06.

conditions such as renal failure, atrial fibrillation, and heart failure (Laurent et al., 2001; Rahman, 2017; Niiranen et al., 2019). Peripheral PP has also been associated with cardiovascular outcomes (Madhavan et al., 1994; Benetos et al., 1997; Mitchell et al., 1997), however, such observation has been attributed to the interplay between peripheral PP and arterial stiffness.

Beyond its effects on cardiovascular events, cfPWV has been also shown to better predict cognitive decline than measures of BP (Marfella and Paolisso, 2016). The emerging MRI literature has often highlighted a relationship between arterial stiffness, WMHs and white matter microstructure (Shrestha et al., 2009; Rosano et al., 2013; Singer et al., 2014; Badji et al., 2019). In particular, DTI studies looking at the effect of cfPWV on the white matter microstructure showed consistently that several white matter tracts are particularly vulnerable to increased arterial stiffness, among which is the CC, a key white matter tract altered in AD (Badji et al., 2019). Interestingly, cfPWV was recently found to better predict the microstructural integrity of the CC when compared with measures of 24 h SBP, 24 h PP and AIx in participants between 65 and 75 years old (Badji et al., 2020). However, to the best of our knowledge, no other study has yet compared different markers of arterial stiffness

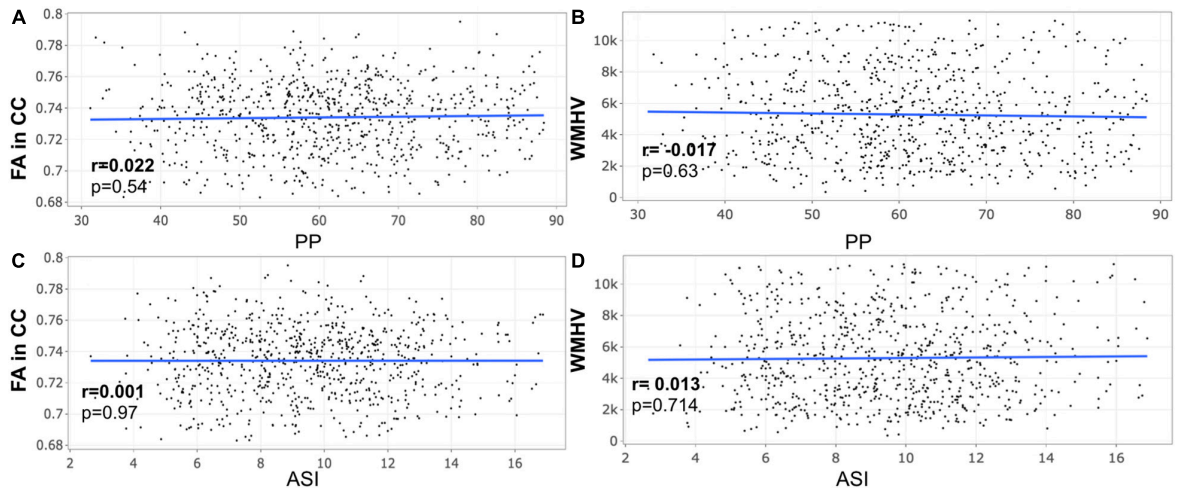


FIGURE 4 | Scatter plot for partial correlation analysis of either pulse pressure (PP) or stiffness Index (ASI) with the fractional anisotropy of the corpus callosum (FA in CC) or the white matter hyperintensity volume (WMHV) in 788 participants over 75 years old. Significant *p*-values are in bold (adjusted threshold with FDR was 0.0125). Covariates included is sex. An additional analysis was performed with both age and sex as covariates showing similar results. **(A–D)** *p* values > 0.0125.

on brain integrity, nor has included measures of ASI before the present study.

In the emerging literature, the correlation between ASI and cfPWV has been found convincing (r = 0.65, p < 0.001) (Millasseau et al., 2002). The relationship between ASI, age and BP was even found similar to that between cfPWV, age and BP which further supported the concept that ASI and cfPWV are influenced by similar factors (Millasseau et al., 2002). Studies looking at the effect of ASI on brain integrity would therefore add value to the already published literature in terms of similitude and differences of such markers. This will in turn hopefully help clinicians in their choice of markers of vascular aging with respect to the outcome of interest.

Our study presents the first evidence that peripheral PP better predicts white matter integrity compared to ASI in participants of the UK Biobank younger than 75 years old. This finding implies that ASI from plethysmography may not be a reliable measure of vascular aging in older adults, and may therefore not be used to estimate cerebrovascular integrity in older adults.

A number of reasons can explain this result. The contour of the pulse waveform is essentially determined by characteristics of the heart such as ventricular ejection and those of large arteries which are altered with increasing age (Avolio et al., 1983; Millasseau et al., 2002; Alty et al., 2007; Russo et al., 2011). In older individuals, the systolic and diastolic peaks in the contour of the arterial waveform become difficult to identify (McVeigh et al., 1999; Alty et al., 2007). This was already demonstrated by McVeigh et al. (1999) who measured the arterial waveform shapes in a group of people of different ages. Increased arterial stiffness in older adults elevates arterial pressure wave propagation, causing the reflected wave to arrive back at the aorta during the systolic rather than the diastolic phase of the cardiac cycle, thereby escalating the SBP and contributing to a widening of PP (Laurent et al., 2005; Vlachopoulos et al., 2011; Pase et al., 2012). The time between the peaks of forward and reflected waves assessed using plethysmography appeared thereby reduced in older subjects (Millasseau et al., 2002). In addition, studies looking at age-related changes in shape characteristics in individual fingers and toes using frequency spectrum analysis (Oliva et al., 1976; Sherebrin and Sherebrin, 1990) showed that there is a general reduction in the harmonic components of the pulse in older subjects (Shirouzu et al., 1998) which makes it further difficult to estimate ASI using plethysmography technique in older adults.

Arterial Stiffness Index, Pulse Pressure, and Brain Integrity After 75 Years Old

As mentioned in the introduction, peripheral PP is determined by brachial SBP and DBP, and the relative contribution of these is a function of age. In young adults, both DBP and SBP increase, whereas in the elderly SBP increases and DBP reduces with age, which escalates PP (Wills et al., 2011). The association among higher SBP, mean BP, DBP, peripheral PP, and WMH is consistent in many previous studies during adulthood (Singer et al., 2014; Badji et al., 2019). Likewise, the association between high BP in middle age (age 40–64 years) and increased risk for vascular dementia is well established (Kennelly et al., 2009; Launer et al., 2010; Ninomiya et al., 2011). However, studies looking at these associations at an older age are sparse and there is no consensus on the association between BP and dementia in individuals aged 75 and above (Peng et al., 2017). In addition, information about the impact of BP and arterial stiffness measures on white matter integrity in people over 75 years old is still lacking.

Nevertheless, a recent study investigated the association between BP measures longitudinally, the internal carotid arteries (ICA) blood flow velocity parameters, and age-related WMH in a well-characterized 694 community-dwelling cohort of older adults over 70 years old (Aribisala et al., 2014). Results from this study showed that no association was found between peripheral

PP and WMH measures (both WMH volume or Fazekas), agreeing well with the results of the present study. Looking at the results in detail, Aribisala et al. (2014) also showed that the size of WMH at the age of 73 years was weakly associated with mean BP and DBP at the age of 70 years old. Similar but even weaker associations were seen between WMH and BP at the age of 73 years (Aribisala et al., 2014). In addition, Peng et al. (2017) reported no association between BP levels nor peripheral PP at the age of 70–75 years and the incidence of vascular dementia.

Altogether, these results could be explained by different reasons. Indeed, both SBP and DBP can reduce at an older age. This phenomenon has a multifactorial etiology such as frailty, polymedication, improper/non-adjusted medication, heart failure, kidney failure, and so on and so forth. The integrity of the brain has a critical dependence on a nearly impeccable vascular supply, it is therefore not excluded that a decline in BP happens as a result of brain damage in the pathogenesis of dementia, just as much as the multifactorial-related decline in BP can further damage cerebrovascular integrity leading to dementia. Such a decline in BP could weaken the association between increased BP levels, white matter changes, and the incidence of vascular dementia later in life (Skoog et al., 1996). Although individuals with any dementia diagnosis or neurological condition were excluded from the present study, some of our participants over 75 years old may be in the early stage of dementia, before clinical symptoms appear. This could explain the significant association found between decreased peripheral PP and increased WMHs in individuals between 65 and 75 years, and the non-significant association between peripheral PP and either FA or WMHs in participants over 75 years old.

Another issue with BP measures in general in late life is the lack of information regarding the dose of exposure (and untreated exposure) in most studies, including this one. Those with a new-onset PP increase may not have an immediate risk of brain injury but those with prolonged PP elevation that continues into late life are likely at very high risk. Effects of treatment only compound these dose-dependent associations that are typically unmeasured.

Strengths and Limitations

The strength of this study lies in the use of a large community-dwelling cohort from the United Kingdom and well-validated imaging-derived data used across all researchers accessing the UK Biobank data. To the best of our knowledge this is the first study comparing different markers of arterial stiffness on brain integrity including ASI from plethysmography. Including comparisons of drug-naive participants and those on antihypertensive treatments would have been interesting. Unfortunately, none of the women included in the present study presented information about antihypertensive medication history, therefore we could not have included it. Likewise, excluding participants with heart conditions such as valve diseases, cardiac arrhythmias or heart failure and participants with renal or hepatic failure was not possible due to the lack of information in the UK Biobank database. Finally, although we did not find any relationship between either peripheral PP or ASI and white matter integrity after 75 years, we must acknowledge that we had less participants (n = 788) compared to other groups (n = 3,015–17,984). Fewer subjects may imply less power to detect such association. In this study, we looked for the first time at the relationship between peripheral PP, ASI and white matter microstructure after the age of 75 years. Although our finding may question the nature of the relationship between markers of vascular aging and white matter damage in individuals over 75 years old, it certainly needs to be replicated in a larger study before being able to draw an accurate conclusion.

CONCLUSION

This study is the first to investigate the relationship between ASI and peripheral PP with the white matter integrity as assessed by FA metric and WMHV volumes in participants of the UK Biobank. Our results show that peripheral PP predicts white matter integrity better than ASI in participants younger than 75 years old. These results suggest that ASI from plethysmography should not be used to estimate cerebrovascular integrity in older adults. In addition, no significant relationship was found between either peripheral PP or ASI and white matter integrity after 75 years old. A decline of BP in the pathogenesis of dementia could weaken the association between increased BP levels, white matter alteration, and the incidence of vascular dementia at a late stage in life (Skoog et al., 1996).

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: UK Biobank is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million United Kingdom participants. The database is regularly augmented with additional data and is globally accessible to approved researchers undertaking vital research into the most common and life-threatening diseases. Requests to access these datasets should be directed to https://www.ukbiobank.ac.uk/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the UK Biobank has approval from the Institutional Review Boards, namely, the North West Multi-centre Research Ethics Committee for the United Kingdom, from the National Information Governance Board for Health and Social Care for England and Wales, and from the Community Health Index Advisory Group for Scotland (https://www.ukbiobank.ac.uk/wp-content/uploads/2011/05/EGF20082.pdf). All participants gave informed consent for the study via a touch-screen interface that required agreement for all individual statements on the consent form as well as the participant's signature on an electronic pad (http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Consent_form.pdf). Written informed consent for participation

was not required for this study in accordance with the National Legislation and the Institutional Requirements.

AUTHOR CONTRIBUTIONS

AB: design of the study, analysis, statistics, writing, submission of the article, and revision of the manuscript. JC-A and HG: design of the study and writing and revision of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Canada Research Chair in Quantitative Magnetic Resonance Imaging (950-230815), Canadian Institutes of Health Research (CIHR FDN-143263 and CIHR IAP-224175), Canada Foundation for Innovation (32454 and 34824), Fonds de Recherche du Québec – Santé (28826), Natural Sciences and Engineering Research Council of Canada (RGPIN-2019-07244), Canada First Research Excellence Fund (IVADO and TransMedTech), Courtois NeuroMod project, Quebec Bio-Imaging Network (5886 and 35450), and CRIUGM and Merck Sharp & Dohme Corp Program of the Faculty of Medicine of the Université de Montréal. AB was supported by a Doctoral TransMedTech Excellence Scholarship, Mitacs Globalink Research Award, and Training Course Abroad scholarship from the Québec Bio-Imaging Network. HG was the holder of an investigator award from the *Fonds de Recherche du Québec – Santé* (FRSQ) and Heart and Stroke Foundation of Canada (HSFC).

ACKNOWLEDGMENTS

We would like to acknowledge Alexandru Foias for helping with data management.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.856782/full#supplementary-material

Supplementary Figure 1 | Scatter plots between age and peripheral PP, ASI, FA in the CC and WMHV respectively.

REFERENCES

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., et al. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* 166, 400–424. doi: 10.1016/j.neuroimage.2017.10.034

Alty, S. R., Angarita-Jaimes, N., Millasseau, S. C., and Chowienczyk, P. J. (2007). Predicting arterial stiffness from the digital volume pulse waveform. *IEEE Trans. Biomed. Eng.* 54, 2268–2275. doi: 10.1109/tbme.2007.897805

Andersson, J. L. R., and Sotiropoulos, S. N. (2015). Non-parametric representation and prediction of single- and multi-shell diffusion-weighted MRI data using Gaussian processes. *NeuroImage* 122, 166–176. doi: 10.1016/j.neuroimage.2015.07.067

Andersson, J. L. R., and Sotiropoulos, S. N. (2016). An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage* 125, 1063–1078. doi: 10.1016/j.neuroimage.2015.10.019

Anstey, K. J., Cherbuin, N., Budge, M., and Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes. Rev.* 12, e426–e437. doi: 10.1111/j.1467-789x.2010.00825.x

Aribisala, B. S., Morris, Z., Eadie, E., Thomas, A., Gow, A., Valdés Hernández, M. C., et al. (2014). Blood pressure, internal carotid artery flow parameters, and age-related white matter hyperintensities. *Hypertension* 63, 1011–1018. doi: 10.1161/HYPERTENSIONAHA.113.02735

Avolio, A. P., Chen, S. G., Wang, R. P., Zhang, C. L., Li, M. F., and O'Rourke, M. F. (1983). Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 68, 50–58. doi: 10.1161/01.cir.68.1.50

Badji, A., de la Colina, A. N., Boshkovski, T., Sabra, D., Karakuzu, A., Robitaille-Grou, M.-C., et al. (2020). A cross-sectional study on the impact of arterial stiffness on the corpus callosum, a key white matter tract implicated in Alzheimer's disease. *J. Alzheimers. Dis.* 77, 591–605. doi: 10.3233/JAD-200668

Badji, A., Sabra, D., Bherer, L., Cohen-Adad, J., Girouard, H., and Gauthier, C. J. (2019). Arterial stiffness and brain integrity: A review of MRI findings. *Ageing Res. Rev.* 53:100907. doi: 10.1016/j.arr.2019.05.001

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., and Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement.* 11, 718–726.

Benetos, A., Safar, M., Rudnichi, A., Smulyan, H., Richard, J. L., Ducimetieère, P., et al. (1997). Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 30, 1410–1415. doi: 10.1161/01.hyp.30.6.1410

Boutouyrie, P., Tropeano, A. I., Asmar, R., Gautier, I., Benetos, A., Lacolley, P., et al. (2002). Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients. *Hypertension* 39, 10–15. doi: 10.1161/hy0102.099031

Chowienczyk, P. J., Kelly, R. P., MacCallum, H., Millasseau, S. C., Andersson, T. L., Gosling, R. G., et al. (1999). Photoplethysmographic assessment of pulse wave reflection: blunted response to endothelium-dependent beta2-adrenergic vasodilation in type II diabetes mellitus. *J. Am. Coll. Cardiol.* 34, 2007–2014. doi: 10.1016/s0735-1097(99)00441-6

Collins, R., and UK Biobank Steering Committee (2007). *UK Biobank: Protocol For a Large-Scale Prospective Epidemiological Resource*. Manchester: UK biobank coordinating Centre.

Elgendi, M. (2012). On the analysis of fingertip photoplethysmogram signals. *Curr. Cardiol. Rev.* 8, 14–25.

Fernandes, V. R. S., Polak, J. F., Cheng, S., Rosen, B. D., Carvalho, B., Nasir, K., et al. (2008). Arterial stiffness is associated with regional ventricular systolic and diastolic dysfunction: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 28, 194–201. doi: 10.1161/ATVBAHA.107.156950

Franklin, S. S., Khan, S. A., Wong, N. D., Larson, M. G., and Levy, D. (1999). Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation* 100, 354–360. doi: 10.1161/01.cir.100.4.354

Glasser, S. P., Halberg, D. L., Sands, C., Gamboa, C. M., Muntner, P., and Safford, M. (2014). Is pulse pressure an independent risk factor for incident acute coronary heart disease events? The REGARDS study. *Am. J. Hypertens.* 27, 555–563. doi: 10.1093/ajh/hpt168

Griffanti, L., Zamboni, G., Khan, A., Li, L., Bonifacio, G., Sundaresan, V., et al. (2016). BIANCA (Brain Intensity AbNormality Classification Algorithm): A new tool for automated segmentation of white matter hyperintensities. *Neuroimage* 141, 191–205. doi: 10.1016/j.neuroimage.2016.07.018

Gunarathne, A., Patel, J. V., Gammon, B., Hughes, E. A., and Lip, G. Y. H. (2008). Impact of mean arterial blood pressure on higher arterial stiffness indices in South Asians compared to white Europeans. *J. Hypertens.* 26, 1420–1426. doi: 10.1097/HJH.0b013e3282ffb42a

Iulita, M. F., Noriega de la Colina, A., and Girouard, H. (2018). Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? *J. Neurochem.* 144, 527–548. doi: 10.1111/jnc.14235

Kaess, B. M., Rong, J., Larson, M. G., Hamburg, N. M., Vita, J. A., Levy, D., et al. (2012). Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 308, 875–881. doi: 10.1001/2012.jama.10503

Kennelly, S. P., Lawlor, B. A., and Kenny, R. A. (2009). Blood pressure and dementia - a comprehensive review. *Ther. Adv. Neurol. Disord.* 2, 241–260. doi: 10.1177/1756285609103483

Kivipelto, M., Helkala, E. L., Laakso, M. P., Hänninen, T., Hallikainen, M., Alhainen, K., et al. (2001). Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322, 1447–1451. 11408299doi: 10.1136/bmj.322.7300.1447

Launer, L. J., Hughes, T., Yu, B., Masaki, K., Petrovitch, H., Ross, G. W., et al. (2010). Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension* 55, 1352–1359. doi: 10.1161/HYPERTENSIONAHA.109.147389

Launer, L. J., Masaki, K., Petrovitch, H., Foley, D., and Havlik, R. J. (1995). The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 274, 1846–1851.

Laurent, S., Boutouyrie, P., and Lacolley, P. (2005). Structural and genetic bases of arterial stiffness. *Hypertension* 45, 1050–1055. doi: 10.1161/01.HYP.0000164580.39991.3d

Laurent, S., Boutouyrie, P., Asmar, R., Gautier, I., Laloux, B., Guize, L., et al. (2001). Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients. *Hypertension* 37, 1236–1241. doi: 10.1161/01.hyp.37.5.1236

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., et al. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur. Heart J.* 27, 2588–2605. doi: 10.1093/eurheartj/ehl254

Longstreth, W. T., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. *Stroke* 27, 1274–1282. doi: 10.1161/01.str.27.8.1274

Madhavan, S., Ooi, W. L., Cohen, H., and Alderman, M. H. (1994). Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* 23, 395–401.

Maillard, P., Mitchell, G. F., Himali, J. J., Beiser, A., Tsao, C. W., Pase, M. P., et al. (2016). Effects of arterial stiffness on brain integrity in young adults from the Framingham heart study. *Stroke* 47, 1030–1036. doi: 10.1161/STROKEAHA.116.012949

Marfella, R., and Paolisso, G. (2016). Increased arterial stiffness trumps on blood pressure in predicting cognitive decline in low-risk populations. *Hypertension* 67, 30–31. doi: 10.1161/HYPERTENSIONAHA.115.06450

Matsui, Y., Kario, K., Ishikawa, J., Eguchi, K., Hoshide, S., and Shimada, K. (2004). Reproducibility of arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive patients. *Hypertens. Res.* 27, 851–857. doi: 10.1291/hypres.27.851

McVeigh, G. E., Bratteli, C. W., Morgan, D. J., Alinder, C. M., Glasser, S. P., Finkelstein, S. M., et al. (1999). Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. *Hypertension* 33, 1392–1398. doi: 10.1161/01.hyp.33.6.1392

Millasseau, S. C., Guigui, F. G., Kelly, R. P., Prasad, K., Cockcroft, J. R., Ritter, J. M., et al. (2000). Noninvasive assessment of the digital volume pulse. Comparison with the peripheral pressure pulse. *Hypertension* 36, 952–956. doi: 10.1161/01.hyp.36.6.952

Millasseau, S. C., Kelly, R. P., Ritter, J. M., and Chowienczyk, P. J. (2002). Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clin. Sci.* 103, 371–377. doi: 10.1042/cs1030371

Mitchell, G. F., Hwang, S.-J., Vasan, R. S., Larson, M. G., Levy, D., Benjamin, E. J., et al. (2010). Response to letters regarding article, "arterial stiffness and cardiovascular events: the framingham heart study". *Circulation* 122:e515. doi: 10.1161/circulationaha.110.967141

Mitchell, G. F., Moyeì, L. A., Braunwald, E., Rouleau, J.-L., Bernstein, V., Geltman, E. M., et al. (1997). Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. *Circulation* 96, 4254–4260. doi: 10.1161/01.cir.96.12.4254

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., et al. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 40, 570–582. doi: 10.1016/j.neuroimage.2007.12.035

Mugler, J. P. III (2014). Optimized three-dimensional fast-spin-echo MRI: Optimized 3D Fast-Spin-Echo MRI. *J. Magn. Reson. Imaging* 39, 745–767.

Nichols, W. W. (2005). Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am. J. Hypertens.* 18, 3S–10S. doi: 10.1016/j.amjhyper.2004.10.009

Niiranen, T. J., Kalesan, B., Mitchell, G. F., and Vasan, R. S. (2019). Relative contributions of pulse pressure and arterial stiffness to cardiovascular disease: the Framingham heart study. *Hypertension* 73, 712–717.

Ninomiya, T., Ohara, T., Hirakawa, Y., Yoshida, D., Doi, Y., Hata, J., et al. (2011). Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension* 58, 22–28. doi: 10.1161/HYPERTENSIONAHA.110.163055

Nir, T. M., Jahanshad, N., Villalon-Reina, J. E., Isaev, D., Zavaliangos-Petropulu, A., Zhan, L., et al. (2017). Fractional anisotropy derived from the diffusion tensor distribution function boosts power to detect Alzheimer's disease deficits. *Magn. Reson. Med.* 78, 2322–2333. doi: 10.1002/mrm.26623

Novak, V., and Hajjar, I. (2010). The relationship between blood pressure and cognitive function. *Nat. Rev. Cardiol.* 7, 686–698.

Oliva, I., Ipser, J., Roztocil, K., and Guttenbergerová, K. (1976). Fourier analysis of the pulse wave in obliterating arteriosclerosis. *Vasa* 5, 95–100.

Pase, M. P. (2012). Modifiable vascular markers for cognitive decline and dementia: the importance of arterial aging and hemodynamic factors. *J. Alzheimers. Dis.* 32, 653–663. doi: 10.3233/JAD-2012-120565

Pase, M. P., Herbert, A., Grima, N. A., Pipingas, A., and O'rourke, M. F. (2012). Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. *Intern. Med. J.* 42, 808–815. doi: 10.1111/j.1445-5994.2011.02645.x

Peng, M., Chen, G., Tang, K. L., Quan, H., Smith, E. E., Faris, P., et al. (2017). Blood pressure at age 60–65 versus age 70–75 and vascular dementia: a population based observational study. *BMC Geriatr.* 17:252. doi: 10.1186/s12877-017-0649-3

Qiu, C., and Fratiglioni, L. (2015). A major role for cardiovascular burden in age-related cognitive decline. *Nat. Rev. Cardiol.* 12, 267–277. doi: 10.1038/nrcardio.2014.223

Qiu, C., Winblad, B., and Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* 4, 487–499. doi: 10.1016/S1474-4422(05)70141-1

Rahman, M. (2017). Faculty opinions recommendation of ambulatory pulse wave velocity is a stronger predictor of cardiovascular events and all-cause mortality than office and ambulatory blood pressure in hemodialysis patients. *Fac. Opin.* 70, 148–157. doi: 10.1161/HYPERTENSIONAHA.117.09023

Rosano, C., Watson, N., Chang, Y., Newman, A. B., Aizenstein, H. J., Du, Y., et al. (2013). Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. *Hypertension* 61, 160–165. doi: 10.1161/HYPERTENSIONAHA.112.198069

Russo, C., Jin, Z., Takei, Y., Hasegawa, T., Koshaka, S., Palmieri, V., et al. (2011). Arterial wave reflection and subclinical left ventricular systolic dysfunction. *J. Hypertens.* 29, 574–582. doi: 10.1097/HJH.0b013e328342ca56

Said, M. A., Eppinga, R. N., Lipsic, E., Verweij, N., and van der Harst, P. (2018). Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. *J. Am. Heart Assoc.* 7:e007621. doi: 10.1161/JAHA.117.007621

Sherebrin, M. H., and Sherebrin, R. Z. (1990). Frequency analysis of the peripheral pulse wave detected in the finger with a photoplethysmograph. *IEEE Trans. Biomed. Eng.* 37, 313–317. doi: 10.1109/10.52332

Shirouzu, S., Shirouzu, E., Tsuda, Y., and Sugano, H. (1998). "Circulatory parameter extraction from digital plethysmogram. I. Waveform analysis of digital plethysmogram," in *Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Vol.20 Biomedical Engineering Towards the Year 2000 and Beyond (Cat. No.98CH36286)*, Vol. 6 (Piscataway, NJ: IEEE), 3087–3089. doi: 10.1109/iembs.1998.746144

Shrestha, I., Takahashi, T., Nomura, E., Ohtsuki, T., Ohshita, T., Ueno, H., et al. (2009). Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis. *Hypertens. Res.* 32, 869–874. doi: 10.1038/hr.2009.121

Singer, J., Trollor, J. N., Baune, B. T., Sachdev, P. S., and Smith, E. (2014). Arterial stiffness, the brain and cognition: a systematic review. *Ageing Res. Rev.* 15, 16–27. doi: 10.1016/j.arr.2014.02.002

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., et al. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet* 347, 1141–1145. doi: 10.1016/s0140-6736(96)90608-x

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505.

Stang, A., Moebus, S., Möhlenkamp, S., Dragano, N., Schmermund, A., Beck, E.-M., et al. (2006). Algorithms for converting random-zero to automated oscillometric blood pressure values, and vice versa. *Am. J. Epidemiol.* 164, 85–94. doi: 10.1093/aje/kwj160

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., et al. (2015). UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 12:e1001779. doi: 10.1371/journal.pmed.1001779

Tolppanen, A.-M., Solomon, A., Soininen, H., and Kivipelto, M. (2012). Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. *J. Alzheimers. Dis.* 32, 531–540. doi: 10.3233/JAD-2012-120802

Tsao, C. W., Seshadri, S., Beiser, A. S., and Westwood, A. J. (2013). Relations of arterial stiffness and endothelial function to brain aging in the community. *Neurology* 81, 984–991. doi: 10.1212/WNL.0b013e3182a43e1c

Vaccarino, V., Holford, T. R., and Krumholz, H. M. (2000). Pulse pressure and risk for myocardial infarction and heart failure in the elderly. *J. Am. Coll. Cardiol.* 36, 130–138. doi: 10.1016/s0735-1097(00)00687-2

Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 55, 1318–1327. doi: 10.1016/j.jacc.2009.10.061

Vlachopoulos, C., O'Rourke, M., and Nichols, W. W. (2011). *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. Boca Raton, FL: CRC press.

Wang, R., Fratiglioni, L., Kalpouzos, G., Lövdén, M., Laukka, E. J., Bronge, L., et al. (2017). Mixed brain lesions mediate the association between cardiovascular risk burden and cognitive decline in old age: A population-based study. *Alzheimers. Dement.* 13, 247–256. doi: 10.1016/j.jalz.2016.06.2363

Wiesmann, M., Kiliaan, A. J., and Claassen, J. A. (2013). Vascular aspects of cognitive impairment and dementia. *J. Cereb. Blood Flow Metab.* 33, 1696–1706. doi: 10.1038/jcbfm.2013.159

Wills, A. K., Lawlor, D. A., Matthews, F. E., Sayer, A. A., Bakra, E., Ben-Shlomo, Y., et al. (2011). Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med.* 8:e1000440. doi: 10.1371/journal.pmed.1000440

World Health Organization (2015). *The World Health Report 2008: Primary Health Care Now More Than Ever. 2008*. Geneva: World Health Organization.

Yaffe, K., Vittinghoff, E., Pletcher, M. J., Hoang, T. D., Launer, L. J., Whitmer, R., et al. (2014). Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation* 129, 1560–1567. doi: 10.1161/CIRCULATIONAHA.113.004798

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 27 June 2022
doi: 10.3389/fnagi.2022.786253

Neural Dysconnectivity in the Hippocampus Correlates With White Matter Lesions and Cognitive Measures in Patients With Coronary Artery Disease

*Jianhua Niu†, Jingchen Zhang†, Jueyue Yan, Zhipeng Xu, Xing Fang, Jingyu You, Zhihai Liu, Weifang Wu and Tong Li**

Department of Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Purpose: Recent neuroimaging reports have shown the microstructural changes in coronary artery disease (CAD) and its correlation with cognitive dysfunction while little is known about the functional characteristics of CAD. We hypothesize that functional characteristics may give clues to underlying pathology in CAD and its link with cognitive dysfunction. Degree centrality (DC), a graph-based assessment of network organization was performed to explore the neural connectivity changes in CAD patients compared with healthy controls and their correlation with cognitive measures.

Methods: Thirty CAD patients and 36 healthy controls were included in our study. All participants underwent functional magnetic resonance imaging (fMRI) of the brain. We performed DC analysis to identify voxels that showed changes in whole-brain functional connectivity with other voxels. DC was measured by the fMRI graph method and comparisons between the two groups were done. All participants underwent neuropsychological assessment (Montreal Cognitive Assessment, MoCA and Mini-Mental State Examination, MMSE).

Results: Our data analysis included 30 CAD patients (59.90 ± 7.53 years) and 36 HCs (61.61 ± 6.19 years). CAD patients showed a greater prevalence of white matter lesions using the Fazekas score than healthy controls ($P < 0.001$). Importantly, CAD patients showed significantly lower ($P < 0.001$) MoCA and MMSE scores compared with healthy controls. CAD patients showed significantly decreased DC value ($P < 0.001$) in the right hippocampus (hippocampus_R), right lingual gyrus (lingual_R), and significantly increased DC value ($P < 0.001$) in the left middle frontal gyrus (Frontal_Mid_L) when compared with healthy controls respectively. DC value in the hippocampus_R significantly correlated ($P < 0.00$) with MMSE and MoCA scores in CAD patients. Fazekas scores in CAD patients showed a significant correlation ($P < 0.001$) with the DC value in the hippocampus_R.

Conclusion: These findings suggest that reduced cerebral neural connectivity in CAD may contribute to their cognitive impairment and white matter microstructural damage.

Keywords: Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), Fazekas score, functional magnetic resonance imaging (fMRI), coronary artery disease (CAD)

OPEN ACCESS

Edited by:
Helene Girouard,
Université de Montréal, Canada

Reviewed by:
Paul Alan Nyquist,
Johns Hopkins Medicine, United States
Atef Badji,
Université de Montréal, Canada

***Correspondence:**
Tong Li
drli@zju.edu.cn

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *30 September 2021*
Accepted: *26 May 2022*
Published: *27 June 2022*

Citation:
Niu J, Zhang J, Yan J, Xu Z, Fang X, You J, Liu Z, Wu W and Li T (2022) Neural Dysconnectivity in the Hippocampus Correlates With White Matter Lesions and Cognitive Measures in Patients With Coronary Artery Disease. Front. Aging Neurosci. 14:786253. doi: 10.3389/fnagi.2022.786253

INTRODUCTION

Coronary artery disease (CAD) is caused by the build of plaque in the wall of arteries that supply blood to the heart; plaques cause narrowing or blockage that could reduce blood flow to the heart which may lead to a heart attack. Increasing evidence suggests an association between CAD and cognitive impairment even in the absence of ischemic stroke (Burkauskas et al., 2016, 2018; Lowenstern and Wang, 2019). The potential mechanism underlying this association include cerebral atherosclerosis and hypoperfusion, which may have been linked with cerebral small vessel disease (CSVD) (Berry et al., 2019).

Neuroimaging reports have shown that CAD is associated with white matter lesions (Ikram et al., 2008; Vidal et al., 2010), and cerebral infarcts (Geerlings et al., 2010) which are radiological indicators of small vessel disease; reports have also shown that CAD is associated with transient ischemic attacks (TIA) (Adams et al., 2003) and gray matter microstructural changes (DeCarli et al., 1999). Nonetheless, very little is known about the neural network changes that occur in the brain of CAD patients; understanding the underlying mechanisms may bring insight into the cerebral changes and cognitive impairment that occur during the disease mechanism.

Magnetic resonance imaging (MRI) reports have mostly focused on the microstructural changes that occur in CAD patients. CAD patients tend to present with reduced gray matter and white matter microstructure compared with controls (Almeida et al., 2012; Vuorinen et al., 2014; Anazodo et al., 2015); it is also suggested that CAD patients showed cortical thickness in multiple regions of the brain (Almeida et al., 2012; Vuorinen et al., 2014). Importantly, reports (Deckers et al., 2017; Elman et al., 2019; Faulkner et al., 2021; Liang et al., 2021) have shown the association between CAD and the risk for cognitive impairment or dementia but very little is known about the association between this link. However, it is suggested that the association between cognitive impairment and CAD may be linked with underlying risk factors (such as hypertension, diabetes mellitus which have been suggested to be linked with cognitive dysfunction), atherosclerosis, and hypoperfusion.

To date, very little is known about the functional characteristics of the brain in CAD patients which may give clues to the underlying mechanisms. Degree centrality (DC), assessed by functional magnetic resonance imaging (fMRI) has acquired incredible consideration lately. This graph-based assessment of network organization reflects the number of instantaneous functional connections between a region and the rest of the brain within the entire connectivity matrix of the brain. In that, DC can assess how much a node influences the entire brain and integrates information across functionally segregated brain regions. Voxel-wise centrality maps have provided novel insights into patterns and complexity of functional connectivity in Alzheimer's disease (AD) (Guo et al., 2017).

Our current study focused on network architecture to investigate the intrinsic dysconnectivity pattern in whole-brain functional networks at the voxel level in CAD patients compared with healthy controls. We chose DC because its measures take into account a given region's relationship with the entire functional connectome and not just its relation to individual regions or to separate larger components; therein, DC allows one to capture the complexity of the functional connectome as a whole. We also assessed the correlation between DC changes and their clinical cognitive assessment scores. We hypothesize that functional characteristics may give clues to underlying pathology in CAD and its link with cognitive dysfunction.

MATERIALS AND METHODS

This observational cross-sectional study was done at the First Affiliated Hospital of Zhejiang University School of Medicine from September 2020 to July 2021. The inclusion criteria for CAD patients were as follows: (1) age between 35 and 80 years; (2) diagnosed with CAD (Johansen et al., 2021); and (3) could cooperate during magnetic resonance imaging. The exclusion criteria were as follows: the presence of carotid artery stenosis or pseudo-occlusion, stroke, and patients who could not cooperate during MR imaging.

The control group was individuals who attended our hospital for annual health check-ups and had no history of neurologic or cardiovascular diseases.

All participants were evaluated for cardiovascular risk factors, medical history, medication use and had a comprehensive cardiovascular physical examination by a cardiologist. The study was approved by the Ethics Committee of First Affiliated Hospital of Zhejiang University School of Medicine. Participants recruited provided written informed consent before enrolling in the study.

Neuropsychological Examinations

All participants underwent a Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) which are examinations to screen for cognitive decline. These examinations have a total score of 30 and a score lower than 26 indicates worse cognition in MoCA while a score lower than 24 indicates worse cognition in MMSE.

Magnetic Resonance Imaging Protocol

Whole-brain MRI data were acquired at the Center for Brain Imaging Science and Technology, First Affiliated Hospital of Zhejiang University School on a Siemens MAGNETOM Prisma 3T scanner (Siemens, Erlangen, Germany). All participants were placed in the machine with foam padding around the head to reduce motion; they were asked to keep still with their eyes closed during imaging.

An echo-planar imaging sequence was used to acquire the functional images with the following: 60 axial slices, thickness/gap = 2.0/0mm, in-plane resolution = 64 × 64, repetition time (TR) = 2,000 ms, echo time (TE) = 34 ms, flip angle = 62° and field of view (FOV) = 220 mm × 220 mm. Anatomical T1-weighted whole brain magnetization-prepared rapid gradient echo images were obtained using the following: 160 sagittal slices, slice thickness/gap = 1.2/0 mm, in-plane resolution = 512 × 512, TR = 5,000 ms, TE = 2.9 ms, inversion time (TI) = 700 ms, flip angle = 4° and FOV = 256 mm × 256 mm.

Processing of MRI Data

SPM8[1] was used to implement pre-processing of all fMRI data while data processing was done with Data Processing Assistant for Resting-State fMRI.[2] The initial 10 volumes of the functional images were discarded to remove initial transient effects and to allow the participant to adjust to the scanner noise before pre-processing. The rest of the fMRI images were acquired with slice timing for the acquisition delay between slices and correction of head motion. All participants who were under imaging had less than 1.5 mm maximum displacement in x, y, or z and 1.5° angular motion during imaging. Spatial normalization and resampling to 3 mm voxels were used to acquire realigned images while a Gaussian filter (6 mm FWHM) was used to spatially smoothen the images. Smoothened images were filtered using a typical temporal bandpass (0.01–0.08 Hz) to reduce low-frequency drift, physiological high-frequency respiratory and cardiac noise. Linear trends were removed within each time series. Lastly, spurious variances from several sources were removed by linear regression including six head motion parameters, along with average signals from cerebrospinal fluid and white matter.

Calculation of DC

Voxel-based whole-brain correlation analysis on pre-processed fMRI was done to calculate voxel-wise DC as previously described (Li et al., 2016). Pearson's correlation coefficients (r) were done between all pairs of brain voxels in the gray matter mask. We then converted the Pearson's correlation data to normally distributed Fisher's Z-scores and constructed the whole-brain functional network by thresholding each correlation at $r > 0.25$ as previously reported (Buckner et al., 2009). DC for a given voxel was calculated as the sum of the significant connections at the individual level. Voxel-wise DC values were also converted into a Z-score map using the Fisher-Z transformation to improve normality. Positive correlations were considered in the DC calculation due to the uncertainty of interpretation and detrimental effects on test-retest reliability.

To assess the DC difference between CAD patients and HC, a two-sample t-test was performed using REST. AlphaSim, a program based on Monte Carlo simulation and implemented in AFNI,[3] was used for multiple comparison corrections. Monte Carlo simulations determine the random distribution of cluster size for a given per voxel threshold (Ledberg et al., 1998). Statistical difference was defined as $P < 0.05$ and cluster size > 198 voxels, corresponding to a corrected $P < 0.05$. The correction was confined within the gray matter mask and was determined by Monte Carlo simulations (Ledberg et al., 1998).

White Matter Lesion Rating Using the Fazekas Scale

White matter lesions (WML) were rated based on FLAIR and T2-W cerebral images using the Fazekas scale. Scores ranged from 0 to 3 as previously reported (Han et al., 2018). A modification of suggested rating scales was used to describe different types of hyperintense signal abnormalities around the ventricles (periventricular white matter hyperintensities, PWMH) and in the deep white matter (DWMH) as previously reported (Fazekas et al., 1987).

Statistical Analysis

SPSS (version 24) was used for our statistical analysis. Continuous variables were displayed as mean ± standard deviation, number (%) as appropriate. To assess the correlation between DC changes and clinical features of CAD, multivariable linear regression was used while adjusting for risk factors (age, gender, hypertension, and dyslipidemia). *P* values less than 0.05 were considered statistically significant.

