Cognitive and Neuroimaging Markers of Vascular Cognitive Impairment

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Abstract

Detection of incipient cognitive impairment and dementia pathophysiology is critical to identifying preclinical populations and target potentially disease modifying interventions towards them. There are currently concerted efforts for such detection in Alzheimer's disease (AD). By contrast, the examination of cognitive markers and their relationship to biomarkers for vascular cognitive impairment (VCI) is far less established, despite VCI being highly prevalent and often concomitantly presenting with AD. Critically, vascular risk factors are currently associated with the most viable treatment options via pharmacological and non-pharmacological intervention, hence developing selective and sensitive methods for the identification of vascular factors have important implications for modifying dementia disease trajectories. As outlined in Chapter one, this thesis focuses on uncovering spatial navigation deficits in established and preclinical VCI and investigates potential brain dysconnectivity in the frontoparietal regions and overlapping navigation systems. Chapter two reveals egocentric orientation deficits in established VCI to distinguish it from AD. In Chapter three, the VCI case study, RK, who previously displayed spatial navigation deficits is followed up three years after initial diagnosis. Results suggest an ongoing egocentric orientation deficit whilst there are improvements in cognitive scores assessed using conventional neuropsychological assessments. Diffusion tensor imaging (DTI) analysis suggests reduced superior longitudinal fasciculus (SLF) integrity to parietal segments. Chapter four shows that a novel test battery of navigation and ERP components capture deficits that precede the onset of general cognitive decline assessed by typical neuropsychological assessment in preclinical VCI. Taken together, this research advances our conceptual understanding of the pathological changes to cognition that characterise VCI and at-risk individuals.

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My acknowledgements would not complete without recognising my parents Susan and Michael. Thank you for raising tenacious and determined children.

Finally, this thesis is a love letter to my 16-year-old self on GCSE results day in August 2003. You are smart, you are capable, and you can do this. It's just that the time was wrong.

I, Louis Renoult (primary supervisor), confirm that any required taught courses have been satisfactorily completed:

Author's declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Parts of this work have been presented at conferences and published in academic journals.

Ethical approval

Ethical approval for the work in this thesis has been granted by the Faculty of Medicine and Health Sciences Ethics Committee at the University of East Anglia.

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Puthusseryppady, V., Manley, E., **Lowry, E.,** Patel, M., & Hornberger, M. (2020). Impact of road
network structure on dementia-related missing incidents: a spatial buffer approach. *Scientific reports*, *10*(1), 1-9.

Puthusseryppady, V., Emrich-Mills, L., **Lowry, E.,** Patel, M., & Hornberger, M. (2020). Spatial disorientation in Alzheimer's disease: the missing path from virtual reality to real world. *Frontiers in Aging Neuroscience*, *12*.

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Abbreviations

ACA	anterior cerebral artery
ACE	Addenbrookes cognitive examination
AD	Alzheimer's disease
APOE	Apolipoprotein E subtype
BMET	Brief Memory and Executive Test
BMI	body mass index
CAA	cerebral amyloid angiopathy
COT	Clock Orientation Test
dBP	diastolic blood pressure
DMN	default mode network
DSST	digit symbol substitution test
DTI	diffusion tensor imaging
DWRT	delayed word recall test
EEG	Electroencephalogram
ERP	Event Related Potentials
FCSRT	Free and Cued Selective Reminding Test
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
lh SLFP	left hemisphere superior longitudinal fasciculus parietal
lh SLFT	left hemisphere superior longitudinal fasciculus temporal
MCA	middle cerebral artery
MCI	mild cognitive impairment
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
MTL	medial temporal lobe
OCS	Oxford cognitive screen

PCA	posterior cerebral artery
PCC	posterior parietal cortex
PFC	prefrontal cortex
rh SLFP	right hemisphere superior longitudinal fasciculus parietal
rh SLFT	right hemisphere superior longitudinal fasciculus temporal
RAVLT	Rey Auditory Verbal Learning Test
ROC	receiver operating characteristics
RSC	retrosplenial cortex
sBP	systolic blood pressure
SHQ	Sea Hero Quest
SLF	superior longitudinal fasciculus
TMT	Trail making task
VCI	Vascular Cognitive Impairment
VOSP	Visual Object and Space Perception Battery
VST	Virtual Supermarket Test
WFT	word fluency test
WM	white matter
WMH	white matter hyperintensities

Impact of COVID-19

At the start of this PhD project, the study outlined in Chapter four was intended to be longitudinal in nature, with a follow-up scheduled 18 months after the initial testing sessions. Data collection started for this study in November 2019 and in addition to the participants discussed in Chapter four, a further 17 participants had been recruited and screened but were unable to attend testing sessions due to the UK going into a lockdown. In addition to this, MRI brain scans were scheduled to take place at the Norfolk and Norwich University Hospital from May to June 2020 for all the study participants in Chapter four. Due to the impact of the COVID-19 pandemic all the above was unable to take place.

Maternity Leave

From July 2020 to May 2021, I had a break in study to have my daughter.

Chapter 1: General Introduction

Published Paper

Lowry, E., Puthusseryppady, V., Johnen, A. K., Renoult, L., & Hornberger, M. (2021). Cognitive and neuroimaging markers for preclinical vascular cognitive impairment. *Cerebral Circulation-Cognition and Behavior*, *2*, 100029.

Introduction

Cardiovascular disease and cognitive impairment is an increasing public health problem (Roth et al., 2018). Evidence is emerging to suggest almost a third of dementias can be prevented by modifying lifestyle factors, namely our cardiovascular health (Livingston et al., 2020). Accumulating evidence suggests a link between cardiovascular health, changes in brain structure and subsequent cognitive deterioration. The pathophysiology is intricate, spanning a wide variety of genetic, lifestyle, environmental and health related exposures (Littlejohns et al., 2019). Although cardiovascular interactions are thought to be implicated in a variety of neurodegenerative disorders (Sweeney et al., 2018). The most established link is with Vascular Cognitive Impairment (VCI).

VCI is an umbrella term for conditions related to disrupted cerebral blood flow to the brain and subsequent cognitive decline. Traditionally, post-stroke dementia (dementia following stroke-related brain injury) was considered the main contributor to VCI, however it is now clear that it only represents a small portion of VCI, with other incipient neurovascular changes (subcortical, multi-infarct and mixed dementias) significantly contributing to VCI (Skrobot et al., 2017). This also dovetails with findings showing that up to 80% of dementia patients show vascular pathology at autopsy (Sachdev et al., 2014; Toledo et al., 2013) and there appears to be a

reciprocal relationship between neurovascular and neurodegenerative pathology (Attems & Jellinger, 2014). Importantly, cognitive decline in VCI can be insidious and evolve over many years without 'classic' stroke symptomology. In the next section, I will review current cognitive markers used in VCI before exploring preclinical cognitive measures and their neural correlates.

The aim of this review is to examine the current evidence of cognitive marker correlates to VCI pathology. I begin by examining the existing evidence concerning the neuroimaging profile of symptomatic VCI and its cognitive characteristics. Next, I discuss midlife risk factors that predict VCI. Then I discuss preclinical cognitive hallmarks of VCI informed by insights from neuropsychological assessment, network connectivity and ERP/EEG experimental findings. Finally, I discuss the potential utility of spatial navigation as a mechanism of assessing cognitive decline, followed by limitations of current cognitive assessments and the need for future cognitive test development to inform diagnostic assessment. As well as intervention outcome measures for preclinical VCI. In turn, these tests will inform earlier detection of vascular changes and allow implementation of disease intervention approaches.

Pathophysiology of symptomatic VCI

Hallmark physiological features leading to the development of VCI include; large vessel infarct, microinfarct, macroscopic haemorrhages and microbleeds, lacunar infarcts, white matter hyperintensities (WMH), arteriolosclerosis (hardening of the arteries) and atherosclerosis (plaque build-up narrowing arteries) (see, Figure 1) (for review, see Dichgans & Leyes, 2017).

The occurrence of large or small infarcts is recognised to cause cognitive decline. Large vessel disease associated with VCI relates to arteriolosclerosis in large vessels and cardiac embolic events characterised by a sudden onset and have stepwise deterioration, typically associated with stroke. It can consist of multi infarcts (cortical and subcortical) or a single strategic infarct. By contrast, small vessel disease is characterised by multiple small, ischemic white matter change dilation of perivascular spaces and cortical microinfarcts and microhaemorrhages lacunar infarcts and diffuse ischaemic white matter lesions. Lacunar infarcts are typically 2-15mm noncortical in nature and are caused by occlusion of a single penetrating branch of a large cerebral artery. MRI correlates of small vessel disease include multiple lacunes, extensive white matter hyperintensities (small white matter lesions) and subcortical hyperintensities (Wardlaw et al., 2013). Global reductions in cerebral perfusion can result in transient or permanent ischemia leading to cognitive disturbance and both macroscopic intracerebral haemorrhage and microbleeds as well as loss of white matter and grey matter can also be associated with VCI (Dichgans & Leyes, 2017).

Recent findings suggest cumulative intracranial small vessel changes rather than large cortical lesions play a major role in VCI (Kalaria, 2012). These microinfarcts cannot be easily delineated and cognitive and functional decline can be subtle and take place over a number of years before subjective complaints become apparent. Predominant locations of these pathological features include the carotid artery, Circle of Willis and proximal branches of the middle cerebral artery, anterior cerebral artery and posterior cerebral artery, whilst other regions include the white matter tracts running between the basal ganglia, internal and external capsules (Kalaria, 2012). More recently, there have been attempts to redefine VCI to include mild and major forms and

subtypes (Skrobot et al., 2017), to overcome the lack of availability of a consistently used diagnostic criteria. Although, it is not clear how widely this has been adopted.

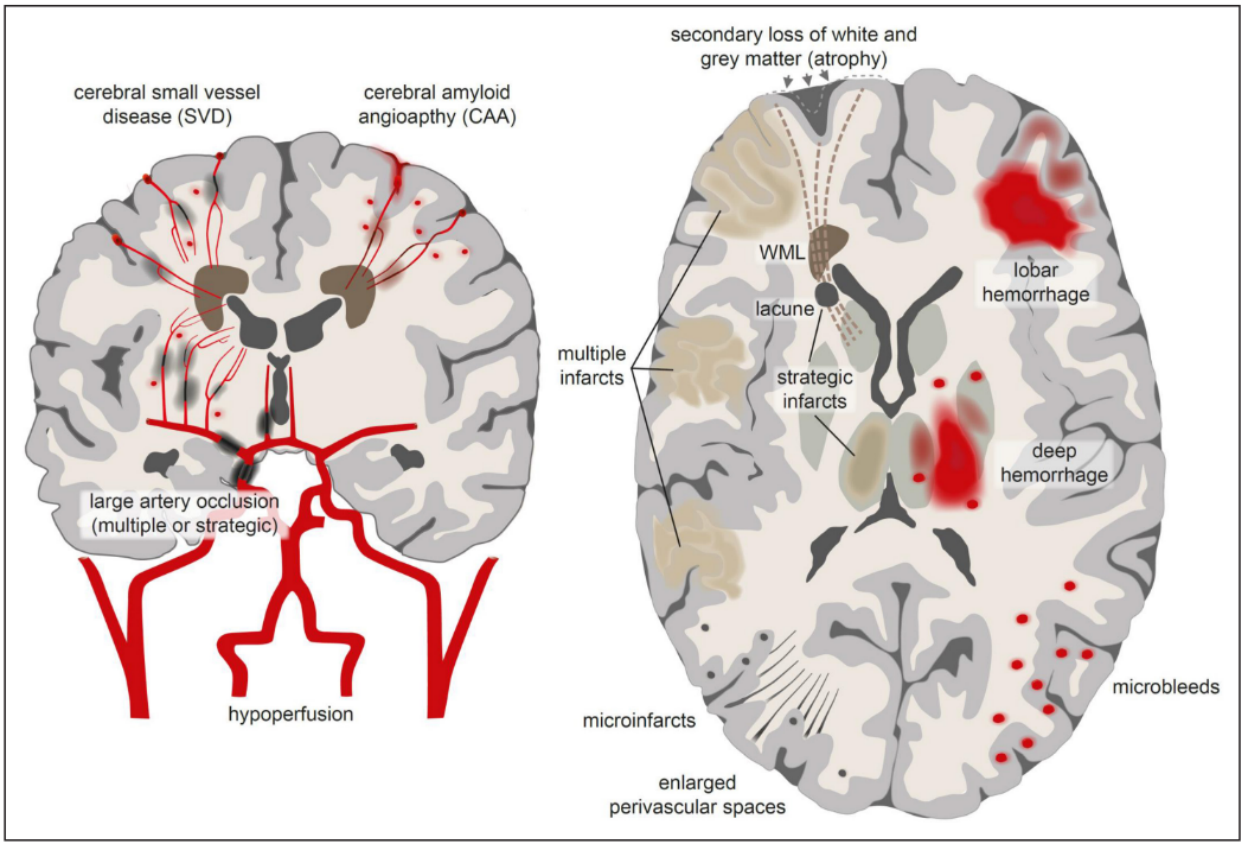

Figure 1. Major mechanisms underlying vascular cognitive impairment. Left image indicates vascular causes. Right image indicates brain parenchymal lesions associated with VCI. Figure adopted from Dichgans & Leys, 2017.

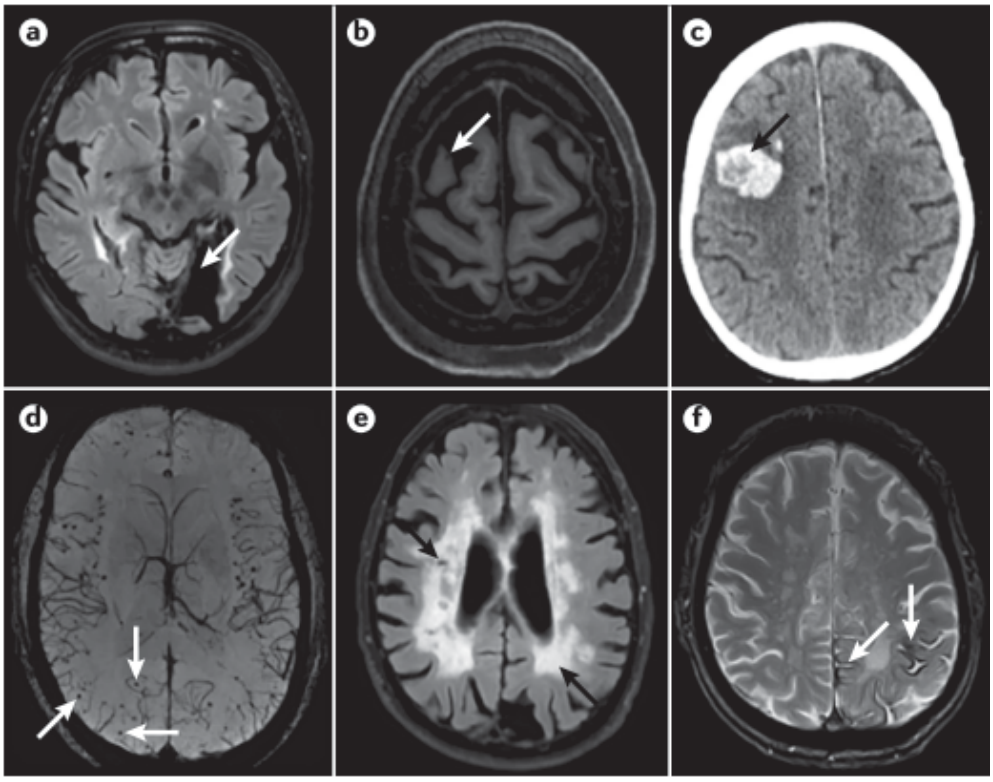

Figure 2. MRI manifestations of cerebrovascular disease leading to VCI symptomology. (A) Large vessel infarct detected using fluid-attenuated inversion recovery (FLAIR) sequences (B) Microinfarct detected using T1-weighted MRI (C) Macroscopic Haemorrhage detected using CT (D) Multiple microbleeds indicative of cerebral amyloid angiopathy detected using susceptibility- weighted imaging (E) Extensive white matter hyperintensities (WMHs) detected using FLAIR sequences (arrows point to WMHs). (F) Superficial siderosis detected using susceptibility weighted imaging. Figure from van der Flier, et al., 2017.

Neuroimaging characteristics of symptomatic VCI

The current MRI standards to detect VCI are grounded in differing presentations of small vessel disease (STRIVE)(Skrobot et al., 2017; Wardlaw et al., 2013) (see, Table 1.). White matter hyperintensities are thought to be strongly associated with vascular risk factors and cerebrovascular disease (Wardlaw et al., 2013) but guidance stops short of offering predictive markers of VCI. Whilst, VCI neuropathology guidelines (VCING)(Skrobot et al., 2016) conclude the best individual predictors of VCI were at least one large infarct, moderate to severe occipital leptomeningeal cerebral amyloid angiopathy (CAA) and moderate to severe myelin loss

in at least one brain region. Predictive probabilities increase exponentially when a combination of these pathological features were observed. Interestingly, age, gender, Apolipoprotein E (APOE) and Braak stage were not associated with cognitive impairment (Skrobot et al., 2017).

According to a prominent review examining clinicopathological evidence to link cerebrovascular changes to cognitive impairment, the key substrates of vascular and parenchymal change associated with vascular-related cognitive decline show a high frequency with small or micro infarcts in the cortical and subcortical regions, cribriform change and perivascular spacing in the WM, basal ganglia, internal and external capsules and demyelination and oligodendrocyte changes in the white matter (Kalaria, 2016). More moderate associations shown between VCI and plaque build-up and occlusive disease in the Circle of Willis and proximal branches of the MCA, ACA and PCA, cystic infarcts and white matter, basal ganglia and thalamus and hippocampal atrophy and sclerosis in CA1-CA4 (Kalaria, 2016). Whilst, the accumulation of cerebral microbleeds manifest in deficits to executive function and processing speed in frank VCI (Nannoni et al., 2022). This heterogeneous and multifactorial model of VCI makes it difficult to predict the emergence of anatomical damage and associated cognitive impairment.

Table 1. Neuroimaging criteria for Vascular Cognitive Impairment.