RESULTS

We initially enrolled 70 participants (34 CAD and 36 HCs), but 2 CAD patients were excluded because of uncooperating during MR imaging and 2 CAD patients were excluded because of cerebral infarction after MR imaging as shown in **Supplementary Figure 1**. Our data analysis included 30 CAD patients (59.90 ± 7.53 years) and 36 HCs (61.61 ± 6.19 years). Of the 30 CAD patients, 23 (76.67%) were males, 22 (73.33%) had a history of hypertension while 20 (66.67%) had a history of dyslipidemia. **Table 1** shows the demographics and clinical information of our participants. CAD patients showed a greater prevalence of white matter lesions using the Fazekas score than healthy controls ($P < 0.001$, **Table 1**). Importantly, CAD patients showed significantly lower ($P < 0.001$, **Table 1**) MoCA and MMSE scores compared with healthy controls, respectively.

Comparison of DC Values Between CAD and HC

A total of 90 brain regions involved in Anatomical Automatic Labelling (ALL) were analyzed in the study. AAL partitions

TABLE 1 | Demographics and clinical data.

Variable	CAD (n = 30)	HC (n = 36)	*P*-value
Demographic information			
Male sex, No. (%)	23 (67.74%)	20 (80.5%)	0.672
Age (years), mean (SD)	59.90 ± 7.53	61.61 ± 6.19	0.865
Hypertension, No.	22	16	0.722
Diabetes mellitus, No.	0	0	0.909
Hypercholesterolemia, No.	20	15	0.448
Dyslipidemia, No.	20	16	0.468
LVEF,%	57.53 ± 4.16	59.69 ± 3.88	0.052
Smokers, No.	15	8	0.380
Education, years	5.07 ± 1.31	5.11 ± 1.01	0.621
MMSE score	21.07 ± 3.96	29.47 ± 1.29	<0.001
MoCA score	17.96 ± 3.57	26.83 ± 1.73	<0.001
Total Fazekas score	3.93 ± 1.14	0.14 ± 0.35	<0.001
PWMH	1.87 ± 0.76		
DWMH	2.07 ± 0.68		

LVEF, left ventricular ejection fraction; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity.

[1]http://www.fil.ion.ucl.ac.uk/spm

[2]http://restfmri.net/forum/

[3]http://afni.nimh.nih.gov

are provided by Montreal Neurological Institute (MNI). There are 116 regions in the AAL template but only 90 belong in the brain. Before comparison corrections, CAD patients showed significantly decreased DC value ($P < 0.001$; **Table 2**) in the right hippocampus (hippocampus_R), right lingual gyrus (lingual_R), left middle frontal gyrus (Frontal_Mid_L), left superior frontal gyrus (Frontal_Sup_L), and significantly increased DC values in the left middle frontal gyrus (Frontal_Mid_L) ($P < 0.001$). After comparison corrections, CAD patients showed significantly decreased DC values ($P < 0.001$; **Table 2** and **Figure 1**) in the right hippocampus (hippocampus_R), right lingual gyrus (lingual_R), and significantly increased DC values ($P < 0.001$, **Table 2** and **Figure 1**) in the left middle frontal gyrus (Frontal_Mid_L) when compared with healthy controls respectively.

Correlation Between DC Values and Clinical Features in CAD Patients

Degree centrality value in the hippocampus_R significantly correlated ($P < 0.001$, **Table 3**) with MMSE and MoCA scores in CAD patients. Fazekas scores in CAD patients showed a significant correlation ($P < 0.001$, **Table 3**) with the DC value in the hippocampus_R.

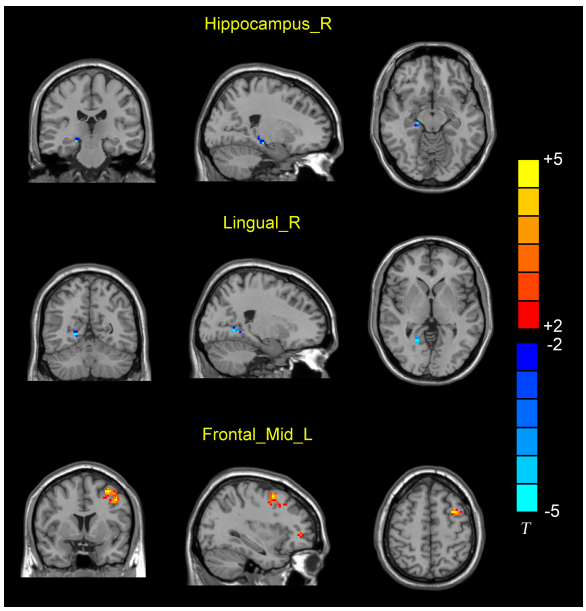


FIGURE 1 | Differences in DC value between CAD patients and HC. Blue represents the decreased DC values in the right hippocampus (hippocampus_R) and right lingual gyrus (lingual_R). Red represents increased DC values in the left middle frontal gyrus (Frontal_Mid_L).

DISCUSSION

Coronary artery disease is thought to affect the brain in multiple ways and recent reports have shown CAD may lead to cognitive impairment; it has been suggested cerebral hypoperfusion, and cardioembolism which may lead to cerebral atherosclerosis may be linked with the underlying mechanism (Xie et al., 2019). A current report suggested that there could be a gradual process at play affecting blood flow and the brain but how it works is still unclear (Rovio et al., 2019). To the best of our knowledge, this is the first study to assess the intrinsic dysconnectivity pattern of brain functional networks in CAD patients by using DC analysis. Our current report showed that CAD patients had significantly lower DC values in the right hippocampus, right lingual gyrus, and left middle frontal gyrus when compared with healthy controls. We also showed that reduced DC value in the right hippocampus correlated with reduced MoCA and MMSE scores and increased Fazekas score in CAD patients.

We observed a significant neural connectivity decrease in the right lingual gyrus of CAD patients compared with HCs. The lingual gyrus is a structure in the brain that is linked to visual processing and is part of the primary visual cortex of the brain (Zhang et al., 2016; Yu et al., 2018). It has been suggested that cardiovascular patients may be at a higher risk of developing visual-related problems (Flammer et al., 2013; Greenberg et al., 2015). Our report suggests that reduced neural connectivity in the right lingual gyrus may affect the vision of CAD patients which may explain the reduced visual acuity in CAD patients compared with healthy controls.

We also showed that CAD patients had significantly increased neural connectivity in the right middle frontal gyrus, which plays a significant role in the reorientation of attention in an individual (Japee et al., 2015). Therefore, we suggest that CAD may cause increased neural connectivity in the right middle frontal gyrus may be a compensatory effect by functional reorganization for the damaged brain tissue in this region to help with cognition.

The hippocampus has been well detailed to be involved in the commonest neurodegenerative disease, Alzheimer's disease, leading to a significant decline in memory function (Allen et al., 2003; Jahn, 2013). This has been validated by implementing approaches that have shown decreases in glucose metabolism and perfusion in the hippocampus (Ishii et al., 2007; Mosconi, 2013). Significant changes in the hippocampus are evident not only in Alzheimer's disease, characterized by

TABLE 2 | Brain regions with significantly decreased DC values in CAD patients compared with HC.

Brain regions	Voxels	BA	MNI coordinates			*P*-value
			X	Y	Z	
Uncorrected						
Frontal_Mid_L	10	47	–30	45	3	<0.001
Frontal_Sup_L	14	32	–18	36	27	<0.001
Hippocampus_R	15	36	21	–24	–12	<0.001
Lingual_R	15	30	21	–57	0	<0.001
Frontal_Mid_L	115	6	–33	6	54	<0.001
Corrected						
Hippocampus_R	15	36	21	–24	–12	<0.001
Lingual_R	15	30	21	–57	0	<0.001
Frontal_Mid_L	115	6	–33	6	54	<0.001

Left middle frontal gyrus (frontal_mid_l), left superior frontal gyrus (frontal_sup_l), right hippocampus (hippocampus_R), right lingual gyrus (lingual_R), and left middle frontal gyrus (Frontal_Mid_L).

TABLE 3 | Correlation between DC values and clinical implications in CAD patients.

Variable	MMSE[a]		MoCA[a]		Fazekas score	
	β Coefficient (95% CI)	*P* value	β Coefficient (95% CI)	*P* value	β Coefficient (95% CI)	*P* value
Hippocampus_R	0.106 (0.047 –0.165)	<0.001	0.074 (0.044 –0.122)	<0.001	–0.598 (–0.821 –0.376)	<0.001
Lingual_R	–0.005 (–0.051 –0.041)	0.840	–0.036 (0.033 –0.091)	0.120	–0.116 (–0.304 –0.073)	0.230
Frontal_Mid_L	0.021 (–0.016 –0.057)	0.266	0.032 (0.022 –0.059)	0.167	0.118 (–0.035 –0.27)	0.131

[a]*Adjusted for age, hypertension, years of education, and gender.*
Right hippocampus (hippocampus_R), right lingual gyrus (lingual_R), and left middle frontal gyrus (Frontal_Mid_L).

impairment in everyday life but already in its pre-stage, mild cognitive impairment, where cognitive deficits are detectable in neuropsychological assessments without evident everyday life changes (Moon et al., 2018). Besides these functional changes, Schroeter et al. (2009) showed regional atrophy in the hippocampus of Alzheimer's disease patients. Our current report showed CAD patients had significantly reduced neural connectivity in the right hippocampus when compared with healthy controls which may indicate functional dysfunction in the right hippocampus of CAD patients.

Taken together, both functional impairment and adaptation were observed in CAD patients. Decreased DC values (functional impairment) occurred in structures that play a role in visual memory (Lee et al., 2012; Zhang et al., 2016; Zammit et al., 2017); this may be due to cerebral hypoperfusion resulting from the decreased cardiac output as previously reported in CAD patients. Increased DC value was observed in the left middle frontal gyrus, suggesting functional plasticity to compensate for structural damage in the early phase of the disease (Mueller et al., 2020). These functional changes in CAD were associated with cognition, suggesting that neural connectivity changes may give clues to cognition dysfunction in the brain of CAD patients.

Neuropsychological assessments such as MMSE and MoCA have been shown to help assess the cognitive status of an individual. Our report showed a significant correlation between the reduced MMSE and MoCA scores and the reduced neural connectivity in the right hippocampus of CAD patients. Since the hippocampus plays a significant role in cognition (Rubin et al., 2014), the positive correlation between the reduced MoCA and MMSE scores and significantly reduced neural connectivity in the right hippocampus suggests that the reduced neural connectivity network in the right hippocampus reflects the cognitive assessment in CAD patients. Contrarily, visual stimulation is the main input for these neuropsychological assessments. The hippocampus is needed for the comprehension and execution of these neuropsychological examinations. Since the right hippocampus plays a significant role in comprehension, visual input, and visuospatial memories, reduced neural connectivity may affect the visual stimulation which may affect their cognitive status.

A previous report showed a significant correlation between non-calcified coronary plaque volume and total white matter hyperintensity volume (Kral et al., 2013); the authors suggested that coronary plaque in CAD patients affects the white matter lesions. Recently, it has been suggested that the association between cardiovascular diseases and white matter lesions may be linked to hypoperfusion in the cerebral microcirculation resulting from the reduced cardiac output, cardioembolism, and similar underlying risk factors (de Leeuw et al., 2000; Gurol, 2018). Our current report showed that reduced neural connectivity in the right hippocampus significantly correlated with increased white matter lesions on MR images using the Fazekas scale. White matter lesions suggest cerebral small vessel disease (which may be due to hypoperfusion) and are suggested to be linked with cognitive decline and small vessel disease (Wardlaw et al., 2015). Therefore, increased white matter lesions measured with the Fazekas scale and reduced neural connectivity in the right hippocampus may suggest that increased white matter lesions as a result of hypoperfusion may lead to reduced neural connectivity in the right hippocampus.

The pathological mechanism of cognitive decline in CAD patients is still unclear. In our current study, we utilized the functional magnetic resonance (DC sequence) to evaluate the neural connectivity in CAD patients, providing a possibility for further exploring the underlying mechanism. We would like to acknowledge some limitations in our work. To begin with, the cross-sectional design of our study and the small sample size of our participants limits us to conclude the cause and effect; longitudinal studies with larger sample sizes are needed to investigate more on our current study. As with most diagnostic tests, patient cooperation is an obligation. Movement from participants can diminish the quality of the image which may affect the data. Furthermore, we did not evaluate the microstructural integrity of the MRI images; further studies on the microstructural volume of participants may be needed. Our study focused on functional brain MRI measurements while cardiovascular measurement was not evaluated; further studies with a more comprehensive assessment of the heart may be needed. The clinical relevance of MRI procedures was investigated with cognitive parameters and white matter lesions; further studies are needed to assess the clinical importance of MRI measures and cardiovascular measures.

In conclusion, we showed that CAD patients have significantly reduced neural connectivity in the right hippocampus, right lingual gyrus, and left middle frontal gyrus when compared with healthy controls. We also showed that reduced DC value

in the right hippocampus correlated with reduced MoCA and MMSE scores and increased Fazekas score in CAD patients. These findings suggest that reduced cerebral neural connectivity in CAD may contribute to their cognitive impairment and white matter microstructural damage.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by First Affiliated Hospital of Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

This research was supported by Zhejiang Provincial Medical and Health Science and Technology Project (2022ky777).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.786253/full#supplementary-material

Supplementary Figure 1 | Flow chart of the inclusion of participants for the study.

REFERENCES

Adams, R. J., Chimowitz, M. I., Alpert, J. S., Awad, I. A., Cerqueria, M. D., Fayad, P., et al. (2003). Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Stroke* 34, 2310–2322. doi: 10.1161/01.STR.0000090125.28466.E2

Allen, G., Barnard, H., McColl, R., Hester, A. L., Fields, J. A., Weiner, M. F., et al. (2003). Reduced hippocampal functional connectivity in Alzheimer's disease. *Arch. Clin. Neuropsych.* 18, 690–691.

Almeida, O. P., Garrido, G. J., Beer, C., Lautenschlager, N. T., Arnolda, L., and Flicker, L. (2012). Cognitive and brain changes associated with ischaemic heart disease and heart failure. *Eur. Heart J.* 33, 1769–1776. doi: 10.1093/eurheartj/ehr467

Anazodo, U. C., Shoemaker, J. K., Suskin, N., Ssali, T., Wang, D. J., and St Lawrence, K. S. (2015). Impaired Cerebrovascular Function in Coronary Artery Disease Patients and Recovery Following Cardiac Rehabilitation. *Front. Aging Neurosci.* 7:224. doi: 10.3389/fnagi.2015.00224

Berry, C., Sidik, N., Pereira, A. C., Ford, T. J., Touyz, R. M., Kaski, J. C., et al. (2019). Small-Vessel Disease in the Heart and Brain: current Knowledge, Unmet Therapeutic Need, and Future Directions. *J. Am. Heart Assoc.* 8:e011104. doi: 10.1161/JAHA.118.011104

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J. Neurosci.* 29, 1860–1873. doi: 10.1523/JNEUROSCI.5062-08.2009

Burkauskas, J., Brozaitiene, J., Bunevicius, A., Neverauskas, J., Zaliunaite, V., and Bunevicius, R. (2016). Association of Depression, Anxiety, and Type D Personality with Cognitive Function in Patients with Coronary Artery Disease. *Cogn. Behav. Neurol.* 29, 91–99. doi: 10.1097/WNN.0000000000000093

Burkauskas, J., Lang, P., Bunevicius, A., Neverauskas, J., Buciute-kauskiene, M., and Mickuviene, N. (2018). Cognitive function in patients with coronary artery disease: a literature review. *J. Int. Med. Res.* 46, 4019–4031. doi: 10.1177/0300060517751452

de Leeuw, F. E., de Groot, J. C., Oudkerk, M., Kors, J. A., Hofman, A., van Gijn, J., et al. (2000). Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* 54, 1795–1801. doi: 10.1212/wnl.54.9.1795

DeCarli, C., Reed, T., Miller, B. L., Wolf, P. A., Swan, G. E., and Carmelli, D. (1999). Impact of apolipoprotein E epsilon4 and vascular disease on brain morphology in men from the NHLBI twin study. *Stroke* 30, 1548–1553. doi: 10.1161/01.str.30.8.1548

Deckers, K., Schievink, S. H. J., Rodriquez, M. M. F., van Oostenbrugge, R. J., van Boxtel, M. P. J., Verhey, F. R. J., et al. (2017). Coronary heart disease and risk for cognitive impairment or dementia: systematic review and meta-analysis. *PLoS One* 12:e0184244. doi: 10.1371/journal.pone.0184244

Elman, J. A., Panizzon, M. S., Logue, M. W., Gillespie, N. A., Neale, M. C., Reynolds, C. A., et al. (2019). Genetic risk for coronary heart disease alters the influence of Alzheimer's genetic risk on mild cognitive impairment. *Neurobiol. Aging* 84, 237.e5–237.e12. doi: 10.1016/j.neurobiolaging.2019.06.001

Faulkner, K. M., Uchmanowicz, I., Lisiak, M., Cichon, E., Cyrkot, T., and Szczepanowski, R. (2021). Cognition and Frailty in Patients With Heart Failure: a Systematic Review of the Association Between Frailty and Cognitive Impairment. *Front. Psychiatry* 12:713386. doi: 10.3389/fpsyt.2021.713386

Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., and Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am. J. Roentgenol.* 149, 351–356. doi: 10.2214/ajr.149.2.351

Flammer, J., Konieczka, K., Bruno, R. M., Virdis, A., Flammer, A. J., and Taddei, S. (2013). The eye and the heart. *Eur. Heart J.* 34, 1270–1278. doi: 10.1093/eurheartj/eht023

Geerlings, M. I., Appelman, A. P., Vincken, K. L., Algra, A., Witkamp, T. D., Mali, W. P., et al. (2010). Brain volumes and cerebrovascular lesions on MRI in patients with atherosclerotic disease. The SMART-MR study. *Atherosclerosis* 210, 130–136. doi: 10.1016/j.atherosclerosis.2009.10.039

Greenberg, P., Chen, A., and Wu, W.-C. (2015). Sudden Vision Loss and Cardiovascular Risk Factors in African Americans: the Jackson Heart Study. *Ophthal. Epidemiol.* 22, 116–122. doi: 10.3109/09286586.2015.1012273

Guo, Z., Liu, X., Li, J., Wei, F., Hou, H., Chen, X., et al. (2017). Fractional amplitude of low-frequency fluctuations is disrupted in Alzheimer's disease with depression. *Clin. Neurophysiol.* 128, 1344–1349. doi: 10.1016/j.clinph.2017.05.003

Gurol, M. E. (2018). Atrial fibrillation and FLAIR/T2 white matter hyperintensities on MRI. *J. Neurol. Neurosurg. Psychiatry* 89, 1–2. doi: 10.1136/jnnp-2017-316290

Han, F., Zhai, F. F., Wang, Q., Zhou, L. X., Ni, J., Yao, M., et al. (2018). Prevalence and Risk Factors of Cerebral Small Vessel Disease in a Chinese Population-Based Sample. *J. Stroke* 20, 239–246. doi: 10.5853/jos.2017.02110

Ikram, M. A., van Oijen, M., de Jong, F. J., Kors, J. A., Koudstaal, P. J., Hofman, A., et al. (2008). Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke* 39, 1421–1426. doi: 10.1161/STROKEAHA.107.501106

Ishii, K., Soma, T., Kono, A. K., Sofue, K., Miyamoto, N., Yoshikawa, T., et al. (2007). Comparison of regional brain volume and glucose metabolism between

patients with mild dementia with lewy bodies and those with mild Alzheimer's disease. *J. Nucl. Med.* 48, 704–711. doi: 10.2967/jnumed.106.035691

Jahn, H. (2013). Memory loss in Alzheimer's disease. *Dialogues Clin. Neurosci.* 15, 445–454.

Japee, S., Holiday, K., Satyshur, M. D., Mukai, I., and Ungerleider, L. G. (2015). A role of right middle frontal gyrus in reorienting of attention: a case study. *Front. Syst. Neurosci.* 9:23. doi: 10.3389/fnsys.2015.00023

Johansen, M. C., Gottesman, R. F., Kral, B. G., Vaidya, D., Yanek, L., Becker, L., et al. (2021). Association of Coronary Artery Atherosclerosis With Brain White Matter Hyperintensity. *Stroke* 52, 2594–2600. doi: 10.1161/STROKEAHA.120.032674

Kral, B. G., Nyquist, P., Vaidya, D., Yousem, D., Yanek, L. R., Fishman, E. K., et al. (2013). Relation of subclinical coronary artery atherosclerosis to cerebral white matter disease in healthy subjects from families with early-onset coronary artery disease. *Am. J. Cardiol.* 112, 747–752. doi: 10.1016/j.amjcard.2013.05.002

Ledberg, A., Akerman, S., and Roland, P. E. (1998). Estimation of the probabilities of 3D clusters in functional brain images. *Neuroimage* 8, 113–128. doi: 10.1006/nimg.1998.0336

Lee, A. C., Yeung, L. K., and Barense, M. D. (2012). The hippocampus and visual perception. *Front. Hum. Neurosci.* 6:91. doi: 10.3389/fnhum.2012.00091

Li, S., Ma, X., Huang, R., Li, M., Tian, J., Wen, H., et al. (2016). Abnormal degree centrality in neurologically asymptomatic patients with end-stage renal disease: a resting-state fMRI study. *Clin. Neurophysiol.* 127, 602–609. doi: 10.1016/j.clinph.2015.06.022

Liang, X., Huang, Y., and Han, X. (2021). Associations between coronary heart disease and risk of cognitive impairment: a meta-analysis. *Brain Behav.* 11:e02108. doi: 10.1002/brb3.2108

Lowenstern, A., and Wang, T. Y. (2019). Rethinking Cognitive Impairment in the Management of Older Patients With Cardiovascular Disease. *J. Am. Heart Assoc.* 8:e011968. doi: 10.1161/JAHA.119.011968

Moon, S. W., Lee, B., and Choi, Y. C. (2018). Changes in the Hippocampal Volume and Shape in Early-Onset Mild Cognitive Impairment. *Psychiatry Investig.* 15, 531–537. doi: 10.30773/pi.2018.02.12

Mosconi, L. (2013). Glucose metabolism in normal aging and Alzheimer's disease: methodological and physiological considerations for PET studies. *Clin. Transl. Imaging* 1:10. doi: 10.1007/s40336-013-0026-y

Mueller, K., Thiel, F., Beutner, F., Teren, A., Frisch, S., Ballarini, T., et al. (2020). Brain Damage With Heart Failure: cardiac Biomarker Alterations and Gray Matter Decline. *Circ. Res.* 126, 750–764. doi: 10.1161/CIRCRESAHA.119.315813

Rovio, S., Pahkala, K., and Raitakari, O. (2019). Cognitive Decline Before and After Incident Coronary Heart Disease. *J. Am. Coll. Cardiol.* 73, 3051–3053. doi: 10.1016/j.jacc.2019.04.020

Rubin, R. D., Watson, P. D., Duff, M. C., and Cohen, N. J. (2014). The role of the hippocampus in flexible cognition and social behavior. *Front. Hum. Neurosci.* 8:742. doi: 10.3389/fnhum.2014.00742

Schroeter, M. L., Stein, T., Maslowski, N., and Neumann, J. (2009). Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. *Neuroimage* 47, 1196–1206. doi: 10.1016/j.neuroimage.2009.05.037

Vidal, J. S., Sigurdsson, S., Jonsdottir, M. K., Eiriksdottir, G., Thorgeirsson, G., Kjartansson, O., et al. (2010). Coronary artery calcium, brain function and structure: the AGES-Reykjavik Study. *Stroke* 41, 891–897. doi: 10.1161/STROKEAHA.110.579581

Vuorinen, M., Damangir, S., Niskanen, E., Miralbell, J., Rusanen, M., Spulber, G., et al. (2014). Coronary heart disease and cortical thickness, gray matter and white matter lesion volumes on MRI. *PLoS One* 9:e109250. doi: 10.1371/journal.pone.0109250

Wardlaw, J. M., Valdes Hernandez, M. C., and Munoz-Maniega, S. (2015). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *J. Am. Heart Assoc.* 4:001140. doi: 10.1161/JAHA.114.001140

Xie, W., Zheng, F., Yan, L., and Zhong, B. (2019). Cognitive Decline Before and After Incident Coronary Events. *J. Am. Coll. Cardiol.* 73, 3041–3050. doi: 10.1016/j.jacc.2019.04.019

Yu, T., Li, Y., Fan, F., Cao, H., Luo, X., Tan, S., et al. (2018). Decreased Gray Matter Volume of Cuneus and Lingual Gyrus in Schizophrenia Patients with Tardive Dyskinesia is Associated with Abnormal Involuntary Movement. *Sci. Rep.* 8:12884. doi: 10.1038/s41598-018-31186-y

Zammit, A. R., Ezzati, A., Katz, M. J., Zimmerman, M. E., Lipton, M. L., Sliwinski, M. J., et al. (2017). The association of visual memory with hippocampal volume. *PLoS One* 12:e0187851. doi: 10.1371/journal.pone.0187851

Zhang, L., Qiao, L., Chen, Q., Yang, W., Xu, M., Yao, X., et al. (2016). Gray Matter Volume of the Lingual Gyrus Mediates the Relationship between Inhibition Function and Divergent Thinking. *Front. Psychol.* 7:1532. doi: 10.3389/fpsyg.2016.01532

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 28 June 2022
doi: 10.3389/fnagi.2022.885787

Sex-Specific Associations of Diabetes With Brain Structure and Function in a Geriatric Population

Elias G. Thomas[1,2]*, *Hanneke Rhodius-Meester*[1,3], *Lieza Exalto*[4], *Sanne A. E. Peters*[5,6,7], *Liselotte van Bloemendaal*[1], *Rudolf Ponds*[8] *and Majon Muller*[1]

[1] Department of Internal Medicine, Geriatrics Section, Amsterdam Cardiovascular Science, Amsterdam University Medical Centre, Amsterdam UMC, Amsterdam, Netherlands, [2] Department of Internal Medicine, Amsterdam Public Health Institute, Amsterdam UMC, Amsterdam, Netherlands, [3] Department of Neurology, Alzheimer Center Amsterdam, Amsterdam Neuroscience, VU University Amsterdam, Amsterdam UMC, Amsterdam, Netherlands, [4] Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, Netherlands, [5] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands, [6] The George Institute for Global Health, Imperial College London, London, United Kingdom, [7] The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia, [8] Department of Medical Psychology, Amsterdam University Medical Centers, Amsterdam, Netherlands

OPEN ACCESS

Edited by:
Knut Engedal,
Vestfold Hospital Trust, Norway

Reviewed by:
Marie-Pierre Moisan,
INRAE Nouvelle-Aquitaine Bordeaux, France
Henrik Schirmer,
Akershus University Hospital, Norway

***Correspondence:**
Elias G. Thomas
g.thomas@amsterdamumc.nl

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *28 February 2022*
Accepted: *20 May 2022*
Published: *28 June 2022*

Citation:
Thomas EG, Rhodius-Meester H, Exalto L, Peters SAE, van Bloemendaal L, Ponds R and Muller M (2022) Sex-Specific Associations of Diabetes With Brain Structure and Function in a Geriatric Population. Front. Aging Neurosci. 14:885787. doi: 10.3389/fnagi.2022.885787

Introduction: Globally, women with dementia have a higher disease burden than men with dementia. In addition, women with diabetes especially are at higher risk for cognitive impairment and dementia compared to men with diabetes. Differences in the influence of diabetes on the cerebral vasculature and brain structure may contribute to these sex-specific differences. We examined sex-specific patterns in the relationship between diabetes and brain structure, as well as diabetes and cognitive function.

Methods: In total, 893 patients [age 79 ± 6.6 years, 446 (50%) women] from the Amsterdam Ageing Cohort with available data on brain structures (assessed by an MRI or CT scan) and cognitive function were included. All patients underwent a thorough standardized clinical and neuropsychological assessment (including tests on memory, executive functioning, processing speed, language). Brain structure abnormalities were quantified using visual scales.

Results: Cross-sectional multivariable regression analyses showed that diabetes was associated with increased incidence of cerebral lacunes and brain atrophy in women (OR 2.18 (1.00–4.72) but not in men. Furthermore, diabetes was associated with decreased executive function, processing speed and language in women [B −0.07 (0.00–0.13), −0.06 (0.02–0.10) and −0.07 (0.01–0.12) resp.] but not in men.

Conclusions: Diabetes is related to increased risk of having lacunes, brain atrophy and impaired cognitive function in women but not in men. Further research is required to understand the time trajectory leading up to these changes and to understand the mechanisms behind them in order to improve preventive health care for both sexes.

Keywords: sex-specific analysis, brain structure, diabetes, cognitive function, vascular aging, vascular cognitive impairment and dementia

INTRODUCTION

The prevalence of diabetes is increasing worldwide, with an expected rise from 537 million adults in 2021 to 783 million in 2045 (Sun et al., 2021). This not only leads to high mortality – more than 6.7 million deaths in 2021 alone – but also to high morbidity, including an increased risk of cognitive impairment and dementia (Arvanitakis et al., 2004; Yaffe et al., 2004; Liu, J. et al., 2018). However, not all individuals are similarly affected by the complications of diabetes. As early as 1979, and as confirmed more recently by cohort studies, it was shown that type 2 diabetes is a stronger risk factor for ischemic heart disease and stroke in women than in men (Kannel and McGee, 1979; Peters et al., 2014, 2020, 2021). Women with type 2 diabetes also have a higher excess risk of cognitive decline and vascular dementia, than their male counterparts, although the extent of these differences are dependent of study populations and their characteristics (Verhagen et al., 2022).

To date, it is unclear why men and women with diabetes are dissimilarly impacted by dementia. Since sex-related differences in the incidence of dementia are only present in the group with vascular dementia – not in Alzheimer's dementia – sex-specific patterns of cerebral vascular pathology may play a role in mediating these differences (Hayden et al., 2006; Chatterjee et al., 2016; Liu et al., 2018). Cerebral small vessel disease (cSVD) – including the presence of microbleeds, white matter hyperintensities and lacunes – is more prevalent in individuals with type 2 diabetes than those without (Troncoso et al., 2008; Moran et al., 2013; Geijselaers et al., 2015; Ter Telgte et al., 2018; Wardlaw et al., 2019). Although little is known about sex-specific susceptibility for cSVD, it seems plausible that the increased susceptibility of women to cerebrovascular complications of diabetes is manifested as an increased susceptibility to disease of the smaller cerebral vessels (Jiménez-Sánchez et al., 2021). In addition, diabetes is associated with increased rates of atrophy (Moran et al., 2013). Again, it is not known whether there are sex-related differences in this association, but it is known that atrophy and cSVD are closely related, and they are sometimes even collectively referred to as "brain structure" or "markers for brain health" (Mahammedi et al., 2021). Our primary goal in the present analysis is to assess if there are sex-specific pattern in the relationship between diabetes and brain structure, including cSVD and atrophy, and cognitive function as their clinical correlates.

METHODS

Study Population

The Amsterdam Aging Cohort is an ongoing longitudinal cohort study which includes patients from the outpatient geriatric clinic at the Amsterdam University Medical Center, location VUmc (Rhodius-Meester et al., 2021). We included 893 patients with brain imaging who attended the memory clinic seeking medical care between February 2016 and June 2021. During this period, almost a patients visiting the memory clinic (89%) were willing to participate in the study. All patients were given a complete standardized comprehensive geriatric assessment (CGA) by trained nurses and doctors. This included an assessment of multiple geriatric domains, including cognition, physical function, nutrition, revision of medication in use and detailed medical history. Cognitive diagnosis – such as dementia (McKhann et al., 1984; Román et al., 1993; Neary et al., 1998; McKeith et al., 2005; Dubois et al., 2007; Rascovsky et al., 2011), mild cognitive impairment (MCI) (Albert et al., 2013), or subjective cognitive decline (SCD) (Studart and Nitrini, 2016) – were evaluated in a multidisciplinary consensus meeting. Our analysis included only patients who underwent brain Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) as part of the diagnostic work-up. All patients gave written informed consent for their data to be used and the study was approved by the local Medical Ethics Committee.

Cardiovascular Risk and Disease

Diabetes mellitus (DM) was defined either as having a history of diabetes or using antidiabetic medication. Other cardiovascular diseases – including coronary disease, heart failure, atrial fibrillation, and peripheral artery disease – were assessed on the basis of medical history and double checked with the patient and their family or carer. We dichotomized smoking status (never smoked v. ever smoked). Blood pressure and gait speed, as well as patient height and weight, were measured during the visit (Odden et al., 2012). Venous blood was drawn from all patients to measure cholesterol levels and non-fasting glucose. Medication as provided by the patient's pharmacy was reviewed with the patient, and with a partner, family member or carer if necessary.

Cerebral Small Vessel Disease

Brain imaging was performed during a patient's first visit using CT ($n = 238$), 1.5T MRI ($n = 162$) and 3T MRI ($n = 478$) devices. The scans were reviewed and scored visually by two trained experts supervised by a clinical radiologist. Atrophy was scored on T1 sequence using visual rating scales ranging from 0 to 4 for medial temporal lobe atrophy (MTA), and from 0 to 3 for global cortical atrophy (GCA) (Harper et al., 2015). The average of the left and right side was used for MTA. White matter hyperintensities were scored on FLAIR/T2 sequence using the Fazekas scale (0–3) (Fazekas et al., 1987), and the number of microbleeds (on susceptibility-weighted imaging) and lacunes were counted. In this manuscript, we refer to either brain atrophy, white matter hyperintensities, lacunes or microbleeds collectively as "brain structure abnormalities."

Cognitive Function

To assess whether the observed differences in brain structure also had a functional impact, cognition was included in the analysis. Cognitive performance was assessed in a standardized manner by trained neuropsychologists and divided into four domains: memory, language, executive function, and processing speed. All patients were assessed using the Mini Mental State Examination (MMSE) and the Geriatric Depression Scale (GDS). Memory was tested with the auditory verbal learning test (Van Der Elst et al., 2005) and Visual Association Test (VAT) (Lindeboom et al., 2002). Language was tested using the Category Fluency Animals Test (Van Der Elst et al., 2006) and the VAT naming test, a

TABLE 1 | Patient characteristics stratified for sex.

	Total ***n* = 893**	**Men** ***n* = 447**	**Women** ***n* = 446**	***P*-value**
Age in years	79.6 ± 6.6	79.1 ± 6.4	79.9 ± 6.7	0.096
Living situation	487 (54.5%)	330 (74.0%)	157 (35.1%)	**<0.001**
Independent, with partner	329 (36.8%)	89 (20.0%)	240 (53.7%)	
Independent, alone	32 (3.6%)	10 (2.2%)	22 (4.9%)	
Institutionalized	45 (5.0%)	17 (3.8%)	28 (6.3%)	
Other				
Level of education				**<0.001**
Low education	180 (20.1%)	81 (18.1%)	99 (22.2%)	
Medium level education	317 (35.1%)	137 (30.7%)	176 (39.4%)	
Higher education or university	396 (44.3%	225 (50.4%)	171 (38.3%)	
Diabetes[a]	176 (19.7%)	105 (23.4%)	71 (15.9%)	0.004
Antidiabetic medication				
Oral	112 (12.5%)	69 (15.4%)	43 (9.6%)	**0.009**
Insulin	42 (4.7%)	28 (6.3%)	14 (3.1%)	**0.028**
Cardiovascular diseases				
Coronary disease	225 (25.2%)	155 (34.8%)	70 (15.7%)	**<0.001**
Heart failure	90 (10.1%)	56 (12.6%)	34 (7.6%)	0.014
Atrial fibrillation	153 (17.1%)	87 (19.5%)	66 (14.8%)	0.060
CVA/TIA	186 (20.8%)	111 (24.9%)	75 (16.8%)	**0.003**
Peripheral artery disease	33 (3.6%)	16 (3.6%)	17 (3.8%)	0.861
Cardiovascular risk factors				
Alcohol consumption in units/week	1 (0–5)	2 (0–7)	1 (0–5)	**0.003**
Smokers or ex-smokers	505 (56.6%)	289 (64.8%)	216 (48.3%)	**<0.001**
Hypertension	466 (52.2%)	228 (51.1%)	238 (53.2%)	0.525
Hypercholesterolemia	221 (24.7%)	115 (25.8%)	106 (23.7%)	0.473
Glucose in mmol/L	6.9 ± 2.6	6.9 ± 2.9	6.4 ± 2.5	0.302
BMI in kg/m^2	25.7 ± 4.6	26.1 ± 4.2	25.3 ± 4.9	**0.012**
Systolic BP in mmHg	145.8 ± 21.8	144.5 ± 21.3	147.0 ± 22.3	0.100
Diastolic BP in mmHg	80.6 ± 10.4	79.7 ± 10.5	81.4 ± 10.3	**0.014**
LDL in mmol/L	2.56 ± 0.98	2.62 ± 0.98	2.47 ± 0.97	0.959
HDL in mmol/L	1.58 ± 0.47	1.58 ± 0.47	1.58 ± 0.47	0.101
eGFR CKD-EPI in ml/min/1.73 m²	67.2 ± 16.2	67.0 ± 16.4	67.4 ± 16.0	0.755
Statin use	525 (58.8%)	208 (46.6%)	160 (35.8%)	**0.001**
Blood pressure lowering agents				
Diuretics	147 (16.4%)	71 (15.9%)	76 (17.0%)	0.663
RAAS-inhibition	171 (19.1%)	90 (20.2%)	81 (18.1%)	0.434
Calcium-antagonists	63 (7.0%)	37 (8.3%)	26 (5.8%)	0.148
Beta-blockers	105 (11.7%)	61 (13.7%)	44 (9.8%)	0.075
Anticoagulation				
DOAC/VKA	168 (18.8%)	96 (21.5%)	72 (16.1%)	**0.038**
Platelet inhibition	288 (32.2%)	169 (37.9%)	119 (26.6%)	**<0.001**
MMSE	24 (21–26)	25 (22–28)	24 (21–28)	**0.008**
GDS	3 (1–5)	3 (1–5)	3 (1–5)	0.093
Brain imaging				
MTA or GCA > 2	493 (55.2%)	282 (63.2%)	211 (47.2%)	**0.007**
WMH >2	227 (25.4%)	108 (24.2%)	119 (26.6%)	0.398
Lacunes ≥ 1	204 (22.8%)	112 (25.1%)	92 (20.6%)	0.098
Microbleeds ≥ 3	163 (18.3%)	90 (20.2%)	73 (16.3%)	0.213

(Continued)

TABLE 1 | Continued

	Total $n = 893$	Men $n = 447$	Women $n = 446$	*P*-value
Cognitive diagnosis				0.085
SCD	124 (13.8%)	62 (13.9%)	62 (13.9%)	
MCI	267 (29.8%)	148 (33.2%)	119 (26.6%)	
Dementia	502 (56.2%)	236 (52.9%)	266 (59.5%)	

Data are presented as mean ± SD, n (%) or median [interquartile range]. Differences were tested with independent t-test for continuous variables and chi-square tests for categorical and for not normally distributed continuous variables.

BMI, body mass index; BP, blood pressure; CVA, cerebrovascular accident; DOAC, Direct Oral Anti-Coagulant; GCA, Global Cortical Atrophy; MCI, Mild Cognitive Impairment; MTA, Medial Temporal lobe Atrophy; TIA, Transient Ischemic Attack; SCD, Subjective Cognitive Decline; VKA, Vitamin K Antagonist; WMH, White Matter Hyperintensities.

[a]*type I or II diabetes, not specified in our data collection.*

The bold values indicate the p values which are statistically significant.

component of the VAT. Processing speed was examined with the Stroop Color-Word test (SCWT) (Van der Elst et al., 2006) and the Trail Making Test-A (TMT-A) (Reitan, 1955). Finally, executive function was assessed with the Behavioral Assessment of the Dysexecutive Rule-changing test (BADS) (Burrell and Piguet, 2015) while correcting for speed using the SCWT and the TMT. For the purposes of the analysis, all test results were converted to Z-scores or inverse Z-scores. A higher Z-score indicates poorer performance.

Statistical Analysis

Baseline characteristics for men, women, and the total population are reported as mean (SD), or median (interquartile range) for categorical variables. Differences between groups were analyzed using Student's *T*-test, the Mann-Whitney *U*-test, the Kruskal Wallis test, ANOVA and chi-square testing where appropriate. First, logistic regression analyses were performed to assess the association of diabetes with brain structures separately for men and women. For the logistic regression analysis, we dichotomized the scores of the visual rating scale and the values for microbleeds and lacunes. A cut-off value of two or more was used for the imaging scores of atrophy (MTA and/or CGA) and WMH (Rhodius-Meester et al., 2017). Microbleeds were dichotomized as present or not present, and a value of one or more was adopted a cut-off for lacunes (Henneman et al., 2009; Jokinen et al., 2011). Second, linear regression analyses were performed to assess the association of diabetes with cognitive functioning separately for men and women. All analyses were adjusted for age (model 1), and additionally for smoking and alcohol consumption (model 2), and hypertension and cardiovascular disease (coronary disease, heart failure, atrial fibrillation, stroke or TIA and peripheral arterial disease) (model 3). In addition, we adjusted for presence of subjective complaints, mild cognitive impairment, or dementia (data not shown). For the analyses of functional cognitive measures, furthermore, we corrected all models for level of education. A p-value < 0.05 was considered statistically significant. Data were analyzed with SPSS software, version 26 (IBM Corp, Armonk, NY, USA).