Diagnostic criteria	
VICING (Skrobot et al., 2017)	1 large infract, moderate to severe occipital leptomeningeal CAA, moderate to severe myelin loss in at least one brain region
Cerebrovascular disease and mechanisms of cognitive impairment (Kalaria, 2016)	high frequency with small or micro infarcts in the cortical and subcortical regions, cribriform change and perivascular spacing in the WM, basal ganglia, internal and external capsules, demyelination and oligodendrocyte changes in the white matter, plaque build-up and occlusive disease in the Circle of Willis and proximal branches of the MCA, ACA and PCA, cystic infarcts and WM, basal ganglia and thalamus and hippocampal atrophy and sclerosis in CA1-CA4
California criteria (Chui, 1992)	2 or more ischemic strokes and one infarct outside the cerebellum
NINDS-AIREN (Roman, 1993)	multiple large-vessel stroke, single strategically placed infarct' (angular gyrus, thalamus, basal forebrain or posterior carotid artery or anterior carotid artery territories), multiple basal ganglia and white matter lacune's, extensive periventricular white matter lesions
Statement from the American Heart Association (Gorelick et al., 2011)	One or more of the following; one or more large vessel infarct, extensive or strategically placed ingle infarct (typically thalamus or basal ganglia), more than 2 infarcts outside the brainstem, extensive and confluent WM lesions, strategically placed intracerebral haemorrhage or 2 intracerebral haemorrhages
Vascular Cognitive Impairment (van der Flier et al., 2018)	macroscopic infarcts, microscopic infarcts, haemorrhages, microbleeds, WMHs, neuronal / volume loss, oligodendrocyte loss, astrocytosis, micro gliosis

Cognitive characteristics of symptomatic VCI

Most brief cognitive screening tests to detect decline in general cognition are tailored towards the detection of Alzheimer's disease and are therefore, largely based on temporal lobe based episodic memory deficits. By contrast, in VCI the site of lesions is critical to determine the patient's cognitive impact. Not surprisingly, characterisation of cognitive deficits in VCI has been highly unspecific as diagnostic criteria cover many cognitive domains. For example, executive function, language, visuospatial processing and episodic memory deficits have been all highlighted as key behavioural markers of VCI (Hachinski et al., 2006; Sachdev et al., 2014), further underlining the non-specific detection of cognitive impairment so far. However, the VASCOG diagnostic criteria (Sachdev et al., 2014) are more specific and state that disturbances to frontal and executive processes (slowed information processing, reduced set-shifting ability and poorer working memory) are more prominent in VCI.

According to VASCOG, timed executive function neuropsychological assessments may be sensitive for the detection of VCI. Subsets from the Montreal Cognitive Assessment (MoCA) were thought to be the most sensitive and brief for detecting VCI impairments. Domains of immediate and delayed memory via word recall, orientation (testing date, month, year, day, place, city) and verbal fluency (required to name maximum number of words in one minute that begin with the letter F) are deemed important to delineate a diagnosis of VCI from other dementias. However, as stated above, VCI can often accompany AD and hence it is not clear whether episodic memory measures can really delineate VCI from AD. Therefore, it is recommended to use either more specific vascular impairment screening measures such as Brief Memory and Executive Test (BMET)(Brookes et al., 2015) or The Oxford Cognitive Screen

(OCS) (Demeyere et al., 2015), as well as more specific fronto-parietal neuropsychological measures, such as the Trail Making Test (TMT) (Reitan, 1958) to measure cognitive flexibility, as well as set-shifting and attentional paradigms. However, it becomes quickly clear that none of these measures were specifically developed for gradual VCI and are better suited towards an acute onset of stepwise cognitive dysfunction, such as stroke. Hence might fall short of detecting any incipient cognitive changes to inform diagnostic and intervention pathways.

There are currently concerted efforts for such detection for Alzheimer's disease (AD). By contrast, the examination of cognitive markers and their relationship to biomarkers for Vascular Cognitive Impairment (VCI) is far less established, despite VCI being highly prevalent and often concomitantly presenting with AD. Critically, vascular risk factors are currently associated with the most viable treatment options via pharmacological and non-pharmacological intervention, hence early identification of vascular factors have important implications for modifying dementia disease trajectories. In the following sections, I examine the risk factors which contribute to the onset on VCI and associated cognitive and neuroimaging markers.

Method

Several procedures were followed to ensure a comprehensive review of the literature relevant to this narrative review. First, a review of peer-reviewed journals was undertaken using a wide range of key terms including; vascular cognitive impairment, preclinical vascular dementia, midlife cardiovascular risks. Cross-sectional, longitudinal and retrospective studies were reviewed with a focus on experimental studies exploring midlife cognitive and anatomical brain changes, the reference section for each article was searched for additional relevant articles.

Databases used included; Neurosynth, Science Direct, PsycARTICLES, PsycINFO, PubMed and Google Scholar. The following publications were searched independently Stroke, Brain, Hypertension, NeuroImage clinical. For the purpose of this review, I define preclinical VCI as a slowing or decline in cognitive or brain function which is associated with the presence of cardiovascular risk factors, before the expression of noticeable symptoms or a clinical criteria is met for VCI. I excluded articles containing diabetes type 1, CADISIL, CAA, post-stroke VCI.

The literature review revealed, the most prevalent risk factors were hypertension, high cholesterol, diabetes type 2 and elevated BMI (see, Table 2.). These were deemed appropriate to investigate as they are a) identifiable with standard clinical assessment, b) modifiable with pharmacological or behavioural intervention and c) highly prevalent within the general population. Each risk factor was then reviewed with a search term postfix of dementia, vascular dementia, vascular cognitive impairment, cognition, cognitive decline, cognitive function, impairment, midlife, middle age, preclinical, prodromal, brain change, visuospatial, executive function, episodic memory, MRI, DMN, EEG, ERP, P300 P3, P3A and connectivity. Based on these findings I was able to establish associated cognitive functions affected in midlife and track the later life outcomes. The cognitive domains featured in the following sections were established after this review of the literature which showed repeated deficits in these areas.

1 Table 2. Midlife VCI-Risk factors predictive of cognitive impairment.

Study Type	$\bar{x}$ age at baseline	Risk Factor	Follow up ($\bar{x}$ years)	Outcome Measure	Domain	Summary	Reference
Retrospective cohort study	46	CAIDE risk score sig measures; Cholesterol >25.9mg /dl, BMI >30KG/M, sBP >140mm Hg, smoking	36	Dementia diagnosis (unspecified)	non-specific	Modifiable risk factors at midlife are predictive of later-life dementia	(Exalto et al., 2014)
Epidemiological cohort study	53	Composite; Diabetes 200 mg/dL, sBP ≥140 mm Hg, dBP 90mm Hg, BMI 25-32%, APOE-ε4 carrier, Lower cognitive function	25	MCI or Dementia diagnosis (unspecified)	non-specific	Cardiovascular risk factors and low cognitive function predicts MCI and dementia 20yrs later	(Knopman et al., 2001)
Epidemiological cohort study	50	CAIDE risk score sig measures; Age >47yrs, Education <10yrs, sBP >140 mmHg, Total cholesterol 6·5 mmol/L, BMI >30KG/M2, Inactivity <30mins p/w, APOE-ε4 carrier Sex: male	21	Diagnosis of dementia (unspecified)	non-specific	Midlife cardiovascular risk predicts dementia 20yrs later	(Kivipelto et al., 2006)
Epidemiological cohort study	58	Higher lipid level: total cholesterol (200-239 mg/dL) and triglycerides (200-500 mg/dL)	20	Z-scores of DWRT, DSST, WFT	General cognition	Midlife elevated lipid level predictive of 20-year decline on cognition. Association of high LDL and triglycerides	(Power et al., 2018)

		LDL; 130-159 mg/dL and 160-189 mg/dL		DSST	Executive function, processing speed, sustained attention	greater in DWRT with APOE-ε4 Elevated midlife LDL predictive of selective cognitive decline	
Meta-analysis	54	BMI 27.58 kg/m2 sBP 120.26mm Hg dBP 73.27mm Hg Total Cholesterol 214.99mg/dL, Glucose level 107.21mg/dL	20	Composite score of; DWR, DSS, and WF	memory recall, processing speed and sustained attention, phonemic fluency	Composite score cardiovascular risk associated with declined cognitive performance over time	(Gonzalez et al., 2018)
Retrospective cohort study	43	High Cholesterol ≥240 mg/dl Borderline cholesterol 200-239 mg/dl	17	Dementia diagnosis (AD sig, VaD trend)	non-specific	57% greater risk of AD 26% greater risk of VaD 50% greater of VaD 23% greater risk of AD	(Solomon et al., 2009)
Epidemiology cohort study	57	Hypertension sBP >140mmHg, dBP 90 mm Hg Prehypertension sBP >120mm Hg, dBP ns	20	Z-scores; DWRT, DSST, WFT DSST	General cognition Executive function, processing speed, sustained attention	Midlife hypertension predicts cognitive decline, DSST most sensitive to preclinical stage. Yet, elevated blood pressure at late life was not associated with cognitive decline	(Gottesman et al., 2014)
Epidemiology cohort study	25	Hypertension (BP variability)	25	DSST, RAVLT	Processing speed, sustained attention, verbal memory	Long-term BP variability for 25 years beginning in young adulthood was associated with worse psychomotor speed and verbal memory tests in midlife. Stroop test lacked sensitivity	(Yano et al., 2014)