To determine whether male or female sex and CVD was associated with a higher risk of cSVD to a greater degree than these factors individually, we added an interaction term to the regression analysis, testing multiplicative interaction. To assess additive interaction, we calculated RERI (Relative Risk due to Interaction) (Knol et al., 2007; Knol and VanderWeele, 2012). For this analysis, when the combined risk of sex and CVD was higher than the sum of the risks associated with the individual factors, the interaction between sex and CVD was considered to constitute an additional risk factor. A RERI above zero indicated that interaction between female sex and cardiac disease had an additional effect on the outcome; a RERI below zero indicated that this was the case for the interaction between male sex and cardiac disease. In the RERI analysis, we also corrected for age, smoking, and alcohol consumption, analogous to the logistic regression analyses. These analyses were performed in R (R Core Team, 2020).

RESULTS

A total of 893 patients were included in the analysis (**Table 1**). The mean (SD) age was 79.6 years (73–86.2) and 50% were women. The prevalence of diabetes was 23.3% in men and 15.7% in women ($p = 0.004$), and men with diabetes were more often insulin-dependent compared to women (6.3% for men, 3.1% for women, $p = 0.03$). Women lived alone more often than men and their level of education was lower. Further, women had a lower prevalence of cardiovascular disease, consumed less alcohol, smoked less, had a lower body mass index (BMI) and a slightly higher diastolic BP, and they used less statins and anticoagulation drugs (**Table 1**). Women had slightly lower Mini-Mental State Examination scores, GDS, and men had higher brain atrophy scores. No differences in cognitive diagnosis were observed between men and women. Stratified analyses for sex and diabetes showed that differences in cardiovascular risk between men and women were more pronounced in those with diabetes compared to the total population (**Supplementary Table 1**).

Sex Differences in the Relationship Between Diabetes and Brain Structure

The sex-specific logistic regression analyses of the relation between diabetes and brain structures showed that in women, the presence of diabetes was significantly associated with an increased risk of having brain atrophy and lacunes (**Table 2**).

TABLE 2 | The sex-specific relation of diabetes with changes in brain structure in older men and women ($N = 893$).

	Men, $n = 447$ OR (95% CI)	Women, $n = 446$ OR (95% CI)	Interaction[a] OR (95% CI)	p-value[b]
Atrophy				
Non-diabetic	Ref	Ref	Ref	
Diabetic (model 1)	1.14 (0.60–2.18)	2.16 (1.00–4.67)*	1.22 (0.50–2.94)	$p = 0.66$
Diabetic (model 2)	1.17 (0.60–2.29)	2.46 (1.11–5.42)*	1.32 (0.46–2.79)	$p = 0.77$
Diabetic (model 3)	1.00 (0.51–1.96)	2.18 (1.00–4.72)*	1.17 (0.48–2.87)	$p = 0.71$
WMH				
Non-diabetic	Ref	Ref		
Diabetic (model 1)	1.20 (0.76–1.89)	1.11 (0.65–1.89)	0.88 (0.47–4.00)	$p = 0.70$
Diabetic (model 2)	1.15 (0.72–1.84)	1.09 (0.63–1.88)	0.85 (0.45–1.60)	$p = 0.61$
Diabetic (model 3)	1.01 (0.63–1.62)	1.04 (0.61–1.79)	0.78 (0.41–1.49)	$p = 0.45$
Microbleeds				
Non-diabetic	Ref	Ref		
Diabetic (model 1)	0.59 (0.26–1.32)	0.82 (0.31–2.20)	1.04 (0.32–3.34)	$p = 0.67$
Diabetic (model 2)	0.65 (0.28–1.49)	0.86 (0.31–2.32)	0.97 (0.30–3.13)	$p = 0.95$
Diabetic (model 3)	0.46 (0.20–1.00	0.75 (0.28–2.03)	0.93 (0.29–3.01)	$p = 0.90$
Lacunes				
Non-diabetic	Ref	Ref		
Diabetic (model 1)	1.68 (0.92–3.04)	2.60 (1.24–2.46)*	1.10 (0.49–6.91)	$p = 0.82$
Diabetic (model 2)	1.64 (0.87–3.07)	2.72 (1.24–5.93)*	1.00 (0.41–2.10)	$p = 0.84$
Diabetic (model 3)	1.38 (0.74–2.56)	2.40 (1.13–5.07)*	0.95 (0.37–1.91)	$p = 0.63$

WMH, White Matter Hyperintensities.
Data are presented as OR with (95% CI).
Model 1: adjusted for age.
Model 2: adjusted for age, smoking and alcohol consumption.
Model 3: Adjusted for age, hypertension, hypercholesterolemia, and presence of CVD (coronary disease, heart failure, atrial fibrillation, CVA or TIA, peripheral arterial disease).
**p-value < 0.05.*
[a]*Interaction term (sex multiplied by diabetes) added to the logistic regression.*
[b]*Statistical significance of the interaction term in the logistic regression analysis.*

Age-adjusted odds ratios were 2.16 (95% CI 1.00–4.67) and 2.60 (95% CI 1.24–2.46). However, in men, diabetes was not associated with an increased risk of having brain structure abnormalities. Additional adjustments for cardiovascular risk factors and disease (model 2 and 3) did not change these effect estimates (**Table 2**). Adjusting for cognitive diagnosis (subjective complaints, mild cognitive impairment, or dementia) did not change the effect estimates (data not shown). Diabetes was not associated with an increased risk of WMH and microbleeds. When adding an interaction term to the regression, we did not find a significant interaction of sex with diabetes. When assessing additive interaction using RERI analysis, a trend was seen toward an increased risk for women with diabetes of atrophy and lacunes (RERI 0.45 for the presence of atrophy and female sex, and 0.48 for the presence of lacunes and female sex) (**Supplementary Table 2**).

Sex Differences in the Relationship Between Diabetes and Cognitive Performance

The sex-specific linear regression analyses of the relation between diabetes and cognitive performance showed that diabetes in women was associated with a significantly lower score of executive function (beta z-score 0.07; 95% CI 0.00–0.14), processing speed (beta 0.06; 95% CI 0.90–0.95), and language (beta 0.07; 95% CI 0.01–0.12) (**Table 3**). In men, diabetes was not associated with cognitive performance. Additional adjustments for cardiovascular risk and disease, and cognitive diagnosis did not change the effect estimates (data for cognitive diagnosis not shown). We observed an interaction of sex and diabetes: women with diabetes were at increased risk for impaired processing speed (B 0.17 (0.03–0.33), $p = 0.04$). We observed no interaction between diabetes and sex in the other cognitive domains.

DISCUSSION

In this study of 893 patients attending a geriatric outpatient memory clinic, we found that the presence of diabetes was associated with an increased risk of having brain structure abnormalities, specifically lacunes and atrophy, in women but not in men. We also found an additive interaction between female sex and these brain structure abnormalities, as tested by a RERI analysis. This finding complements previous studies which showed that women with diabetes may be more at risk of multiple forms of vascular pathology than men with diabetes, including coronary heart disease, stroke, and vascular dementia (Huxley et al., 2006; Peters et al., 2014; Chatterjee et al., 2016). It could be argued that other age-mediated cardiovascular risk factors such

TABLE 3 | The sex specific relation of diabetes with cognitive performance in older men and women ($N = 893$).

	Men B (95% CI)	Women B (95% CI)	Interaction[a] B (95% CI)	*p*-value[b]
Memory				
Non-diabetic	Ref	Ref	Ref	
Diabetic (model 1)	0.02 (−0.09 to 0.03)	0.02 (−0.07 to 0.03)	0.09 (−0.26 to 0.46)	0.59
Diabetic (model 2)	0.03 (−0.09 to 0.02)	0.02 (−0.07 to 0.03)	0.10 (−0.26 to 0.47)	0.57
Diabetic (model 3)	0.03 (−0.08 to 0.02)	0.01 (−0.06 to 0.03)	0.10 (−0.27 to 0.47)	0.59
Executive function				
Non-diabetic	Ref	Ref		
Diabetic (model 1)	−0.02 (−0.09 to 0.04)	−0.07 (−0.14 to 0.00)*	−0.04 (−0.36 to 0.28)	0.81
Diabetic (model 2)	−0.02 (−0.09 to 0.04)	−0.06 (−0.13 to 0.01)	−0.03 (−0.32 to 0.32)	0.98
Diabetic (model 3)	−0.01 (−0.06 to 0.06)	−0.07 (−0.13 to 0.00)*	−0.01 (−0.33 to 0.32)	0.97
Processing speed				
Non-diabetic	Ref	Ref		
Diabetic (model 2)	−0.03 (−0.08 to 0.01)	−0.06 (−0.10 to 0.02)*	0.19 (0.03 to 0.34)	**0.02**
Diabetic (model 3)	−0.03 (−0.08 – 0.02)	−0.06 (−0.10 to 0.01)*	0.18 (0.02 to 0.33)	**0.03**
Diabetic (model 1)	−0.02 (−0.07 to 0.01)	−0.06 (−0.10 to 0.02)*	0.17 (0.03 to 0.33)	**0.04**
Language				
Non-diabetic	Ref	Ref		
Diabetic (model 1)	−0.01 (−0.06 to 0.04)	−0.07 (−0.12 to 0.01)*	−0.18 (−0.53 to 0.17)	0.31
Diabetic (model 2)	−0.01 (−0.05 to 0.07)	−0.06 (−0.12 to 0.00)	−0.12 (−0.48 to 0.22)	0.14
Diabetic (model 3)	0.00 (−0.05 to 0.04)	−0.07 (−0.012 to 0.01)*	−0.14 (−0.49 to 0.21)	0.43

Data are presented as unstandardized B with (95% CI).
A negative B signifies a correlation with worse Z-scores, e.g. with worse cognitive performance.
Model 1: adjusted for age and level of education; Model 2: adjusted for age, level of education, smoking and alcohol consumption; Model 3: Adjusted for age, level of education, presence of CVD (coronary disease, heart failure, atrial fibrillation, CVA or TIA, peripheral arterial disease), hypertension and hypercholesterolemia.
**p-value linear regression < 0.05.*
[a]*Interaction term (sex multiplied by diabetes) added to the logistic regression.*
[b]*Statistical significance of the interaction term in the logistic regression analysis.*
The bold values indicate the p values which are statistically significant.

as hypertension and cardiac disease play a role in mediating the relationship between diabetes and brain structure abnormalities. However, we show that this relationship was independent of age, lifestyle, cardiovascular risk factors, and cardiac disease.

Additionally, we found that diabetes was significantly associated with worse cognitive performance in terms of executive function, processing speed and language, in the women in our population but not in the men. An interaction between sex and diabetes was also observed for processing speed, further strengthening the hypothesis of a true sex difference. These findings are in line with a recent study showing that women with diabetes have a higher risk of accelerated cognitive decline than men with diabetes (Verhagen et al., 2022). Sex-dependent physiology, as well as socio-cultural differences between men and women, may be the cause of these differences. We postulate a number of hypotheses below which may explain the association between diabetes and brain structure abnormalities as it is seen in women but not in men.

Pathophysiological Differences

Mechanisms which may affect susceptibility to the vascular complications of diabetes include altered coagulation, oxidative stress, endothelial dysfunction and impaired vasodilation (Kautzky-Willer et al., 2016; de Ritter et al., 2020). Women with diabetes might be in a more pro-thrombotic state than men, which may lead to lacunes and atrophy, and a more general decline in brain health, even when the prevalence of diabetes is similar in both sexes (Smith et al., 2012; Neergaard-Petersen et al., 2014). They generally also have greater levels of systemic inflammation and more oxidative stress than men with diabetes, leading to impaired vascular reactivity, which is specifically associated with the occurrence of lacunes (Mrgan et al., 2018). Sex-dependent differences in vascular physiology may therefore render women more susceptible to the cerebrovascular complications of diabetes, and also lead to functional decline.

Levels of central adiposity in men and women with diabetes may also be of importance. There is evidence to suggest that women have a poorer cardiovascular risk profile than men when they are diagnosed with diabetes, especially when central adiposity is measured (Paul et al., 2012; Peters et al., 2016a). This may be the result of a longer period of development of diabetes in women: women are more insulin-sensitive in middle age, and their insulin sensitivity deteriorates more than in men before they reach the diagnosis of diabetes. A longer period of time before a formal diagnosis of diabetes can be made may also lead to an increased occurrence of other risk factors such as abdominal adiposity, and to higher levels of subclinical damage mediated by hyperglycemia (Woodward et al., 2015; Peters et al., 2016b).

Abdominal adiposity is independently related to brain structure abnormalities, including silent lacunary infarcts, and therefore may mediate the increased prevalence in women with diabetes by comparison with men (Yamashiro et al., 2014).

Furthermore, there is little awareness in the field of geriatrics about the long-term cardiovascular effects of pregnancy-related complications, as well as other women-specific factors such as timing of menopause and gestational diabetes (Keskin et al., 2015; Kuh et al., 2018). These important cardiovascular parameters are therefore often not registered in medical files, as is the case in our dataset (Wilkins-Haug et al., 2015). It has long been known that menopausal status and the timing of menopause influence cardiovascular risk, abdominal obesity, occurrence of DM, and clinical course of dementia (Archer, 2009; Gong et al., 2021; Hickey and Mishra, 2021). They may therefore also have affected the clinical outcome in our study. Further studies investigating the long-term effects of DM should therefore include sex-specific cardiovascular risk factors to assess their impact on brain structure and cognitive function.

Sex-Related Differences in Current Care

As a consequence of ongoing lower inclusion rates of women in studies investigating the long-term effects of diabetes, at least in part, it is unclear which mechanisms lead to the poorer clinical outcome of women with diabetes (Norhammar and Schenck-Gustafsson, 2013). However, there are several scientific findings which may play a role. Social gender norms have a profound influence on patients' disease perception, moment of referral, interpretation of symptoms and the likelihood of receiving guideline-recommended treatment. In the case of diabetes, evidence shows that women diagnosed with diabetes attain glycemic targets less often, and are screened less for the complications of diabetes (Choe et al., 2018). Risk factor targets for co-morbid cardiovascular disease are also less often achieved in women (Ferrara et al., 2008; Wannamethee et al., 2012; Rossi et al., 2013; de Jong et al., 2020). Since early intervention in diabetes improves long-term outcome, this may also have implications for the incidence of (cerebral) complications (Group UPDS, 1998). The same truth holds for cognitive impairment: women with dementia are generally referred later than men (Howard et al., 1998; Sourial et al., 2020). Women might therefore experience delay in receiving adequate supporting care when experiencing cognitive impairment. Hence, inequities in the recognition and treatment of (cardiovascular) risk factors for dementia, as well as the recognition and treatment of dementia itself, may play a role in the occurrence of sex-related differences in the cerebral complications of diabetes.

Strengths and Limitations

A major strength of our study is the standardized work-up of a large group of "real-life" patients. We included a multi-domain assessment which was part of medical routine care. Because of this integration in regular care practice, routinely used measurements and tools were used, facilitating the translation of our research to clinical practice. In addition, we combined these clinically used parameters with imaging markers as well as extensive neuropsychological testing, bridging the gap between etiological research and clinical practice. Our study has also several limitations. Firstly, because of our cross-sectional design, we cannot draw conclusions about the causality of our findings. We balanced this with logistic regression models in which we corrected for confounding factors. Related to this, we have no data showing possible differences between brain structure at the time of diagnosis of diabetes, and later life. It is possible that women with diabetes already have worse brain health at this time, and that it is not a direct consequence of diabetes, but merely coexists due to other pathological processes. Furthermore, HbA1c and time since diagnosis of DM were not included in our dataset. We were therefore unable to assess the influence of glycemic regulation. We did include non-fasted glucose, which was similar for men and women, in our baseline characteristics. Also, it is remarkable that the mean age in our sample is similar for men and women. Since the life expectancy in women exceeds the life expectancy in men, we would expect a higher mean age for women. The similar age for men and women may reflect underlying gender bias in referral to our clinic. However, it may also be explained by other forms of sampling bias not related sex or gender. Furthermore, as mentioned before, women-specific pathology was hardly registered at all in our patient files. A history of gestational diabetes, polycystic ovary syndrome and premature menopause contribute to the excess risk of diabetic complications and diabetes (Soedamah-Muthu et al., 2004; Huxley et al., 2006; Peters et al., 2014). Furthermore, preeclampsia is related to structural brain damage later in life (Siepmann et al., 2017). Lastly, premature menopause is additionally associated with poorer cognitive performance and a higher risk of dementia later in life (Ryan et al., 2014). However, the precise relationship between cerebrovascular disease and pregnancy-related cardiovascular disease remains unclear, since a recent review concluded that gestational hypertension is not related to cerebral stroke (Lo et al., 2020). Finally, other factors that affect the social position of patients and therefore their quality of care – such as class, cultural background, and variables associated with poorer referral and poorer health care provision in general – were not available in our study (Vaccarino et al., 2002; LaVeist et al., 2003).

In conclusion, this sex-specific analysis of the association between diabetes and its cerebrovascular complications shows that diabetes is significantly associated with brain structure abnormalities and function in women but not in men. We can only speculate on the nature of these differences, and whether they are dependent on gender or sex. Although we did not find a statistically significant interaction between female sex and diabetes, the differences in associations for men and women are striking and underline the importance of the sex-specific analysis of clinical data. Further research should at least include data on abdominal obesity and female-specific risk factors such as pregnancy-related complications and menopause, and more studies are needed to elucidate the mechanisms which contribute to the association between diabetes, brain structure and cognition in women. Elucidating the sex-specific relationships between diabetes and cSVD may help to understand the gap in burden of dementia and help to achieve more equity in the care for this group of patients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data is not publicly available since it contains clinical privacy-sensitive patient information. Requests to access these datasets should be directed to majon.muller@amsterdamumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee of the Amsterdam UMC, location VUmc. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study conception and design and data collection: ET, MM, and HR-M. Analysis and interpretation of the results: ET, MM, HR-M, and SP. Draft manuscript preparation: ET, MM, HR-M, LE, SP, RP, and LB. All authors reviewed the results and approved the final version of the manuscript.

FUNDING

HR-M was recipient of the Memorabel Dementia Fellowship 2021 (ZonMw project number 10510022110004). Also, we acknowledge the support from the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation (CVON 2018-28 and 2012-06 Heart Brain Connection), Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development, and the Royal Netherlands Academy of Sciences.

ACKNOWLEDGMENTS

We would like to thank Dr. S.P. Thomas for his proofreading of the manuscript and perpetual moral support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.885787/full#supplementary-material

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2013). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Focus* 11, 96–106. doi: 10.1176/appi.focus.11.1.96

Archer, D. (2009). Premature menopause increases cardiovascular risk. *Climacteric* 12(sup1), 26–31. doi: 10.1080/13697130903013452

Arvanitakis, Z., Wilson, R. S., Bienias, J. L., Evans, D. A., and Bennett, D. A. (2004). Diabetes mellitus and risk of Alzheimer's disease and decline in cognitive function. *Arch. Neurol.* 61, 661–666. doi: 10.1001/archneur.61.5.661

Burrell, J. R., and Piguet, O. (2015). Lifting the veil: how to use clinical neuropsychology to assess dementia. *J. Neurol. Neurosurg. Psychiatry* 86, 1216–1224. doi: 10.1136/jnnp-2013-307483

Chatterjee, S., Peters, S. A., Woodward, M., Arango, S. M., Batty, G. D., Beckett, N., et al. (2016). Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care*. 39, 300–307. doi: 10.2337/dc15-1588

Choe, S.-A., Kim, J. Y., Ro, Y. S., and Cho, S.-I. (2018). Women are less likely than men to achieve optimal glycemic control after 1 year of treatment: a multi-level analysis of a Korean primary care cohort. *PLoS One* 13, e0196719. doi: 10.1371/journal.pone.0196719

de Jong, M., Oskam, M. J., Sep, S. J., Ozcan, B., Rutters, F., Sijbrands, E. J., et al. (2020). Sex differences in cardiometabolic risk factors, pharmacological treatment and risk factor control in type 2 diabetes: findings from the Dutch Diabetes Pearl cohort. *BMJ Open Diabetes Res. Care* 8, e001365. doi: 10.1136/bmjdrc-2020-001365

de Ritter, R., de Jong, M., Vos, R. C., van der Kallen, C. J., Sep, S. J., Woodward, M., et al. (2020). Sex differences in the risk of vascular disease associated with diabetes. *Biol. Sex Differ.* 11, 1–11. doi: 10.1186/s13293-019-0277-z

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. *Lancet Neurol.* 6, 734–746. doi: 10.1016/S1474-4422(07)70178-3

Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., and Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am. J. Neuroradiol.* 8, 421–426. doi: 10.2214/ajr.149.2.351

Ferrara, A., Mangione, C. M., Kim, C., Marrero, D. G., Curb, D., Stevens, M., et al. (2008). Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care*. 31, 69–74. doi: 10.2337/dc07-1244

Geijselaers, S. L., Sep, S. J., Stehouwer, C. D., and Biessels, G. J. (2015). Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. *Lancet Diabetes Endocrinol.*. 3, 75–89. doi: 10.1016/S2213-8587(14)70148-2

Gong, J., Harris, K., Peters, S. A., and Woodward, M. (2021). Reproductive factors and the risk of incident dementia: results from the UK Biobank. doi: 10.21203/rs.3.rs-359787/v1

Group UPDS (1998). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352, 837–853. doi: 10.1016/S0140-6736(98)07019-6

Harper, L., Barkhof, F., Fox, N. C., and Schott, J. M. (2015). Using visual rating to diagnose dementia: a critical evaluation of MRI atrophy scales. *J. Neurol. Neurosurg. Psychiatry* 86, 1225–1233. doi: 10.1136/jnnp-2014-310090

Hayden, K. M., Zandi, P. P., Lyketsos, C. G., Khachaturian, A. S., Bastian, L. A., Charoonruk, G., et al. (2006). Vascular risk factors for incident Alzheimer's disease and vascular dementia: the Cache County study. *Alzheimer's Dis. Assoc. Disord.* 20, 93–100. doi: 10.1097/01.wad.0000213814.43047.86

Henneman, W. J., Sluimer, J. D., Cordonnier, C., Baak, M. M., Scheltens, P., Barkhof, F., et al. (2009). MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. *Stroke* 40, 492–498. doi: 10.1161/STROKEAHA.108.516286

Hickey, M., and Mishra, G. D. (2021). Timing and type of menopause and risk of cardiovascular disease. *Menopause* 28, 477–479. doi: 10.1097/GME.0000000000001747

Howard, B. V., Cowan, L. D., Go, O., Welty, T. K., Robbins, D. C., Lee, E. T., et al. (1998). Adverse effects of diabetes on multiple cardiovascular disease risk factors in women: the Strong Heart Study. *Diabetes care*. 21, 1258–1265. doi: 10.2337/diacare.21.8.1258

Huxley, R., Barzi, F., and Woodward, M. (2006). Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 332, 73–78. doi: 10.1136/bmj.38678.389583.7C

Jiménez-Sánchez, L., Hamilton, O. K., Clancy, U., Backhouse, E. V., Stewart, C. R., Stringer, M. S., et al. (2021). Sex differences in Cerebral Small Vessel Disease: a systematic review and meta-analysis. *Front. Neurol*. 12, 756887. doi: 10.3389/fneur.2021.756887

Jokinen, H., Gouw, A., Madureira, S., Ylikoski, R., Van Straaten, E., Van Der Flier, W., et al. (2011). Incident lacunes influence cognitive decline: the LADIS study. *Neurology*. 76, 1872–1878. doi: 10.1212/WNL.0b013e31821d752f

Kannel, W. B., and McGee, D. L. (1979). Diabetes and cardiovascular risk factors: the Framingham study. *Circulation*. 59, 8–13. doi: 10.1161/01.CIR.59.1.8

Kautzky-Willer, A., Harreiter, J., and Pacini, G. (2016). Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr. Rev*. 37, 278–316. doi: 10.1210/er.2015-1137

Keskin, F., Ozyazar, M., Pala, A., Elmali, A., Yilmaz, B., Uygunoglu, U., et al. (2015). Evaluation of cognitive functions in gestational diabetes mellitus. *Exp. Clin. Endocrinol. Diabetes*. 123, 246–251. doi: 10.1055/s-0034-1395634

Knol, M. J., van der Tweel, I., Grobbee, D. E., Numans, M. E., and Geerlings, M. I. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *Int. J. Epidemiol*. 36, 1111–1118. doi: 10.1093/ije/dym157

Knol, M. J., and VanderWeele, T. J. (2012). Recommendations for presenting analyses of effect modification and interaction. *Int. J Epidemiol*. 41, 514–520. doi: 10.1093/ije/dyr218

Kuh, D., Cooper, R., Moore, A., Richards, M., and Hardy, R. (2018). Age at menopause and lifetime cognition: findings from a British birth cohort study. *Neurology*. 90:e1673–e81. doi: 10.1212/WNL.0000000000005486

LaVeist, T. A., Nuru-Jeter, A., and Jones, K. E. (2003). The association of doctor-patient race concordance with health services utilization. *J. Public Health Policy* 24, 312–323. doi: 10.2307/3343378

Lindeboom, J., Schmand, B., Tulner, L., Walstra, G., and Jonker, C. (2002). Visual association test to detect early dementia of the Alzheimer's type. *J. Neurol. Neurosurg. Psychiatry* 73, 126–133. doi: 10.1136/jnnp.73.2.126

Liu, C.-L., Lin, M.-Y., Hwang, S.-J., Liu, C.-K., Lee, H.-L., and Wu, M.-T. (2018). Factors associated with type 2 diabetes in patients with vascular dementia: a population-based cross-sectional study. *BMC Endocr. Disord*. 18, 1–7. doi: 10.1186/s12902-018-0273-z

Liu, J., Rutten-Jacobs, L., Liu, M., Markus, H. S., and Traylor, M. (2018). Causal impact of type 2 diabetes mellitus on cerebral small vessel disease: a Mendelian randomization analysis. *Stroke*. 49, 1325–1331. doi: 10.1161/STROKEAHA.117.020536

Lo, C. C. W., Lo, A. C., Leow, S. H., Fisher, G., Corker, B., Batho, O., et al. (2020). Future cardiovascular disease risk for women with gestational hypertension: a systematic review and meta-analysis. *J. Am. Heart Assoc.* 9, e013991. doi: 10.1161/JAHA.119.013991

Mahammedi, A., Wang, L., Williamson, B., Khatri, P., Kissela, B., Sawyer, R., et al. (2021). Small vessel disease, a marker of brain health: what the radiologist needs to know. *Am. J. Neuroradiol*. 43, 650–660. doi: 10.3174/ajnr.A7302

McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'brien, J., Feldman, H., et al. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 65, 1863–1872. doi: 10.1212/01.wnl.0000187889.17253.b1

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34, 939-. doi: 10.1212/WNL.34.7.939

Moran, C., Phan, T. G., Chen, J., Blizzard, L., Beare, R., Venn, A., et al. (2013). Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care* 36, 4036–4042. doi: 10.2337/dc13-0143

Mrgan, M., Gram, J., Hecht Olsen, M., Dey, D., Linde Nørgaard, B., Gram, J., et al. (2018). Sex differences in coronary plaque composition evaluated by coronary computed tomography angiography in newly diagnosed Type 2 diabetes: association with low-grade inflammation. *Diabetic Med*. 35, 1588–1595. doi: 10.1111/dme.13768

Neary, D., Snowden, J. S., Gustafson, L., Passant, U., Stuss, D., Black, S., et al. (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 51, 1546–1554. doi: 10.1212/WNL.51.6.1546

Neergaard-Petersen, S., Hvas, A.-M., Kristensen, S. D., Grove, E. L., Larsen, S. B., Phoenix, F., et al. (2014). The influence of type 2 diabetes on fibrin clot properties in patients with coronary artery disease. *Thromb. Haemost*. 112, 1142–1150. doi: 10.1160/th14-05-0468

Norhammar, A., and Schenck-Gustafsson, K. (2013). Type 2 diabetes and cardiovascular disease in women. *Diabetologia* 56, 1–9. doi: 10.1007/s00125-012-2694-y

Odden, M. C., Peralta, C. A., Haan, M. N., and Covinsky, K. E. (2012). Rethinking the association of high blood pressure with mortality in elderly adults: the impact of frailty. *Arch. Intern. Med*. 172, 1162–1168. doi: 10.1001/archinternmed.2012.2555

Paul, S., Thomas, G., Majeed, A., Khunti, K., and Klein, K. (2012). Women develop type 2 diabetes at a higher body mass index than men. *Diabetologia* 55, 1556–1557. doi: 10.1007/s00125-012-2496-2

Peters, S. A., Carcel, C., Millett, E. R., and Woodward, M. (2020). Sex differences in the association between major risk factors and the risk of stroke in the UK Biobank cohort study. *Neurology* 95, e2715–e2726. doi: 10.1212/WNL.0000000000010982

Peters, S. A., Huxley, R. R., and Woodward, M. (2014). Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. *The Lancet*. 383, 1973–1980. doi: 10.1016/S0140-6736(14)60040-4

Peters, S. A., Huxley, R. R., and Woodward, M. (2016a). Sex differences in body anthropometry and composition in individuals with and without diabetes in the UK Biobank. *BMJ Open* 6, e010007. doi: 10.1136/bmjopen-2015-010007

Peters, S. A., Singhateh, Y., Mackay, D., Huxley, R. R., and Woodward, M. (2016b). Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis. *Atherosclerosis* 248, 123–131. doi: 10.1016/j.atherosclerosis.2016.03.016

Peters, T. M., Holmes, M. V., Richards, J. B., Palmer, T., Forgetta, V., Lindgren, C. M., et al. (2021). Sex differences in the risk of coronary heart disease associated with type 2 diabetes: a mendelian randomization analysis. *Diabetes Care*. 44, 556–562. doi: 10.2337/dc20-1137

R Core Team. (2020). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. Available online at: https://www.R-project.org/

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., et al. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 134, 2456–2477. doi: 10.1093/brain/awr179

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *J. Consult. Psychol*. 19, 393. doi: 10.1037/h0044509

Rhodius-Meester, H. F., Benedictus, M. R., Wattjes, M. P., Barkhof, F., Scheltens, P., Muller, M., et al. (2017). MRI visual ratings of brain atrophy and white matter hyperintensities across the spectrum of cognitive decline are differently affected by age and diagnosis. *Front. Aging Neurosci.* 9, 117. doi: 10.3389/fnagi.2017.00117

Rhodius-Meester, H. F. M., van de Schraaf, S. A., Peters, M. J., Kleipool, E. E., Trappenburg, M. C., and Muller, M. (2021). Mortality risk and its association with geriatric domain deficits in older outpatients: the amsterdam ageing cohort. *Gerontology* 67, 194–201. doi: 10.1159/000512048

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J., Masdeu, J., Garcia, J., et al. (1993). Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology* 43, 250. doi: 10.1212/WNL.43.2.250

Rossi, M. C., Cristofaro, M. R., Gentile, S., Lucisano, G., Manicardi, V., Mulas, M. F., et al. (2013). Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD Annals initiative. *Diabetes Care* 36, 3162–3168. doi: 10.2337/dc13-0184

Ryan, J., Scali, J., Carriere, I., Amieva, H., Rouaud, O., Berr, C., et al. (2014). Impact of a premature menopause on cognitive function in later life. *BJOG* 121, 1729–1739. doi: 10.1111/1471-0528.12828

Siepmann, T., Boardman, H., Bilderbeck, A., Griffanti, L., Kenworthy, Y., Zwager, C., et al. (2017). Long-term cerebral white and gray matter changes after preeclampsia. *Neurology*. 88, 1256–1264. doi: 10.1212/WNL.0000000000003765

Smith, E. E., Schneider, J. A., Wardlaw, J. M., and Greenberg, S. M. (2012). Cerebral microinfarcts: the invisible lesions. *Lancet Neurol.* 11, 272–282. doi: 10.1016/S1474-4422(11)70307-6

Soedamah-Muthu, S. S., Chaturvedi, N., Toeller, M., Ferriss, B., Reboldi, P., Michel, G., et al. (2004). Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care*. 27, 530–537. doi: 10.2337/diacare.27.2.530

Sourial, N., Arsenault-Lapierre, G., Margo-Dermer, E., Henein, M., and Vedel, I. (2020). Sex differences in the management of persons with dementia following a subnational primary care policy intervention. *Int. J. Equity Health* 19, 1–6. doi: 10.1186/s12939-020-01285-2

Studart, A. N., and Nitrini, R. (2016). Subjective cognitive decline: the first clinical manifestation of Alzheimer's disease? *Dement Neuropsychol.* 10, 170–177. doi: 10.1590/S1980-5764-2016DN1003002

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B. B., et al. (2021). IDF diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract*. 183, 109119. doi: 10.1016/j.diabres.2021.109119

Ter Telgte, A., van Leijsen, E. M., Wiegertjes, K., Klijn, C. J., Tuladhar, A. M., and de Leeuw, F.-E. (2018). Cerebral small vessel disease: from a focal to a global perspective. *Nat. Rev. Neurol.* 14, 387–398. doi: 10.1038/s41582-018-0014-y

Troncoso, J. C., Zonderman, A. B., Resnick, S. M., Crain, B., Pletnikova, O., and O'Brien, R. J. (2008). Effect of infarcts on dementia in the Baltimore longitudinal study of aging. *Ann. Neurol.* 64, 168–176. doi: 10.1002/ana.21413

Vaccarino, V., Abramson, J. L., Veledar, E., and Weintraub, W. S. (2002). Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation* 105, 1176–1181. doi: 10.1161/hc1002.105133

Van Der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., and Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *J. Int. Neuropsychol. Soc*. 11, 290–302. doi: 10.1017/S1355617705050344

Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., and Jolles, J. (2006). The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment*. 13, 62–79. doi: 10.1177/1073191105283427

Van Der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., and Jolles, J. (2006). Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J. Int. Neuropsychol. Soc*. 12, 80–89. doi: 10.1017/S1355617706060115

Verhagen, C., Janssen, J., Biessels, G. J., Johansen, O. E., and Exalto, L. G. (2022). Females with type 2 diabetes are at higher risk for accelerated cognitive decline than males: CAROLINA-COGNITION study. *Nutr. Metab. Cardiovasc. Dis*. 32, 355–364. Available online at: https://doi.org/10.1016/j.numecd.2021.10.013

Wannamethee, S., Papacosta, O., Lawlor, D., Whincup, P., Lowe, G., Ebrahim, S., et al. (2012). Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. *Diabetologia* 55, 80–87. doi: 10.1007/s00125-011-2284-4

Wardlaw, J. M., Smith, C., and Dichgans, M. (2019). Small vessel disease: mechanisms and clinical implications. *Lancet Neurol.* 18, 684–696. doi: 10.1016/S1474-4422(19)30079-1

Wilkins-Haug, L., Celi, A., Thomas, A., Frolkis, J., and Seely, E. W. (2015). Recognition by women's health care providers of long-term cardiovascular disease risk after preeclampsia. *Obstet. Gynecol.* 125, 1287–1292. doi: 10.1097/AOG.0000000000000856

Woodward, M., Peters, S. A., and Huxley, R. R. (2015). Diabetes and the female disadvantage. *Women's Health* 11, 833–839. doi: 10.2217/wh e.15.67

Yaffe, K., Blackwell, T., Kanaya, A., Davidowitz, N., Barrett-Connor, E., and Krueger, K. (2004). Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology*. 63, 658–663. doi: 10.1212/01.WNL.0000134666.64593.BA

Yamashiro, K., Tanaka, R., Tanaka, Y., Miyamoto, N., Shimada, Y., Ueno, Y., et al. (2014). Visceral fat accumulation is associated with cerebral small vessel disease. *Eur. J. Neurol*. 21, 667–673. doi: 10.1111/ene.12374

Conflict of Interest: HR-M performs contract research for Combinostics. All funding is paid to her institution.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 22 July 2022
DOI 10.3389/fnagi.2022.914360

OPEN ACCESS

EDITED BY
Ivana Hollan,
Norwegian University of Science and Technology, Norway

REVIEWED BY
Neil Bodagh,
Kingston Hospital, United Kingdom
Vida Demarin,
International Institute for Brain Health, Croatia
Andriy Yabluchanskiy,
The University of Oklahoma Health Sciences Center, United States

*CORRESPONDENCE
Shawn N. Whitehead
shawn.whitehead@schulich.uwo.ca

SPECIALTY SECTION
This article was submitted to Cellular and Molecular Mechanisms of Brain-aging, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 06 April 2022
ACCEPTED 06 July 2022
PUBLISHED 22 July 2022

CITATION
Myers SJ, Jiménez-Ruiz A, Sposato LA and Whitehead SN (2022) Atrial cardiopathy and cognitive impairment. *Front. Aging Neurosci.* 14:914360. doi: 10.3389/fnagi.2022.914360

Atrial cardiopathy and cognitive impairment

Sarah J. Myers[1], Amado Jiménez-Ruiz[2], Luciano A. Sposato[2] and Shawn N. Whitehead[1]*

[1]Department of Anatomy and Cell Biology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [2]Department of Clinical Neurological Sciences, University Hospital, Western University, London, ON, Canada

Cognitive impairment involves complex interactions between multiple pathways and mechanisms, one of which being cardiac disorders. Atrial cardiopathy (AC) is a structural and functional disorder of the left atrium that may be a substrate for other cardiac disorders such as atrial fibrillation (AF) and heart failure (HF). The association between AF and HF and cognitive decline is clear; however, the relationship between AC and cognition requires further investigation. Studies have shown that several markers of AC, such as increased brain natriuretic peptide and left atrial enlargement, are associated with an increased risk for cognitive impairment. The pathophysiology of cognitive decline in patients with AC is not yet well understood. Advancing our understanding of the relationship between AC and cognition may point to important treatable targets and inform future therapeutic advancements. This review presents our current understanding of the diagnosis of AC, as well as clinical characteristics and potential pathways involved in the association between AC and cognitive impairment.

KEYWORDS

heart failure, cognitive impairment, atrial cardiopathy, dementia, atrial fibrillation

Introduction

Atrial cardiopathy (AC) is a recently described structural and functional disorder of the left atrium (LA). The lack of a standardized definition for this condition reflects the heterogeneous nature in the spectrum of disorders affecting the LA, resulting in an increased risk of thromboembolic events. Potential biomarkers of AC include imaging, electrophysiological, and serum abnormalities. AC may also be a substrate for multiple primary cardiac disorders, including atrial fibrillation (AF) and heart failure (HF), and has been linked to increased risk for stroke and higher stroke mortality (Ahmad et al., 2020; Edwards et al., 2020). While the link between AF and HF and cognition is clear, data on AC and cognition are scarce (Aldrugh et al., 2017; Rosler and Schnabel, 2020). This review summarizes the relevant anatomical and functional pathways involved in AC and the epidemiology, diagnosis, clinical characteristics, prognosis, and potential treatments for AC and cognitive impairment. An overview of the proposed relationship between AC and cognitive impairment is shown (**Figure 1**).

Diagnostic criteria

A range of diagnostic criteria for AC has been proposed, including the use of echocardiography, electrocardiography, cardiac magnetic resonance imaging (MRI), and blood serum markers (Yaghi et al., 2017). An overview of these diagnostic criteria is provided (**Table 1**).

Echocardiography can be used to evaluate LA diameter or volume, with LA enlargement being considered a marker of AC (Goldberger et al., 2015). The most reliable measure is the LA volume index, although it is more rarely reported (Healey et al., 2019; Kamel et al., 2019). LA enlargement is also associated with a higher rate of cardiovascular events and cardiovascular death (Menichelli et al., 2020). Other echocardiography markers of AC include spontaneous echocardiographic contrast and reduced LA appendage flow velocity (Yaghi et al., 2017). Both of which are also associated with an increased risk of thrombus formation (Leung et al., 1994; Lee et al., 2014).

Multiple electrocardiogram measures may be used as markers of AC, such as PR interval and P-wave terminal force in V1 (Cheng et al., 2009; Yaghi et al., 2017). A prolonged PR interval indicates first-degree atrioventricular block, a risk factor for AF (Cheng et al., 2009). P-wave terminal force measures electrical conduction and atrial dysfunction can cause this to elevate (Yaghi et al., 2017). Further, disorders detected using electrocardiogram, such as paroxysmal supraventricular tachycardia and Bayes syndrome, may also indicate AC (Yaghi et al., 2017).

LA fibrosis, which can be detected through cardiac MRI as delayed uptake of gadolinium, is also used as a marker of AC (Siebermair et al., 2017). LA fibrosis is characterized by collagen deposits and disorganized myocytes, resulting in LA dysfunction and arrhythmias such as AF (Nattel, 2017).

Lastly, brain natriuretic peptide (BNP) and cardiac troponin are blood serum biomarkers of cardiac disease that can be used to detect AC (Yaghi et al., 2017). Chronic elevation of troponin and BNP have been associated with worse outcomes such as stroke or death (Hijazi et al., 2014).

Evidence linking atrial cardiopathy with dementia

Several markers of AC have been associated with dementia risk, including LA enlargement, increased BNP, and electrocardiographic markers, but the relationship is still unclear. AC and cognitive impairment share important risk factors such as age, hypertension, heart failure, diabetes, and obesity. Therefore, confounding variables may account for the increased risk of dementia in patients with AC, and further studies are required to investigate this association. The current evidence linking markers of AC and dementia is presented below.

Left atrial enlargement

LA size is a known risk factor for cardiovascular events, including AF, stroke, and HF, and may be present in both systolic and diastolic heart dysfunction (Khoo et al., 2011; Menichelli et al., 2020). It can be easily measured through non-invasive tests such as transthoracic echocardiography and is considered an important cardiovascular risk factor. Evidence supporting the direct role for LA enlargement as a cause of cognitive impairment is scarce. A prospective study involving older adults from outpatient cardiology clinics found that LA diameter was independently associated with decreased cognitive function, especially regarding language and memory domains, but no changes in whole brain volume (Alosco et al., 2013). A previous study reported a positive correlation between LA size and white matter hyperintensities, a surrogate marker of cognitive dysfunction in the elderly (Oh et al., 2012).

LA size and function have also been linked to cognitive impairment through diverse mechanisms in patients with HF and AF. LA enlargement directly correlates with left ventricular diastolic dysfunction and chronic LA pressure to volume overload, common findings in HF (Zile et al., 2011). In a study including community-based elderly individuals, LA enlargement and the presence of AF were significantly associated with decreased cognitive function in a cross-sectional analysis; however, with a longitudinal follow-up time of 5 years, only AF was associated with increased cognitive impairment (Zhang et al., 2019).

Increased brain natriuretic peptide

The relationship between BNP levels (a known marker of AC) and cognitive impairment/dementia has been well evaluated. Broadly, BNP levels have been associated with both cognitive function as well as future risk of dementia. It remains unknown if increased BNP is a marker of dementia risk or has a causative role. BNP may serve as an indicator of cognitive function in individuals with pre-existing cardiovascular disease. In a study including adults greater than 55 years of age with known heart disease, it was found that higher BNP levels are associated with worse cognitive function (Gunstad et al., 2006).

Apolipoprotein-E (APOE) polymorphisms, particularly APOE e4, are significant risk factors for neurological disorders, such as Alzheimer's disease. There is evidence that APOE e4 may also be a risk factor for cardiovascular disease. Further, APOE e4 carriers have significantly higher BNP levels than non-carriers in individuals with HF (Pasqualetti et al., 2017). In Alzheimer's disease patients, BNP levels are also higher in those that carry an APOE e4 allele (Begic et al., 2019). Contrarily, healthy individuals that carry at least one APOE e4 allele have

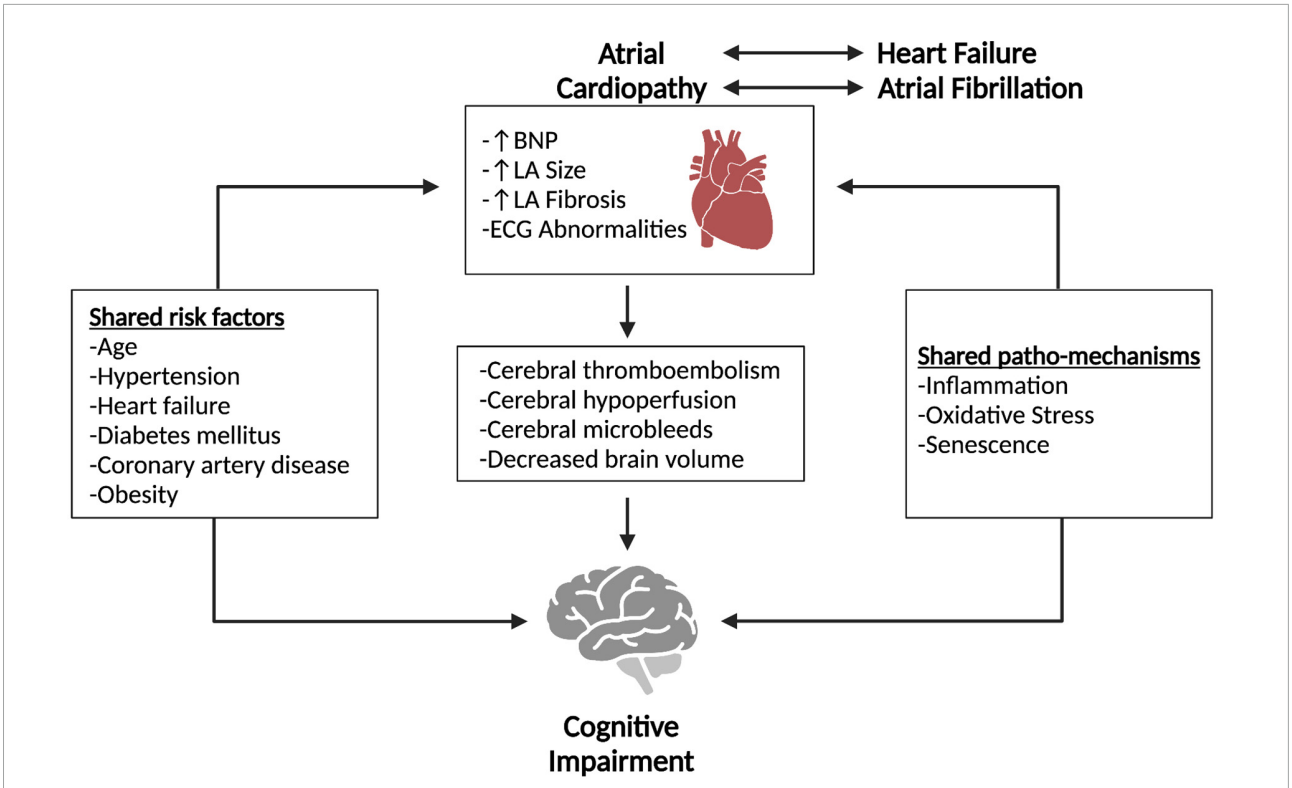


FIGURE 1
Overview of proposed relationship between atrial cardiopathy and cognitive impairment. Atrial cardiopathy, atrial fibrillation and heart failure all share multiple risk factors and patho-mechanisms with cognitive impairment. The effects of atrial cardiopathy potentially predispose individuals to cognitive impairment. Pathways that lead from atrial cardiopathy to cognitive impairment may include cerebral thromboembolism, hypoperfusion, microbleeds, and brain volume loss. Created with Biorender.com.

TABLE 1 Proposed diagnostic criteria for AC.

Diagnostic method	Metrics	AC criteria
Echocardiography	LA volume or volume index; LA diameter or diameter index; LA area or area index	↑ LA size ↓ LA flow velocity
Electrocardiography	PR Interval P-wave terminal force in V1	↑ PR interval ↑ P-wave terminal force in V1
Cardiac MRI	Uptake of gadolinium	↑ LA fibrosis (decreased uptake of gadolinium)
Blood serum biomarkers	BNP Levels Cardiac troponin levels	↑ BNP ↑ Cardiac troponin

significantly lower BNP levels than non-carriers (Begic et al., 2019). This suggests that comorbidities may alter the interplay between APOE e4 status and BNP levels.

The implications for the relationship between BNP levels and cognitive status are not limited to individuals with pre-existing cardiovascular comorbidities. In a population-based study of participants without dementia or cardiovascular disease, higher BNP levels were associated with subclinical brain damage, such as smaller total brain volume (Zonneveld et al., 2017). Also in the general population, within a normal BNP range, higher levels of BNP have been associated with mild cognitive impairment (Kara et al., 2017).

Age is also an important factor when considering the relationship between BNP and cognitive function. In general, BNP levels increase with age, even in individuals without any cardiovascular disease (Redfield et al., 2002). BNP levels have been associated with structural brain changes in both younger and older (>60 years of age) individuals, but the structural changes are accompanied by cognitive deficits only in the older population (Veugen et al., 2018).

Beyond the association between BNP and current cognitive status, it is also a risk factor for future cognitive decline. Multiple longitudinal studies, with follow-up times from 10 to 14 years, found that BNP is an independent risk factor for dementia/cognitive decline (Tynkkynen et al., 2015; Mirza et al., 2016; Nagata et al., 2019; McGrath et al., 2020). Further, when looking specifically at an elderly population greater than 75 years of age, with a 5-year follow-up, BNP was again a predictor of worsening cognitive function (Kerola et al., 2010).

BNP is an established marker of AC; however, it is also a marker of HF and AF, both of which are known risk factors for dementia (Santangeli et al., 2012; Chen et al., 2018; Bailey et al., 2021). Importantly, cognitive function may be further impaired in individuals diagnosed with both HF and AF (Myserlis et al., 2017). The commonality of BNP as a marker of AC, HF and AF, raises the question of whether AC is just a bystander, or is it the shared pathophysiological link between AF, HF, and dementia. There is strong evidence for the association between BNP and cognitive impairment, but further studies are required to tease apart the role of AC in this relationship and to better understand the pathophysiologic mechanisms.

Electrocardiographic abnormalities

In the last decade, several studies have found abnormal P-wave indices (PWIs) to be independent risk factors for cardioembolic ischemic stroke (Kamel et al., 2015; Maheshwari et al., 2017; Chen and Soliman, 2019). PWIs include several electrocardiographic measures such as P-wave axis, P-wave duration, advanced interatrial block, P-wave area, P-wave dispersion, and P-wave terminal force in V1. Most PWIs require automated software, except for the P-wave axis which is the most reported PWI. Electrocardiographic changes are common in the elderly population, probably reflecting functional and structural changes of the aging heart (Chiao and Rabinovitch, 2015). In a study of 80 centenarians (mean age 101.4 $\pm$ 1.5 years), less than 30% had a normal P wave, and almost half of them had an interatrial block (Martinez-Selles et al., 2016).

Although less studied, there may be a relationship between PWIs and cognitive impairment. Data from the community-based cohort Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study with 25-year follow-up and 13,714 participants showed that abnormal PWIs are associated with increased risk of cognitive impairment, independently of the presence of AF and ischemic stroke (Gutierrez et al., 2019). The underlying mechanisms between PWIs and cognitive dysfunction are unknown but may involve subclinical cerebral infarcts and decreased brain perfusion resulting in chronic subcortical ischemia.

Interatrial block on electrocardiogram may also be a valuable marker for different clinical outcomes, including stroke and dementia. Its presence may predict AF, stroke, cognitive impairment, and underlying AC based on atrial remodeling (Bayes de Luna et al., 2017).

The prospective BAYES registry included elderly patients with structural heart disease and absence of AF who were followed for a median of 22 months. Results suggest interatrial block (including both partial and advanced interatrial block) may be a risk factor for cognitive impairment (Martinez-Selles et al., 2020). This finding was also true for patients with mild cognitive impairment (Herrera et al., 2020).

Pathophysiology of atrial cardiopathy-related cognitive impairment

Observational studies suggest that AC itself (in the absence of HF or AF) is a risk factor for stroke and cognitive impairment (Kamel et al., 2016; Freedman et al., 2020). However, as mentioned in previous sections, the pathophysiology of cognitive dysfunction in patients with AC is unknown and research in this field is highly needed. The most likely mechanism is increased LA thrombogenicity leading to cerebral micro and macroembolism, similar to what has been described in AF (Moretti and Caruso, 2020; Moroni et al., 2020). Additionally, the pathophysiological association between AC and cognitive impairment can be explained by the coexistence of AF and HF. The role of these comorbidities as causes of dementia and cognitive impairment in patients with AC are discussed below.

Atrial fibrillation

Aging leads to changes in cardiac tissue structure and function (including the LA and LA appendage) and is a leading risk factor for cardiovascular disease (Chiao and Rabinovitch, 2015). Although the exact molecular mechanisms and the clinical consequences of atrial aging are unknown, epicardial fat seems to be an essential source of cytokines stimulating myocardial remodeling through connective tissue proliferation (Pandit et al., 2016). Atrial fibrotic remodeling is a distinctive feature of AC, promoting electrical and autonomic remodeling, thus facilitating the development of both AF and cardioembolism (Jalini et al., 2019; Shen et al., 2019). Chronic inflammatory markers, including CRP, TNF-a, IL-2, IL-6, and IL-8, are increased in patients with AF and may provide an inflammatory background similar to what is seen in other age-related conditions, providing a common mechanistic pathway between AC, stroke, and cognitive impairment (Aviles et al., 2003; Guo et al., 2012; Diener et al., 2019; Forloni, 2020).

AF is a known risk factor for stroke, increasing the risk by a factor of 4–5 (Wolf et al., 1991). While there is a clear relationship between AF and cognitive decline, the literature is inconclusive on whether risk of cognitive impairment is independent of stroke risk in individuals with AF. A meta-analysis reported that AF is associated with cognitive decline in patients with and without stroke (Kalantarian et al., 2013). However, other studies have reported that the AF-related risk of dementia can be explained by brain infarcts, with the majority of infarcts being silent (Sposato et al., 2017; Kühne et al., 2022). AF and dementia share multiple risk factors, and while many studies adjust for these risk factors at baseline, they have short

follow-up times and are not always reassessed (Rivard et al., 2022). Further, subclinical AF could be a confounding cause of dementia in patients with AC. Additional investigations, with longer follow-up times and larger cohorts, are still required to determine if there is a causal link between AF and dementia.

Our understanding of the shared patho-mechanisms between AC and cognitive impairment is still developing, but they are likely similar to those that have been implicated in AF. Mechanisms involved in AF, such as inflammation, oxidative stress, and senescence have been extensively reviewed elsewhere (Guo et al., 2021; Sagris et al., 2021; Ihara and Sasano, 2022).

Heart failure

HF is associated with a 27% increased risk of dementia (Wolters et al., 2018). Low cardiac output in patients with HF can result in reduced cerebral blood flow leading to hypoperfusion of brain structures critical for cognitive function (Adelborg et al., 2017). Impaired vascular autoregulation resulting in white matter injury, neurohormonal dysregulation, systemic inflammation, and cerebral microvascular dysfunction may also contribute to generating a state of chronic cerebral hypoxia leading to brain microinfarcts and neurodegeneration (Adelborg et al., 2017). The latter may be enhanced by oxidative stress, dendritic spine loss, glial activation, and programmed cell death (Jinawong et al., 2021).

Local atrophy of structures involved in memory and other cognitive domains (such as the parahippocampal gyrus) are prominent in patients with HF without clinical dementia (Meguro et al., 2017). This may constitute a treatable and potentially preventable risk factor for cognitive impairment. In a community-based sample of older adults, different left venticle function markers (including echocardiographic parameters and BNP levels) were also associated with structural and functional changes in the brain and not entirely explained by associated risk factors.

Evidence from the ARIC-PET (Atherosclerosis Risk in Communities-positron emission tomography) Study revealed a significant association between florbetapir (a high-affinity beta-amyloid radiotracer) uptake and left ventricular structure and using positron emission tomography (Johansen et al., 2019). Whether these structural and functional changes in heart tissue precede or occur concurrently with amyloid deposition remains unknown.

Atrial dysfunction manifested as HF with preserved ejection fraction may also be linked to cognitive dysfunction. Subclinical ischemic stroke was common in patients with HF with preserved ejection fraction and no prior AF diagnosis and is associated with measurable cognitive deficits in the ARIC cohort (Cogswell et al., 2017). One possible explanation may be undiagnosed paroxysmal AF or AC. AC has also been linked to increased brain amyloid deposition using positron emission tomography, without a similar association in individuals with AF (Johansen et al., 2020).

Conclusion

Cognitive impairment is a multifactorial disease state with complex interactions between various mechanistic pathways, including neurodegenerative and vascular injury. However, clinical and subclinical cardiac disease may be an important piece of this puzzle and a treatable target for therapeutic intervention. AC may be a substrate for multiple cardiac disorders, such as AF and HF. The association between cognition and both AF and HF is well evaluated but the literature examining AC and cognition is scarce. As our knowledge of AC advances, we will develop a better understanding of AC as a predictor or indicator of cognitive decline. The relationship between AC and dementia may help inform future diagnostic and therapeutic advancements and warrants further investigation. Since there are no proven disease-modifying therapies for dementia, large-scale, multicenter collaborative efforts to evaluate preventive strategies including oral anticoagulants, risk factors modifications, and anti-inflammatory agents are needed.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding

SM was a CGS-M and OGS scholar. SW received funding from CIHR, CCNA, and CFREF-BrainsCAN.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Adelborg, K., Horváth-Puhó, E., Ording, A., Pedersen, L., Sørensen, H. T., and Henderson, V. W. (2017). Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *Eur. J. Heart Fail.* 19, 253–260.

Ahmad, M., Singleton, M., Bhave, P., Kamel, H., and Soliman, E. (2020). Atrial cardiopathy and stroke mortality in the general population. *Int. J. Stroke* 15, 650–656.

Aldrugh, S., Sardana, M., Henninger, N., Saczynski, J. S., and Mcmanus, D. D. (2017). Atrial fibrillation, cognition and dementia: a review. *J. Cardiovasc. Electrophysiol.* 28, 958–965.

Alosco, M. L., Gunstad, J., Jerskey, B. A., Clark, U. S., Hassenstab, J. J., Xu, X., et al. (2013). Left atrial size is independently associated with cognitive function. *Int. J. Neurosci.* 123, 544–552.

Aviles, R. J., Martin, D. O., Apperson-Hansen, C., Houghtaling, P. L., Rautaharju, P., Kronmal, R. A., et al. (2003). Inflammation as a risk factor for atrial fibrillation. *Circulation* 108, 3006–3010.

Bailey, M., Soliman, E., Mcclure, L., Howard, G., Howard, V., Judd, S., et al. (2021). Relation of atrial fibrillation to cognitive decline (from the reasons for geographic and racial differences in stroke [regards] study). *Am. J. Cardiol.* 148, 60–68.

Bayes de Luna, A., Baranchuk, A., Alberto Escobar, Robledo, L., Masso Van, Roessel, A., et al. (2017). Diagnosis of interatrial block. *J. Geriatr. Cardiol.* 14, 161–165.

Begic, E., Hadzidedic, S., Kulaglic, A., Ramic-Brkic, B., Begic, Z., and Causevic, M. (2019). SOMAscan-based proteomic measurements of plasma brain natriuretic peptide are decreased in mild cognitive impairment and in Alzheimer's dementia patients. *PLoS One* 14:e0212261. doi: 10.1371/journal.pone.0212261

Chen, L. Y., and Soliman, E. Z. (2019). P wave indices-advancing our understanding of atrial fibrillation-related cardiovascular outcomes. *Front. Cardiovasc. Med.* 6:53. doi: 10.3389/fcvm.2019.00053

Chen, L., Norby, F., Gottesman, R., Mosley, T., Soliman, E., Agarwal, S., et al. (2018). Association of atrial fibrillation with cognitive decline and dementia over 20 years: the aric-cs (atherosclerosis risk in communities neurocognitive study). *J. Am. Heart Assoc.* 7:e007301. doi: 10.1161/JAHA.117.007301

Cheng, S., Keyes, M. J., Larson, M. G., Mccabe, E. L., Newton-Cheh, C., Levy, D., et al. (2009). Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 301, 2571–2577.

Chiao, Y. A., and Rabinovitch, P. S. (2015). The aging heart. *Cold Spring Harb. Perspect. Med.* 5:a025148.

Cogswell, R. J., Norby, F. L., Gottesman, R. F., Chen, L. Y., Solomon, S., Shah, A., et al. (2017). High prevalence of subclinical cerebral infarction in patients with heart failure with preserved ejection fraction. *Eur. J. Heart Fail.* 19, 1303–1309. doi: 10.1002/ejhf.812

Diener, H. C., Hart, R. G., Koudstaal, P. J., Lane, D. A., and Lip, G. Y. H. (2019). Atrial fibrillation and cognitive function: JACC review topic of the week. *J. Am. Coll. Cardiol.* 73, 612–619. doi: 10.1016/j.jacc.2018.10.077

Edwards, J., Healey, J., Fang, J., Yip, K., and Gladstone, D. (2020). Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. *J. Am. Heart Assoc.* 9:e013227. doi: 10.1161/JAHA.119.013227

Forloni, G. (2020). Alzheimer's disease: from basic science to precision medicine approach. *BMJ Neurol. Open* 2:e000079.

Freedman, B., Kamel, H., Van Gelder, I. C., and Schnabel, R. B. (2020). Atrial fibrillation: villain or bystander in vascular brain injury. *Eur. Heart J. Suppl.* 22, M51–M59.

Goldberger, J. J., Arora, R., Green, D., Greenland, P., Lee, D. C., Lloyd-Jones, D. M., et al. (2015). Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. *Circulation* 132, 278–291.

Gunstad, J., Poppas, A., Smeal, S., Paul, R., Tate, D., Jefferson, A., et al. (2006). Relation of brain natriuretic peptide levels to cognitive dysfunction in adults >55 years of age with cardiovascular disease. *Am. J. Cardiol.* 98, 538–540.

Guo, G., Watterson, S., Zhang, S. D., Bjourson, A., Mcgilligan, V., Peace, A., et al. (2021). The role of senescence in the pathogenesis of atrial fibrillation: a target process for health improvement and drug development. *Ageing Res. Rev.* 69:101363. doi: 10.1016/j.arr.2021.101363

Guo, Y., Lip, G. Y., and Apostolakis, S. (2012). Inflammation in atrial fibrillation. *J. Am. Coll. Cardiol.* 60, 2263–2270.

Gutierrez, A., Norby, F. L., Maheshwari, A., Rooney, M. R., Gottesman, R. F., Mosley, T. H., et al. (2019). Association of abnormal P-wave indices with dementia and cognitive decline over 25 years: ARIC-NCS (the atherosclerosis risk in communities neurocognitive study). *J. Am. Heart Assoc.* 8:e014553. doi: 10.1161/JAHA.119.014553

Healey, J. S., Gladstone, D. J., Swaminathan, B., Eckstein, J., Mundl, H., Epstein, A. E., et al. (2019). Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the navigate esus randomized clinical trial. *JAMA Neurol.* 76, 764–773. doi: 10.1001/jamaneurol.2019.0617

Herrera, C., Bruna, V., Abizanda, P., Diez-Villanueva, P., Formiga, F., Torres, R., et al. (2020). Relation of interatrial block to cognitive impairment in patients >/= 70 years of age (from the cambiad case-control study). *Am. J. Cardiol.* 136, 94–99. doi: 10.1016/j.amjcard.2020.09.008

Hijazi, Z., Oldgren, J., Andersson, U., Connolly, S. J., Ezekowitz, M. D., Hohnloser, S. H., et al. (2014). Importance of persistent elevation of cardiac biomarkers in atrial fibrillation: a RE-LY substudy. *Heart* 100, 1193–1200. doi: 10.1136/heartjnl-2013-304872

Ihara, K., and Sasano, T. (2022). Role of inflammation in the pathogenesis of atrial fibrillation. *Front. Physiol.* 13:862164. doi: 10.3389/fphys.2022.862164

Jalini, S., Rajalingam, R., Nisenbaum, R., Javier, A. D., Woo, A., and Pikula, A. (2019). Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology* 92, e288–e294.

Jinawong, K., Apaijai, N., Chattipakorn, N., and Chattipakorn, S. C. (2021). Cognitive impairment in myocardial infarction and heart failure. *Acta Physiol. (Oxf)* 232:e13642.

Johansen, M. C., Mosley, T. H., Knopman, D. S., Wong, D. F., Ndumele, C., Shah, A. M., et al. (2020). Associations between atrial cardiopathy and cerebral amyloid: the ARIC-PET study. *J. Am. Heart Assoc.* 9:e018399.

Johansen, M. C., Mosley, T. H., Knopman, D. S., Wong, D. F., Wagenknecht, L. E., Shah, A. M., et al. (2019). Associations between left ventricular structure. Function, and cerebral amyloid: the ARIC-PET study. *Stroke* 50, 3622–3624.

Kalantarian, S., Stern, T. A., Mansour, M., and Ruskin, J. N. (2013). Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann. Intern. Med.* 158, 338–346.

Kamel, H., Longstreth, W. T., Tirschwell, D. L., Kronmal, R. A., Broderick, J. P., Palesch, Y. Y., et al. (2019). The AtRial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: rationale and methods. *Int. J. Stroke* 14, 207–214. doi: 10.1177/1747493018799981

Kamel, H., Okin, P. M., Elkind, M. S., and Iadecola, C. (2016). Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 47, 895–900.

Kamel, H., O'neal, W. T., Okin, P. M., Loehr, L. R., Alonso, A., and Soliman, E. Z. (2015). Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann. Neurol.* 78, 670–678. doi: 10.1002/ana.24482

Kara, K., Mahabadi, A., Weimar, C., Winkler, A., Neumann, T., Kalsch, H., et al. (2017). N-terminal Pro-B type natriuretic peptide is associated with mild cognitive impairment in the general population. *J. Alzheimers Dis.* 55, 359–369.

Kerola, T., Nieminen, T., Hartikainen, S., Sulkava, R., Vuolteenaho, O., and Kettunen, R. (2010). B-type natriuretic peptide as a predictor of declining cognitive function and dementia-a cohort study of an elderly general population with a 5-year follow-up. *Ann. Med.* 42, 207–215. doi: 10.3109/07853891003652542

Khoo, C. W., Krishnamoorthy, S., Lim, H. S., and Lip, G. Y. (2011). Assessment of left atrial volume: a focus on echocardiographic methods and clinical implications. *Clin. Res. Cardiol.* 100, 97–105. doi: 10.1007/s00392-010-0222-y

Kühne, M., Krisai, P., Coslovsky, M., Rodondi, N., Müller, A., Beer, J. H., et al. (2022). Silent brain infarcts impact on cognitive function in atrial fibrillation. *Eur. Heart J.* 43, 2127–2135.

Lee, J. M., Shim, J., Uhm, J. S., Kim, Y. J., Lee, H. J., Pak, H. N., et al. (2014). Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. *Am. J. Cardiol.* 113, 963–969. doi: 10.1016/j.amjcard.2013.11.058

Leung, D. Y., Black, I. W., Cranney, G. B., Hopkins, A. P., and Walsh, W. F. (1994). Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. *J. Am. Coll. Cardiol.* 24, 755–762. doi: 10.1016/0735-1097(94)90025-6

Maheshwari, A., Norby, F. L., Soliman, E. Z., Koene, R. J., Rooney, M. R., O'neal, W. T., et al. (2017). Abnormal P-wave axis and ischemic stroke: the ARIC

study (atherosclerosis risk in communities). *Stroke* 48, 2060–2065. doi: 10.1161/STROKEAHA.117.017226

Martinez-Selles, M., Martinez-Larru, M. E., Ibarrola, M., Santos, A., Diez-Villanueva, P., Bayes-Genis, A., et al. (2020). Interatrial block and cognitive impairment in the bayes prospective registry. *Int. J. Cardiol.* 321, 95–98. doi: 10.1016/j.ijcard.2020.08.006

Martinez-Selles, M., Masso-Van Roessel, A., Alvarez-Garcia, J., Garcia De La Villa, B., Cruz-Jentoft, A. J., Vidan, M. T., et al. (2016). Interatrial block and atrial arrhythmias in centenarians: prevalence, associations, and clinical implications. *Heart Rhythm* 13, 645–651. doi: 10.1016/j.hrthm.2015.10.034

McGrath, E., Himali, J., Levy, D., Conner, S., Decarli, C., Pase, M., et al. (2020). Growth differentiation factor 15 and Nt-probnp as blood-based markers of vascular brain injury and dementia. *J. Am. Heart Assoc.* 9:e014659. doi: 10.1161/JAHA.119.014659

Meguro, T., Meguro, Y., and Kunieda, T. (2017). Atrophy of the parahippocampal gyrus is prominent in heart failure patients without dementia. *ESC Heart Fail.* 4, 632–640. doi: 10.1002/ehf2.12192

Menichelli, D., Sciacqua, A., Cangemi, R., Andreozzi, P., Del Sole, F., Violi, F., et al. (2020). Atrial fibrillation pattern, left atrial diameter and risk of cardiovascular events and mortality. A prospective multicenter cohort study. *Int. J. Clin. Pract.* 75:e13771. doi: 10.1111/ijcp.13771

Mirza, S., De Bruijn, R., Koudstaal, P., Van Den Meiracker, A., Franco, O., Hofman, A., et al. (2016). The N-terminal pro B-type natriuretic peptide, and risk of dementia and cognitive decline: a 10-year follow-up study in the general population. *J. Neurol. Neurosurg. Psychiatry* 87, 356–362. doi: 10.1136/jnnp-2014-309968

Moretti, R., and Caruso, P. (2020). Small vessel disease-related dementia: an invalid neurovascular coupling? *Int. J. Mol. Sci.* 21:1095. doi: 10.3390/ijms21031095

Moroni, F., Ammirati, E., Hainsworth, A. H., and Camici, P. G. (2020). Association of white matter hyperintensities and cardiovascular disease: the importance of microcirculatory disease. *Circ. Cardiovasc. Imaging* 13:e010460. doi: 10.1161/CIRCIMAGING.120.010460

Myserlis, P., Malli, A., Kalaitzoglou, D., Kalaitzidis, G., Miligkos, M., Kokkinidis, D., et al. (2017). Atrial fibrillation and cognitive function in patients with heart failure: a systematic review and meta-analysis. *Heart Fail. Rev.* 22, 1–11.

Nagata, T., Ohara, T., Hata, J., Sakata, S., Furuta, Y., Yoshida, D., et al. (2019). NT-proBNP and risk of dementia in a general Japanese elderly population: the Hisayama study. *J. Am. Heart Assoc.* 8:e011652. doi: 10.1161/JAHA.118.011652

Nattel, S. (2017). Molecular and cellular mechanisms of atrial fibrosis in atrial fibrillation. *JACC Clin. Electrophysiol.* 3, 425–435.

Oh, J. E., Shin, J. W., Sohn, E. H., Jung, J. O., Jeong, S. H., Song, H. J., et al. (2012). Effect of cardiac function on cognition and brain structural changes in dementia. *J. Clin. Neurol.* 8, 123–129.

Pandit, S. V., Anumonwo, J., and Jalife, J. (2016). Atrial fibrillation susceptibility in obesity: an excess adiposity and fibrosis complicity? *Circ. Res.* 118, 1468–1471. doi: 10.1161/CIRCRESAHA.116.308686

Pasqualetti, G., Seghieri, M., Santini, E., Rossi, C., Vitolo, E., Giannini, L., et al. (2017). P2X(7) receptor and apoe polymorphisms and survival from heart failure: a prospective study in frail patients in a geriatric unit. *Aging Dis.* 8, 434–441. doi: 10.14336/AD.2016.1202

Redfield, M., Rodeheffer, R., Mahoney, D., Jacobsen, S., and Burnett, J. (2002). Plasma BNP to screen for systolic dysfunction in the community: importance of using age- and sex-specific partition values. *J. Am. Coll. Cardiol.* 39, 200A–201A.

Rivard, L., Friberg, L., Conen, D., Healey, J. S., Berge, T., Boriani, G., et al. (2022). Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. *Circulation* 145, 392–409.

Rosler, A., and Schnabel, R. (2020). [Atrial fibrillation and impairment of cognition-importance for geriatrics]. *Z. Gerontol. Geriatr.* 54, 704–707. doi: 10.1007/s00391-020-01754-x

Sagris, M., Vardas, E. P., Theofilis, P., Antonopoulos, A. S., Oikonomou, E., and Tousoulis, D. (2021). Atrial fibrillation: pathogenesis, predisposing factors, and genetics. *Int. J. Mol. Sci.* 23:6.

Santangeli, P., Di Biase, L., Bai, R., Mohanty, S., Pump, A., Brantes, M., et al. (2012). Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 9, 1761–1768.

Shen, M. J., Arora, R., and Jalife, J. (2019). Atrial myopathy. *JACC Basic Transl. Sci.* 4, 640–654.

Siebermair, J., Kholmovski, E. G., and Marrouche, N. (2017). Assessment of left atrial fibrosis by late gadolinium enhancement magnetic resonance imaging: methodology and clinical implications. *JACC Clin. Electrophysiol.* 3, 791–802.

Sposato, L. A., Ruíz Vargas, E., Riccio, P. M., Toledo, J. B., Trojanowski, J. Q., Kukull, W. A., et al. (2017). Milder Alzheimer's disease pathology in heart failure and atrial fibrillation. *Alzheimers Dement.* 13, 770–777. doi: 10.1016/j.jalz.2016.12.002

Tynkkynen, J., Laatikainen, T., Salomaa, V., Havulinna, A., Blankenberg, S., Zeller, T., et al. (2015). NT-proBNP and the risk of dementia: a prospective cohort study with 14 years of follow-up. *J. Alzheimers Dis.* 44, 1007–1013.

Veugen, M., Henry, R., Brunner-La Rocca, H., Dagnelie, P., Schram, M., Van Agtmaal, M., et al. (2018). Cross-sectional associations between cardiac biomarkers. Cognitive performance, and structural brain changes are modified by age: the Maastricht study. *Arterioscler. Thromb. Vasc. Biol.* 38, 1948–1958. doi: 10.1161/ATVBAHA.118.311082

Wolf, P. A., Abbott, R. D., and Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 22, 983–988.

Wolters, F. J., Segufa, R. A., Darweesh, S. K. L., Bos, D., Ikram, M. A., Sabayan, B., et al. (2018). Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement.* 14, 1493–1504.

Yaghi, S., Kamel, H., and Elkind, M. S. V. (2017). Atrial cardiopathy: a mechanism of cryptogenic stroke. *Expert Rev. Cardiovasc. Ther.* 15, 591–599.

Zhang, M. J., Norby, F. L., Lutsey, P. L., Mosley, T. H., Cogswell, R. J., Konety, S. H., et al. (2019). Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: the ARIC-NCS. *J. Am. Heart Assoc.* 8:e013197. doi: 10.1161/JAHA.119.013197

Zile, M. R., Gottdiener, J. S., Hetzel, S. J., Mcmurray, J. J., Komajda, M., Mckelvie, R., et al. (2011). Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation* 124, 2491–2501.

Zonneveld, H., Ikram, M., Hofman, A., Niessen, W., Van Der Lugt, A., Krestin, G., et al. (2017). N-terminal Pro-B-type natriuretic peptide and subclinical brain damage in the general population. *Radiology* 283, 205–214.

frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 24 August 2022
DOI 10.3389/fnagi.2022.821866

OPEN ACCESS

EDITED BY
Kristy A. Nielson,
Marquette University, United States

REVIEWED BY
Aurel Popa-Wagner,
University of Medicine and Pharmacy of Craiova, Romania

*CORRESPONDENCE
Antoine Hakim
ahakim@toh.ca

SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 24 November 2021
ACCEPTED 05 August 2022
PUBLISHED 24 August 2022

CITATION
Hakim A (2022) Perspectives on the complex links between depression and dementia.
Front. Aging Neurosci. 14:821866.
doi: 10.3389/fnagi.2022.821866

Perspectives on the complex links between depression and dementia

Antoine Hakim[1,2]*

[1]Brain and Mind Research Institute, University of Ottawa, Ottawa, ON, Canada, [2]Division of Neurology, University of Ottawa, Ottawa, ON, Canada

This review highlights that depression is a growing health problem for the individual, and because of its high frequency in most societies, a growing burden on health care budgets. The focus of the review is the physiological links between depression and dementia, specifically Alzheimer's disease. It suggests that depression is a significant risk factor for cognitive decline and explores the pathways that may lead depressed individuals to suffer this outcome. This review shows that depression and a number of its precursors activate pro-inflammatory mediators. These lead to cerebral small vessel disease with the consequent reduction in cerebral blood flow, which is known to precede cognitive decline. Thus, the impact of depression on the physiological events that lead to dementia is identical to the impact of other dementia risk factors recently reviewed. Depression is distinct, however, in being a relatively treatable condition, but the impact of treating depression on later cognitive decline is not always positive, leading to the hypothesis that only the antidepressants that attenuate inflammation alleviate subsequent cognitive decline.

KEYWORDS

depression, dementia, inflammation, cerebral small vessel disease, treatment, risk factors

Introduction

Caring for dementia patients is consuming growing portions of the health care budgets of many countries. The recognition that certain risk factors increase the risk for dementia provides the possibility of reducing this burden by intensifying efforts to reduce and control the risk factors. In a recent article (Hakim, 2021), a hypothesis was presented that a sequence of physiological events links dementia risk factors to their cognitive outcomes. It was proposed that in the presence of a risk factor, the sequence that leads to dementia is triggered by inflammation which leads to cerebral small vessel disease. This results in a reduction of cerebral perfusion, which precedes the appearance of any clinical evidence for cognitive impairment. Data were presented to highlight this sequence in three recognized dementia risk factors: obesity, sedentary lifestyle, and insufficient sleep. Depression is recognized as a risk factor for dementia, and the current

literature review explores the pathway from depression to dementia and suggests that it follows the same sequence of physiological events that link other risk factors to dementia. A significant difference between depression and the other risk factors is the possibility that some antidepressant medications may alleviate this risk to cognitive decline. This benefit, however, may be limited to the antidepressants that reduce inflammation.

Dementia and depression are growing problems

All published estimates agree that the number of people affected by dementia will substantially increase over time, mainly due to projected trends in population aging and growth. The GBD2019 Dementia Forecasting Collaborators estimate the number of people with dementia globally will increase from 57.4 million in 2019 to 152.8 million in 2050 (GBD 2019 Dementia Forecasting Collaborators, 2022). Wittenberg et al. (2020) in 2020 projected that the number of older people with dementia will more than double in the next 25 years.

When dementia is estimated by age group, a clear correlation is evident between aging and prevalence of the condition. Gautrin et al. (1990) calculated dementia prevalence to be 1% for ages 65–74, 4% for ages 75–84, and 10.5% for 85 and over. In contrast, depression is not more prevalent with age even though its prevalence is also rising in many jurisdictions. A community-based study of American adults found that the 1-year frequency of major depressive disorder (MDD) rose from 3.33 to 7.06% between 1991–92 and 2001–02 (Compton, 2006). An analysis of the Minnesota Multiphasic Personality Inventory (MMPI), which consists of data on 63,706 American college students and 13,870 high school students revealed that younger adults were 6–8 times more likely than older adults to meet the criteria for clinical depression in 2007 compared to peers in 1938 (Twenge et al., 2010). In a Swedish population studied approximately every 10 years, it was shown that the risk for depression in young adults had increased 10-fold from 1957 to 1972 compared to the period from 1947 to 1957 (Hagnell, 1989; Hagnell et al., 1993). A data brief from the US department of Health and Human Services reported in September 2020 that the percentage of adults who experienced any symptoms of depression was highest among those aged 18–29 (21.0%), followed by those aged 45–64 and those older than 65 (18.4%), and lastly by those aged 30–44 (16.8%). For all degrees of depression severity, women were more likely to be affected than men (Villarroel and Terlizzi, 2020). There is thus a concordance of studies showing that the incidence of depression is rising and that the younger adult age groups are more likely to develop depression, with onset at increasingly earlier ages (Hidaka, 2012). We may therefore be in the middle of an epidemic of depression, and its impact on cognitive functions is worthy of further analysis.

Depression increases the risk for dementia

Cognitive decline in later life has been associated with many factors; a review of these factors revealed a link between depression and the onset of dementia (Steffens et al., 2004). In a 14-year longitudinal study which followed 4,922 healthy men aged 71–89 years, 18.3% developed dementia. Interestingly, the men who were older and had a history of depression were at greater risk of developing dementia (Almeida et al., 2017). The authors concluded that the link between depression and cognitive decline was evident during the initial 5 years of follow-up. Zeki Al Hazzouri et al. (2018) reported in the Northern Manhattan Study (2018) that greater depressive symptoms, adjusted for other variables, were significantly associated with worse baseline episodic memory in populations. Greater depressive symptoms were significantly related to poorer baseline episodic memory function (β [95% confidence interval] = −0.21 [−0.33 to −0.10],p = 0.0003) even when the models had been adjusted for socio-demographics, vascular risk factors, and medications for behavioral and mental health issues (Zeki Al Hazzouri et al., 2018). Gatchel et al. (2019), in a longitudinal study of 276 cognitively unimpaired older adults, showed that worsening depressive symptoms were significantly associated with declining cognition. Finally, researchers have concluded that half of the patients with major depressive disorders showed cognitive and memory impairments (Köhler et al., 2010). Norton et al. (2014) predicted that depression accounted for 5–11% of all Alzheimer's disease cases. There is therefore concordant evidence in the literature that depression is a significant risk factor for cognitive decline.