Epidemiological cohort study	71	Prediabetes HbA1c level ≥5.8% Diabetes HbA1c level ≥7.1%	9	MMSE	General cognition	Prediabetes and diabetes at 71 were independently associated with accelerated cognitive decline	(Marseglia et al., 2019)
Retrospective cohort study	≥50	Diabetes HbA1c level ≥6.5%	8	Diagnosis of dementia (unspecified)	Non-specific	Diabetes at midlife increases the risk of dementia at follow up	(Hsu et al., 2011)
Epidemiological cohort study	62	Diabetes HbA1c level ≥6.68%	14	DSST	Executive function, processing speed, sustained attention	DM at midlife affects cog flexibility and visuospatial abilities but not memory. Word List and Mosaic Task lacked sensitivity	(Degen et al., 2016)
Epidemiological cohort study	57	Diabetes HbA1c level ≥6.5%	20y	DSST, WFT	Processing speed, executive function, language, verbal fluency	DM at midlife associated with significant cognitive decline over 20 years compared to controls	(Rawlings et al., 2014)
Meta-analysis	50	BMI ≥25KG/M2	3-36	AD and VAD diagnosis	non-specific	Overweight in midlife associated with dementia but continuous BMI in late-life was not associated with dementia	(Anstey et al., 2011)
Epidemiological cohort study	36-43	BMI ≥25KG/M2 Gains in waist circumference	30	VMT, Letter Search, Simple RT task	Memory, processing speed, reaction time	Longer exposure to elevated BMI and greater waist circumference at midlife associated with lower cognitive function at 60yrs	(Masi et al., 2018)

BMI = body mass index, sBP = systolic blood pressure, dPB = diastolic blood pressure, APOE-ε4 = Apolipoprotein E subtype 4, LDL = low-density lipoproteins, HbA1c = Hemoglobin A, DWRT = Delayed Word Recall Test, DSST = Digit Symbol Substitution Test, WFT = Word Fluency Test, RAVLT = Rey Auditory Verbal Learning Test, TMT = Trail Making Test, MMSE = Mini Mental State Examination

Preclinical VCI

There is a distinct lack of specificity on the diagnostic criteria for cognitive symptoms in VCI. Indeed, cognitive diagnostic tests in Alzheimer's disease (AD) are largely based on episodic memory deficits, due to the initial impact of AD pathophysiology on medial temporal lobe structures. By contrast, lesion sites in VCI are more heterogeneous and hence symptoms can range from virtually none to multiple cognitive functions being affected. It is therefore not surprising that the characterisation of cognitive deficits in VCI has been highly heterogenous to date. Detection of VCI specific changes in preclinical VCI is therefore even less established, despite offering significant treatment potential.

A different approach is to outline which cardiovascular risk factors predict later-life cognitive impairment. Table 2. Clearly denotes those individuals with VCI risk factors in midlife show a cognitive decline overtime. Below, I review current, limited evidence on more domain-specific cognitive measures associated with established VCI risk factors and examine network connectivity and ERP/EEG contributions to explore potential strategies for the early identification of VCI

Executive function

Cardiovascular risk is consistently associated with performance decline when high executive demands are required from participants, such as attention and processing speed, similar to clinical VCI and VASCOG criteria. For example, hypertension appears to have the biggest impact on executive function, motor speed and attention and this is most pertinent for hypertension at midlife but not at later-life (Iadecola & Gottesman, 2019). Cognitive decline linked to hypertension was shown over a 20-year community-based cohort study (Yano et al., 2014). The cognitive battery used in this study consisted of the Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST) and Word Fluency Test (WFT) administered over three time points over 20 years. Results showed that, on composite scores, individuals with high or variable hypertension had greater decline over the 20 year duration, compared to individuals with healthy blood pressure, and this effect was independent of age, sex, race, education, body mass index, diabetes mellitus, alcohol consumption, smoking status, ApoE-ε4 genotype, and stroke history (Gottesman et al., 2014). The Digit Symbol Substitution Test was the most sensitive measure to detect this decline. Baseline measures of the Digit Symbol Substitution Test at age 75 years have also been shown to predict the onset of more general cognitive decline, mobility and mood when adjusted for the presence of white matter hyperintensities (Rosano et al., 2016). Although the Digit Symbol Substitution Test is sensitive to the presence of wider cognitive dysfunction, it has low specificity. Indeed slower processing speeds as detected by this test may serve to identify disorders of cognition, mobility and even mood (Jaeger, 2018).

Other studies have explored the link of hypertension to processing speed, and the underlying neural changes. For example, it has been shown that hypertension among middle aged men (high systolic blood pressure >140 mm Hg) predicted lower grey matter volumes in the

supplementary motor area, superior frontal gyrus, anterior cingulate cortex, and left middle temporal gyrus (Gianaros et al., 2006). Low grey matter volume in the supplementary motor area also predicted slower completion times of the Trail Making Test (part B) and poorer recall of items from a four-word short-term working memory test, independent of age, total brain tissue volume, educational history, severity of carotid atherosclerosis, and the extent of periventricular and subcortical white matter lesions (Gianaros et al., 2006). Similarly, diffusion tensor imaging (DTI) studies reported that people with hypertension showed significantly reduced integrity of white matter in the bilateral superior longitudinal fasciculus compared to healthy controls (Li et al., 2015) impacting on their processing speed – this change being of particular interest given the propensity for injury to white matter tracts in clinically established VCI (Prins & Scheltens, 2015).

In addition to hypertension, older adults with type 2 diabetes have shown increased mean diffusivity, as measured via DTI, reflecting microstructural white matter abnormalities in the superior longitudinal fasciculus, the uncinate fasciculus, the inferior longitudinal fasciculus, and the genu and splenium of the corpus callosum (Reijmer et al., 2013). This was associated with reduced information processing speed (z scores of; Trail Making Test, Stroop Test, Digit Symbol Substitution Test) and worse verbal memory performance (Rey Auditory Verbal Learning Test) compared to age matched controls, independent of age, sex, estimated IQ, total white matter hyperintensity load, and presence of cerebral infarcts. Cognitive deficits in type 2 diabetic individuals have been found to be weaker in younger adults but still detectable (Awad et al., 2004), although poor glaucomic control seems to increase the severity of cognitive complaints (McCrimmon et al., 2012). Furthermore, in middle age individuals with type 2 diabetes, white matter abnormalities have also been detected using DTI (Hsu et al., 2012), despite no changes shown via resting state fMRI connectivity. Indicating more

specific white matter alterations without necessarily affecting the functional connectivity of brain regions. Given that individuals with type 2 diabetes demonstrate greater structural abnormalities characteristic of VCI (white matter hyperintensities and lacunar infarcts) compared to healthy controls, it is promising that these changes appear to be associated with identifiable cognitive markers for symptom identification and tracking.

The presence of executive function decline in VCI is also supported by findings from a prospective study examining changes to cerebral blood flow in healthy older adults with the APOE-ε4 allele dementia-risk-gene (Haijar et al., 2015). Results showed that APOE-ε4 allele carriers had lower cerebral blood flow, and the effects of this on cognitive performance (Trail Making Test and the Hopkins Verbal Learning Test) were made worse by the co-occurrence of hypertension. However, critically, in individuals with clinically significant hypertension, only those with lower cerebral blood flow demonstrated the negative association between APOE-ε4 and executive function on the Trail Making Test (part B), compared to individuals with higher cerebral blood flow. Yet, there was no interaction between hypertension, APOE-ε4 and cerebral blood flow with respect to the memory recall measured by the Hopkins Verbal Learning Test (Haijar et al., 2015), suggesting that hypertension in individuals at risk of dementia with lower cerebral blood flow impairs executive function selectively. This also implies that greater cerebral blood flow may act as a protective factor against cognitive deficits in APOE-ε4 individuals. This is further confirmed by a cluster analysis investigating the implication of hypertension on cognition, mood and mobility in healthy older adults (Hajjar et al., 2009). Results showed an association between hypertension, reduced Trail Making Test (part B) performance, depressive symptoms and slower speed. Whereas, consistent with more recent findings, memory measures (Hopkins Verbal Learning Test; immediate recall, delayed recall and recognition) did not reveal such associations (Hajjar et

al., 2009). This therefore illustrates that visuospatial and set-shifting deficits in individuals at high cardiovascular risk can serve as a potential cognitive marker of VCI, but memory tests may be less sensitive.

Finally, individuals with high composite cardiovascular risk scores also show increased activation change in the left parietal cortex, associated with greater executive demand in the Flanker task, compared to low risk persons (Chuang et al., 2014), establishing a connection between aggregated cardiovascular risk and parietal-mediated cognitive deficits. This nicely dovetails with the DTI findings in the superior longitudinal fasciculus and is consistent with the view that VCI cognitive and functional impairment is frequently more fronto-parietal in nature, as opposed to hippocampal-dependent episodic memory problems that are traditionally associated with AD.

Visuospatial function

Besides the prevalent executive function changes, VCI also often presents clinically with visuospatial deficits, this also seems true before the onset of clinical symptoms. For example, findings from a longitudinal cohort study suggests a steeper decline in visuospatial performance with age for individuals diagnosed with diabetes type 2 at midlife, compared to those diagnosed at a later stage (Degen et al., 2016). For those individuals with midlife diabetes, decline over time was observed for the digit symbol test and for visuospatial imagery (where participants are required to count the surfaces of three-dimensional geometrical figures), compared to individuals diagnosed at a later stage (Degen et al., 2016). Assessments of word fluency, visual search and verbal recall tasks did not reveal any deficits, suggesting a specific effect of long-term type 2 diabetes in domains of visuospatial processing and processing speed, but not memory.