The risk factors for depression

It is now widely appreciated that depression can have a number of precursors and social determinants (Slavich and Irwin, 2014). Exposure to early life stressors such as social stressors, social isolation, and the inability to form attachments are all possible risk factors for depression (Panksepp, 2003; Watt and Panksepp, 2009). Early maltreatment has been associated with late-life depression and suicide risk (Comijs et al., 2013). Watt and Panksepp (2009) conceptualize depression as arising from an evolutionarily preserved "shutdown mechanism" resulting from protracted separation distress in early life. These types of stressors have been linked to inflammation and changes in immune function which may lead to both depression and dementia.

In 2003, Eisenberger et al. (2003), demonstrated that with increasing social distress greater activity could be observed in the anterior cingulate cortex, an area implicated in generating the aversive experience of physical pain. A study done

by Slavich and Irwin (2014), examined young adults who were exposed to social stressors while monitoring markers of inflammatory activity and brain activity using fMRI. Social stress exposure resulted in significant increases in a soluble receptor for tumor necrosis factor alpha and interleukin-6. The TNF-alpha receptor increases were associated with greater activity in the dorsal anterior cingulate cortex and anterior insula. These regions have been previously associated with processing rejection-related distress. A second study by Muscatell et al. (2015) showed that higher levels of neuronal activity in the amygdala in response to stress was associated with greater increases in inflammation.

Overall, these studies suggest that proinflammatory cytokines are the crucial mediators between the risk factors and their depression consequences often evident as sad mood, chronic feeling of fatigue, social withdrawal, and anhedonia. Therefore, targeting inflammation may offer new opportunities for preventing and treating depression.

The pathogenesis of cognitive decline. Alzheimer's disease is the major contributor to dementia

Crous-Bou et al. (2017) state that Alzheimer's disease accounts for 60–80% of dementias, making it the most common precursor of cognitive decline. In that condition the hallmark pathological criteria have included elevated levels of amyloid-beta peptide and hyperphosphorylated tau which accumulates intracellularly and becomes microscopically evident as neurofibrillary tangles. Recent evidence, however, suggests that a decline in cerebral blood flow precedes these pathological hallmarks of Alzheimer's disease, potentially by many years. In an extensive study by Iturria-Medina et al. (2016), where multiple simultaneous measurements of regional cerebral perfusion and other biomarkers of Alzheimer's disease were made, a decline in cerebral perfusion preceded all other pathological hallmarks of Alzheimer's disease. Bangen et al. (2018) have subsequently confirmed that reduced regional cerebral blood flow relates to poorer cognition in adults with type 2 diabetes. More recently, Bracko et al. (2021) confirmed the crucial role that a reduction in cerebral blood flow plays in Alzheimer's disease.

The pathways from depression to dementia

Depression is associated with a reduction in cerebral blood flow

Multiple studies have shown that cerebral blood flow is reduced in the setting of depression. Popa-Wagner et al. (2015) eloquently described in 2015 how dysfunction of cerebral autoregulation in aging can impair CBF and increase susceptibility to hypoxia and ischemia. Using arterial spin labeling, Cooper et al. (2020) compared cerebral blood flow (CBF) between 164 individuals suffering from major depression and 94 healthy controls. They reported reduced CBF in the right parahippocampus, thalamus, fusiform, and middle temporal gyri along with bilateral insula regions in depressed patients compared to controls. This confirmed the results obtained by Meyer et al. (1973) who showed that in severe depression there is bilateral hemispheric reduction of CBF. Takano et al. (2006) reported that the regional CBF (rCBF) in depressed patients was decreased compared to normal controls in widespread areas including the frontal lobe and limbic regions such as the cingulate cortex and parahippocampal gyrus. Oda et al. (2003) showed in depressed patients that rCBF in the frontal lobe, temporal lobe, and anterior cingulate gyrus were reduced regardless of the presence of subcortical hyperintensities. Where there was MRI hyperintensity, however, patients displayed reduced rCBF in the thalamus, basal ganglia, and brainstem a long with the cortical areas. In addition, the white matter hyperintensity scale was negatively correlated with rCBF in subcortical brain regions, such as the thalamus and right basal ganglia (Oda et al., 2003).

Depression also modifies vascular risk factors (Hakim, 2011). The effect of emotions on heart and blood vessel function was investigated. It was found that sadness created a distinctive pattern, showing slight increases in blood pressure and vascular resistance, and a reduction in the pumping capacity of the heart (Sinha et al., 1992). Thus, the reduction in CBF seen in depressed individuals may partially be the result of the impact of sadness on vascular risk factors.

Cerebral small vessel disease is evident in depressed individuals

Depression is as immense a risk factor for small vessel disease as high blood pressure (Wang et al., 2014). People who are depressed have abnormalities in the same brain regions known to be at risk for the development of small covert white matter strokes (Aizenstein et al., 2011). Greater depressive symptoms, after adjusting for sociodemographic, behavioral, and vascular risk factor variables, are correlated with smaller cerebral parenchymal fraction (β [95% confidence interval] = −0.56 [−1.05 to −0.07], p = 0.02) and increased odds of subclinical brain infarcts (odds ratio [95% confidence interval] = 1.55 [1.00–2.42], p = 0.05) (Zeki Al Hazzouri et al., 2018). Although this publication concludes that increased symptoms of depression were not significantly linked to white matter hyper-intensity volume, numerous magnetic resonance imaging (MRI) investigations have demonstrated that late life depression is related to the increased prevalence of white matter

hyper-intensities on MRI (Krishnan et al., 2004; Taylor et al., 2005, 2013; Chen et al., 2006; Herrmann et al., 2008; Firbank et al., 2012).

The role of inflammation in depression

Possibly the most important mechanism associating depression with cognitive decline is how the immune system responds to persistent depression. This topic was extensively covered recently in the excellent article by Dafsari and Jessen (2020), where it was concluded that depressed patients exhibit chronic inflammation. Elevations in the interleukin system and tissue necrosis factor (TNFα) and C-reactive protein (CRP) have been reported in depressed patients, frequently associated with a simultaneous decrease in anti-inflammatory regulation (Dowlati et al., 2010; Felger and Lotrich, 2013). Miller and Raison (2016) concluded from meta-analyses that the most consistent biomarkers of inflammation in patients with depression were the peripheral blood interleukins, such as interleukin (IL)-1β, IL-6, TNFα, and CRP. Polymorphisms in inflammatory cytokine genes have been linked to depression and the individual's response to therapy. These polymorphisms are for genes such as IL-Iβ, TNFα, and CRP (Bufalino et al., 2013). Other genes that have been linked to depression come from meta-analyses of genome-wide association studies and are associated with the immune system's response to pathogens (Raison and Miller, 2013). It has been shown that if non-depressed persons are given inflammatory cytokines such as IFNα the onset of signs of depression occurs (Reichenberg et al., 2001; Bonaccorso et al., 2002; Capuron et al., 2002; Harrison et al., 2009). In addition, if cytokines like TNFα, or components of the inflammatory signaling pathway like cyclooxygenase 2, can be reduced, then the signs of depression can be reduced in individuals with various medical conditions such as rheumatoid arthritis, psoriasis and cancer, and major depressive disorder (Tyring et al., 2006; Köhler et al., 2014; Abbott et al., 2015). These findings highlight that depression has a large influence on the inflammatory pathways.

The impacts of treating depression

Depression can be managed by a variety of means, including psychotherapy, electroconvulsive therapy, and anti-depressant medication. This review will focus on the more prevalent therapy, namely oral antidepressants.

There is considerable debate on the impact of treating depression on the subsequent development of dementia. Coupland et al. (2019) presented evidence from a case-control study in which they reported that anticholinergic antidepressants such as Paxil and other tricyclic antidepressants may actually increase rather than decrease the risk of subsequent Alzheimer's disease. Similar negative impact on cognition is attributed to SSRI's (Wang et al., 2016). Consequently, when faced with a patient suffering from depression, the possibility of offering psychotherapy rather than medical therapy should be considered, and in the latter case, the impact of the specific drug being considered on dementia risk should be reviewed before it is prescribed.

The literature describes a number of physiological impacts attributed to the use of antidepressants.

On inflammation

Findings suggest that some antidepressants possess significant anti-inflammatory properties (Tynan et al., 2012; Walker, 2013; Jeon and Kim, 2017). Along with their impact on the cells of the peripheral immune system, selective serotonin reuptake inhibitors (SSRIs) can limit microglial and astroglial inflammatory processes (Dafsari and Jessen, 2020). As an example, fluoxetine causes the downregulation of genes involved in the pro-inflammatory response pathways such as the activation of IL-6 signaling and nuclear factor kappa b (NF-κb) signaling, and of TNFα signaling-related molecules (Patrício et al., 2015). Further, the dopamine enhancer bupropion inhibits pro-inflammatory cytokine production and lowers production of TNFα and interferon γ in mice (Brustolim et al., 2006). Researchers have shown that SSRIs (e.g., sertraline, fluoxetine, and paroxetine) likely inhibit microglial TNFα and nitrous oxide production. In mixed glial cell cultures, serotonin, and norepinephrine reuptake inhibitors (SNRIs) such as the MAO inhibitor moclobemide and selective noradrenaline reuptake inhibitors are anti-inflammatory (Vollmar et al., 2008; Bielecka et al., 2010). The reduction in neuroinflammation resulting from the noradrenaline reuptake inhibitor was also able to partially restore microglial function (Heneka et al., 2015). Popa-Wagner et al. (2014) suggested in 2014 that inflammation may be one pathophysiologic mechanism that contributes to treatment resistance in depression.

The effects of antidepressant treatment on microglial activation in patients with MDD were studied by using 18F-FEPPA PET. It revealed that the longer patients went without treatment, the greater the microglial activation was. However, if the patients were given antidepressants, the increase in microglial activation was no longer observed (Setiawan et al., 2018). The anticholinergic effects of some tricyclic antidepressant drugs have been shown to raise the risk of dementia possibly through accelerated glial transition to a neurodegenerative phenotype (Gamage et al., 2020).

Thus, there is a clear link for both depression and dementia to the inflammatory process, and the ability of

any antidepressant approach or treatment to moderate the inflammatory load may be key to its success in reducing dementia.

Other physiological impacts of antidepressants that have been reported to date include.

On cerebral hemodynamics

Bench et al. (1995) performed early scans of patients suffering from depression and then rescanned the same patients following treatment with an antidepressant medication. They found that recovery from depression was linked to increases in rCBF flow in the same areas in which focal decreases in this parameter were described in the depressed state compared with normal subjects. Similar findings in another study described patients with depression having reduced blood flow to the left frontal brain region. However, with the antidepressant medication venlafaxine, the blood flow was restored (Navarro et al., 2004). Ishizaki et al. (2008) showed that following pharmacotherapy rCBF improved remarkably in the left dorsolateral medial prefrontal cortex (PFC) and the right parietooccipital regions while decreased CBF in some other regions of the PFC did not significantly improve. In a sample of older patients, Wei et al. (2018) reported that rCBF increases were linked to reductions in depressive symptoms. This led the authors to state that their observations were consistent with the vascular depression hypothesis in late-life depression.

On incidence of dementia

Antidepressant treatment may reduce cognitive decline (Mossello et al., 2008). It is estimated that the incidence of dementia would decline by 4% in the population if antidepressant treatment is applied (Mossello et al., 2008). Bartels et al. (2020) sought to determine the result of antidepressant drug classes on the risk for developing dementia using multiple treatment intervals. The researchers analyzed data of 62,317 individuals with an incident dementia diagnosis who were included in the German Disease Analyzer database and compared outcomes to those of controls matched by age and sex. They conducted logistic regression analyses, which were adjusted for health insurance status and comorbid diseases linked to dementia or antidepressant treatment, to evaluate the links between dementia incidence and treatment with four major classes of antidepressant drug, as well as 14 of the most commonly prescribed individual antidepressants. Results showed an association between treatment for 2 years or longer with any antidepressant and a lower risk for dementia among 17 of 18 comparisons. Particularly for long-term treatment, tricyclic antidepressants were linked to a reduction in the incidence of dementia. Long-term treatment with escitalopram (OR = 0.66; 95% CI, 0.5–0.89) was associated with the lowest risk for dementia on an individual antidepressant basis.

However, it is important to emphasize that antidepressant medications have a host of risks, contradictions and side effects that must be considered for each individual prior to starting treatment. As has been stated, some antidepressants may be ineffective or even have negative effects on cognition (Lu and Tune, 2003; Wang et al., 2016; Moraros et al., 2017).

Summary and conclusion

This review highlights that depression is a risk factor for dementia and details the physiological steps that link depression to its negative cognitive function. These steps begin with activation of inflammatory mediators, followed by a decline in the density of cerebral small vessels, which then leads to a drop in cerebral blood flow. This sequence is evident in the brains of depressed individuals when they are still cognitively normal but predicts the eventual decline in memory function.

The multifaceted physiological consequences of depression described here conform to the already outlined pattern for other recognized risks for dementia such as obesity, sedentary lifestyle and inadequate sleep (Hakim, 2021). The major difference between depression and the other cognitive risk factors is the possibility of offering various therapeutic modalities to the affected individuals.

This review cautions, however, that some antidepressant medications may worsen the cognitive impact of depression and recommends a careful evaluation of the proposed therapy on the subsequent decline in cognitive function. In addition, the use of social supports to reduce cognitive decline and depression should also be considered. Reducing social isolation has been shown to potentially delay the onset of dementia (Xiang et al., 2021). Positive social support was shown to reduce the risk of dementia whereas negative support increased the risk among persons aged 50 years and over (Khondoker et al., 2017). Overall, high quality social relationships appear to be important for overall cognitive health and can also reduce depression in older people (Murata et al., 2017).

With the identification of the proposed intermediary steps to link depression and other risk factors to cognitive decline, research can focus on identifying and neutralizing the inflammatory mediators, with the goal of interrupting the negative impact they have on cognitive function.

Author contributions

AH reviewed the literature, wrote the manuscript, and approved the submitted version.

Acknowledgments

The author would like to acknowledge his gratitude to the University of Ottawa Brain and Mind Research Institute and to Sarah Schock, for their support and contributions in the production of this manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Abbott, R., Whear, R., Nikolaou, V., Bethel, A., Coon, J. T., Stein, K., et al. (2015). Tumour necrosis factor-α inhibitor therapy in chronic physical illness: a systematic review and meta-analysis of the effect on depression and anxiety. *J. Psychosom. Res.* 79, 175–184. doi: 10.1016/j.jpsychores.2015.04.008

Aizenstein, H. J., Andreescu, C., Edelman, K. L., Cochran, J. L., Price, J., Butters, M. A., et al. (2011). fMRI correlates of white matter hyperintensities in late-life depression. *Am. J. Psychiatry* 168, 1075–1082. doi: 10.1176/appi.ajp.2011.10060853

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., and Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Transl. Psychiatry* 7:e1117. doi: 10.1038/tp.2017.90

Bangen, K. J., Werhane, M. L., Weigand, A. J., Edmonds, E. C., Delano-Wood, L., Thomas, K. R., et al. (2018). Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes. *Front. Aging Neurosci.* 10:270. doi: 10.3389/fnagi.2018.00270

Bartels, C., Belz, M., Vogelgsang, J., Hessmann, P., Bohlken, J., Wiltfang, J., et al. (2020). To be continued? Long-term treatment effects of antidepressant drug classes and individual antidepressants on the risk of developing dementia: a german case-control study. *J. Clin. Psychiatry* 81:19m13205. doi: 10.4088/JCP.19m13205

Bench, C. J., Frackowiak, R. S. J., and Dolan, R. J. (1995). Changes in regional cerebral blood flow on recovery from depression. *Psychol. Med.* 25, 247–261. doi: 10.1017/S0033291700036151

Bielecka, A. M., Paul-Samojedny, M., and Obuchowicz, E. (2010). Moclobemide exerts anti-inflammatory effect in lipopolysaccharide-activated primary mixed glial cell culture. *Naunyn Schmiedebergs Arch. Pharmacol.* 382, 409–417. doi: 10.1007/s00210-010-0535-4

Bonaccorso, S., Marino, V., Puzella, A., Pasquini, M., Biondi, M., Artini, M., et al. (2002). Increased depressive ratings in patients with hepatitis C receiving interferon-α-based immunotherapy are related to interferon-α-induced changes in the serotonergic system. *J. Clin. Psychopharmacol.* 22, 86–90. doi: 10.1097/00004714-200202000-00014

Bracko, O., Cruz Hernández, J. C., Park, L., Nishimura, N., and Schaffer, C. B. (2021). Causes and consequences of baseline cerebral blood flow reductions in Alzheimer's disease. *J. Cereb. Blood Flow Metab.* 41, 1501–1516. doi: 10.1177/0271678X20982383

Brustolim, D., Ribeiro-dos-Santos, R., Kast, R. E., Altschuler, E. L., and Soares, M. B. P. (2006). A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. *Int. Immunopharmacol.* 6, 903–907. doi: 10.1016/j.intimp.2005.12.007

Bufalino, C., Hepgul, N., Aguglia, E., and Pariante, C. M. (2013). The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. *Brain. Behav. Immun.* 31, 31–47. doi: 10.1016/j.bbi.2012.04.009

Capuron, L., Gumnick, J. F., Musselman, D. L., Lawson, D. H., Reemsnyder, A., Nemeroff, C. B., et al. (2002). Neurobehavioral effects of interferon-α in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26, 643–652. doi: 10.1016/S0893-133X(01)00407-9

Chen, P. S., McQuoid, D. R., Payne, M. E., and Steffens, D. C. (2006). White matter and subcortical gray matter lesion volume changes and late-life depression outcome: a 4-year magnetic resonance imaging study. *Int. Psychogeriatr.* 18, 445–456. doi: 10.1017/S1041610205002796

Comijs, H. C., Van Exel, E., Van Der Mast, R. C., Paauw, A., Oude Voshaar, R., and Stek, M. L. (2013). Childhood abuse in late-life depression. *J. Affect Disord.* 147, 241–246. doi: 10.1016/j.jad.2012.11.010

Compton, W. (2006). Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991–1992 and 2001–2002. *Am. J. Psychiatry* 163, 2141–2147. doi: 10.1176/appi.ajp.163.12.2141

Cooper, C. M., Chin Fatt, C. R., Liu, P., Grannemann, B., Carmody, T., Almeida, J. R. C., et al. (2020). Discovery and replication of cerebral blood flow differences in major depressive disorder. *Mol. Psychiatry* 25, 1500–1510. doi: 10.1038/s41380-019-0464-7

Coupland, C. A. C., Hill, T., Dening, T., Morriss, R., Moore, M., and Hippisley-Cox, J. (2019). Anticholinergic drug exposure and the risk of dementia. *JAMA Intern. Med.* 179, 1084–1093. doi: 10.1001/jamainternmed.2019.0677

Crous-Bou, M., Minguillón, C., Gramunt, N., and Molinuevo, J. L. (2017). Alzheimer's disease prevention: from risk factors to early intervention. *Alzheimers Res. Ther.* 9:71. doi: 10.1186/s13195-017-0297-z

Dafsari, F. S., and Jessen, F. (2020). Depression—an underrecognized target for prevention of dementia in Alzheimer's disease. *Transl. Psychiatry* 10:160. doi: 10.1038/s41398-020-0839-1

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., et al. (2010). A meta-analysis of cytokines in major depression. *Biol. Psychiatry* 67, 446–457. doi: 10.1016/j.biopsych.2009.09.033

Eisenberger, N. I., Lieberman, M. D., and Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science* 302, 290–292. doi: 10.1126/science.1089134

Felger, J. C., and Lotrich, F. E. (2013). Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience* 246, 199–229. doi: 10.1016/j.neuroscience.2013.04.060

Firbank, M. J., Teodorczuk, A., Van Der Flier, W. M., Gouw, A. A., Wallin, A., Erkinjuntti, T., et al. (2012). Relationship between progression of brain white matter changes and late-life depression: 3-Year results from the LADIS study. *Br. J. Psychiatry* 201, 40–45. doi: 10.1192/bjp.bp.111.098897

Gamage, R., Wagnon, I., Rossetti, I., Childs, R., Niedermayer, G., Chesworth, R., et al. (2020). Cholinergic modulation of glial function during aging and chronic neuroinflammation. *Front. Cell Neurosci.* 14:577912. doi: 10.3389/fncel.2020.577912

Gatchel, J. R., Rabin, J. S., Buckley, R. F., Locascio, J. J., Quiroz, Y. T., Yang, H. S., et al. (2019). Longitudinal association of depression symptoms with cognition and cortical amyloid among community-dwelling older adults. *JAMA Netw. Open* 2:e198964. doi: 10.1001/jamanetworkopen.2019.8964

Gautrin, D., Froda, S., Tetreault, H., and Gauvreau, D. (1990). Canadian projections of cases suffering from Alzheimer's disease and senile dementia of Alzheimer type oer the period 1986-2031. *Can. J. Psychiatry* 35, 162–165. doi: 10.1177/070674379003500211

GBD 2019 Dementia Forecasting Collaborators (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 7, e105–e125. doi: 10.1016/S2468-2667(21)00249-8

Hagnell, O. (1989). Repeated incidence and prevalence studies of mental disorders in a total population followed during 25 years the Lundby Study, Sweden. *Acta Psychiatr. Scand.* 79, 61–77. doi: 10.1111/j.1600-0447.1989.tb05216.x

Hagnell, O., Ojesjo, L., Otterbeck, L., and Rorsman, B. (1993). Prevalence of mental disorders, personality traits and mental complaints in the Lundby Study: a point prevalence study of the 1957 Lundby cohort of 2612 inhabitants of a geographically defined area who were re-examined in 1972 regardless of domicile. *Scand. J. Soc. Med. Suppl.* 21, 1–77.

Hakim, A. M. (2011). Depression, strokes and dementia: new biological insights into an unfortunate pathway. *Cardiovasc. Psychiatry Neurol.* 2011:649629. doi: 10.1155/2011/649629

Hakim, A. M. (2021). A Proposed hypothesis on dementia: inflammation, small vessel disease, and hypoperfusion is the sequence that links all harmful lifestyles to cognitive impairment. *Front. Aging Neurosci.* 13:679837. doi: 10.3389/fnagi.2021.679837

Harrison, N. A., Brydon, L., Walker, C., Gray, M. A., Steptoe, A., and Critchley, H. D. (2009). Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry* 66, 407–414. doi: 10.1016/j.biopsych.2009.03.015

Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., et al. (2015). Neuroinflammation in Alzheimer's disease. *Lancet Neurol.* 14, 388–405. doi: 10.1016/S1474-4422(15)70016-5

Herrmann, L. L., Le Masurier, M., and Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 79, 619–624. doi: 10.1136/jnnp.2007.124651

Hidaka, B. H. (2012). Depression as a disease of modernity: explanations for increasing prevalence. *J. Affect. Disord.* 140, 205–214. doi: 10.1016/j.jad.2011.12.036

Ishizaki, J., Yamamoto, H., Takahashi, T., Takeda, M., Yano, M., and Mimura, M. (2008). Changes in regional cerebral blood flow following antidepressant treatment in late-life depression. *Int. J. Geriatr. Psychiatry* 23, 805–811. doi: 10.1002/gps.1980

Iturria-Medina, Y., Sotero, R. C., Toussaint, P. J., Mateos-Pérez, J. M., Evans, A. C., and The Alzheimer's Disease Neuroimaging Initiative (2016). Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat. Commun.* 7:11934. doi: 10.1038/ncomms11934

Jeon, S. W., and Kim, Y. K. (2017). Inflammation-induced depression: its pathophysiology and therapeutic implications. *J. Neuroimmunol.* 313, 92–98. doi: 10.1016/j.jneuroim.2017.10.016

Khondoker, M., Rafnsson, S. B., Morris, S., Orrell, M., and Steptoe, A. (2017). Positive and negative experiences of social support and risk of dementia in later life: an investigation using the english longitudinal study of ageing. *J. Alzheimers Dis.* 58, 99–108. doi: 10.3233/JAD-161160

Köhler, O. E., Benros, M., Nordentoft, M., Farkouh, M. E., Iyengar, R. L., Mors, O., et al. (2014). Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71, 1381–1391. doi: 10.1001/jamapsychiatry.2014.1611

Köhler, S., Van Boxtel, M. P. J., Van Os, J., Thomas, A. J., O'Brien, J. T., Jolles, J., et al. (2010). Depressive symptoms and cognitive decline in community-dwelling older adults. *J. Am. Geriatr. Soc.* 58, 873–879. doi: 10.1111/j.1532-5415.2010.02807.x

Krishnan, K. R. R., Taylor, W. D., McQuoid, D. R., MacFall, J. R., Payne, M. E., Provenzale, J. M., et al. (2004). Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol. Psychiatry* 55, 390–397. doi: 10.1016/j.biopsych.2003.08.014

Lu, C. J., and Tune, L. E. (2003). Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am. J. Geriatr. Psychiatry* 11, 458–461. doi: 10.1097/00019442-200307000-00009

Meyer, J. S., Shimazu, K., Fukuuchi, Y., Ouchi, T., Okamoto, S., Koto, A., et al. (1973). Impaired neurogenic cerebrovascular control and dysautoregulation after stroke. *Stroke* 4, 169–186. doi: 10.1161/01.STR.4.2.169

Miller, A. H., and Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* 16, 22–34. doi: 10.1038/nri.2015.5

Moraros, J., Nwankwo, C., Patten, S. B., and Mousseau, D. D. (2017). The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: a systematic review and meta-analysis. *Depress. Anxiety* 34, 217–226. doi: 10.1002/da.22584

Mossello, E., Boncinelli, M., Caleri, V., Cavallini, M. C., Palermo, E., Di Bari, M., et al. (2008). Is antidepressant treatment associated with reduced cognitive decline in Alzheimer's disease? *Dement. Geriatr. Cogn. Disord.* 25, 372–379. doi: 10.1159/000121334

Murata, C., Saito, T., Tsuji, T., Saito, M., and Kondo, K. (2017). A 10-year follow-up study of social ties and functional health among the old: the AGES project. *Int. J. Environ. Res. Public Health* 14:717. doi: 10.3390/ijerph14070717

Muscatell, K. A., Dedovic, K., Slavich, G. M., Jarcho, M. R., Breen, E. C., Bower, J. E., et al. (2015). Greater amygdala activity and dorsomedial prefrontal-amygdala coupling are associated with enhanced inflammatory responses to stress. *Brain Behav. Immun.* 43, 46–53. doi: 10.1016/j.bbi.2014.06.201

Navarro, V., Gastó, C., Lomeña, F., Torres, X., Mateos, J. J., Portella, M. J., et al. (2004). Prognostic value of frontal functional neuroimaging in late-onset severe major depression. *Br. J. Psychiatry* 184, 306–311. doi: 10.1192/bjp.184.4.306

Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., and Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* 13, 788–794. doi: 10.1016/S1474-4422(14)70136-X

Oda, K., Okubo, Y., Ishida, R., Murata, Y., Ohta, K., Matsuda, T., et al. (2003). Regional cerebral blood flow in depressed patients with white matter magnetic resonance hyperintensity. *Biol. Psychiatry* 53, 150–156. doi: 10.1016/S0006-3223(02)01548-2

Panksepp, J. (2003). Feeling the pain of social loss. *Science* 302, 237–239. doi: 10.1126/science.1091062

Patrício, P., Mateus-Pinheiro, A., Irmler, M., Alves, N. D., Machado-Santos, A. R., Morais, M., et al. (2015). Differential and converging molecular mechanisms of antidepressants' action in the hippocampal dentate gyrus. *Neuropsychopharmacology* 40, 338–349. doi: 10.1038/npp.2014.176

Popa-Wagner, A., Buga, A. M., Popescu, B., and Muresanu, D. (2015). Vascular cognitive impairment, dementia, aging and energy demand. A vicious cycle. *J. Neural Transm.* 122, S47–S54. doi: 10.1007/s00702-013-1129-3

Popa-Wagner, A., Buga, A. M., Tica, A. A., and Albu, C. V. (2014). Perfusion deficits, inflammation and aging precipitate depressive behaviour. *Biogerontology* 15, 439–448. doi: 10.1007/s10522-014-9516-1

Raison, C. L., and Miller, A. H. (2013). The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Mol. Psychiatry* 18, 15–37. doi: 10.1038/mp.2012.2

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., et al. (2001). Cytokine-associated emotional and cognitive disturbances in humans. *Arch. Gen. Psychiatry* 58, 445–452. doi: 10.1001/archpsyc.58.5.445

Setiawan, E., Attwells, S., Wilson, A. A., Mizrahi, R., Rusjan, P. M., Miler, L., et al. (2018). Association of translocator protein total distribution volume with duration of untreated major depressive disorder: a cross-sectional study. *Lancet Psychiatry* 5, 339–347. doi: 10.1016/S2215-0366(18)30048-8

Sinha, R., Lovallo, W. R., and Parsons, O. A. (1992). Cardiovascular differentiation of emotions. *Psychosom. Med.* 54, 422–435. doi: 10.1097/00006842-199207000-00005

Slavich, G. M., and Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol. Bull.* 140, 774–815. doi: 10.1037/a0035302

Steffens, D. C., Welsh-Bohmer, K. A., Burke, J. R., Plassman, B. L., Beyer, J. L., Gersing, K. R., et al. (2004). Methodology and preliminary results from the neurocognitive outcomes of depression in the elderly study. *J. Geriatr. Psychiatry Neurol.* 17, 202–211. doi: 10.1177/0891988704269819

Takano, H., Kato, M., Inagaki, A., Watanabe, K., and Kashima, H. (2006). Time course of cerebral blood flow changes following electroconvulsive therapy in depressive patients - Measured at 3 time points using single photon emission computed tomography. *Keio J. Med.* 55, 153–160. doi: 10.2302/kjm.55.153

Taylor, W. D., MacFall, J. R., Payne, M. E., McQuoid, D. R., Steffens, D. C., Provenzale, J. M., et al. (2005). Greater MRI lesion volumes in elderly depressed subjects than in control subjects. *Psychiatry Res. Neuroimaging* 139, 1–7. doi: 10.1016/j.pscychresns.2004.08.004

Taylor, W. D., Zhao, Z., Ashley-Koch, A., Payne, M. E., Steffens, D. C., Krishnan, R. R., et al. (2013). Fiber tract-specific white matter lesion severity Findings in late-life depression and by AGTR1 A1166C genotype. *Hum. Brain Mapp.* 34, 295–303. doi: 10.1002/hbm.21445

Twenge, J. M., Gentile, B., DeWall, C. N., Ma, D., Lacefield, K., and Schurtz, D. R. (2010). Birth cohort increases in psychopathology among young Americans, 1938-2007: a cross-temporal meta-analysis of the MMPI. *Clin. Psychol. Rev.* 30, 145–154. doi: 10.1016/j.cpr.2009.10.005

Tynan, R. J., Weidenhofer, J., Hinwood, M., Cairns, M. J., Day, T. A., and Walker, F. R. (2012). A comparative examination of the anti-inflammatory effects

of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain Behav. Immun.* 26, 469–479. doi: 10.1016/j.bbi.2011.12.011

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., et al. (2006). Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 367, 29–35. doi: 10.1016/S0140-6736(05)67763-X

Villarroel, M. A., and Terlizzi, E. P. (2020). *Symptoms of Depression Among Adults: United States, 2019*. Hyattsville: NCHS Data Brief.

Vollmar, P., Haghikia, A., Dermietzel, R., and Faustmann, P. M. (2008). Venlafaxine exhibits an anti-inflammatory effect in an inflammatory co-culture model. *Int. J. Neuropsychopharmacol.* 11, 111–117. doi: 10.1017/S1461145707007729

Walker, F. R. (2013). A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology* 67, 304–317. doi: 10.1016/j.neuropharm.2012.10.002

Wang, C., Gao, S., Hendrie, H. C., Kesterson, J., Campbell, N. L., Shekhar, A., et al. (2016). Antidepressant use in the elderly is associated with an increased risk of dementia. *Alzheimer Dis. Assoc. Disord.* 30, 99–104. doi: 10.1097/WAD.0000000000000103

Wang, L., Leonards, C. O., Sterzer, P., and Ebinger, M. (2014). White matter lesions and depression: a systematic review and meta-analysis. *J. Psychiatr. Res.* 56, 56–64. doi: 10.1016/j.jpsychires.2014.05.005

Watt, D. F., and Panksepp, J. (2009). Depression: an evolutionarily conserved mechanism to terminate separation distress? a review of aminergic, peptidergic, and neural network perspectives. *Neuropsychoanalysis* 11, 7–15. doi: 10.1080/15294145.2009.10773593

Wei, W., Karim, H. T., Lin, C., Mizuno, A., Andreescu, C., Karp, J. F., et al. (2018). Trajectories in cerebral blood flow following antidepressant treatment in late-life depression: support for the vascular depression hypothesis. *J. Clin. Psychiatry* 79:18m12106. doi: 10.4088/JCP.18m12106

Wittenberg, R., Hu, B., Jagger, C., Kingston, A., Knapp, M., Comas-Herrera, A., et al. (2020). Projections of care for older people with dementia in England: 2015 to 2040. *Age Ageing* 49, 264–269. doi: 10.1093/ageing/afz154

Xiang, X., Lai, P. H. L., Bao, L., Sun, Y., Chen, J., Dunkle, R. E., et al. (2021). Dual trajectories of social isolation and dementia in older adults: a population-based longitudinal study. *J. Aging Health* 33, 63–74. doi: 10.1177/0898264320953693

Zeki Al Hazzouri, A., Caunca, M. R., Nobrega, J. C., Nobrega, J. C., Elfassy, T., Cheung, Y. K., et al. (2018). Greater depressive symptoms, cognition, and markers of brain aging: Northern Manhattan Study. *Neurology* 90, e2077–e2085. doi: 10.1212/WNL.0000000000005639

frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 15 September 2022
DOI 10.3389/fnagi.2022.931715

OPEN ACCESS

EDITED BY
Eszter Farkas,
University of Szeged, Hungary

REVIEWED BY
Matthew Lennon,
University of New South Wales, Australia
Shraddha Sapkota,
University of California, Davis, United States

*CORRESPONDENCE
Geir Selbaek
geir.selbaek@aldringoghelse.no

SPECIALTY SECTION
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 29 April 2022
ACCEPTED 25 August 2022
PUBLISHED 15 September 2022

CITATION
Selbaek G, Stuebs J, Engedal K, Hachinski V, Hestad K, Trevino CS, Skjellegrind H, Wedatilake Y and Strand BH (2022) Blood pressure trajectories over 35 years and dementia risk: A retrospective study: The HUNT study.
Front. Aging Neurosci. 14:931715.
doi: 10.3389/fnagi.2022.931715

Blood pressure trajectories over 35 years and dementia risk: A retrospective study: The HUNT study

Geir Selbaek[1,2,3]*, Josephine Stuebs[1,2,3], Knut Engedal[1,2], Vladimir Hachinski[4], Knut Hestad[5,6], Cathrine Selnes Trevino[1,2], Håvard Skjellegrind[7,8], Yehani Wedatilake[1,9] and Bjørn Heine Strand[1,2,10]

[1]Norwegian National Centre for Aging and Health, Vestfold Hospital Trust, Tønsberg, Norway, [2]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway, [3]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [4]Department of Clinical Neurological Sciences, Robarts Research Institute, University of Western Ontario, London, ON, Canada, [5]Department of Research, Innlandet Hospital Trust, Brumunddal, Norway, [6]Department of Health and Nursing Science, Faculty of Health and Social Sciences, Inland Norway University of Applied Sciences, Elverum, Norway, [7]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, HUNT Research Centre, Norwegian University of Science and Technology, Levanger, Norway, [8]Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway, [9]The Research Centre for Age-Related Functional Decline and Disease, Innlandet Hospital Trust, Ottestad, Norway, [10]Department of Physical Health and Ageing, Norwegian Institute of Public Health, Oslo, Norway

High blood pressure is a well-established risk factor of dementia. However, the timing of the risk remains controversial. The aim of the present study was to compare trajectories of systolic blood pressure (SBP) over a 35-year follow-up period in the Health Survey in Trøndelag (HUNT) from study wave 1 to 4 in people with and without a dementia diagnosis at wave 4 (HUNT4). This is a retrospective cohort study of participants aged ≥ 70 years in HUNT4, where 9,720 participants were assessed for dementia. In the HUNT study all residents aged ≥ 20 years have been invited to four surveys: HUNT1 1984–86, HUNT2 1995–97, HUNT3 2006–08 and HUNT4 2017–19. The study sample was aged 70–102 years (mean 77.6, *SD* 6.0) at HUNT4, 54% were women and 15.5% had dementia, 8.8% had Alzheimer's disease (AD), 1.6% had vascular dementia (VaD) and 5.1% had other types of dementia. Compared to those without dementia at HUNT4, those with dementia at HUNT4 had higher SBP at HUNT1 and HUNT2, but lower SBP at HUNT4. These differences at HUNT1 and 2 were especially pronounced among women. Results did not differ across birth cohorts. For dementia subtypes at HUNT4, the VaD group had a higher SBP than the AD group at HUNT2 and 3. Age trajectories in SBP showed that the dementia group experienced a steady increase in SBP until 65 years of age and a decrease from 70 to 90 years. SBP in the no- dementia group increased until 80 years before it leveled off from 80 to 90 years.

The present study confirms findings of higher midlife SBP and lower late-life SBP in people with dementia. This pattern may have several explanations and it highlights the need for close monitoring of BP treatment in older adults, with frequent reappraisal of treatment needs.

KEYWORDS

blood pressure, dementia, trajectory, cohort study, Alzheimer, vascular dementia

Introduction

Dementia is a chronic, progressive syndrome which affects cognition, behavior, and daily life functioning. The steeply rising prevalence of dementia presents an immense individual, societal and economic burden. In 2019, there were 57,4 million persons with dementia globally. This number is projected to increase to 152,8 million by 2050 (GBD Dementia Forecasting Collaborators, 2022). In Norway, 101,000 persons have dementia, set to exceed 236,000 by 2050 (Gjøra et al., 2021). With a few exceptions, such as antiretroviral therapy for HIV-associated dementia, treatment of vascular diseases causing dementia and the recently FDA approved monoclonal antibody, aducanumab, there is at present no disease-modifying treatment available for any of the diseases causing dementia. However, modifiable lifestyle risk factors for dementia may be a target for intervention. The recent Lancet commission on dementia prevention, intervention and care identified 12 modifiable risk factors and estimated that more than 40% of dementia cases could be delayed or prevented by excluding these risk factors (Livingston et al., 2020).

Hypertension is one of these risk factors. It has been suggested that the observed decrease in dementia incidence over the last decades is partly due to better blood pressure (BP) control, especially in people with midlife hypertension (Satizabal et al., 2016). Ample evidence suggests that midlife hypertension is associated with an increased risk of dementia (McGrath et al., 2017; Abell et al., 2018). However, as age increases the association is attenuated and might even be reversed. Previous studies have found that hypotension in old age may be associated with an increased risk of dementia (Hestad et al., 2005; Qiu et al., 2009; Gabin et al., 2017). Alternatively, both late-life hypertension and hypotension may be associated with an increased risk of dementia (Walker et al., 2019). This may be due to reverse causality. The development of degenerative brain disorder may induce a decrease in BP. This is particularly relevant for the most common dementia disorder, Alzheimer's disease (AD), in which the degenerative process starts in the brain decades before cognitive and functional impairment become apparent (Frisoni et al., 2022). The association between hypertension and risk of AD is still not well understood. Whereas there seems to be a rather robust association between midlife diastolic hypertension and AD risk, the results regarding midlife systolic hypertension and AD risk are conflicting (Walker et al., 2017). Few studies have investigated the association between midlife hypertension and risk of vascular dementia (VaD) but the association between hypertension and risk of VaD seems to be more robust than for AD (Walker et al., 2017). Sex differences in the association between hypertension and dementia risk are not well characterized and a recent review concluded that studies rarely, and inconsistently analyzed or reported sex effects (Blanken and Nation, 2020). Two recent studies indicated that sex differences exist both for risk of dementia (Gong et al., 2021) and the risk of memory decline (Anstey et al., 2021).

To be able to intervene in clinical settings, we need precise information on patterns of how risk factors change over the life course. However, very few studies have been able to follow the trajectories of blood pressure from early or midlife until late life. A recent review identified only four trajectory studies reporting on risk of all-cause dementia and three studies reporting on risk of AD or VaD. Only two of the studies had a follow-up longer than 10 years (Peters et al., 2020).

The present study aims to test the hypothesis that midlife hypertension is associated with dementia in late life, but that this association is attenuated and even reversed with increasing age. Furthermore, we hypothesize that different risk profiles exist between men and women, older and younger age groups, and between participants with AD and VaD.

Materials and methods

Study population

In this retrospective cohort study, we employed data from the Trøndelag Health (HUNT) study for our analyses. The HUNT study is a unique database of questionnaire data, clinical measurements, and biological samples from the former Nord-Trøndelag county's population from 1984 onward. The study includes data from persons 20 years or older, gathered during four waves: HUNT1 (1984–1986), HUNT2 (1995–1997), HUNT3 (2006–2008), and HUNT4 (2017–2019). In each HUNT wave, data were collected over a 2-year period

(Åsvold et al., 2022). In HUNT4 all participants who were 70 years and older were invited to participate in the HUNT4 70+ study (Gjøra et al., 2021) where they underwent cognitive assessments.

Our study population included participants from the HUNT4 70+ study, born 1914–49. Among a total of 9,904 participants, those with missing dementia assessment at HUNT4 (n = 178) and/or no BP measurements in any waves, HUNT1-HUNT4 (n = 6) were excluded. A total of 9,720 individuals were included in the analysis. In this study population of HUNT4-participants, we studied systolic blood pressure (SBP) trajectories retrospectively during the HUNT1-HUNT4 waves and analyzed them by dementia status at HUNT4.

Procedures for diagnosis of dementia or mild cognitive impairment

In HUNT4 70+, dementia diagnoses were set by experts from a diagnostic group of nine medical doctors with both scientific and clinical expertise (geriatrics, neurology or old-age psychiatry). A diagnosis was made for each case by two experts independently, applying the DSM-5 diagnostic criteria to classify the following conditions: no cognitive impairment, mild cognitive impairment (mild neurocognitive disorder), dementia (major neurocognitive disorder) and dementia subtypes; AD, VaD, Lewy body dementias (LBD), frontotemporal dementia (FTD), mixed dementia, other specified dementia and unspecified dementia (Gjøra et al., 2021). If no consensus for the diagnosis was reached a third expert was consulted. During the diagnostic process the experts had access to all relevant information from the HUNT4 70+ dataset, such as cognitive tests, patient history, physical diseases including stroke, function in activities of daily living, neuropsychiatric symptoms assessment and a structured interview with the closest family proxy.

Blood pressure, dementia status and covariates

BP (mmHg) was measured in HUNT1–4. In the study population 75% had BP measured at all waves (HUNT1–4), 90% had a BP measurement from at least 3 waves, 96% had a BP measurement from at least two waves, and 4% had a BP measurement from only one wave. Participants were included if there was at least one valid BP measurement in HUNT1–4 and a valid dementia assessment at HUNT4.

Dementia status was categorized as no dementia and dementia. Dementia subtypes were categorized as AD, VaD and "other dementia." The category "other dementia" included LBD, FTD, mixed dementia, other specified dementia, and unspecified dementia.

Time dependent covariates at HUNT1–4 included self-reported antihypertensive medication use (yes/no), daily smoker (never, ever, current) and history of stroke (yes/no). Obesity was defined as body mass index [calculated as weight (in kilograms) divided by squared height (in meters)] $\geq$ 30 and included as a dichotomous time dependent variable. Time invariant covariates included the following: birth year, sex (male/female) and education level (compulsory, secondary, tertiary) obtained from the National Education Data Base (registry based data). Missing values for education (n = 25) were imputed as compulsory education. Missing values for history of stroke (n = 70) for HUNT2–4 were imputed based on reports on previous HUNT-study waves.

Procedures for blood pressure assessment

At HUNT1 BP was assessed using a mercury sphygmomanometer, by trained nurses or technicians. BP was recorded twice in the seated position after resting for a minimum of 5 min (Gabin et al., 2017). In HUNT1 the mean of the first and the second readings was used to calculate mean systolic or diastolic BP.

In HUNT2-HUNT4, three repeated automated oscillometric BP-measurements were recorded at 1-min intervals. The measurements were started after the participant was seated for 2 min with the cuff on the arm, and the arm resting steadily on a table. The mean of the second and third readings were used to calculate mean systolic or diastolic BP.

In HUNT2, measurements were done at the stationary assessment team in the five larger municipalities by oscillometry., using a Critikon Dinamap monitor (845XT and XL9301) (Gabin et al., 2017).

In the HUNT3 study, BP and heart rate were measured using a Critikon Dinamap (8,100) based on oscillometry (Krokstad et al., 2013). Dinamap XL model 9301 (Johnson & Johnson Medical Inc.) was also used for the measurements by the mobile team in the 19 smaller municipalities in both HUNT2 and HUNT3. The Dinamap XL model 9301 measures mean arterial pressure directly, and hence does not estimate it from systolic and diastolic pressure. In HUNT4 the Dinamap CARESCAPE V100 (GE Healthcare) with GE TruSignal for pulse oximetry was used, also based on automatic oscillometry.

Cognitive assessments

In HUNT4 70+ the following cognitive assessment instruments were applied:

The Montreal Cognitive Assessment (MoCA) scale is a multidomain cognitive screening instrument that tests memory, visuospatial and executive functions, naming, attention, abstraction, language, and orientation. Scores range from 0 to 30; higher scores indicate better cognitive function (Nasreddine et al., 2005).

The Word list from the Consortium to Establish a Registry for Alzheimer's Diseases (CERAD) (ten-word immediate and delayed memory test) tests memory with a list of 10 words that the person being tested is asked to recall after each of three initial presentations (immediate recall) (score 0–30) and again after 10 min (delayed recall) (score 0–10) (Morris et al., 1989). In nursing home patients with moderate to severe dementia, the Severe Impairment Battery 8-item version was applied (Schmitt et al., 2013).

Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK Southeast 251687) and the Norwegian Center for Research Data (NSD 571736). Participation in the HUNT studies was based on an informed written consent.

Statistical methods

Stata 16 was used for all analyses. SBP was used as the outcome in a random intercept and random slope multilevel mixed-effects linear regression model with HUNT study survey as time variable (1–4) and dementia status at HUNT4 as independent variable. Year of birth, sex, and educational level were added to the model as time invariant adjustment variables, while BP medication use, obesity, daily smoking, and history of stroke were allowed to vary over the HUNT surveys 1–4 and treated as time dependent covariates in the regression model. All interactions between age, sex and dementia status were included. SBP values by dementia status, sex and survey time point were predicted from the regression model *post hoc* using the margins command. Stratified predictions were performed to investigate differences between men and women, between age groups (birth years 1914–34 vs. 1935–49), and between dementia subtypes. Analyses were run on the total study population (n = 9720) in a minimally adjusted model with these variables included: dementia, time, time*dementia, birth year, sex, as well as in the study population with non-missing values for all the adjustment variables (n = 9484).

In a second multilevel mixed-effects linear regression model analysis (random intercept and random slope), age was used as the time variable, thus the age trajectories by dementia status at HUNT4 70+ were modeled. Age was included as a linear and quadratic term and the interactions with dementia status were included. The model was adjusted by all the adjustment variables mentioned above and performed on the sample with non-missing values for all the adjustment variables (n = 9484).

Since only two BP measurements were performed in HUNT1 and three BP measurements were taken in HUNT2–4, we did three sensitivity analyses using the same SBP measurement at all surveys; first we used the first SBP measurement at all surveys, secondly, we used the second measurement at all surveys, and lastly we used the mean from reading number one and two for all surveys.

Results

At HUNT4 the mean age was 77.6 years (*SD* 6.0) (range 70–102) and 54% were women. In 1984, the initial year of the HUNT study (HUNT1), the mean age was 44.1 years (*SD* 6.4) (range 35–70). During cognitive assessments at HUNT4, 1503 (15.5%) were found to have dementia, of which 856 (8.8%) had AD, 156 (1.6%) had VaD and 491 (5.1%) had other types of dementia. In the total sample, mean SBP increased from 129.2 (*SD* 15.9) mmHg in HUNT1 to 138.8 (*SD* 19.2) mmHg in HUNT2 and remained stable from HUNT2 to HUNT3 (137.6 mmHg, *SD* 18.9) and HUNT4 (139.4 mmHg, *SD* 20.2). Descriptive characteristics of the population from HUNT1 to HUNT4, by dementia status at HUNT4 are presented in **Table 1**.

Systolic blood pressure trajectories by all-cause dementia status at HUNT4, adjusted for confounders

SBP from HUNT1 to HUNT4 comparing those with and without dementia is presented in (**Figure 1A**) total sample adjusted for sex and age, (**Figure 1B**) complete cases sample adjusted for sex and age and (**Figure 1C**) complete cases fully adjusted for sex, age, antihypertensive use, obesity, smoking status and history of stroke.

Adjusted by sex and birth year (centered at 1939, and 45% men), the SBP trajectory for those with dementia, for HUNT study waves 1–4 was 131.8, 143.3, 138.4, 132.2 mmHg, respectively. For those without dementia the SBP trajectory was 128.7, 137.9, 137.8, 140.7 mmHg from HUNT1–4 (**Figure 1A**). Thus, compared to those without dementia, those with dementia at HUNT4, had higher SBP levels at both HUNT1 (3.1 mmHg higher, 95%CI 2.1, 4.2) and at HUNT2 (5.3 mmHg higher, 95%CI 4.3, 6.4) (**Table 2**). At HUNT3 the SBP levels were similar (0.6 mmHg higher, 95%CI −0.6, 1.8), and at HUNT4 the pattern was reversed; the BP level was 8.5 mmHg lower (95%CI −9.6, −7.3) in the dementia group. In the sample with no missing

10.3389/fnagi.2022.931715

TABLE 1 Characteristics of the study participants at the HUNT surveys (HUNT1–4: 1984, 1995, 2006, 2017) by dementia status (assessed at HUNT4).

Characteristic	No dementia at HUNT4				Dementia at HUNT4			
	HUNT1 1984	HUNT2 1995	HUNT3 2006	HUNT4 2017	HUNT1 1984	HUNT2 1995	HUNT3 2006	HUNT4 2017
No. of participants with BP measurements	7,295	7,267	7,214	8,181	1,358	1,316	1,138	1,403
Age mean (SD), years	43.7 (5.7)	55.3 (5.7)	66.4 (5.6)	76.8 (5.5)	50.5 (7.5)	62.1 (7.5)	72.6 (7.1)	82.5 (7.2)
Women (%)	3,993 (54.7)	3,976 (54.7)	3,904 (54.1)	4,373 (53.4)	814 (59.9)	794 (60.3)	673 (59.1)	809 (57.7)
Men (%)	3,302 (45.3)	3,291 (45.3)	3,309 (45.9)	3,808 (46.6)	544 (40.1)	522 (39.7)	465 (40.9)	594 (42.3)
Education (%)								
Compulsory	1,670 (22.9)	1,634 (22.5)	1,565 (21.7)	1,835 (22.4)	610 (44.9)	581 (44.1)	481 (42.3)	613 (43.7)
Secondary	3,200 (43.9)	3,169 (43.6)	3,142 (43.5)	3,475 (42.5)	517 (38.1)	509 (38.7)	434 (38.1)	535 (38.1)
Tertiary	2,425 (33.2)	2,464 (33.9)	2,507 (34.7)	2,871 (35.1)	231 (17)	226 (17.2)	223 (19.6)	255 (18.2)
Systolic BP mean (SD) mm Hg	128.2 (15.2)	137.5 (18.4)	137.1 (18.5)	140.1 (19.9)	134.7 (18.2)	146.1 (21.7)	140.8 (20.7)	134.9 (21.6)
Antihypertensive use (%)	301 (4.1)	843 (11.6)	2,519 (34.8)	4,130 (65.7)	125 (9.1)	285 (21.6)	554 (48.4)	538 (65.2)
Smoking status (%)								
Current	1,595 (25.2)	1,507 (20.9)	814 (11.6)	493 (6.2)	313 (26.5)	269 (20.7)	121 (11.1)	71 (6.6)
Previous	1,837 (29.0)	2,497 (34.6)	2,971 (42.2)	4,025 (50.5)	303 (25.6)	430 (33.1)	432 (39.9)	536 (50.0)
Never	2,904 (45.9)	3,209 (44.5)	3,248 (46.2)	3,457 (43.4)	567 (47.9)	601 (46.2)	529 (48.9)	466 (43.4)
Obesity (BMI > 30) (%)	438 (6.0)	1,139 (15.7)	1,765 (24.4)	1,696 (21.4)	132 (9.7)	274 (20.9)	304 (26.8)	396 (29.9)
History of stroke (%)	8 (0.1)	49 (0.7)	254 (3.5)	653 (8.8)	7 (0.5)	21 (1.6)	92 (8.0)	226 (23.2)

BMI, body mass index; BP, blood pressure; HUNT, The Trøndelag Health Study. Missing N in antihypertensive use: 1,007, 1,132, 1,330, 2,607 in HUNT1,2,3,4, respectively; missing N in smoking status: 2,198, 1,207, 1,605, 672 in HUNT1,2,3,4, respectively; missing N in obesity: 1,070, 1,148, 1,362, 473 in HUNT1,2,3,4, respectively; missing N in history of stroke: 1,008, 1,131, 1,319, 1,363 in HUNT1,2,3,4, respectively.

values for all confounders (n = 9,484), the SBP trajectories by dementia status at HUNT4 were similar to the full sample (N = 9,720), except that there was a slightly smaller difference at HUNT4; the level was 5.3 mmHg lower (95%CI −6.9, −3.8) in the dementia group (Figure 1B and Table 2). In a fully adjusted model, with education, antihypertensive medication, smoking, obesity and stroke, results were minimally attenuated and almost identical to those adjusted only for age and birth year (Figure 1C and Table 2).

Systolic blood pressure trajectories by dementia status at HUNT4: Differences according to sex, birth cohort and dementia subtype (fully adjusted model, complete case sample n = 9484)

The SBP difference between the no dementia group and the dementia group at HUNT4, over the four HUNT waves is shown in Figure 2 and Table 2, with stratification by (Figure 2A) sex, (Figure 2B) birth cohort and (Figure 2C) type of dementia.

Compared with the no dementia group, women in the dementia group had a higher SBP at HUNT1 and HUNT2 and a lower SBP at HUNT4. There was no difference between the groups at HUNT3. In men, SBP was higher in the dementia group at HUNT2 and lower in the dementia group at HUNT4, whereas there was no difference between the groups at HUNT1 and HUNT3. The difference in SBP according to dementia status at HUNT4, was significantly larger in women compared to that in men at HUNT1 (p = 0.003) and HUNT2 (p < 0.001), while the difference was similar across sexes at HUNT3 (p = 0.43) and HUNT4 (p = 0.72) (Figure 2A and Table 2).

The difference in SBP according to dementia status at HUNT4 was similar across birth cohorts (Figure 2B and Table 2).

For those without dementia the SBP trajectory was 129.1, 137.8, 137.3, 139.7 mmHg from HUNT1–4 (almost identical to the trajectories described above for the full sample). For those with AD the SBP trajectory was 131.2, 141.3, 136.8, 134.0 mmHg from HUNT1–4, and for those with VaD the SBP trajectory was 133.7, 147.7, 143.3, 137.6 mmHg from HUNT1–4. Thus, there were substantial differences among dementia subtypes. Compared to the no dementia group, the VaD group had a higher SBP at HUNT1, HUNT2 and HUNT3, but there was no difference at HUNT4. Compared

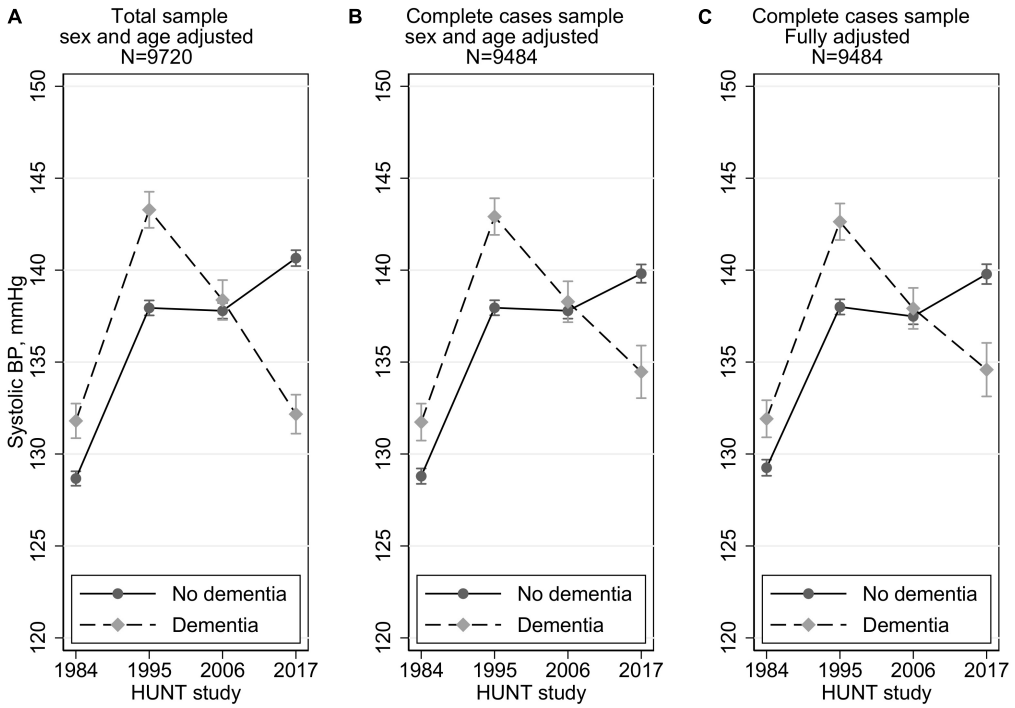


FIGURE 1
Systolic blood pressure trajectories by dementia status (yes/no) at HUNT4 70+ in 2017–19 with 95% confidence intervals. Multilevel mixed methods with random intercept and slope. In the fully adjusted models in C, these time-dependent variables are included: blood pressure medication (yes/no), smoking (current, previous, never), obesity (yes/no), and history of stroke (yes/no), and the following time-invariant variables: education (compulsory, secondary, tertiary), birth year, and sex.

TABLE 2 Absolute difference in SBP (mmHg) at HUNT1, HUNT2, HUNT3 and HUNT4, respectively, for those with dementia at HUNT4 vs those without dementia at HUNT4 (95% CI).

	Number of participants (%)	HUNT1 1984	HUNT2 1995	HUNT3 2006	HUNT4 2017
All					
Model 1	9,720	3.1 (2.1, 4.2)	5.3 (4.3, 6.4)	0.6 (−0.6, 1.8)	−8.5 (−9.6, −7.3)
Model 2	9,484	2.9 (1.8, 4.1)	5.0 (3.9, 6.0)	0.5 (−0.7, 1.7)	−5.3 (−6.9, −3.8)
Model 3	9,484	2.7 (1.6, 3.7)	4.6 (3.6, 5.7)	0.4 (−0.8, 1.6)	−5.2 (−6.7, −3.7)
By sex (A), model 3					
Men	4,313 (45.5)	0.9 (−0.7, 2.6)	2.4 (0.7, 4.0)	−0.2 (−2.0, 1.6)	−5.0 (−7.3, −2.8)
Women	5,171 (54.5)	4.2 (2.8, 5.6)	6.2 (4.8, 7.6)	0.8 (−0.8, 2.3)	−5.6 (−7.6, −3.5)
By birth cohort (B), model 3					
Born 1935 or later	7,247 (76.4)	2.5 (0.9, 4.0)	4.5 (3.0, 6.1)	2.1 (0.4, 3.8)	−2.1 (−4.1, −0.01)
Born before 1935	2,237 (23.6)	4.3 (2.8, 5.9)	4.8 (3.2, 6.4)	1.4 (−0.4, 3.1)	−4.4 (−6.8, −2.0)
Dementia type (C), model 3					
No dementia	8,037 (84.7)	–	–	–	–
AD	831 (8.8)	2.1 (0.8, 3.5)	3.4 (2.1, 4.8)	−0.6 (−2.1, 0.9)	−5.7 (−7.7, −3.7)
VaD	147 (1.5)	4.6 (1.6, 7.6)	9.9 (6.9, 12.9)	6.0 (2.6, 9.3)	−2.1 (−6.2, 2.0)
Other dementias	469 (4.9)	3.0 (1.3, 4.8)	5.2 (3.4, 7.0)	0.6 (−1.4, 2.6)	−5.2 (−7.8, −2.6)

Model 1 Total sample (N = 9,720), age and sex adjusted; Model 2 Complete cases sample (N = 9,484), age and sex adjusted; Model 3 Complete cases sample (N = 9,484), adjusted by age, sex, education, and histories of blood pressure medication, smoking, obesity, and stroke.

to the no dementia group, the AD group had a higher SBP at HUNT1, HUNT2 and a lower SBP at HUNT4. There was no difference at HUNT3. Those with VaD had significantly higher SBP than those with AD, both at HUNT2 (6.5 mmHg higher, $p < 0.001$) and HUNT3 (6.5 mmHg higher, $p < 0.001$) (Figure 2C and Table 2). The VaD group had similar SBP as the AD group at HUNT1 ($p = 0.14$) and HUNT4 ($p = 0.12$).

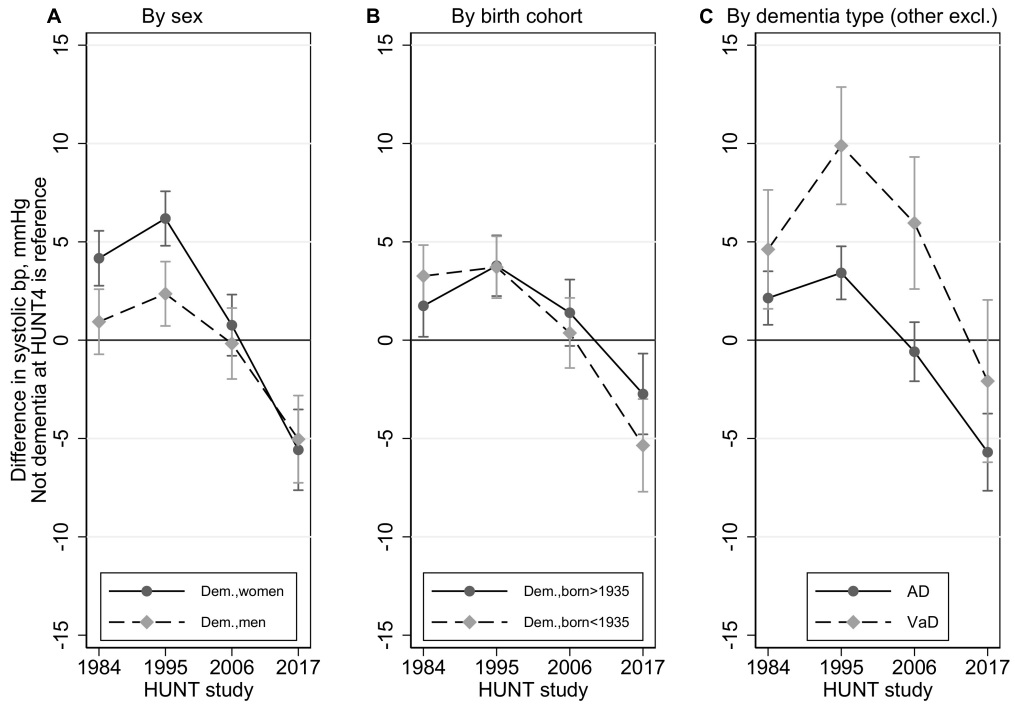


FIGURE 2
Trajectories in difference in systolic blood pressure between those with dementia at HUNT4 70+ (2017–19) vs those without dementia (reference line 0) by sex, birth cohort, and dementia type (restricted to AD and VaD) with 95% confidence intervals. Multilevel mixed methods with random intercept and slope. In all models, these time-dependent variables are included: blood pressure medication (yes/no), smoking (current, previous, never), obesity (yes/no), and history of stroke (yes/no), and the following time invariant variables: education (compulsory, secondary, tertiary), birth year, and sex.

The SBP of the "other dementias" group did not differ from the AD group from HUNT1-HUNT4 (Table 2).

Age trajectories

Fully adjusted age trajectories in SBP between those with and without dementia at HUNT4 70+ are presented in Figure 3. By visual inspection we saw in the dementia group a steady increase in SBP until 65 years of age, a stable level from 65 to 70 and a steady decrease from 70 to 90 years of age. In the no dementia group we saw that SBP increased until age 80 before it leveled off from 80 to 90.

Compared to the no dementia group the dementia group had higher SBP from 45 to 75 years of age. At 80 and 85 years of age there was no difference between the groups and at 90 years of age the dementia group had lower SBP than the no dementia group.

Sensitivity analyses

Using alternative BP measurements in the analyses did not impact the main findings (results not shown). Using the first BP measurement across all HUNT surveys 1–4, instead of the mean of two readings, shifted the BP slightly upwards for all groups. Thus,

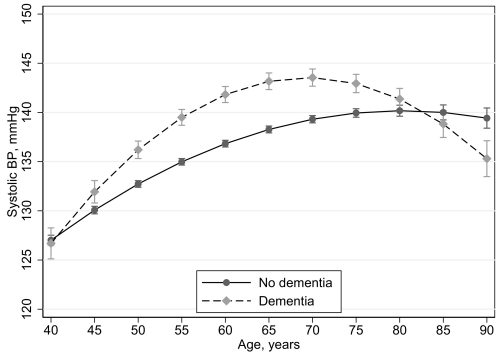


FIGURE 3
Age trajectories in systolic blood pressure between those with dementia at HUNT4 70+ (2017–19) vs those without dementia with 95% confidence intervals. Multilevel mixed methods with random intercept. In all models, these time-dependent variables are included: blood pressure medication (yes/no), smoking (current, previous, never), obesity (yes/no), and history of stroke (yes/no), and the following time invariant variables: education (compulsory, secondary, tertiary), and sex.

the choice of BP measure was robust and did not affect our conclusions.

Discussion

In this retrospective population-based cohort study, we found that persons with dementia had a higher SBP in HUNT1-HUNT2 but a lower SBP in HUNT4. The decrease in SBP in the dementia group started 10–20 years prior to dementia diagnosis at HUNT4. The results were largely confirmed in both the AD and VaD groups. Although the overall pattern of SBP trajectories remained the same across sex and age groups, some differences between groups were observed.

A pattern with higher BP in midlife but lower BP in late life in persons with dementia, compared to persons without dementia was demonstrated in the seminal study by Skoog et al. (1996) and has later been confirmed in several studies (Qiu et al., 2005; Li et al., 2007; Abell et al., 2018). However, studies on midlife hypertension cover a wide age range. Also in the present study, the age range of the participants at each assessment spans more than 30 years. However, when considering the sample in two age groups (35–49 and 50–70 years at HUNT1), we found that the pattern with higher SBP at HUNT1 and HUNT2 and lower SBP at HUNT4, in those with dementia at HUNT4 remained the same in both age groups. When modeling age trajectories of SBP we found substantial differences between the groups. The dementia group had an increase in SBP until the age of 70 and a significant drop in SBP afterward. The no dementia group experienced a slower increase in SBP but no significant drop in SBP in old age. These findings indicate that higher SBP is associated with an increased risk for dementia over a long period, from 45 years until 75 years of age and that it is only in later life that lower SBP is associated with a higher risk of dementia. These findings highlight the importance of monitoring SBP closely in older people with dementia as antihypertensive medication might need to be adjusted or even deprescribed to avoid negative outcomes, such as increased morbidity and mortality (Benetos et al., 2015). Furthermore, current evidence does not show any clear benefit of initiation of antihypertensive treatment in older age groups (Benetos et al., 2019).

Potential mechanisms that may explain the association between hypertension and dementia risk are multifaceted. It seems that higher BP and older age have a synergistic deleterious effect on the structural and functional integrity of the cerebral microcirculation (Ungvari et al., 2021). Hypertension leads to dysregulation of cerebral blood flow. This in turn exposes the cerebral microvessels to hemodynamic instability causing pathological changes termed small vessel disease. This includes endothelial dysfunction, lipohyalinosis, fibrinoid necrosis, lacunes and microhaemorrhages (McGrath et al., 2017). All these events are associated with cognitive decline. Chronic hypertension may also disrupt blood-brain-barrier (BBB) function impeding transport of essential substances into the brain and transport of waste products out of the brain. Furthermore, BBB disruption promotes neuroinflammation, synaptic dysfunction and myelin damage contributing to cognitive decline and dementia and exacerbate amyloid pathologies associated with Alzheimer's disease (Ungvari et al., 2021). Chronic hypertension is also associated with arteriosclerosis and cardiac failure, both conditions which may negatively affect cerebral blood flow and thereby cause cognitive decline. Long-standing hypertension may induce a state of hypoperfusion in the brain. It has been postulated that brain hypoperfusion is involved in the pathogenesis of AD, by constituting an upstream event before amyloid formation (De la Torre, 2018).

There might be several explanations as to why midlife hypertension, but not late-life hypertension is associated with dementia. Hypertension usually begins long before the neurodegenerative process and it acts as a powerful contributor to cognitive impairment in midlife (Veldsman et al., 2020). While hypertension is one of very few contributors to cognitive impairment in midlife, its contribution might be obscured by several other factors in late life, such as neurodegeneration because of AD. Other factors associated with development of dementia, such as people with dementia becoming more immobile, more fragile and being underweight, might in combination contribute to a decrease in blood pressure along the disease course. Recently, a new evolutionary interpretation of the brain's circulation has been proposed, indicating that the brain circulation comprises complementary low-pressure and high-pressure systems (the ambibaric brain). This model highlights the need for the development of methods of assessing the best blood pressure for the individual brains and for close monitoring of BP to optimize brain health (Hachinski and Østergaard, 2021).

Most previous studies report that dementia and AD are more common in women than in men whereas VaD is more common in men (Cao et al., 2020). This was also found in our recent study using the same HUNT4 70+ group as the present study (Gjøra et al., 2021). Suggested explanations for this sex difference include longevity (women live longer than men), biological differences (hormones, epigenetics, frailty), differences in cognitive performance and gendered social roles and opportunities (Andrew and Tierney, 2018). Recent studies have indicated that sex differences in dementia prevalence may be influenced by sex differences in the profile of dementia risk factors. A recent review concluded that higher midlife SBP was associated with a greater risk of all-cause dementia, AD and VaD in women compared to men (Blanken and Nation, 2020). Another recent study found that mid-adulthood hypertension was associated with increased dementia risk in women, but not in men (Gilsanz et al., 2017). A large UK biobank study found that the association between several midlife

cardiovascular risk factors and risk of dementia did not differ between the sexes, but BP affected men and women differently. The relationship between higher SBP and dementia risk was U-shaped in men but had a dose-response relationship in women. This difference was not affected by antihypertensive use and was consistent across dementia subtypes, like AD and VaD (Gong et al., 2021). Our study strengthens the idea that sex differences exist since SBP was higher at HUNT1 in the dementia group only in women. Furthermore, the difference in SBP between those with and without dementia was larger in women than in men at both HUNT1 and HUNT2. These differences remained when the analysis was adjusted for antihypertensive use and other risk factors which may differ between the sexes.

The association between midlife hypertension and AD risk is unclear, with most studies showing consistent association between increased midlife diastolic BP and AD risk, whereas studies regarding increased midlife BP and AD risk are conflicting. An association between late-life hypotension and AD risk has been documented in several studies (Walker et al., 2017). Our study confirms a clear pattern of SBP trajectory and AD risk, where a higher SBP in midlife and a lower SBP in late life was associated with a diagnosis of AD in late life.

The evidence supporting an association between midlife hypertension and increased VaD risk is stronger than for AD risk but the results regarding BP and VaD risk in old age are conflicting. Only a few studies have addressed this specifically (Walker et al., 2017). A registry-based study of 4.28 million individuals found that higher SBP was associated with increased VaD risk, irrespective of preceding transient ischemic attack or stroke but no inverse association in old age (Emdin et al., 2016). Our findings confirm that people with VaD have higher SBP in midlife than those with AD. Additionally we found that SBP decreases substantially in the VaD group with increasing age. However, not to the extent that VaD was associated with lower SBP compared to the no dementia group, as observed in the AD group at HUNT4. Comparisons between the AD and VaD group should be interpreted with caution as there probably is considerable overlap with a large group of people with mixed AD and VaD pathology (Custodio et al., 2017). One could argue that most dementias constitute a mix, often including AD pathology with a typical case harboring several pathologies (Boyle et al., 2018).

Strengths and limitations

The main strength of the present study is the large population-based sample, a follow-up period of more than 30 years and a thorough consensus-based method for diagnosing dementia and subtypes of dementia. By including nursing-home patients, the sample covers all levels of dementia. Furthermore, BP was measured in a standardized way and 75% of the participants had BP measurements at all four assessments. We were able to adjust for several potential confounders, limiting the chance of residual confounding.

There are a few limitations that should be taken into consideration when interpreting the results. We did not have information about race/ethnicity. However, recent reports show that only 1.6% of the population 67 + in the catchment area of the present study had a minority background (StatBank Norway, 2022). Hence, the present results may not be generalized to groups beyond a Nordic population. Although the diagnostic process conforms to the quality indicators of population-based dementia studies, the reliance on data collected by others and the lack of biomarker data may make the diagnosis less valid, especially regarding subtypes of dementia. The lack of cognitive assessments prior to HUNT4 is a major limitation. It is reasonable to assume that the participants did not have dementia at HUNT1 and HUNT2 and that very few if any had dementia at HUNT3. However, it is difficult to gauge the importance of reverse causality, especially because of disease development in the preclinical stage in some of the dementia subtypes. Even though the participation rate is relatively high, some selection bias is likely. A study on non-participation in HUNT3 showed that those who did not participate had lower socioeconomic status, higher mortality and a higher prevalence of chronic diseases (Krokstad et al., 2013). Another limitation is the substantial amount of self-reported data, which is inherent to most large-scale population studies. Even though we have adjusted for the most common confounders residual confounding cannot be excluded. Finally, our study may be prone to survival bias. This would most likely attenuate the association between the exposure in midlife (BP) and the outcome (dementia).

Conclusion

In the present study, dementia was associated with systolic hypertension in midlife but not in late life. In general, the same pattern existed across sex, age groups and types of dementia although some variation was apparent. Our findings underline that the trajectories of blood pressure should be closely monitored in clinical practice and the need for continuing antihypertensive treatment should be reappraised regularly. Separate blood pressure targets for men and women may need to be developed. To identify the ideal blood pressure for the individual brain is an urgent question in personalized medicine. Future studies should also include measurements of standing and sitting/lying blood pressure since orthostatic instability may contribute to the cognitive impairment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Regional Committee for Medical and Health Research Ethics in Norway. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GS, JS, CT, and BS were responsible for the conception and the design of the study. JS prepared the dataset. BS, GS, YW, and JS contributed to the analysis of data. GS and BS wrote the first draft. All authors gave input to the analysis plan, contributed to data interpretation and critical revisions of the manuscript, read, and approved the final manuscript.

Funding

Data collection in HUNT was largely publicly funded. The preparation of this manuscript was done without any external funding. Data collection took place as part of the four waves of the Trøndelag Health Study (HUNT), a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), the Trøndelag County Council, the Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Conflict of interest

GS participated in an advisory board meeting with BIOGEN.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abell, J. G., Kivimaki, M., Dugravot, A., Tabak, A. G., Fayosse, A., Shipley, M., et al. (2018). Association between systolic blood pressure and dementia in the Whitehall II cohort study: Role of age, duration, and threshold used to define hypertension. *Eur. Heart J.* 39, 3119–3125. doi: 10.1093/eurheartj/ehy288

Andrew, M. K., and Tierney, M. C. (2018). The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men? *Womens Health* 14:1745506518817995. doi: 10.1177/1745506518817995

Anstey, K. J., Peters, R., Mortby, M. E., Kiely, K. M., Eramudugolla, R., Cherbuin, N., et al. (2021). Association of sex differences in dementia risk factors with sex differences in memory decline in a population-based cohort spanning 20-76 years. *Sci. Rep.* 11:7710. doi: 10.1038/s41598-021-86397-7

Åsvold, B. O., Langhammer, A., Rehn, T. A., Kjelvik, G., Grøntvedt, T. V., Sørgjerd, E. P., et al. (2022). Cohort profile update: The HUNT study, Norway. *Int. J. Epidemiol.* dyac095. doi: 10.1093/ije/dyac095 [Epub ahead of print].

Benetos, A., Petrovic, M., and Strandberg, T. (2019). Hypertension Management in Older and Frail Older Patients. *Circ. Res.* 124, 1045–1060. doi: 10.1161/CIRCRESAHA.118.313236

Benetos, A., Rossignol, P., Cherubini, A., Joly, L., Grodzicki, T., Rajkumar, C., et al. (2015). Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians. *JAMA* 314, 170–180. doi: 10.1001/jama.2015.7517

Blanken, A. E., and Nation, D. A. (2020). Does Gender Influence the Relationship Between High Blood Pressure and Dementia? Highlighting Areas for Further Investigation. *J. Alzheimers Dis.* 78, 23–48. doi: 10.3233/JAD-200245

Boyle, P. A., Yu, L., Wilson, R. S., Leurgans, S. E., Schneider, J. A., and Bennett, D. A. (2018). Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann. Neurol.* 83, 74–83. doi: 10.1002/ana.25123

Cao, Q., Tan, C. C., Xu, W., Hu, H., Cao, X. P., Dong, Q., et al. (2020). The Prevalence of Dementia: A Systematic Review and Meta-Analysis. *J. Alzheimers Dis.* 73, 1157–1166. doi: 10.3233/JAD-191092

Custodio, N., Montesinos, R., Lira, D., Herrera-Pérez, E., Bardales, Y., and Valeriano-Lorenzo, L. (2017). Mixed dementia: A review of the evidence. *Dement Neuropsychol.* 11, 364–370. doi: 10.1590/1980-57642016dn11-040005

De la Torre, J. (2018). The Vascular Hypothesis of Alzheimer's Disease: A Key to Preclinical Prediction of Dementia Using Neuroimaging. *J. Alzheimers Dis.* 63, 35–52. doi: 10.3233/JAD-180004

Emdin, C. A., Rothwell, P. M., Salimi-Khorshidi, G., Kiran, A., Conrad, N., and Callender, T. (2016). Blood Pressure and Risk of Vascular Dementia: Evidence From a Primary Care Registry and a Cohort Study of Transient Ischemic Attack and Stroke. *Stroke* 47, 1429–1435. doi: 10.1161/STROKEAHA.116.012658

Frisoni, G. B., Altomare, D., Thal, D. R., Ribaldi, F., Van der kant, R., and Ossenkoppele, R. (2022). The probabilistic model of Alzheimer disease: The amyloid hypothesis revised. *Nat. Rev. Neurosci.* 23, 53–66. doi: 10.1038/s41583-021-00533-w

Gabin, J. M., Tambs, K., Saltvedt, I., Sund, E., and Holmen, J. (2017). Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: The HUNT Study. *Alzheimers Res. Ther.* 9:37. doi: 10.1186/s13195-017-0262-x

GBD Dementia Forecasting Collaborators. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 7: e105–e125

Gilsanz, P., Mayeda, E. R., Glymour, M. M., Quesenberry, C. P., Mungas, D. M., Decarli, C., et al. (2017). Female sex, early-onset hypertension, and risk of dementia. *Neurology* 89, 1886–1893. doi: 10.1212/WNL.0000000000004602

Gjøra, L., Strand, B. H., Bergh, S., Borza, T., Braekhus, A., Engedal, K., et al. (2021). Current and Future Prevalence Estimates of Mild Cognitive Impairment, Dementia, and Its Subtypes in a Population-Based Sample of People 70 Years and Older in Norway: The HUNT Study. *J. Alzheimers Dis.* 79, 1213–1226. doi: 10.3233/JAD-201275

Gong, J., Harris, K., Peters, S. A. E., and Woodward, M. (2021). Sex differences in the association between major cardiovascular risk factors in midlife and dementia: A cohort study using data from the UK Biobank. *BMC Med.* 19:110. doi: 10.1186/s12916-021-01980-z

Hachinski, V., and Østergaard, L. (2021). The Ambibaric Brain: Pathophysiological and Clinical Implications. *Stroke* 52:e259–e262. doi: 10.1161/STROKEAHA.120.033492

Hestad, K., Kveberg, B., and Engedal, K. (2005). Low blood pressure is a better predictor of cognitive deficits than the apolipoprotein e4 allele in the oldest old. *Acta Neurol Scand* 111, 323–328. doi: 10.1111/j.1600-0404.2005.00397.x

Krokstad, S., Langhammer, A., Hveem, K., Holmen, T. L., Midthjell, K., Stene, T. R., et al. (2013). Cohort Profile: The HUNT Study, Norway. *Int. J. Epidemiol.* 42, 968–977. doi: 10.1093/ije/dys095

Li, G., Rhew, I. C., Shofer, J. B., Kukull, W. A., Breitner, J. C., Peskind, E., et al. (2007). Age-varying association between blood pressure and risk of dementia in those aged 65 and older: A community-based prospective cohort study. *J. Am. Geriatr. Soc.* 55, 1161–1167. doi: 10.1111/j.1532-5415.2007.01233.x

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., and Banerjee, S. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 396, 413–446. doi: 10.1016/S0140-6736(20)30367-6

McGrath, E. R., Beiser, A. S., Decarli, C., Plourde, K. L., Vasan, R. S., Greenberg, S. M., et al. (2017). Blood pressure from mid- to late life and risk of incident dementia. *Neurology* 89, 2447–2454. doi: 10.1212/WNL.0000000000004741

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., Van belle, G., Fillenbaum, G., et al. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 39, 1159–1165. doi: 10.1212/WNL.39.9.1159

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Peters, R., Peters, J., Booth, A., and Anstey, K. J. (2020). Trajectory of blood pressure, body mass index, cholesterol and incident dementia: Systematic review. *Br. J. Psychiatry* 216, 16–28. doi: 10.1192/bjp.2019.156

Qiu, C., Winblad, B., and Fratiglioni, L. (2005). The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* 4, 487–499. doi: 10.1016/S1474-4422(05)70141-1

Qiu, C., Winblad, B., and Fratiglioni, L. (2009). Low diastolic pressure and risk of dementia in very old people: A longitudinal study. *Dement Geriatr. Cogn. Disord.* 28, 213–219. doi: 10.1159/000236913

Satizabal, C. L., Beiser, A. S., Chouraki, V., Chêne, G., Dufouil, C., and Seshadri, S. (2016). Incidence of Dementia over Three Decades in the Framingham Heart Study. *N. Engl. J. Med.* 374, 523–532. doi: 10.1056/NEJMoa1504327

Schmitt, F. A., Saxton, J., Ferris, S. H., Mackell, J., and Sun, Y. (2013). Evaluation of an 8-item Severe Impairment Battery (SIB-8) vs. the full SIB in moderate to severe Alzheimer's disease patients participating in a donepezil study. *Int. J. Clin. Pract.* 67, 1050–1056. doi: 10.1111/ijcp.12188

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., et al. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet* 347, 1141–1145. doi: 10.1016/S0140-6736(96)90608-X

StatBank Norway (2022). *[Immigrants and Norwegian borne with immigrant parents, by age, country background, statistic variable, year and region* [Online]. Oslo: Statistics Norway.