White matter hyperintensity volume in healthy mid-life adults has also been associated with reduced visuospatial abilities, as assessed using the Hooper Visual Organisation Test(Au et al., 2006). Visuospatial memory and organization performance were worse in participants with greater white matter hyperintensity volumes, as compared to participants with low white matter hyperintensity volumes. A similar pattern of performance was observed for visual scanning and motor speed, assessed by the Trail Making Test. In contrast, verbal memory, abstract reasoning and naming showed no significant differences between individuals with low versus high volume white matter hyperintensity.

Further research shows that young adults with a family history of hypertension (first degree relative systolic with blood pressure >140 mmHg before 60 years old) also have different neural activations during a visuospatial n-back task, compared to controls, despite equivalent task performance(Haley et al., 2008). Relative to controls, individuals with a family history of hypertension exhibited lower activation to the visuospatial n-back task in the right inferior parietal lobule and the right inferior temporal gyrus, and substantially more deactivation in the posterior cingulate (Haley et al., 2008), indicating subtle changes in visuospatial mechanisms in healthy individuals with a predisposition to VCI risk-factors.

Episodic memory

Deficits in episodic memory are less often associated with VCI and more apparent in AD. However, there have been some interesting findings from studies with at VCI-risk individuals, suggesting that brain regions involved in episodic memory are also affected by early neurovascular change. In a cross-sectional study, reduced scores in immediate and delayed Emotional Memory and free recall in the California Verbal Learning Test were found

in middle aged individuals with type 2 diabetes, compared to healthy controls. In contrast, working memory, sustained attention and verbal fluency were unaffected (Yau et al., 2009). DTI analysis showed that white matter microstructural abnormalities were present among individuals with diabetes and were predominantly located in the frontal and temporal regions, particularly the left temporal stem (Yau et al., 2009). These DTI findings may explain the lower memory performance present among diabetics, after accounting for age, metabolic dysregulation and hypertension. This is supported by a further cross-sectional study indicating that older adults with type 2 diabetes had poorer performance on the Rey Complex Figure Test (memory recall condition) and longer completion times in the Stroop test (Moran et al., 2013). These results were associated with grey matter loss in the anterior cingulate and medial frontal lobes, and with white matter loss in frontal and temporal regions. Interestingly, longer diabetes duration (≥15yrs) was associated with impairments in visuospatial and inhibition domains, with reduced performance in the Rey Complex Figure Test (copy condition), digit symbol coding and digit search over time (Moran et al., 2013).

In addition, older adults with greater cardiovascular burden have been shown to have an accelerated decline in episodic memory, working memory, and perceptual speed over time compared to lower risk individuals (Song et al., 2020). Episodic memory was assessed using Word List Memory, Word List Recall, Word List Recognition and immediate and delayed recall of the Wechsler Memory Scale-revised. Working memory was evaluated using the Digit Span and digit ordering tasks. Perceptual speed was tested using the Symbol Digit Modalities Test, Number Comparison, and 2 indices from a modified Stroop Test. MRI analysis revealed that reduced episodic and working memory performance was associated with smaller volumes of the hippocampus, whilst reduced perceptual speed was linked to greater volume of white matter hyperintensities (Song et al., 2020). This is supported by an

earlier study examining cognition in mild cognitive impairment (MCI) individuals with hippocampal atrophy compared with MCI individuals with severe white matter hyperintensities. Results show equally impaired episodic memory performance (using an object-colour association task) for both groups but with additional impairment for the MCI individuals with white matter hyperintensities in tests tapping verbal and spatial working memory abilities and attentional control processes (Nordahl et al., 2005). This potentially suggests white matter hyperintensities reflect disruption to the white matter tracts (dorsolateral prefrontal cortex and connected neural circuits), which result in diminished executive control processes critical to working memory, that may in turn impair episodic memory function (Nordahl et al., 2005).

This account of insidious pathology in VCI-risk populations indicates that early manifestations of VCI may also span medial temporal and related networks. However, at this stage it is unclear whether these episodic memory impairments are in line with age-related memory decline, concomitant AD or a collateral effect of VCI. Regardless, it emerges that the cognitive changes in preclinical VCI might more affect networks of brain regions, instead of discrete areas, in particular when white matter tracts are affected. In the following section I will review therefore how potentially the network connectivity between brain regions might be affected in preclinical VCI and how this will impact on the cognitive symptomology.

Structural Changes

fMRI

Disruptions to the default mode network (DMN) is of major interest in preclinical dementia. The DMN consists of a network with three major subdivisions: the ventral medial prefrontal cortex, the dorsal medial prefrontal cortex and the posterior cingulate cortex and adjacent

precuneus plus the lateral parietal cortex (Greicius et al., 2004; Raichle, 2015) that co-activate when subjects are at rest and de-activate when subjects become engaged in external cognitive tasks. It is thought that DMN dysconnectivity could represent a biomarker for preclinical AD and this may be related to cerebrovascular function (Chand et al., 2017; Haight et al., 2015). Cerebrovascular reactivity was significantly reduced in the posterior cingulate/precuneus and anterior cingulate areas of the DMN for those with hypertension and prehypertension (defined as either systolic blood pressure >= 130 mmHg, diastolic blood pressure >= 85 mmHg or use of blood pressure medication) as compared to healthy controls (Haight et al., 2015). Similarly, MCI patients with evidence of cerebrovascular infarcts also showed differing underlying (de)activation patterns compared to MCI individuals free from infarcts, during an n-back task, even though neuropsychological scores were similar (Papma et al., 2013). Results indicate impaired deactivation in the precuneus/ posterior cingulate cortex, for those MCI individuals with infarcts. Additionally, greater activation was observed in the anterior cingulate gyrus during differing memory loads compared to MCI patients without infarcts. To suggest a differing working memory load fMRI response between groups and potentially indicating different DMN connectivity for preclinical VCI individuals as compared to early stage AD individuals and would also nicely dovetail with the white matter changes reported in preclinical VCI (though see, (de Leeuw et al., 2001)).

Frontal networks, including the salience network primarily composed of the anterior insula and the dorsal cingulate cortex, involved in sustained attention and task switching, have also been implicated in dysconnectivity in MCI individuals with elevated mean systolic blood pressure (150 mmHg), compared to healthy aged matched controls (Chand et al., 2017). The resting state fMRI study in MCI, healthy age matched controls and young adults showed that the salience network, particularly its dorsal sub-network, modulates the interactions between

the DMN and the central executive network in young adults and healthy aging. This pattern of modulation in the salience network was interrupted in MCI and the degree of disruption was associated with lower overall cognitive scores on the MoCA (Chand et al., 2017). Importantly, the authors commented that the effect was particularly pronounced in the MCI individuals due to their elevated blood pressure and more pervasive 'executive' impairments assessed by the MoCA, TMT, Stroop interference and verbal frequency. Based on these findings, salience network changes might be indicative of measuring frontally mediated executive impairment and associated vascular pathophysiology in MCI. This would also dovetail with findings showing that dysfunction to the DMN/ salience networks and associated functional impairment may be predictive biomarkers of later-life VCI (Lockhart et al., 2012; Zhang et al., 2013).

ERP/EEG

Network dysfunction can not only be measured via fMRI but also via EEG derived measures such as event-related potentials (ERPs) or frequency analyses. This approach has been successfully employed to patients presented with clinical dementia syndromes(Pedroso et al., 2012). The P300 component in particular, has been suggested as a physiological marker of preclinical AD (Lai et al., 2010). P300 is thought to be evoked by the rapid detection of environmental changes and is associated with domains of working memory as well as attention and characterized by a positive deflection with a latency between 250 and 500ms (Lee et al., 2013). A classic paradigm for evoking the P300 response is the oddball task, where participants have to detect rare stimuli among frequently occurring standard stimuli. 'Oddball' target stimuli typically evoke a response that is maximal at parietal electrode sites (P3b), whilst novel stimuli evoke a response that is maximal at frontal sites (P3a;(Linden, 2005)). These novel and target P300 components can be used to evaluate cognitive decline

(Lai et al., 2010) and evidence suggests that decreased P300 amplitude is associated with reduced language, memory and executive function performance in AD (Lee et al., 2013). Additionally, non-clinical older adults with reduced cognitive ability (MoCA score <25) demonstrate reduced P300 amplitude compared to age matched controls and healthy young adults(Newsome et al., 2013). Reduced P300 latencies have also been observed in MCI and in AD, compared to healthy controls (for a review see, Howe et al., 2014).

Importantly, one study reported that VCI and AD could be differentiated by including novel stimuli in an auditory oddball paradigm (Yamaguchi et al., 2000). Results showed that the novel P300 amplitude (P3a) was markedly reduced in VCI patients, but that it was preserved in AD and controls (Yamaguchi et al., 2000). Further, source localisation studies indicate that VCI patients have an impaired parietal-to-frontal and parietal-to-central connectivity during the oddball paradigm (200-300ms after stimuli onset) compared to controls, showing a weakened outgoing connectivity from parietal regions (Wang et al., 2014b, 2016). This response appears different compared to AD groups where a shift of maximum intensity location during the P300 response occurs from the frontal-to-temporal lobes (Tsolaki et al., 2017). The P300 component could also be a promising biomarker in preclinical individuals as the ‘oddball’ response in middle age type 2 diabetics (Hazari et al., 2015) and hypertensive older adults (Cicconetti et al., 2007) includes increased P300 latencies compared to healthy controls. Taken together, the evidence suggests this differing ERP response may reflect dysconnectivity between posterior and anterior structures in at VCI-risk individuals – reminiscent of white matter tract dysfunctions in preclinical and clinical VCI individuals.

Spatial orientation as a tool to detect cognitive decline?

Neuroanatomy of spatial orientation

However, one particularly striking aspect emerging from our review is that despite parietal functions, areas, and connections being commonly affected in VCI, cognitive and neural measures rarely tapped into those. In addition, the fronto-parietal network and superior longitudinal fasciculus (white matter tract connecting parietal, temporal with prefrontal regions) is heavily implicated in underpinning executive function (Fuentes-Claramonte et al., 2021; Sasson et al., 2012) but also likely plays into parietal dysfunction in VCI. Interestingly, this white matter tract is also thought to play a role in spatial processing (Smith et al., 2011). As such, investigations into parietal mediated spatial orientation could be a potentially novel and more specific approach towards VCI and may help to discriminate between VCI and AD pathology.

Spatial orientation is an important cognitive function used in everyday life. It allows us to navigate familiar or new environments, locate and interact with objects and have a frame of reference in our memory to successfully navigate and maintain a trajectory from one location to the next (Coughlan., 2018) It is widely considered there are two frames of spatial navigation that work in parallel and integrate spatial coordinates. Our egocentric frame of reference is concerned with the spatial relation between objects or landmarks and the self. It is focused on processing spatial information from a person-centred perspective. While our allocentric frame of reference involves the spatial relation between the position of objects and landmarks relative to each other and is focused on map-based representations. Both frames are informed by spatial information from multi-faceted person-to-object centred and environmental cues (Colombo et al., 2017). Both frames are required for everyday navigation

with egocentric and allocentric processes shifting as a function of navigational demands (McNaughton et al., 2006). Path integration is integral to spatial navigation as it allows an individual to keep track of and return to their starting location on the basis of visual, self-motion, vestibular and proprioceptive feedback which represent current position and heading direction in references to a permanent location (Etienne & Jeffery, 2004; Knierim et al., 2014; McNaughton et al., 2006). This process involves translating distance travelled with changes in direction of movement either relative to our allocentric or egocentric orientation (Burgess, 2006). Multisensory (visual, self-motion, vestibular and proprioceptive) feedback combine egocentric and allocentric frames of reference, allowing path integration to continuously update this information, allowing one to keep track of one's position in space (Coughlan et al., 2018b; Rieser, 1989).

Research shows egocentric referencing is vital for self-orientation of small and familiar environments (Wang & Spelke, 2000), such as navigating around your home or to a local shop. Whereas allocentric referencing is employed when navigating a new route or city for the first time. Both processes are continuously updated by information from visual, motor-movement, vestibular and proprioceptive mechanisms (McNaughton et al., 2006). It is thought that typically we preferentially rely on egocentric referencing as a quick and automatic way of remembering spatial information (Diwadkar & McNamara, 2016; Waller & Hodgson, 2006). Though, spatial navigation is most effective when we integrate both egocentric and allocentric frames (Waller & Hodgson, 2006).

Egocentric orientation relies more on the prefrontal and parietal cortex to localise the position of objects relative to the body (Arnold et al., 2014; Goodale & Milner, 1992), the precuneus then uses these location cues to form the basis of an egocentric representation of the surrounding space, integrating self-motion cues with the egocentric reference frame (Wolbers

& Wiener, 2014). Though, the body of evidence examining the neural correlates of the egocentric frame, is largely informed from posterior parietal cortex (PPC) lesion patients. The dorsal ventral stream (Whitwell et al., 2014), an established theoretical network starting at the primary visual cortex extending to the parietal cortex is thought to determine the position of objects relative to the body in order to act and guide navigation (Goodale & Milner, 1992). Typically discussed in the context of hemispatial neglect, studies show the PPC is not only involved in the perception of visual information but also the internal representation of it. The PPC is thought to be a multimodal 'hub' for egocentric presentations integrating visual, motor and somatosensory input used to encode objects for reaching towards (Byrne et al., 2007; Cavina-Pratesi et al., 2018; Desmurget et al., 1999; Meek et al., 2013), movement with respect to landmarks and the imagination of scenes from the person-centred perspective (Colombo et al., 2017). The caudate nucleus (Cook & Kesner, 1988), medial parietal lobe and precuneus (Burgess, 2006a, 2008; Colombo et al., 2017) are all implicated in landmark position, attention and the integration of egocentric information. There is also evidence of frontoparietal networks involved in egocentric spatial processing (Vallar et al., 1999), as well as domains of spatial working memory and executive function (Burgess et al., 2007).

Whereas allocentric orientation is reliant on the formation of maps using place, grid and boundary vector cells situated mainly in the medial temporal lobe (Lester et al., 2017), which fire in specific spatial locations regardless of the persons orientation (Aguirre et al., 1996). Parahippocampal involvement is also vital for scene construction (Coughlan et al., 2018b). The integration of egocentric and allocentric frames occurs in the retrosplenial cortex (RSC), which is a critical interface between the medial temporal and medial parietal regions (Alexander & Nitz, 2015). Dorsal-medial regions of the RSC are thought to be implicated in orientating and recalling unseen locations from a current position in space, whilst ventro-

lateral portions were more linked to updating and integrating scene information (Burles et al., 2017). The RSC is primarily involved with the translation of egocentric and allocentric information (Byrne et al., 2007; Takahashi et al., 1997), this path integration acts to combine heading direction from a parietal and person-centred reference with hippocampal landmark information to provide a more integrated representation of the environment (for illustration see, figure 3). Though, no single brain region serves as the primary underpinning of egocentric or allocentric navigation, instead a network of interacting brain structures subserving spatial navigational processes are thought to dynamically interact (for a review, see Ekstrom et al., 2017).

Spatial orientation and pathological aging

Spatial navigation deteriorates in healthy aging but appears more focused to allocentric strategies while egocentric remain intact (Gazova et al., 2013; Li & King, 2019). Spatial navigation is an established marker of cognitive impairment in AD(Coughlan et al., 2018b) We largely understand that in AD allocentric and egocentric orientation is impaired and this is also present in the preclinical and prodromal stages (Coughlan et al., 2019). It is thought so effective as brain regions underpinning spatial navigation overlap with AD pathophysiology (see, Figure. 3). By contrast the pathophysiology of VCI is far more heterogenous. Yet, from the above review there appears to be emerging evidence to suggest the frontoparietal network may be one of the first regions to show dysfunction in preclinical VCI (Lowry et al., 2021; Veldsman, Tai, et al., 2020), which overlap with brain regions involved in spatial navigation.

Table 3.Typical neural substrates of cognitive symptoms of VCI compared to AD.

	Frontal	**Parietal**	**Temporal**
VCI	+++	++	+
AD	+	+	+++

Strength of symptoms, + low; ++ moderate; +++ high

Innovative and novel virtual reality tests of spatial navigation can be easily applied in clinical settings and appear more robust than traditional validated tests of spatial navigation (Mitolo et al., 2015; Schinazi et al., 2013). Computer generated environments unlike the 'real world' are able to maintain well controlled testing conditions and determine the navigational complexity and provide test environments which can isolate egocentric and allocentric processes. Previous studies using tests of virtual reality have shown that in patients with AD typically both the egocentric and allocentric frame of reference are impaired, which is thought to be underpinned by widespread neurodegeneration in medial temporal, parietal and frontal bran regions (Irish et al., 2015; Jheng & Pai, 2009; Pengas et al., 2010; Serino et al., 2015; Serino & Riva, 2013).