Ungvari, Z., Toth, P., Tarantini, S., Prodan, C. I., Sorond, F., Merkely, B., et al. (2021). Hypertension-induced cognitive impairment: From pathophysiology to public health. *Nat. Rev. Nephrol.* 17, 639–654. doi: 10.1038/s41581-021-00430-6

Veldsman, M., Tai, X. Y., Nichols, T., Smith, S., Peixoto, J., Manohar, S., et al. (2020). Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nat. Commun.* 11:4340. doi: 10.1038/s41467-020-18201-5

Walker, K. A., Power, M. C., and Gottesman, R. F. (2017). Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: A Review. *Curr. Hypertens. Rep.* 19, 24–24. doi: 10.1007/s11906-017-0724-3

Walker, K. A., Sharrett, A. R., Wu, A., Schneider, A. L. C., Albert, M., and Lutsey, P. L. (2019). Association of Midlife to Late-Life Blood Pressure Patterns With Incident Dementia. *JAMA* 322, 535–545. doi: 10.1001/jama.2019.10575

frontiers | Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 15 September 2022
DOI 10.3389/fnagi.2022.886023

OPEN ACCESS

EDITED BY
Helene Girouard,
Université de Montréal, Canada

REVIEWED BY
Kai Li,
Peking University, China
Michelangela Barbieri,
University of Campania Luigi Vanvitelli, Italy

*CORRESPONDENCE
Paola Nicolini
paolanikolini@fastwebnet.it

SPECIALTY SECTION
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 28 February 2022
ACCEPTED 25 August 2022
PUBLISHED 15 September 2022

CITATION
Nicolini P, Lucchi T, Abbate C, Inglese S, Tomasini E, Mari D, Rossi PD and Vicenzi M (2022) Autonomic function predicts cognitive decline in mild cognitive impairment: Evidence from power spectral analysis of heart rate variability in a longitudinal study. *Front. Aging Neurosci.* 14:886023. doi: 10.3389/fnagi.2022.886023

Autonomic function predicts cognitive decline in mild cognitive impairment: Evidence from power spectral analysis of heart rate variability in a longitudinal study

Paola Nicolini[1]*, Tiziano Lucchi[1], Carlo Abbate[1,2], Silvia Inglese[1], Emanuele Tomasini[1,2], Daniela Mari[3], Paolo D. Rossi[1] and Marco Vicenzi[4,5]

[1]Geriatric Unit, Internal Medicine Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2]IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy, [3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [4]Dyspnea Lab, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [5]Cardiovascular Disease Unit, Internal Medicine Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Background: Despite the emerging clinical relevance of heart rate variability (HRV) as a potential biomarker of cognitive decline and as a candidate target for intervention, there is a dearth of research on the prospective relationship between HRV and cognitive change. In particular, no study has addressed this issue in subjects with a diagnosis of cognitive status including cognitive impairment.

Objective: To investigate HRV as a predictor of cognitive decline in subjects with normal cognition (NC) or Mild Cognitive Impairment (MCI). Specifically, we tested the literature-based hypothesis that the HRV response to different physical challenges would predict decline in different cognitive domains.

Methods: This longitudinal study represents the approximately 3-year follow-up of a previous cross-sectional study enrolling 80 older outpatients (aged $\geq$ 65). At baseline, power spectral analysis of HRV was performed on five-minute electrocardiographic recordings at rest and during a sympathetic (active standing) and a parasympathetic (paced breathing) challenge. We focused on normalized HRV measures [normalized low frequency power (LFn) and the low frequency to high frequency power ratio (LF/HF)] and on their dynamic response from rest to challenge (Δ HRV). Extensive neuropsychological testing was used to diagnose cognitive status at baseline and to evaluate cognitive change over the follow-up *via* annualized changes in cognitive Z-scores. The association between Δ HRV and cognitive change was explored by means of linear regression, unadjusted and adjusted for potential confounders.

Results: In subjects diagnosed with MCI at baseline a greater response to a sympathetic challenge predicted a greater decline in episodic memory [adjusted model: Δ LFn, standardized regression coefficient (β) = −0.528, p = 0.019; Δ LF/HF, β = −0.643, p = 0.001] whereas a greater response to a parasympathetic challenge predicted a lesser decline in executive functioning (adjusted model: Δ LFn, β = −0.716, $p < 0.001$; Δ LF/HF, β = −0.935, $p < 0.001$).

Conclusion: Our findings provide novel insight into the link between HRV and cognition in MCI. They contribute to a better understanding of the heart-brain connection, but will require replication in larger cohorts.

KEYWORDS

autonomic nervous system, cognition, episodic memory, executive function, heart rate variability, mild cognitive impairment, longitudinal study, older adults

Introduction

Mild cognitive impairment (MCI) is a transitional state lying along the continuum between normal cognitive aging and dementia (Petersen et al., 2018). It is characterized by slight cognitive deficits with no or minimal impairment in the activities of daily living (Petersen et al., 2018). MCI is emerging as a major health issue because it is considered to be the prodromal stage of dementia (Petersen et al., 2018) and because it will affect an ever-growing number of individuals. In fact, its prevalence increases with age (Petersen et al., 2018) and is bound to soar with the exponential aging of the population [United Nations [UN], and Department of Economic and Social Affairs Population Division [DESA], 2020]. In Italy, the prevalence of MCI has been reported to reach 34% in those over 90 (Pioggiosi et al., 2006).

Heart rate variability (HRV) is the physiological phenomenon by which the heart rate (HR) changes from beat to beat, producing fluctuations in the time intervals between adjacent R waves (RR intervals) on an electrocardiographic (ECG) recording (Malik et al., 1996; Laborde et al., 2017; Shaffer and Ginsberg, 2017). HRV reflects the influence on sinus node activity of the two branches of the autonomic nervous system (ANS)—sympathetic and parasympathetic (Malik et al., 1996; Laborde et al., 2017; Shaffer and Ginsberg, 2017)—and HRV analysis therefore provides a simple and reliable method for the assessment of autonomic function in clinical research (Nicolini et al., 2012).

An increasing number of cross-sectional studies have indicated an association between cognition and HRV. They have enrolled older subjects with neurocognitive disorders (for reviews see Cheng et al., 2020; Liu et al., 2022) or generally healthy individuals across the age spectrum [for a review see Forte et al. (2019a)], more seldom within the geriatric age range (e.g., Dalise et al., 2020).

The link between cognition and HRV appears to be related to their common neural substrate which is the Central Autonomic Network (CAN). The CAN is a complex network of central nervous system regions that are implicated in both cognitive processing and in the autonomic regulation of cardiovascular function (Thayer et al., 2009; Silvani et al., 2016). It encompasses brain structures such as the hippocampus, insula, locus coeruleus and prefrontal cortex, which project to preganglionic neurons of the sympathetic and parasympathetic nervous system. Thus, the CAN represents the neuroanatomical correlate of the brain-heart axis (Silvani et al., 2016). Also, autonomic dysfunction can lead to blood pressure (BP) dysregulation (Julius and Weder, 1989) which can contribute to cognitive impairment *via* cerebral hypoperfusion (Forte et al., 2019b; Jia et al., 2021).

The clinical relevance of the connection between cognition and HRV lies in the fact that HRV could serve as a potential biomarker of cognitive decline as well as a candidate target for intervention. There is a growing recognition that dementing illnesses follow a chronic disease model in which cognitive symptoms emerge late in the course of the disease process and are predated by pathological changes and/or neural dysfunction occurring several years before (Tan et al., 2014). Since traditional cerebrospinal fluid (CSF) and neuroimaging biomarkers are costly and/or invasive and not widely accessible or applicable (Tan et al., 2014), over the last decade particular momentum has been gained by measures of brain activity (Cassani et al., 2018; Engedal et al., 2020). Although data on HRV is still sparse and novel, it is acknowledged that HRV reflects a state of the brain (Ernst, 2017) and as such it is believed to hold considerable promise as an early biomarker of cognitive impairment (Forte et al., 2019a). Also, within the context of scant and controversial pharmacological treatment for MCI (Petersen et al., 2018; Chen et al., 2021; Tampi et al., 2021), HRV-biofeedback is a convenient and increasingly popular method of enhancing HRV

(Lehrer and Gevirtz, 2014; Lehrer et al., 2020) with beneficial effects on cognitive performance across healthy and pathological populations of different ages (Lehrer et al., 2020; Tinello et al., 2021).

Nonetheless, to the best of our knowledge, no study has so far addressed the question of whether HRV can predict cognitive decline in subjects with cognitive impairment or has differentiated between individuals with normal cognition (NC) and MCI. As far as we are aware, there are only six studies in the literature that have investigated the longitudinal association between HRV and cognitive functioning (Britton et al., 2008; Mahinrad et al., 2016; Zeki Al Hazzouri et al., 2017; Knight et al., 2020; Schaich et al., 2020; Costa et al., 2021). Only one has exclusively involved older adults (Mahinrad et al., 2016) and none have included a diagnosis of cognitive status. They are all secondary analyses of large-scale epidemiological studies carried out for other purposes and therefore, despite their large sample sizes, they may suffer from some limitations. These comprise the use of routine ECG recordings and limited cognitive batteries, the lack of cognitive data at baseline, and the paucity of findings concerning episodic memory, and are described at length in the **Supplementary Introduction**.

In an attempt to fill this gap in the literature we report the findings from the 3-year cognitive follow-up of NC and MCI subjects aged ≥ 65 who were enrolled in a previous cross-sectional study on HRV and underwent HRV analysis in resting conditions and during a sympathetic and parasympathetic challenge. The study details have been described elsewhere (Nicolini et al., 2014) and will be recapitulated in the "Baseline assessment" section of the Methods.

We hypothesized that the autonomic response to the two challenges would predict decline in different cognitive domains. In particular, we supposed that the response to the sympathetic challenge would negatively predict decline in episodic memory whereas the response to the parasympathetic challenge would negatively predict decline in executive functioning.

Our assumptions were based on diverse lines of evidence from the literature that have shown that different components of the CAN are differentially involved in cognitive processing and in sympathetic versus parasympathetic autonomic control. Specifically, the hippocampus/parahippocampus, insula and locus coeruleus have been demonstrated to play a role in episodic memory and to generate sympathetic outflow, while the prefrontal cortex has been proved to be responsible for executive functioning and for parasympathetic activity. The evidence supporting these site-specific functions of the CAN is extensively reviewed in the **Supplementary Introduction**. Accordingly, within the more general relationship between cognition and HRV, several cross-sectional studies have found episodic memory to positively correlate with sympathetic HRV (Frewen et al., 2013; Nicolini et al., 2020; Hilgarter et al., 2021) and negatively correlate with parasympathetic HRV (Vasudev et al., 2012; Kim et al., 2018), and a number of investigators have noted a positive association between executive functions and parasympathetic HRV, both cross-sectionally (e.g., Forte et al., 2019a) and longitudinally (Mahinrad et al., 2016; Zeki Al Hazzouri et al., 2017; Knight et al., 2020; Schaich et al., 2020; Costa et al., 2021).

Materials and methods

Baseline assessment

Study population

We considered for inclusion 475 community-dwelling older subjects (aged ≥ 65) who consecutively attended a first geriatric visit at the Geriatric Outpatient Unit of our university hospital from January to December 2012. Referrals were made by general practitioners for a wide spectrum of age-related health problems. Eighty subjects with a known diagnosis of dementia were excluded. Of the remaining 395 subjects, 117 were eligible based on a number of exclusion criteria and were invited to undergo neuropsychological testing (see following sections). Of the 113 subjects who consented to neuropsychological testing, 23 were diagnosed with dementia and excluded, leaving 90 subjects with a diagnosis of NC or MCI. Of these, 5 declined further participation, so that 85 subjects (n = 44 NC and n = 41 MCI) were asked to take part in the subsequent clinical and autonomic assessment, which was carried out within 1 month from the neuropsychological assessment. Of the 85 participants, 2 were excluded during the autonomic assessment (n = 1 baseline respiratory rate < 9 breaths/min, n = 1 postural vasovagal reaction) and 3 during the HRV analysis (n = 1 paroxysmal supraventricular tachycardia, n = 2 excessive ectopic beats). Thus, the study ultimately enrolled 80 subjects, 40 with NC and 40 with MCI.

Exclusion criteria

Exclusion criteria were conditions precluding HRV analysis as well as diseases and medications with an established and significant effect on HRV. They have been extensively accounted for and referenced in our previous work (Nicolini et al., 2014) and were as follows: (a) non-sinus rhythm (atrial fibrillation and other arrhythmias, paced rhythms), (b) heart disease (coronary artery disease, heart failure), diabetes mellitus, neurological and psychiatric diseases (Parkinson's disease, stroke, major depression) and severe diseases (respiratory, renal, autoimmune and neoplastic), (c) cardioactive medications: beta-blockers, alpha-blockers, centrally-acting calcium-channel blockers, class I and III antiarrhythmic drugs, digoxin, (d) psychotropic medications: tricyclic antidepressants, selective serotonin-noradrenaline reuptake inhibitors, atypical antidepressants, antipsychotics and cholinesterase inhibitors.

Neuropsychological assessment

The neuropsychological assessment was performed by means of a comprehensive battery of tests covering different cognitive domains: episodic memory, executive functioning, language, visuospatial skills and ideomotor praxis. The neuropsychological tests and their references can be found in **Supplementary Table 1**. MCI was diagnosed according to consensus criteria of objective cognitive impairment on neuropsychological testing, essentially preserved daily functioning [i.e., intact basic activities of daily living (BADL) with no or minimal impairment of instrumental activities of daily living (IADL)] and no dementia (Petersen et al., 2018).

Raw neuropsychological test scores were converted to age-, sex- and education-adjusted scores based on published normative data for the Italian population and objective cognitive impairment was defined as having an adjusted score in at least one neuropsychological test below the 10th percentile of the normative score distribution. We selected the 10th percentile threshold, in accordance with several other Authors (e.g., Solfrizzi et al., 2004; Delano-Wood et al., 2009), because we believe that, relative to the 1 and 1.5 standard deviation cut-offs (i.e., the 7th and 16th percentiles), also commonly accepted (Albert et al., 2011), it provides a more appropriate balance between the risk of under- and over-diagnosing MCI.

Clinical assessment

During the clinical assessment we collected information on sociodemographics (age, sex, education), anthropometrics (Body Mass Index), lifestyle habits (alcohol and coffee consumption, physical activity), blood tests for vascular risk (glucose and lipid panel), history of hypertension (defined as current antihypertensive drug therapy), medication history, psychological symptoms [short Geriatric Depression Scale (GDS-s) and State-Trait Personality Inventory-trait anxiety subscale (STPI-TA)] and comorbidity [Cumulative Illness Rating Scale-comorbidity (CIRS-m)]. Functional status was assessed by means of the BADL and IADL scales. The Mini Mental State Examination (MMSE), corrected for age and education, was used to provide a crude measure of global cognitive functioning.

All measures used in the clinical assessment have been referenced in our previous work (Nicolini et al., 2014).

Autonomic assessment

The autonomic assessment was conducted in a quiet room, with dimmed lighting and a comfortable temperature (22–24°C) between 8:30 and 10:30 a.m. in order to minimize the effect of circadian changes in HRV. Participants were instructed to consume a light breakfast and refrain from caffeinated beverages, alcohol, smoking and vigorous physical activity in the 12 h prior to testing. Three-channel ECG recordings for HRV analysis were obtained by means of a digital Holter recorder (Spider View, Sorin Group Company).

The experimental protocol was composed of three stages: (1) supine rest with free breathing (resting condition): 15 min during which the subjects were asked to remain awake, silent and still, breathing spontaneously, (2) active standing (sympathetic challenge): 10 min in which the subjects were asked to remain still and silent, breathing spontaneously, after standing upright in as smooth a motion as possible, and (3) supine paced breathing at 12 breaths/minute (0.2 Hz) (parasympathetic challenge): 15 min during which the subjects breathed, as regularly as possible and at a "comfortable" tidal volume, in time to an electronic metronome set at 24 acoustic signals per minute (2.5 s inspiration, 2.5 s expiration). Given the nature of our study population, this stage was made as simple as possible: the first 10 min were devoted to familiarization with the breathing protocol and, throughout, the subjects were not asked to directly synchronize their breathing rhythm with the metronome but to follow voice indications from the experimenters. To allow for stabilization, only the last 5 min of each stage were analyzed. The spontaneous respiratory rate was visually monitored and subjects with a respiratory rate < 9 breaths/min (i.e., < 0.15 Hz) or > 24 breaths/min (i.e., > 0.40 Hz) were excluded from HRV analysis because, in these conditions, there is a shift of the high frequency power (HF) band that precludes proper interpretation of power spectral analysis (PSA) (Laborde et al., 2017).

Heart rate variability analysis

As far as HRV analysis was concerned, three methodological issues are worth noting. First, it was performed by PSA because the HRV Task Force guidelines (Malik et al., 1996) recommend that 5-min recordings be processed by frequency-domain methods, which are considered more sensitive (Malik and Camm, 1990), and 24-h recordings by time-domain methods, which have greater accuracy and predictive value over longer periods (Malik et al., 1996; Shaffer and Ginsberg, 2017). We employed commercial software (Synescope version 3.10, Sorin Group Company) which conducts PSA by means of the Fast Fourier Transform (FFT), after linear interpolation/resampling at 4 Hz of the discrete event series (to obtain a regularly time-sampled signal) and filtering with a Hanning window (to attenuate leakage effects). Although the software automatically detects non-sinus beats, the recordings were always manually overread by an experienced investigator, blinded to the subjects' cognitive status, in order to ensure correct QRS complex classification and rhythm identification. Since there is no clear indication in the literature as to the amount of ectopic beats that it is acceptable to remove or remove and interpolate, we selected the most restrictive criterion of 1% of the total number of beats (Nicolini et al., 2014). Thus, recordings with excessive atrial or ventricular ectopic beats were excluded from analysis as were those with other arrhythmias.

Second, PSA can yield several different indices: total power (TP, $\approx \leq 0.40$ Hz), very low frequency power (VLF, ≤ 0.04 Hz),

low frequency power (LF, 0.04–0.15 Hz), HF (0.15–0.40 Hz), normalized low frequency power [LFn = LF/(TP-VLF) × 100], normalized high frequency power [HFn = HF/(TP-VLF) × 100] and the low frequency power to high frequency power ratio (LF/HF). We chose to focus on LFn and LF/HF as markers of autonomic function because they can be considered indices of sympathetic activation/parasympathetic withdrawal (e.g., Malik et al., 1996, 2019; Montano et al., 2009) while other measures are less physiologically meaningful. TP only quantifies overall autonomic modulation (Malik et al., 1996). VLF is best assessed over 24 h (Malik et al., 1996; Shaffer and Ginsberg, 2017) and its interpretation is still uncertain (Shaffer and Ginsberg, 2017). The nature of LF is highly controversial and it has been viewed as reflecting prevalently sympathetic modulation (Malik et al., 1996), mixed sympathetic and parasympathetic modulation (Malik et al., 1996; Goldstein et al., 2011), and predominantly parasympathetic modulation (Reyes del Paso et al., 2013). Even if HF is an index of pararasympathetic modulation (Malik et al., 1996; Laborde et al., 2017; Shaffer and Ginsberg, 2017), there is evidence that HFn provides more accurate information on the state of the parasympathetic nervous system (Montano et al., 2009), also because HF is a more highly dispersed variable (Nunan et al., 2010). However, HFn was not taken into account because it is specularly correlated with LFn, which thus shares the same advantages (Montano et al., 2009; Nunan et al., 2010).

Third, we decided to concentrate on the changes of LFn and LF/HF from rest to challenge, i.e., Δ HRV = HRV challenge—HRV rest. This approach is based on the notion that Δ HRV indices are especially sensitive measures of autonomic modulation since they directly quantify the response to a stressor and explore the dynamic range of the ANS (Montano et al., 2009; Malik et al., 2019). Accordingly, much HRV literature uses Δ HRV indices (e.g., Niu et al., 2018; Suga et al., 2019; Knight et al., 2020) and studies in subjects with cognitive impairment by us (Nicolini et al., 2014, 2020) and others (e.g., Mellingsæter et al., 2015) have found differences in challenge-associated but not resting HRV. In particular, active standing Δ LFn and Δ LF/HF reflect sympathetic activation/parasympathetic withdrawal, while paced breathing Δ LFn and Δ LF/HF reflect parasympathetic activation/sympathetic withdrawal.

Follow-up

After approximately 3 years from the baseline assessment, in order to evaluate cognitive change, participants were invited to attend a second neuropsychological evaluation using the same battery of neuropsychological tests employed at baseline. A geriatric assessment was also carried out with the same instruments used to measure functional and global cognitive status at baseline, i.e., the BADL, IADL and MMSE scales.

MCI was diagnosed as previously described. Dementia was diagnosed by means of standard criteria: the National Institute on Aging-Alzheimer's association (NIA-AA) criteria for all-cause and Alzheimer's disease (AD) dementia (McKhann et al., 2011) and the American Heart Association/American Stroke Association (AHA/ASA) criteria for vascular dementia (VAD) (Gorelick et al., 2011). Further details on the diagnosis of dementia are given in the **Supplementary Materials and Methods**.

It should be noted that, although a diagnosis of cognitive status was also made at follow-up, in our study the reference for the diagnosis of cognitive status was taken to be the same time of the HRV assessment, i.e., baseline. Since at baseline subjects with NC and MCI were enrolled in the study while subjects with dementia were excluded from it, our hypotheses were tested only in the two groups of subjects diagnosed with NC and MCI at baseline (also see Limitations).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy. All participants gave written informed consent to participation in the study.

Statistical analysis

Data are reported as mean (standard deviation) for continuous variables and as number (percentage) for categorical variables.

In the two cognitive groups at baseline (NC and MCI) the neuropsychological test scores were compared at baseline and follow-up by means of the paired *t*-test or the Wilcoxon sign-ranked test as appropriate.

Linear regression was performed in the NC and MCI groups at baseline to investigate if the autonomic response at baseline predicted cognitive change from baseline to follow-up. The annualized cognitive change score (see later) was taken as dependent variable while the independent variables were the Δ HRV indices (the variables of interest) as well as potential confounders which were selected *a priori* from the literature according to their being known risk factors for cognitive decline: socio-demographic factors (age, sex and education), physical activity and physical/mental comorbidity (e.g., Roberts and Knopman, 2013). Adjustment was also carried out for baseline cognition and resting HRV. Both simple (unadjusted) and multiple (adjusted) linear regression were conducted.

In accordance with the study hypotheses, two different regression models were fitted for each of the NC and MCI groups: one with the episodic memory change score as the outcome and the sympathetic Δ HRV indices (i.e., active standing Δ LFn and Δ LF/HF) among the predictors (model 1),

the other with the executive functioning change score as the outcome and the parasympathetic Δ HRV indices (i.e., paced breathing Δ LFn and Δ LF/HF) among the predictors (model 2).

Composite scores were computed for episodic memory and executive functioning by means of a Z-score transformation. The raw scores of the individual neuropsychological tests were converted to Z-scores based on the mean and standard deviation of published normative data for the Italian population (see **Supplementary Table 1**) and then averaged to yield a domain-specific score. Scores quantifying response time (i.e., Trail-Making Tests A and B) or number or errors (i.e., Cognitive Estimates total and bizarre) were multiplied by −1 so that lower Z-scores consistently indicated poorer performance. We chose to use such composite cognitive scores because they offer several advantages: they minimize the likelihood of type I error associated with multiple testing, have greater reliability and reduce floor and ceiling effects (Morris et al., 1999; Williams et al., 2019). The cognitive change score for each domain was calculated by subtracting the baseline Z-score from the follow-up Z-score and it was then annualized by dividing it by the number of years of follow-up, so as to account for different follow-up durations among the study participants.

As far as comorbidity was concerned, with the aim of achieving a more parsimonious model, physical and mental comorbidities were combined to create an additive index. The physical burden of illness was measured by the CIRS-m score. Psychological distress was quantified by the GDS-s and STPI-TA scores. For comparability, all three scores were rescaled between 0 and 1 using a simple linear stretch according to the formula X' (rescaled score) = [X (original score) – X min (minimum score value)]/[X max (maximum score value) – X min], and were then summed. The choice to standardize these measures to a common metric by a minimum-maximum normalization rather than a Z-score transformation, as was the case for the cognitive scores, is explained hereafter. First, normative neuropsychological test data for the Italian population are well-established and are the cornerstone of neuropsychological assessment [see e.g., Spinnler and Tognoni (1987) in **Supplementary Table 1**]. On the contrary, normative data for the CIRS-m, GDS-s and STPI-TA scores are either lacking (e.g., for the CIRS-m) or limited by representativeness issues [e.g., norms for the GDS-s are available for mentally and physically healthy older adults in New Zealand (Knight et al., 1983); norms for the STPI-TA are available for a different 10-item form of the STPI-TA in a French study (Bergua et al., 2016)]. Second, although the current study sample could have been taken as a reference for norming, we believed this would have been a less appropriate approach given its relatively small size. Nonetheless, if the three scales are aggregated by using a Z-score transformation based on our sample data, the pattern of significance is unaffected (see **Supplementary Tables 2, 3**).

In order to meet the assumptions of normality and/or homoscedasticity, two outliers (standardized residual > |3|) (Stevens, 2012) were omitted from the regression analyses: one in the NC group for model 2 and one in the MCI group for model 1. None of the omitted (or included) data points were influential (Cooke's distance < 1) (Stevens, 2012). Indeed, retaining all data and repeating the analyses with non-parametric testing (i.e., Spearman's simple and partial correlations) does not substantively change the results despite some expected loss of statistical power (Sedgwick, 2015; see **Supplementary Tables 4, 5**).

The regression models satisfied the assumptions of normality (Shapiro–Wilk's test, $p > 0.05$), homoscedasticity (Breusch Pagan test, $p > 0.05$), independence of errors (Durbin Watson values between 1.5 and 2.5) and no significant multicollinearity [variance inflation factor (VIF) < 5] (Stevens, 2012).

Inflation of type I error due to multiple testing was controlled for by means of the Benjamini–Hochberg procedure (Benjamini and Hochberg, 1995) with the false discovery rate (FDR) set at the conventional level for alpha (5%).

Analyses were performed by means of the statistical packages SPSS version 25.0 (SPSS Inc., Chicago, IL, United States) and R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria) for Windows. A P value ≤ 0.05 was considered statistically significant.

Due to the novelty of the original study no power calculation was performed *a priori* (Nicolini et al., 2014). However, we conducted a power determination analysis for the current sample size with G*power (Faul et al., 2009) based on the data of Mahinrad et al. (2016) from a similarly aged population. Cohen's d for differences in cognitive test scores (Stroop, Letter-Digits Coding and Picture-Word Learning total) between the high and low HRV tertiles (d = 2.7–3.1) was converted to Cohen's f^2 (f^2 = 1.8–2.4) according to Cohen (1988) so as to obtain an effect size estimate for linear regression. Both measures indicated large effect sizes and, in order to be conservative, the lowest f^2 value (f^2 = 1.8) was used in the power analysis. The achieved sample sizes (n = 36 NC, n = 33 MCI) yielded an almost 100% power for multiple linear regression with a 5% alpha level (two tailed) and eight predictors.

Results

The mean duration of the follow-up was 2.8 years (range 2.0–3.6 years). Of the 80 subjects enrolled at baseline (n = 40 NC and n = 40 MCI), 9 were lost to follow-up: 7 due to mortality (n = 2 NC and n = 5 MCI) and 2 due to refusal to participate further (n = 1 NC and n = 1 MCI). Thus, the analyses were performed on 71 subjects: 37 who were diagnosed with NC at baseline and 34 who were diagnosed with MCI at baseline. Over the follow-up, the 37 subjects with NC at baseline either remained NC (n = 25) or evolved to MCI (n = 11) or to dementia (n = 1), while the 34 subjects with MCI at baseline

either remained MCI (n = 22) or reverted to NC (n = 1) or evolved to dementia (n = 11). The study sample at follow-up therefore included 26 subjects with NC, 33 subjects with MCI and 12 subjects with dementia. Among the 12 incident cases of dementia 9 were AD dementia and 3 VAD.

Tables 1, 2 show the neuropsychological test scores at baseline and follow-up in subjects with a baseline diagnosis of NC and MCI respectively. As expected, there was a decline in cognitive performance over time.

Tables 3, 4 show the results of the linear regression in subjects with a baseline diagnosis of NC and MCI respectively. In the NC group Δ HRV indices were not found to be significant predictors of cognitive change; although the association between standing Δ LF/HF and episodic memory decline was significant in the unadjusted model [standardized regression coefficient (β) = −0.395, p = 0.016], it became non-significant after controlling for potential confounders (β = −0.148, p = 0.383). Instead, in the MCI group all Δ HRV indices were significant predictors of cognitive change in both unadjusted and adjusted models. In particular, after adjustment for potential confounders, a greater response to a sympathetic challenge predicted a greater decline in episodic memory (Δ LFn, β = −0.528, p = 0.019; Δ LF/HF, β = −0.643, p = 0.001) whereas a greater response to a parasympathetic challenge predicted a lesser decline in executive functioning (Δ LFn, β = −0.716, $p < 0.001$; Δ LF/HF, β = −0.935, $p < 0.001$).

When the regression analyses were repeated with other Δ HRV indices (TP, LF, HF and time-domain) and with all resting HRV indices (frequency- and time-domain), none were meaningful predictors of cognitive change (with rare and scattered significances not surviving adjustment and/or correction for multiple testing, see Supplementary Tables 6–9).

For reference, the actual values of the HRV indices at rest, during the challenge and their change from rest to challenge are reported in Supplementary Table 10 for LFn and LF/HF and in Supplementary Table 11 for all other indices.

TABLE 1 Neuropsychological test scores at baseline and follow-up in subjects with NC at baseline (n = 37).

Test	Baseline	Follow-up	*P*-value
Episodic memory			
Prose recall	13.3 (2.3)	12.0 (3.1)	**0.021**[a]
ROCF-delayed recall	23.4 (5.3)	20.5 (7.0)	0.066[a]
Executive functions			
Bell Test	34.4 (0.8)	33.9 (1.1)	**0.042**[a]
Digit Cancellation Test	53.5 (5.0)	52.8 (6.4)	0.599[a]
Digit Span Forwards	5.7 (0.9)	5.6 (1.0)	0.827[b]
Digit Span Backwards	4.4 (0.6)	4.5 (0.8)	0.299[a]
Trail-Making Test A	28.8 (12.6)	30.8 (13.8)	0.561[b]
Trail-Making test B	58.5 (32.6)	74.8 (63.6)	0.451[b]
Weigl's Test	12.2 (1.7)	11.4 (2.7)	0.122[b]
Cognitive Estimates-total	10.3 (1.5)	14.2 (3.3)	< **0.001**[a]
Cognitive Estimates-bizarre	1.6 (0.8)	3.5 (2.0)	< **0.001**[a]
Raven's CPM	32.9 (3.8)	31.8 (5.4)	0.421[b]
Letter fluency	37.5 (7.6)	33.9 (8.9)	0.074[a]
Language			
Category fluency	18.6 (3.4)	18.5 (4.5)	0.777[b]
Picture naming	75.0 (2.8)	74.6 (4.3)	0.937[b]
Token Test	33.6 (1.1)	33.0 (2.8)	0.190[a]
Visuospatial skills			
ROCF-copy	34.9 (3.7)	35.0 (2.7)	0.899[b]
Copy of geometric figures	13.7 (0.4)	13.6 (0.8)	0.793[b]
Ideomotor praxis			
De Renzi's test-right upper limb	71.6 (0.8)	71.3 (1.3)	0.210[b]
De Renzi's test-left upper limb	71.0 (1.6)	71.4 (1.0)	0.142[b]

Neuropsychological test scores reported as mean (standard deviation) and demographically-adjusted. Higher scores indicate better cognitive performance except for the Trail-Making and Cognitive Estimates tests for which the reverse applies. [a]Paired t-test, [b]Wilcoxon signed-rank test. Significant results are shown in bold typeface. NC, Normal Cognition; ROCF, Rey-Osterrieth Complex Figure; CPM, Colored Progressive Matrices.

TABLE 2 Neuropsychological test scores at baseline and follow-up in subjects with MCI at baseline (n = 34).

Test	Baseline	Follow-up	*P*-value
Episodic memory			
Prose recall	8.1 (4.7)	7.8 (4.8)	0.656[a]
ROCF-delayed recall	14.3 (7.0)	11.9 (9.7)	**0.027**[b]
Executive functions			
Bell Test	31.5 (2.7)	32.1 (3.5)	0.256[a]
Digit Cancellation Test	50.1 (5.7)	46.9 (8.7)	**0.017**[b]
Digit Span Forwards	5.3 (0.9)	4.9 (1.4)	0.124[b]
Digit Span Backwards	3.7 (0.7)	3.6 (1.4)	0.774[b]
Trail-Making Test A	45.9 (23.8)	53.2 (45.7)	0.970[b]
Trail-Making test B	200.6 (136.8)	244.4 (169.1)	**0.008**[b]
Weigl's Test	9.4 (2.5)	8.6 (2.8)	0.088[a]
Cognitive Estimates-total	13.2 (2.3)	17.8 (3.4)	< **0.001**[a]
Cognitive Estimates-bizarre	2.6 (1.2)	5.1 (2.2)	< **0.001**[a]
Raven's CPM	27.5 (4.7)	29.3 (16.1)	0.428[b]
Letter fluency	30.8 (8.5)	27.8 (10.3)	**0.034**[a]
Language			
Category fluency	13.7 (3.1)	13.5 (4.1)	0.702[a]
Picture naming	70.1 (5.2)	67.1 (7.6)	**0.005**[b]
Token Test	30.8 (2.0)	30.3 (2.8)	0.316[a]
Visuospatial skills			
ROCF-copy	32.1 (4.2)	29.1 (5.9)	**0.006**[b]
Copy of geometric figures	12.4 (1.4)	12.0 (2.5)	0.889[b]
Ideomotor praxis			
De Renzi's test-right upper limb	70.5 (1.8)	69.6 (3.6)	0.136[b]
De Renzi's test-left upper limb	69.9 (1.9)	69.5 (3.6)	0.927[b]

Neuropsychological test scores reported as mean (standard deviation) and demographically-adjusted. Higher scores indicate better cognitive performance except for the Trail-Making and Cognitive Estimates tests for which the reverse applies. [a]Paired t-test, [b]Wilcoxon signed-rank test. Significant results are shown in bold typeface. MCI, Mild Cognitive Impairment; ROCF, Rey-Osterrieth Complex Figure; CPM, Colored Progressive Matrices.

TABLE 3 HRV indices as predictors of cognitive change in subjects with NC at baseline (n = 37).

	Unadjusted model[a]			Adjusted model[b]		
	β	P-value	Q-value[c]	β	P-value	Q-value[c]
Active standing						
Δ LFn (n.u)[†]	0.166	0.327	0.476	0.202	0.234	0.374
Δ LF/HF[†]	−0.395	**0.016**	**0.031**	−0.148	0.383	0.500
Paced breathing						
Δ LFn (n.u)[‡¶]	−0.086	0.617	0.672	0.098	0.630	0.672
Δ LF/HF[‡¶]	−0.143	0.406	0.500	0.071	0.786	0.786

[a]Simple linear regression with the Δ HRV index as independent variable and the annual change in the cognitive Z-score as dependent variable, [b]Multiple linear regression adjusted for age, sex, education, physical activity, morbidity (additive index), resting HRV and baseline cognitive Z-score, [c]P-value corrected for multiple testing by means of the Benjamini–Hochberg procedure with a 5% False Discovery Rate (FDR), [†]Dependent variable: annual change in episodic memory Z-score (model 1), [‡]Dependent variable: annual change in executive functioning Z-score (model 2), [¶]One outlier removed from the analyses. Significant results are shown in bold typeface. NC, Normal Cognition; β, standardized regression coefficient; LFn, normalized low frequency power; n.u, normalized units; LF/HF, low frequency power to high frequency power ratio; Δ index, index during challenge – index at rest.

TABLE 4 HRV indices as predictors of cognitive change in subjects with MCI at baseline (n = 34).

	Unadjusted model[a]			Adjusted model[b]		
	β	P-value	Q-value[c]	β	P-value	Q-value[c]
Active standing						
Δ LFn (n.u)[†¶]	−0.531	**0.001**	**0.003**	−0.528	**0.019**	**0.034**
Δ LF/HF[†¶]	−0.639	**< 0.001**	**< 0.001**	−0.643	**0.001**	**0.003**
Paced breathing						
Δ LFn (n.u)[‡]	−0.658	**< 0.001**	**< 0.001**	−0.716	**< 0.001**	**< 0.001**
Δ LF/HF[‡]	−0.620	**< 0.001**	**< 0.001**	−0.935	**< 0.001**	**< 0.001**

[a]Simple linear regression with the Δ HRV index as independent variable and the annual change in the cognitive Z-score as dependent variable, [b]Multiple linear regression adjusted for age, sex, education, physical activity, morbidity (additive index), resting HRV and baseline cognitive Z-score, [c]P-value corrected for multiple testing by means of the Benjamini–Hochberg procedure with a 5% False Discovery Rate (FDR), [†]Dependent variable: annual change in episodic memory Z-score (model 1), [‡]Dependent variable: annual change in executive functioning Z-score (model 2), [¶]One outlier removed from the analyses. Significant results are shown in bold typeface. MCI, Mild Cognitive Impairment; β, standardized regression coefficient; LFn, normalized low frequency power; n.u, normalized units; LF/HF, low frequency power to high frequency power ratio; Δ index, index during challenge – index at rest.

During paced breathing all subjects breathed at the target respiratory rate of 12 breaths/min, as indicated by the center frequency of the HF peak on PSA (0.2 Hz). Also, the respiratory rate was not significantly different between the two groups, both at rest [14.0 (2.5) NC versus 14.7 (2.9) MCI, t-test: p = 0.276] and during active standing [14.8 (2.7) NC versus 15.6 (3.2) MCI, t-test: p = 0.290], thus excluding any undue influence of respiratory rate on HRV.