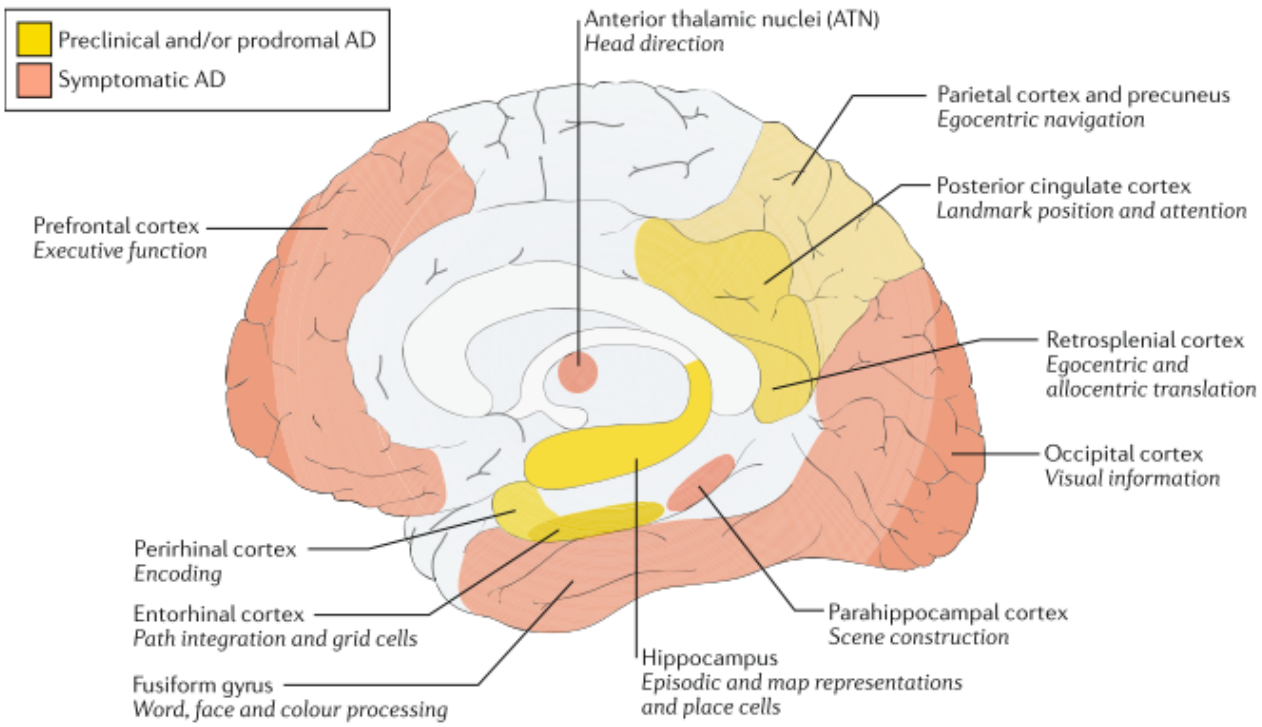

Figure 3. Schematic illustration of the anatomy of spatial navigation in the context of Alzheimer's disease pathophysiology in preclinical, prodromal and symptomatic stages of the disease. Figure originally from Coughlan et al., 2018b.

Tasks that tap into spatial navigation, and more specifically path integration therefore provide a promising ecological, cognitive framework to detect medial temporal and medial parietal pathophysiology. Not surprisingly, path integration has been already explored in AD (Morganti et al., 2013; Ritchie et al., 2018; Serino et al., 2014; Vlček & Laczó, 2014) and the advent of VR based testing has allowed such tests to be clinically available (Morganti et al., 2013; Parizkova et al., 2018; Plancher et al., 2012). We have developed previously such tests, the Virtual Supermarket test and Sea Hero Quest, is now used across many large cohorts and drug trials as it can reliably detect path integration differences in preclinical and clinical dementia populations (Tu et al., 2015, 2017; Coughlan et al., 2019). The VR tasks reliably measures spatial processes of: i) egocentric self-reference navigation; ii) allocentric map-based navigation and iii) heading direction. For example, it is previously shown that the test allows distinction of behavioural variant fronto-temporal dementia (bvFTD) from AD, with AD showing particularly problems in switching between egocentric and allocentric frames during path integration (Tu et al., 2017). Importantly, these switching problems in AD were associated with grey matter atrophy in the RSC (Tu et al., 2015).

In addition to this, and critical to this thesis, a recent case study has shown using the virtual supermarket test and novel bedside assessments of spatial orientation that in fact egocentric orientation deficits, mediated by fronto-parietal structures, may be a promising marker for the identification of vascular pathology (Coughlan et al., 2018a). This coupled with MRI and ERP experimental findings from VCI and at-risk individuals may mark a promising path forward for the development of selective markers focused on connectivity changes across key brain structures.

Conclusion & outlook

There is clearly a disconnect between well-established neural markers of VCI and how they relate to cognitive symptomology. This may be explained by the current lack of a gold standard or single domain cognitive measures to detect VCI, either clinically or preclinically. Instead, current cognitive measures lack the specificity to isolate VCI pathology and sensitivity to detect its earliest symptoms. This might not be a problem per se, however clinically a functional readout of how symptoms change over time, including cognitive problems, is important for disease prevention, management, and tracking.

Taken together, the reviewed evidence suggests that impaired executive function, visuo-spatial and set-shifting ability along with dysconnectivity between the frontal-parietal networks and subcortical structures (cingulate, insula and precuneus) may predict VCI onset. The VASCOG guidelines (Sachdev et al., 2014) highlight that disturbances to frontal and executive processes (slowed information processing, reduced set-shifting ability and poorer working memory) are prominent in VCI. Although this contributes towards identifying the cognitive and biological markers of preclinical VCI, the current clinical measures (MoCA, TMT, DSST…) might not be sensitive or specific enough to detect the earliest VCI changes or disassociate it from incipient AD pathophysiology. Instead, more experimental measures informed by preclinical neural and cognitive change need to be explored to fill the gaps in this research area and aid our understanding of biomarker development of this insidious multifaceted disease.

Although neuroimaging is less accessible for clinical utility, it is clear network approaches should be explored to identify at VCI-risk individuals to help inform more selective cognitive testing. Although, this area of research is in its infancy the present review suggests

neuropsychological assessments which tap into structures affected at the preclinical stage of VCI (see, outcome measures listed in Table. 2) are more appropriate for diagnostic and screening purposes compared to more multi-domain assessments. Yet, new and novel methods assessing self-referential spatial navigation seem to have greater selectivity and specificity than more traditional pen and paper tasks (see, Lowry et al., 2020).

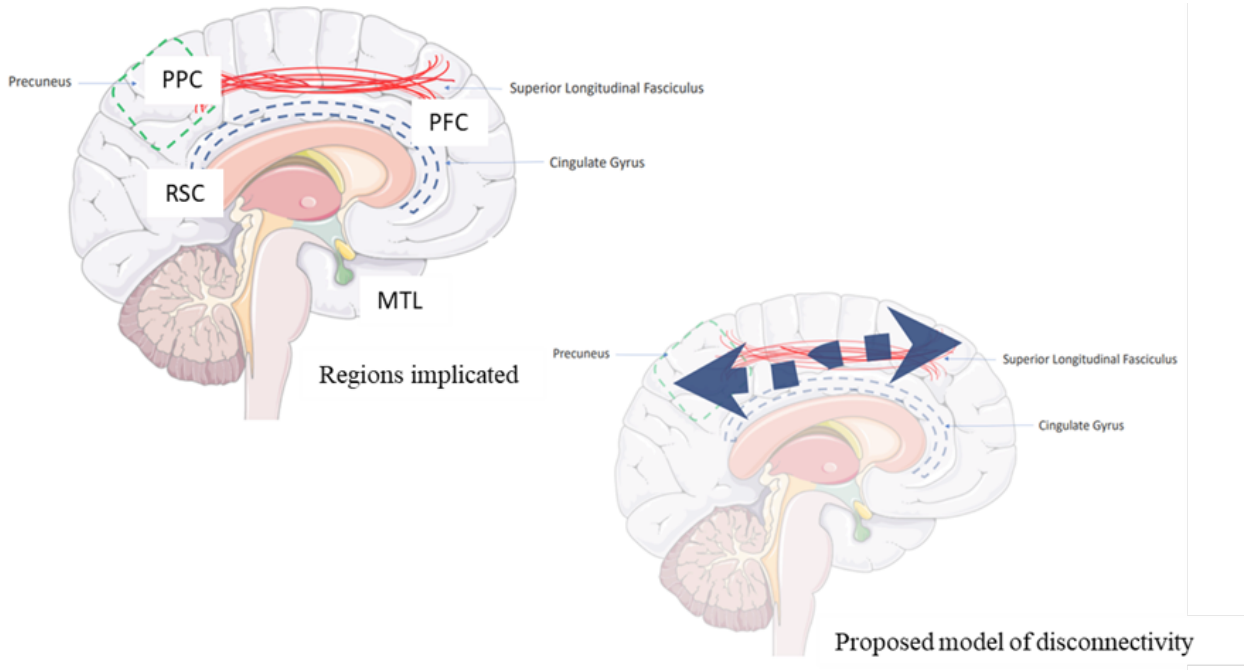

Figure 4. *Schematic illustration of brain regions implicated and potential model of dysconnectivity emerging between parietal sites and connecting anterior regions. Figure originally from Lowry et al., 2021.*

However, the current review is not without limitation. VCI is highly heterogenous in terms of expression, as well as pathogenesis. Therefore, we have not considered the complex interaction of risk factors (for a review, see Van Der Flier et al., 2018), or how they may contribute towards potential different expressions of preclinical VCI. Nor, have I discussed the latter stages of VCI at its clinical threshold or how specific lesion sites may be incorporated into our preliminary model (see, figure 4) of prodromal change. This is due to this review being focused on modifiable mechanisms that contribute to cerebrovascular change with an aim to identify their cognitive fingerprints at an early stage. However,

longitudinal tracking of the risk factors, along with cognitive and neuroimaging markers discussed above, may help identify at-risk individuals and a potential 'sensitive window' to deduce if/or when symptomology could be slowed or halted with appropriate intervention. I also acknowledge that the body of literature examining cognitive and neuroimaging correlates of risk factors that predate VCI is limited and has highlighted the need for further resources and investigation to gain a broader understanding of the preclinical stage. Above, in Figure 4. I have provided a schematic illustration of the brain regions implicated at the prodromal stage of VCI and a potential preliminary model of emerging dysconnectivity.

Growing evidence indicates that cardiovascular risk factors are associated with increased structural and metabolic change in the brain, worse cognitive performance and increased dementia risk. Yet, research is still lacking in detecting these symptoms in preclinical individuals before presentation of frank VCI. However, from the research discussed throughout this review there appears to be an emergence of cognitive dysfunction and connectivity changes in at VCI-risk individuals and as such, a more subtle and sophisticated approach is required to detect these biological and behavioural markers in their earliest manifestations. Focusing investigation into new and novel screening techniques to detect this dysfunction is key to providing clinical utility in order to identify, intervene and track disease progression as well as personalise treatment pathways.

To help close this gap, it is important to identify if there are cognitive or neuroimaging factors that are associated with VCI and the preclinical stage. Specifically, this includes studying if spatial orientation deficits are in fact, a sensitive and selective marker of VCI. This thesis also aims to build on our findings and examine if the spatial orientation deficits observed in VCI patients can be translated to identify at risk individuals in the prodromal

stage. In conclusion, addressing the current limitations of the literature would enhance the understanding of spatial orientation in VCI, to be used as a diagnostic tool.

Thesis aims and objectives

The aims for the experimental chapters outlined in this thesis include:

- To investigate if spatial navigation deficits, namely egocentric orientation, can be used as a sensitive and selective marker of VCI and disassociate from Alzheimer's dementia patients to aid cognitive diagnostic testing.
- Investigate the trajectory of change in spatial orientation deficits over a three-year period in the VCI case study, RK, who originally motivated this line of inquiry and gain a better understanding of the neural correlates of his symptoms.
- Investigate if egocentric orientation deficits exist in at VCI-risk individuals to help inform early disease detection.
- Observe if EEG using the P300 response will reveal differences in fronto-parietal processing in at VCI-risk individuals, in line with our working hypothesis discussed in Chapter 1, indicative of VCI progression.

A conclusion and discussion of the overall chapters will be found in Chapter 5. The novel spatial orientation test battery includes the Virtual Supermarket Test, the Clock Orientation Test and Sea Hero Quest which will be discussed in detail in each chapter. Each experimental chapter will conclude a set of specific hypotheses. The overarching hypotheses of the research thesis are:

- VCI patients will have an egocentric deficit compared to Alzheimer's disease patients who will have an allocentric deficit.
- RK's egocentric orientation deficit will persist and be associated with reduced white matter integrity of the superior longitudinal fasciculus.
- At VCI-risk individuals will have egocentric deficits, reduced P300 amplitude and delayed latency compared to healthy controls.

Chapter 2: Path Integration Changes as a Cognitive Marker for Vascular Cognitive Impairment?

Published paper

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Introduction

Vascular cognitive impairment (VCI) is the second most prevalent cause of cognitive decline after Alzheimer's disease (AD) and is thought to account for ~20% of all dementias (Goodman et al., 2017; Van Der Flier et al., 2018a). Although, individuals with mixed (AD and VCI) pathology are estimated to account for up to 70% of all dementia cases (Toledo et al., 2013). Despite the high prevalence of vascular impairment, its cognitive correlates are still being explored. Clinically, VCI is considered to involve a decline in executive function and higher order cognition such as information processing, planning, set-shifting and working memory (Hachinski et al., 2006; Sachdev et al., 2014). These changes are mostly attributed to micro and macro infarcts in subcortical and cortical regions, as well as their connecting white matter tracts (Beason-Held et al., 2012; van der Flier et al., 2018), in particular affecting frontoparietal networks. Nevertheless, attributing such executive changes to VCI specifically has remained challenging, as deficits in executive function can also present as part of AD or related pathophysiology (Guarino et al., 2019; Neufang et al., 2011). However, the recent development of novel spatial navigation cognitive markers for AD show promise in being more specific to underlying disease pathophysiology (Coughlan., 2018b) and may help to identify cognitive decline specific to VCI. A clear distinction between VCI and AD is essential to both clinician's and patient's as with appropriate intervention VCI can be slowed or halted, whereas AD has a fixed and terminal prognosis.

Spatial navigation has already been explored in AD (see Chapter one; Morganti et al., 2013; Serino et al., 2014; Vlˇcek and Laczó, 2014; Ritchie et al., 2018). In contrast to the exciting findings in AD, less is known about path integration in VCI, despite path integration potentially allowing as well to tap into parietal deficits in VCI (Haight et al., 2015; Maguire et al., 1998; Papma et al., 2013; Wolbers et al., 2004). A previous case study by our group explored path integration in a 65-year-old male with VCI. The findings showed that the vascular patient had normal performance on allocentric orientation but a clear and isolated deficit in egocentric and heading direction sub-components of the path integration tasks (Coughlan et al., 2018a). These findings are consistent with frontoparietal network disruptions typically seen in vascular dementia patients (Beason-Held et al., 2012; Sachdev et al., 2014; van der Flier et al., 2018) and may suggest medial parietal changes impede the egocentric frame of reference and subsequent path integration.

Aims and hypotheses

The current study leads on from this case study by exploring path integration in a group of VCI patients, and importantly comparing them against a group of AD patients and controls. Navigation will be tested using the Virtual Supermarket task where participants move through the virtual environment to a series of locations and are tested on their egocentric, allocentric and heading direction response. It is hypothesised that i) medial parietal mediated egocentric processes will be more affected in VCI; ii) medial temporal mediated allocentric processes will be more affected in AD.

Methods

Participants

Nine early stage vascular cognitive impairment and 10 early stage Alzheimer's disease patients along with 20 healthy controls were recruited from the community using 'Join Dementia Research' to participate in the study at the University of East Anglia as part of the wider The Dementia Research and Care Clinic (TRACC) study. The research was approved by the Faculty of Medicine and Health Sciences Ethics Committee at the University of East Anglia (reference 16/LO/1366) and written informed consent was obtained from all participants. Clinical diagnosis (VCI or AD) was classified by a consultant at the Norfolk and Suffolk Foundation Trust by interviewing the patient, examining neuropsychological assessment scores, structural clinical MRI scans and the patient's medical history which met the diagnostic criteria for VCI (see, VASCOG criteria (Sachdev et al., 2014)) or AD (see, NINCDS-ADRDA criteria (Dubois et al., 2007)). For clarity, the structural MRI profile of VCI was indicated by subcortical infarcts and white matter hyperintensities, whilst volume loss focused to medial temporal lobes was associated with AD pathology. Disease duration was reported by the person's study partner (a spouse or relative). Participants had no history of psychiatric or neurological disease, substance dependence disorder or traumatic brain injury and had normal or corrected-to-normal vision. None of the patients study partners in this experiment reported problems with spatial orientation before dementia onset or a history of developmental topographical disorientation (Iaria et al., 2009). All participants underwent neuropsychological screening, including cognitive screening, episodic memory and spatial memory tasks, Addenbrooke's cognitive examination (ACE-III) (Hsieh et al., 2013), Rey–Osterrieth Complex Figure Test (RCFT) copy and with 3-min delayed recall (Shin et al., 2006), Cube Analysis, Dot Counting and Position Discrimination from the Visual Object and

Space Perception Battery (VOSP) (Warrington & James, 1991), Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984).

Measures and Materials

Virtual Supermarket Task

The Virtual Supermarket Task has been developed by our group previously and used in symptomatic mild cognitive impairment (MCI), AD, frontotemporal dementia (FTD) and VCI patients(Coughlan et al., 2018a; Tu et al., 2015, 2017).The VR task is an ecological test of spatial navigation abilities designed to simulate navigating through a real-world supermarket. An iPad 9.7 (Apple Inc.,) was used to show participants 20-40 second video clips of a moving shopping trolley in the virtual supermarket (Figure. 5A-C). Videos were presented in a first-person perspective and participants are provided with optic flow cues from the moving shopping trolley and changing scenery as it followed different routes to reach a different end point in each trial. The task avoids the use of landmarks or salient features within the environment and limits the demand on episodic memory, reflecting similar tasks in the literature (see Cushman et al., 2008; Morganti et al., 2013; Wolbers et al., 2007) and taps into path integration processes via three core spatial processes: i) egocentric self-reference navigation; ii) allocentric map-based navigation and iii) heading direction. Once the video clip stops, participants indicate in real-life the direction of their starting point (egocentric orientation; Figure 5D). In a second step, participants indicate their finishing location on a birds-eye view map of the supermarket (allocentric orientation; Figure 5E), performance is calculated using the distance error (mm) between this and the coordinates of the actual finishing location. This map-based component provides an assessment of geocentric encoding of the virtual environment. The participant then indicates their heading

direction at the finishing point, which determines the ability to which heading direction was encoded and updated throughout the task. The tasks consists of 14 trials and takes approximately 15 minutes to complete.

Clock Orientation test

The Clock Orientation test has also been developed by our lab(Coughlan et al., 2018a) as a bedside clinical test for egocentric orientation. It requires participants to imagine they are standing in the centre of a large clock, facing a particular number, e.g., the number 3. Participants are then asked "which number is directly behind you?" (Answer: number 9). Next participants are asked to point, in real-life, to the positions of different numbers on the clock face in relation to the number that they are currently facing. For example, "You are facing number 12, can you point to the number 3?" (