The HR was slightly higher in the MCI group both at rest [65.5 (8.8) NC versus 70.5 (10.0) MCI, t-test: p = 0.029], during active standing [70.1 (10.2) NC versus 75.3 (10.2) MCI, Mann–Whitney's U-test: p = 0.062] and during paced breathing [58.1 (7.0) NC versus 62.0 (8.1) MCI, t-test: p = 0.033]. Although this is likely to be a spurious finding in the context of multiple testing, and LFn and LF/HF are not affected by HR (Zaza and Lombardi, 2001), we rerun the analyses adjusting for HR (at rest, standing and paced breathing for the resting, Δ standing and Δ paced breathing HRV indices respectively) and found unchanged results (data not shown).

The characteristics of the three cognitive groups at follow-up (NC, MCI and dementia) are shown in **Supplementary Tables 12, 13**. At baseline, the group who went on to develop dementia was older, had a lower MMSE score and engaged in less physical activity. At follow-up, cognitively impaired subjects unsurprisingly exhibited worse neuropsychological performance than cognitively normal ones. Also, there were no significant between-group differences in the BADL score while the IADL and MMSE scores were lower in subjects with dementia.

Discussion

The aim of our study was to determine whether the baseline response to a sympathetic versus parasympathetic challenge would differentially predict decline in specific cognitive domains over the follow-up in subjects diagnosed with NC and MCI at baseline. In particular, we hypothesized: (1) that the response to a sympathetic challenge would negatively predict decline in episodic memory, and (2) that the response to a parasympathetic challenge would negatively predict decline in executive functioning. While the second hypothesis was confirmed, the first one was not. In particular, significant findings were confined to the MCI group. The

characteristics of the study population were consistent with the relevant literature, the study setting as well as with the exclusion and diagnostic criteria used, and are discussed in the **Supplementary Discussion**.

Response to a parasympathetic challenge

The observation that an increased autonomic response to a parasympathetic challenge predicted a slower decline in executive functioning generally aligns with a large body of cross-sectional studies reporting an association between parasympathetic HRV indices and executive functioning (e.g., Williams et al., 2016, 2019; Forte et al., 2019a). More specifically, it conforms well to findings from the sparse longitudinal studies available in the literature. In particular, the standard deviation of the normal to normal intervals (SDNN), which is largely dependent on the parasympathetic nervous system when recorded under resting conditions (Malik et al., 1996), has been shown to have an inverse relationship with decline in the Letter-Digit Coding Test over a 3-year follow-up (Mahinrad et al., 2016) as well as a direct relationship with performance on the Stroop Test 5 years later (Zeki Al Hazzouri et al., 2017) and the Digit-Symbol Coding Test 10 years later (Schaich et al., 2020). Also, a greater parasympathetic responsivity to cognitive tasks, in terms of HF recovery and reactivity, has been demonstrated to predict an attenuated decline in executive functioning (and, to a lesser degree, in episodic memory) across a 9-year period (Knight et al., 2020). Although this latter study was unable to capture an association between the HF reactivity to an orthostatic challenge and changes in cognitive functioning, two points should be noted. First, the orthostatic stress was less intense since it involved standing from a sitting rather than a supine position. Second, there was no recovery period following the orthostatic challenge and no "true" baseline since HF reactivity was computed as HF during standing minus HF during the recovery epoch of the cognitive challenges. Given that mental stress produces parasympathetic withdrawal (Castaldo et al., 2015), as does orthostatic stress, such methodological choice is bound to reduce the magnitude of the orthostatic HF response and thus the likelihood of detecting any potential association it may have with cognition. Furthermore, even if Britton et al. (2008) concluded for no association between HRV and cognitive impairment, due to the lack of consistency of the observed associations across cognitive domains, they did identify a relationship between lower SDNN and HF and a greater 5-year decrease in the Mill Hill Test, which can be considered a measure of executive functioning (Raven, 1983). Lastly, a very recent study by Costa et al. (2021) has found that greater decline in executive functioning tests like the Digit-Symbol Coding and the Digit Span Forwards and Backwards over 6 years was predicted by greater heart rate fragmentation (HRF). This is a novel HRV metric whose physiological underpinnings are still unresolved, but are likely reflective of a degradation of the parasympathetic nervous system (Costa et al., 2017). The authors do not find an association between cognitive decline and traditional parasympathetic HRV indices [SDNN, the root mean square of successive differences of the normal to normal intervals (RMSSD) and HF], but the use of ECG recordings from in-home overnight polysomnography from an ancillary sleep study is an approach that, albeit convenient, carries some limitations. The presence of sleep-disordered breathing, highly prevalent in the study population (Chen et al., 2015), can have a confounding effect on HRV analysis both because it actually alters autonomic control and because abnormal breathing patterns distort the interpretation of the power spectrum (Tobaldini et al., 2013). The same would be true of leg movements during sleep, which are linked to autonomic activation as well as a potential source of motion artifacts (Guggisberg et al., 2007; Tobaldini et al., 2013). Moreover, despite the fact that the stationarity requirements of spectral analysis warrant the averaging of values from 5-min windows over the entire 12-h period, such averaging obscures detailed information on autonomic modulation (Malik et al., 1996).

Response to a sympathetic challenge

The finding that an increased autonomic response to a sympathetic challenge predicted a faster decline in episodic memory was contrary to our expectations. Indeed, sparse cross-sectional studies have shown that better episodic memory is associated with enhanced sympathetic activation, as indexed by increased sympathetic HRV or decreased parasympathetic HRV. In fact, LF/HF has been found to positively correlate with the episodic memory subdomain of the Montreal Cognitive Assessment (MOCA) score in older adults (Frewen et al., 2013), orthostatic Δ LFn and Δ LF/HF have been reported to positively correlate with the Prose Delayed Recall Z-score in subjects with amnestic MCI (Nicolini et al., 2020), and a stress-induced increase in SDNN has been noticed to positively correlate with the California Verbal Learning Task in healthy individuals of different ages (Hilgarter et al., 2021). Also, resting TP, which is mostly parasympathetically-mediated (Malik et al., 1996), and HF, which is a parasympathetic index, have been found to negatively correlate with Word Recall and Word/Picture Recognition in late-life depression (Vasudev et al., 2012) and with the Seoul Verbal Learning Test in subjects with MCI/dementia (Kim et al., 2018). Along the same lines, Dalise et al. (2020) have described a positive adjusted association between LF/HF and the MMSE score in geriatric outpatients representative of a real-life setting, and it is recognized that, especially at older ages, the MMSE primarily captures episodic memory (Soubelet and Salthouse, 2011; Dichgans and Leys, 2017).

There could be different potential explanations for the association between the sympathetic response and the change in episodic memory being in the opposite direction than anticipated.

First, it could be a paradoxical effect stemming from survivor bias. In fact, low HRV has been demonstrated to increase mortality in older adults (Nicolini et al., 2012) and individuals with higher HRV, by living longer, could have a greater opportunity to develop cognitive impairment. However, this interpretation seems unlikely since, in our study, loss to follow-up was small (11%) and well below the 20–40% threshold recommended for cohort studies (Ramirez-Santana, 2018). Also, sympathetic Δ HRV indices were not significantly different between the mortality and no-mortality groups (see **Supplementary Table 14**).

Second, it could reflect a regression to the mean phenomenon by which, on repeated neuropsychological testing, more extreme scores at baseline tend to converge toward the mean at follow-up, so that there is a negative association between baseline and change cognitive scores. If this is coupled with a positive association between baseline sympathetic Δ HRV indices and baseline episodic memory, the former would then have a negative longitudinal relationship with change in episodic memory, i.e., greater baseline sympathetic Δ HRV indices would be linked to greater episodic memory decline at follow-up. Nonetheless, this does not appear to be plausible because there was no significant cross-sectional association between the Δ HRV indices and cognitive tests at baseline (see **Supplementary Tables 15, 16** and the **Supplementary Discussion**) and because, in any case, regression to the mean was controlled for by adjusting the regression analyses for baseline cognitive scores (Yu and Chen, 2015).

Therefore, it is reasonable to assume that our results do not represent a statistical artifact, but, rather, have a true pathophysiological basis. Support for this view comes from a wealth of functional neuroimaging studies that have primarily focused on individuals with MCI (O'Brien et al., 2010; Sperling et al., 2010; Huijbers et al., 2015), mostly of the amnestic type, but have also spanned the cognitive continuum to include individuals with mild AD dementia (Alsop et al., 2008; Sperling et al., 2010) as well as cognitively normal older adults at genetic risk (Sperling et al., 2010; Rao et al., 2015) or not (Leal et al., 2017) for AD. They have revealed that in these subjects, relatively to controls, there is mostly a hyperactivity of the hippocampal/parahippocampal region (Alsop et al., 2008; O'Brien et al., 2010; Sperling et al., 2010; Huijbers et al., 2015; Rao et al., 2015) and, additionally, that hyperactivity is a longitudinal predictor of greater cognitive decline (O'Brien et al., 2010; Sperling et al., 2010; Huijbers et al., 2015; Rao et al., 2015; Leal et al., 2017), especially in episodic memory (O'Brien et al., 2010; Rao et al., 2015; Leal et al., 2017). These data fit in nicely with the cognitive reserve theory (Stern, 2012) according to which the brain can compensate for damage by engaging neural networks. Within this context, hyperactivity is viewed as a compensatory attempt to maintain cognitive performance in the face of cerebral pathology (Sperling et al., 2010; Stern, 2012). Likewise, hyperactivity is a harbinger of cognitive decline because it signifies that the system is working closer to its maximum capacity, i.e., closer to the threshold beyond which reserve is depleted and compensation is no longer possible (Sperling et al., 2010; Stern, 2012).

Somewhat more recently, similar evidence has emerged for the insula. Hyperactivity of the insular cortex has been demonstrated in subjects with MCI (Scarmeas et al., 2004; Alexopoulos et al., 2012; Alfini et al., 2019), mild AD dementia (Scarmeas et al., 2004) and cognitively normal older adults at genetic risk of AD (Thambisetty et al., 2010; Lin et al., 2017). Also, in subjects with MCI, insular hyperactivity has been associated with greater cognitive decline at follow-up (Devanand et al., 2006).

Although there is little functional (and even structural) neuroimaging work targeting the locus coeruleus, due to the technical challenges of imaging a small brainstem nucleus (Mather, 2021), other lines of research converge toward the notion that it, too, may exhibit an inverse U-shaped activation curve in AD (e.g., Ross et al., 2015). Thus, noradrenergic transmission would be aberrantly increased in the earlier stages and then decline later on (e.g., Ross et al., 2015).

On the whole, it can be conjectured that a greater HRV response to a sympathetic challenge at baseline could be indexing an increased activity of those cerebral regions that generate sympathetic outflow (i.e., the hippocampus/parahippocampus, insula and locus coeruleus) and that such hyperactivation may be signaling the impeding breakdown of compensatory mechanisms. Accordingly, as brain damage progresses, a point will be reached during the follow-up when compensation can no longer occur and there is a rapid deterioration of cognitive performance in the domains underpinned by these brain structures, i.e., episodic memory. It should be noted that the negative (and not positive) longitudinal association between the response to a parasympathetic challenge and executive decline would appear to imply that compensation is not operating here, and a potential reason for this is given the **Supplementary Discussion**.

Strength and limitations

The study has strengths and limitations. The study strengths include its novelty as well as the performance of a detailed and *ad hoc* neuropsychological, autonomic and clinical assessment including extensive neuropsychological testing, the use of two physical maneuvers to differentially challenge the two branches of the ANS and the collection of information on several potential confounders.

A number of limitations must also be acknowledged. Since HRV was not measured at follow-up it was not possible to track the trajectory of autonomic function over time. This would have enabled us to more thoroughly examine the relationship between HRV and cognition by determining how change in HRV associates with change in cognition (Elias and Torres, 2017), an issue which still remains unexplored. Thus, future longitudinal research should include concurrent HRV and cognitive measures.

The sample size was relatively small. Although an *a posteriori* power analysis with a large expected effect size revealed an almost 100% power for multiple linear regression (see "Statistical analysis" section), only in the MCI group the observed effect size was large according to Acock (2014) (standardized beta coefficient > 0.5). Therefore, the study may have been underpowered to detect smaller effect sizes in the NC subjects and our findings will need to be replicated in larger cohorts.

Only the HRV indices that were the main focus of the study (i.e., Δ LFn and Δ LF/HF) were found to be significant predictors of cognitive change. No meaningful results were observed for other Δ HRV indices (time- and frequency-domain) or for all resting HRV indices. This was probably the case because it is generally recognized that, in short-term ECG recordings performed in controlled experimental conditions, there is a greater sensitivity of the spectral and Δ indices (Malik and Camm, 1990; Montano et al., 2009; Malik et al., 2019). The fact that this was not true of other Δ spectral indices (i.e., Δ HF, Δ TP and Δ LF) is likely due to their statistical properties and/or physiological significance. Although HF is an index of parasympathetic modulation it is also a highly dispersed variable (Nunan et al., 2010). TP and LF are indices of joint sympathetic and parasympathetic modulation, which implies that, since sympathetic activity is related to episodic memory and parasympathetic activity is related to executive functioning, a "mixed" measure is less able to capture these domain-specific associations, because their strength is diluted by the presence of a second autonomic component unrelated to the specific cognitive domain. It cannot be excluded that with a larger sample size and/or PSA techniques based on the Welch method, which reduces HRV variance (Stoica and Moses, 2004), our findings could have been different. Also, it should be noted that, even if transformed HRV indices (i.e., LFn and LF/HF) have received ample support in the literature (e.g., Malliani et al., 1998; Montano et al., 2009; Malik et al., 2019) and have been extensively employed in HRV studies across topics (e.g., Niu et al., 2018; Dalise et al., 2020; Sun et al., 2021), they have also been questioned (e.g., Heathers, 2014). Future works should address other measures of sympathetic activity such as plasma adrenaline/noradrenaline levels (Goldstein et al., 2011) and the pre-ejection period (Wiley et al., 2021).

The nature of the sample (i.e., outpatients referred to a Geriatric Unit) can limit the generalizability of our study to the older community-dwelling population at large, and the exclusion of individuals with dementia at baseline implies that HRV was not investigated as a predictor of cognitive decline in this subset of older adults.

Lastly, although the role of HRV as indicator of brain activity is grounded in much literature (see "Introduction," **Supplementary Introduction**, and "Discussion" sections), the study lacked functional neuroimaging which could have provided deeper insight into the complexity of the relationship between HRV, cognition and the activity of specific CAN regions.

Conclusion

Our study is the first to show that the HRV response to a physical challenge predicts cognitive decline in a clinically relevant population of older adults, i.e., subjects with MCI. In particular, a differential effect was observed for the two branches of the ANS and for the episodic memory versus executive functioning domain. These findings contribute to the sparse existing literature on the prospective association between autonomic and cognitive processes, and support the emerging role of HRV as a biomarker for cognitive impairment and, potentially, as a target for intervention. Our results contribute to the understanding of the heart-brain connection, but will require confirmation from future research on larger cohorts with concurrent HRV and cognitive measurements as well as functional neuroimaging data.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PN conceived and designed the study, acquired and interpreted the data, and drafted and critically revised the manuscript. CA, SI, ET, and PR acquired and interpreted the data. DM and TL interpreted the data. MV interpreted and critically revised the data. All authors contributed to the manuscript and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.886023/full#supplementary-material

References

Acock, A. C. (2014). *A Gentle Introduction to Stata*. College Station, TX: Stata Press.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimers Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Alexopoulos, P., Sorg, C., Förschler, A., Grimmer, T., Skokou, M., Wohlschläger, A., et al. (2012). Perfusion abnormalities in mild cognitive impairment and mild dementia in Alzheimer's disease measured by pulsed arterial spin labeling MRI. *Eur. Arch. Psychiatry Clin. Neurosci.* 262, 69–77. doi: 10.1007/s00406-011-0226-2

Alfini, A. J., Weiss, L. R., Nielson, K. A., Verber, M. D., and Smith, J. C. (2019). Resting cerebral blood flow after exercise training in mild cognitive impairment. *J. Alzheimers Dis.* 67, 671–684. doi: 10.3233/JAD-180728

Alsop, D. C., Casement, M., de Bazelaire, C., Fong, T., and Press, D. Z. (2008). Hippocampal hyperperfusion in Alzheimer's disease. *Neuroimage* 42, 1267–1274. doi: 10.1016/j.neuroimage.2008.06.006

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B Stat. Methodol.* 57, 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Bergua, V., Meillon, C., Potvin, O., Ritchie, K., Tzourio, C., Bouisson, J., et al. (2016). Short STAI-Y anxiety scales: Validation and normative data for elderly subjects. *Aging Ment. Health* 20, 987–995. doi: 10.1080/13607863.2015.1051511

Britton, A., Singh-Manoux, A., Hnatkova, K., Malik, M., Marmot, M. G., and Shipley, M. (2008). The association between heart rate variability and cognitive impairment in middle-aged men and women. The Whitehall II cohort study. *Neuroepidemiology* 31, 115–121. doi: 10.1159/000148257

Cassani, R., Estarellas, M., San-Martin, R., Fraga, F. J., and Falk, T. H. (2018). Systematic review on resting-state EEG for Alzheimer's Disease Diagnosis and progression assessment. *Dis. Markers* 2018:5174815. doi: 10.1155/2018/5174815

Castaldo, R., Melillo, P., Bracale, U., Caserta, M., Triassi, M., and Pecchia, L. (2015). Acute mental stress assessment via short term HRV analysis in healthy adults: A systematic review with meta-analysis. *Biomed. Signal. Process. Control* 18, 370–377. doi: 10.1016/j.bspc.2015.02.012

Chen, X., Wang, R., Zee, P., Lutsey, P. L., Javaheri, S., Alcántara, C., et al. (2015). Racial/Ethnic differences in sleep disturbances: The multi-ethnic study of atherosclerosis (MESA). *Sleep* 38, 877–888. doi: 10.5665/sleep.4732

Chen, Y. X., Liang, N., Li, X. L., Yang, S. H., Wang, Y. P., and Shi, N. N. (2021). Diagnosis and treatment for mild cognitive impairment: A systematic review of clinical practice guidelines and consensus statements. *Front. Neurol.* 12:719849. doi: 10.3389/fneur.2021.719849

Cheng, Y. C., Huang, Y. C., and Huang, W. L. (2020). Heart rate variability in patients with dementia or neurocognitive disorders: A systematic review and meta-analysis. *Aust. N. Z. J. Psychiatry* 56, 16–27. doi: 10.1177/0004867420976853

Cohen, J. (1988). *Statistical Power Analysis For The Behavioral Sciences*. Hillsdale, MI: Lawrence Erlbaum Associates.

Costa, M. D., Davis, R. B., and Goldberger, A. L. (2017). Heart rate fragmentation: A new approach to the analysis of cardiac interbeat interval dynamics. *Front. Physiol.* 8:255. doi: 10.3389/fphys.2017.00255

Costa, M. D., Redline, S., Hughes, T. M., Heckbert, S. R., and Goldberger, A. L. (2021). Prediction of cognitive decline using heart rate fragmentation analysis: The multi-ethnic study of atherosclerosis. *Front. Aging Neurosci.* 13:708130. doi: 10.3389/fnagi.2021.708130

Dalise, A. M., Prestano, R., Fasano, R., Gambardella, A., Barbieri, M., and Rizzo, M. R. (2020). Autonomic nervous system and cognitive impairment in older patients: Evidence from long-term heart rate variability in real-life setting. *Front. Aging Neurosci.* 12:40. doi: 10.3389/fnagi.2020.00040

Delano-Wood, L., Bondi, M. W., Sacco, J., Abeles, N., Jak, A. J., Libon, D. J., et al. (2009). Heterogeneity in mild cognitive impairment: Differences in neuropsychological profile and associated white matter lesion pathology. *J. Int. Neuropsychol. Soc.* 15, 906–914. doi: 10.1017/S1355617709990257

Devanand, D. P., Habeck, C. G., Tabert, M. H., Scarmeas, N., Pelton, G. H., Moeller, J. R., et al. (2006). PET network abnormalities and cognitive decline in patients with mild cognitive impairment. *Neuropsychopharmacology* 31, 1327–1334. doi: 10.1038/sj.npp.1300942

Dichgans, M., and Leys, D. (2017). Vascular cognitive impairment. *Circ. Res.* 120, 573–591. doi: 10.1161/CIRCRESAHA.116.308426

Elias, M. F., and Torres, R. V. (2017). The renaissance of heart rate variability as a predictor of cognitive functioning. *Am. J. Hypertens.* 31, 21–23. doi: 10.1093/ajh/hpx150

Engedal, K., Barca, M. L., Høgh, P., Bo Andersen, B., Winther Dombernowsky, N., Naik, M., et al. (2020). The power of EEG to predict conversion from mild cognitive impairment and subjective cognitive decline to dementia. *Dement. Geriatr. Cogn. Disord.* 49, 38–47. doi: 10.1159/000508392

Ernst, G. (2017). Heart-rate variability-more than heart beats? *Front. Public Health* 5:240. doi: 10.3389/fpubh.2017.00240

Faul, F., Erdfelder, E., Buchner, A., and Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav. Res. Methods* 41, 1149–1160. doi: 10.3758/BRM.41.4.1149

Forte, G., Favieri, F., and Casagrande, M. (2019a). Heart rate variability and cognitive function: A systematic review. *Front. Neurosci.* 13:710. doi: 10.3389/fnins.2019.00710

Forte, G., De Pascalis, V., Favieri, F., and Casagrande, M. (2019b). Effects of blood pressure on cognitive performance: A systematic review. *J. Clin. Med.* 9:34. doi: 10.3390/jcm9010034

Frewen, J., Finucane, C., Savva, G. M., Boyle, G., Coen, R. F., and Kenny, R. A. (2013). Cognitive function is associated with impaired heart rate variability in ageing adults: The Irish longitudinal study on ageing wave one results. *Clin. Auton. Res.* 23, 313–323. doi: 10.1007/s10286-013-0214-x

Goldstein, D. S., Bentho, O., Park, M. Y., and Sharabi, Y. (2011). Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. *Exp. Physiol.* 96, 1255–1261. doi: 10.1113/expphysiol.2010.056259

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., et al. (2011). Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 42, 2672–2713. doi: 10.1161/STR.0b013e3182299496

Guggisberg, A. G., Hess, C. W., and Mathis, J. (2007). The significance of the sympathetic nervous system in the pathophysiology of periodic leg movements in sleep. *Sleep* 30, 755–766. doi: 10.1093/sleep/30.6.755

Heathers, J. A. (2014). Everything Hertz: Methodological issues in short-term frequency-domain HRV. *Front. Physiol.* 5:177. doi: 10.3389/fphys.2014.00177

Hilgarter, K., Schmid-Zalaudek, K., Csanády-Leitner, R., Mörtl, M., Rössler, A., and Lackner, H. K. (2021). Phasic heart rate variability and the association with cognitive performance: A cross-sectional study in a healthy population setting. *PLoS One* 16:e0246968. doi: 10.1371/journal.pone.0246968

Huijbers, W., Mormino, E. C., Schultz, A. P., Wigman, S., Ward, A. M., Larvie, M., et al. (2015). Amyloid-β deposition in mild cognitive impairment is associated with increased hippocampal activity, atrophy and clinical progression. *Brain* 138, 1023–1035. doi: 10.1093/brain/awv007

Jia, P., Lee, H. W. Y., Chan, J. Y. C., Yiu, K. K. L., and Tsoi, K. K. F. (2021). Long-term blood pressure variability increases risks of dementia and cognitive decline: A meta-analysis of longitudinal studies. *Hypertension* 78, 996–1004. doi: 10.1161/HYPERTENSIONAHA.121.17788

Julius, S., and Weder, A. B. (1989). Brain and the regulation of blood pressure: A hemodynamic perspective. *Clin. Exp. Hypertens. A* 11, 1–19. doi: 10.3109/10641968909045408

Kim, M. S., Yoon, J. H., and Hong, J. M. (2018). Early differentiation of dementia with Lewy bodies and Alzheimer's disease: Heart rate variability at mild cognitive impairment stage. *Clin. Neurophysiol.* 129, 1570–1578. doi: 10.1016/j.clinph.2018.05.004

Knight, E. L., Giuliano, R. J., Shank, S. W., Clarke, M. M., and Almeida, D. M. (2020). Parasympathetic and sympathetic nervous systems interactively predict change in cognitive functioning in midlife adults. *Psychophysiology* 57:e13622. doi: 10.1111/psyp.13622

Knight, R. G., Waal-Manning, H. J., and Spears, G. F. (1983). Some norms and reliability data for the state–trait anxiety inventory and the zung self-rating depression scale. *Br. J. Clin. Psychol.* 22, 245–249. doi: 10.1111/j.2044-8260.1983.tb00610.x

Laborde, S., Mosley, E., and Thayer, J. F. (2017). Heart rate variability and cardiac vagal tone in psychophysiological research – recommendations for experiment planning, data analysis, and data reporting. *Front. Psychol.* 8:213. doi: 10.3389/fpsyg.2017.00213

Leal, S. L., Landau, S. M., Bell, R. K., and Jagust, W. J. (2017). Hippocampal activation is associated with longitudinal amyloid accumulation and cognitive decline. *eLife* 6:e22978. doi: 10.7554/eLife.22978

Lehrer, P. M., and Gevirtz, R. (2014). Heart rate variability biofeedback: How and why does it work? *Front. Psychol.* 5:756. doi: 10.3389/fpsyg.2014.00756

Lehrer, P., Kaur, K., Sharma, A., Shah, K., Huseby, R., Bhavsar, J., et al. (2020). Heart rate variability biofeedback improves emotional and physical health and performance: A systematic review and meta analysis. *Appl. Psychophysiol. Biofeedback* 45, 109–129. doi: 10.1007/s10484-020-09466-z

Lin, F., Ren, P., Lo, R. Y., Chapman, B. P., Jacobs, A., Baran, T. M., et al. (2017). Insula and inferior frontal gyrus' activities protect memory performance against alzheimer's disease pathology in old age. *J. Alzheimers Dis.* 55, 669–678. doi: 10.3233/JAD-160715

Liu, K. Y., Elliott, T., Knowles, M., and Howard, R. (2022). Heart rate variability in relation to cognition and behavior in neurodegenerative diseases: A systematic review and meta-analysis. *Ageing Res. Rev.* 73:101539. doi: 10.1016/j.arr.2021.101539

Mahinrad, S., Jukema, J. W., van Heemst, D., Macfarlane, P. W., Clark, E. N., de Craen, A. J., et al. (2016). 10-Second heart rate variability and cognitive function in old age. *Neurology* 86, 1120–1127. doi: 10.1212/WNL.0000000000002499

Malik, M., and Camm, A. J. (1990). Heart rate variability. *Clin. Cardiol.* 13, 570–576. doi: 10.1002/clc.4960130811

Malik, M., Hnatkova, K., Huikuri, H. V., Lombardi, F., Schmidt, G., and Zabel, M. (2019). CrossTalk proposal: Heart rate variability is a valid measure of cardiac autonomic responsiveness. *J. Physiol.* 597, 2595–2598. doi: 10.1113/JP277500

Malik, M., Thomas Bigger, J., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., et al. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Eur. Heart J.* 17, 354–381. doi: 10.1093/oxfordjournals.eurheartj.a014868

Malliani, A., Pagani, M., Montano, N., and Mela, G. S. (1998). Sympathovagal balance: A reappraisal. *Circulation* 98, 2640–2643.

Mather, M. (2021). Noradrenaline in the aging brain: Promoting cognitive reserve or accelerating Alzheimer's disease? *Semin. Cell Dev. Biol.* 116, 108–124. doi: 10.1016/j.semcdb.2021.05.013

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R. Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Mellingsæter, M. R., Wyller, T. B., Ranhoff, A. H., Bogdanovic, N., and Wyller, V. B. (2015). Reduced sympathetic response to head-up tilt in subjects with mild cognitive impairment or mild Alzheimer's dementia. *Dement. Geriatr. Cogn. Dis. Extra* 5, 107–115. doi: 10.1159/000375297

Montano, N., Porta, A., Cogliati, C., Costantino, G., Tobaldini, E., Casali, K. R., et al. (2009). Heart rate variability explored in the frequency domain: A tool to investigate the link between heart and behavior. *Neurosci. Biobehav. Rev.* 33, 71–80. doi: 10.1016/j.neubiorev.2008.07.006

Morris, M. C., Evans, D. A., Hebert, L. E., and Bienias, J. L. (1999). Methodological issues in the study of cognitive decline. *Am. J. Epidemiol.* 149, 789–793. doi: 10.1093/oxfordjournals.aje.a009893

Nicolini, P., Ciulla, M. M., De Asmundis, C., Magrini, F., and Brugada, P. (2012). The prognostic value of heart rate variability in the elderly, changing the perspective: From sympathovagal balance to chaos theory. *Pacing Clin. Electrophysiol.* 35, 622–638. doi: 10.1111/j.1540-8159.2012.03335.x

Nicolini, P., Ciulla, M. M., Malfatto, G., Abbate, C., Mari, D., Rossi, P. D., et al. (2014). Autonomic dysfunction in mild cognitive impairment: Evidence from power spectral analysis of heart rate variability in a cross-sectional case-control study. *PLoS One* 9:e96656. doi: 10.1371/journal.pone.0096656

Nicolini, P., Mari, D., Abbate, C., Inglese, S., Bertagnoli, L., Tomasini, E., et al. (2020). Autonomic function in amnestic and non-amnestic mild cognitive impairment: Spectral heart rate variability analysis provides evidence for a brain-heart axis. *Sci. Rep.* 10:11661. doi: 10.1038/s41598-020-68131-x

Niu, S. W., Huang, J. C., Chen, S. C., Lin, H. Y., Kuo, I. C., Wu, P. Y., et al. (2018). Association between age and changes in heart rate variability after hemodialysis in patients with diabetes. *Front. Aging Neurosci.* 10:43. doi: 10.3389/fnagi.2018.00043

Nunan, D., Sandercock, G. R., and Brodie, D. A. (2010). A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin. Electrophysiol.* 33, 1407–1417. doi: 10.1111/j.1540-8159.2010.02841.x

O'Brien, J. L., O'Keefe, K. M., LaViolette, P. S., DeLuca, A. N., Blacker, D., Dickerson, B. C., et al. (2010). Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology* 74, 1969–1976. doi: 10.1212/WNL.0b013e3181e3966e

Petersen, R. C., Lopez, O., Armstrong, M. J., Getchius, T. S. D., Ganguli, M., Gloss, D., et al. (2018). Practice guideline update summary: Mild cognitive impairment: Report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. *Neurology* 90, 126–135. doi: 10.1212/WNL.0000000000004826

Pioggiosi, P. P., Berardi, D., Ferrari, B., Quartesan, R., and De Ronchi, D. (2006). Occurrence of cognitive impairment after age 90: MCI and other broadly used concepts. *Brain Res. Bull.* 68, 227–232. doi: 10.1016/j.brainresbull.2005.06.039

Ramirez-Santana, M. (2018). "Limitations and Biases in Cohort Studies," in *Cohort Studies in Health Sciences*, ed. R. Mauricio Barría (London: IntechOpen), 29–46.

Rao, S. M., Bonner-Jackson, A., Nielson, K. A., Seidenberg, M., Smith, J. C., Woodard, J. L., et al. (2015). Genetic risk for Alzheimer's disease alters the five-year trajectory of semantic memory activation in cognitively intact elders. *Neuroimage* 111, 136–146. doi: 10.1016/j.neuroimage.2015.02.011

Raven, J. (1983). "The Progressive Matrices and Mill Hill Vocabulary Scale in Western Societies," in *Human Assessment and Cultural Factors*, eds S. H. Irvine and J. W. Berry (Boston: Springer), 107–114.

Reyes del Paso, G. A., Langewitz, W., Mulder, L. J., van Roon, A., and Duschek, S. (2013). The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology* 50, 477–487. doi: 10.1111/psyp.12027

Roberts, R., and Knopman, D. S. (2013). Classification and epidemiology of MCI. *Clin. Geriatr. Med.* 29, 753–772. doi: 10.1016/j.cger.2013.07.003

Ross, J. A., McGonigle, P., and Van Bockstaele, E. J. (2015). Locus Coeruleus, norepinephrine and Aβ peptides in Alzheimer's disease. *Neurobiol. Stress* 2, 73–84. doi: 10.1016/j.ynstr.2015.09.002

Scarmeas, N., Habeck, C. G., Zarahn, E., Anderson, K. E., Park, A., Hilton, J., et al. (2004). Covariance PET patterns in early Alzheimer's disease and subjects with cognitive impairment but no dementia: Utility in group discrimination and correlations with functional performance. *Neuroimage* 23, 35–45. doi: 10.1016/j.neuroimage.2004.04.032

Schaich, C. L., Malaver, D., Chen, H., Shaltout, H. A., Zeki Al Hazzouri, A., Herrington, D. M., et al. (2020). Association of heart rate variability with cognitive performance: The multi-ethnic study of atherosclerosis. *J. Am. Heart Assoc.* 9:e013827. doi: 10.1161/JAHA.119.013827

Sedgwick, P. (2015). A comparison of parametric and non-parametric statistical tests. *BMJ* 350:h2053. doi: 10.1136/bmj.h2053

Shaffer, F., and Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Front. Public Health* 5:258. doi: 10.3389/fpubh.2017.00258

Silvani, A., Calandra-Buonaura, G., Dampney, R. A., and Cortelli, P. (2016). Brain-heart interactions: Physiology and clinical implications. *Philos. Trans. A Math. Phys. Eng. Sci.* 374:20150181. doi: 10.1098/rsta.2015.0181

Solfrizzi, V., Panza, F., Colacicco, A. M., D'Introno, A., Capurso, C., Torres, F., et al. (2004). Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* 63, 1882–1891. doi: 10.1212/01.wnl.0000144281.38555.e3

Soubelet, A., and Salthouse, T. A. (2011). Correlates of level and change in the Mini-Mental State Examination. *Psychol. Assess.* 23, 811–818. doi: 10.1037/a0023401

Sperling, R. A., Dickerson, B. C., Pihlajamaki, M., Vannini, P., LaViolette, P. S., Vitolo, O. V., et al. (2010). Functional alterations in memory networks in early Alzheimer's disease. *Neuromol. Med.* 12, 27–43. doi: 10.1007/s12017-009-8109-7

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* 11, 1006–1012. doi: 10.1016/S1474-4422(12)70191-6

Stevens, J. P. (2012). *Applied Multivariate Statistics for the Social Sciences*. New York, NY: Routledge.

Stoica, P., and Moses, R. (2004). *Spectral Analysis of Signals*. Upper Saddle River, NJ: Prentice Hall.

Suga, A., Uraguchi, M., Tange, A., Ishikawa, H., and Ohira, H. (2019). Cardiac interaction between mother and infant: Enhancement of heart rate variability. *Sci. Rep.* 9:20019. doi: 10.1038/s41598-019-56204-5

Sun, J., Zhang, Q., Lin, B., He, M., Pang, Y., Liang, Q., et al. (2021). Association between postoperative long-term heart rate variability and postoperative delirium in elderly patients undergoing orthopedic surgery: A prospective cohort study. *Front. Aging Neurosci.* 13:646253. doi: 10.3389/fnagi.2021.646253

Tampi, R. R., Forester, B. P., and Agronin, M. (2021). Aducanumab: Evidence from clinical trial data and controversies. *Drugs Context* 10, 2021–2027. doi: 10.7573/dic.2021-7-3

Tan, C. C., Yu, J. T., and Tan, L. (2014). Biomarkers for preclinical Alzheimer's disease. *J. Alzheimers Dis.* 42, 1051–1069. doi: 10.3233/JAD-140843

Thambisetty, M., Beason-Held, L., An, Y., Kraut, M. A., and Resnick, S. M. (2010). APOE epsilon4 genotype and longitudinal changes in cerebral blood flow in normal aging. *Arch. Neurol.* 67, 93–98. doi: 10.1001/archneurol.2009.913

Thayer, J. F., Hansen, A. L., Saus-Rose, E., and Johnsen, B. H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann. Behav. Med.* 37, 141–153. doi: 10.1007/s12160-009-9101-z

Tinello, D., Kliegel, M., and Zuber, S. (2021). Does heart rate variability biofeedback enhance executive functions across the lifespan? A systematic review. *J. Cogn. Enhanc.* 1, 126–142. doi: 10.1007/s41465-021-00218-3

Tobaldini, E., Nobili, L., Strada, S., Casali, K. R., Braghiroli, A., and Montano, N. (2013). Heart rate variability in normal and pathological sleep. *Front. Physiol.* 4:294. doi: 10.3389/fphys.2013.00294

United Nations [UN], and Department of Economic and Social Affairs Population Division [DESA] (2020). *World Population Ageing 2020 Highlights: Living Arrangements Of Older Persons*. New York, NY: United Nations.

Vasudev, A., Saxby, B. K., O'Brien, J. T., Colloby, S. J., Firbank, M. J., Brooker, H., et al. (2012). Relationship between cognition, magnetic resonance white matter hyperintensities, and cardiovascular autonomic changes in late-life depression. *Am. J. Geriatr. Psychiatry* 20, 691–699. doi: 10.1097/JGP.0b013e31824c0435

Wiley, C. R., Pourmand, V., Thayer, J. F., and Williams, D. P. (2021). A close examination of the use of systolic time intervals in the calculation of impedance derived cardiac autonomic balance and regulation. *Front. Neurosci.* 15:625276. doi: 10.3389/fnins.2021.625276

Williams, D. P., Thayer, J. F., and Koenig, J. (2016). Resting cardiac vagal tone predicts intraindividual reaction time variability during an attention task in a sample of young and healthy adults. *Psychophysiology* 53, 1843–1851. doi: 10.1111/psyp.12739

Williams, P. G., Cribbet, M. R., Tinajero, R., Rau, H. K., Thayer, J. F., and Suchy, Y. (2019). The association between individual differences in executive functioning and resting high-frequency heart rate variability. *Biol. Psychol.* 148:107772. doi: 10.1016/j.biopsycho.2019.107772

Yu, R., and Chen, L. (2015). The need to control for regression to the mean in social psychology studies. *Front. Psychol.* 5:1574. doi: 10.3389/fpsyg.2014.01574

Zaza, A., and Lombardi, F. (2001). Autonomic indexes based on the analysis of heart rate variability: A view from the sinus node. *Cardiovasc. Res.* 50, 434–442. doi: 10.1016/s0008-6363(01)00240-1

Zeki Al Hazzouri, A., Elfassy, T., Carnethon, M. R., Lloyd-Jones, D. M., and Yaffe, K. (2017). Heart rate variability and cognitive function in middle-age adults: The coronary artery risk development in young adults. *Am. J. Hypertens.* 31, 27–34. doi: 10.1093/ajh/hpx125

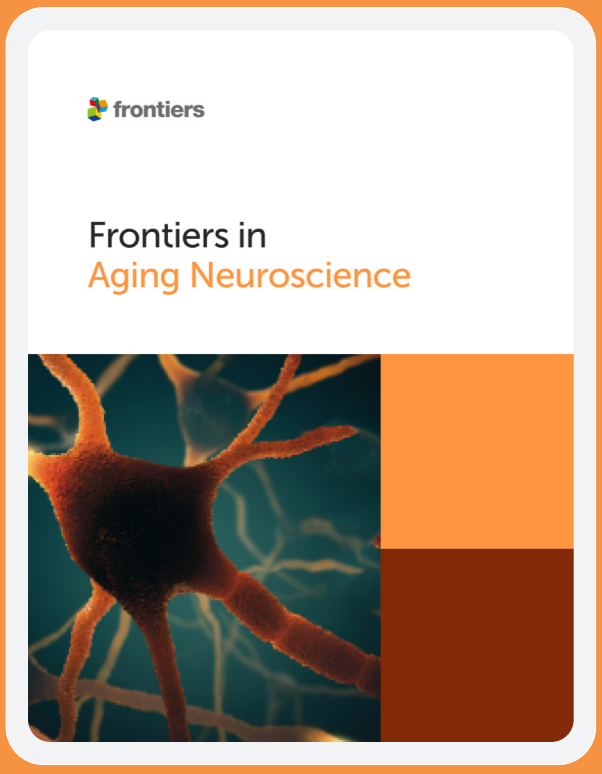
Frontiers in
Aging Neuroscience

Explores the mechanisms of central nervous system aging and age-related neural disease

The third most-cited journal in the field of geriatrics and gerontology, with a focus on understanding the mechanistic processes associated with central nervous system aging.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact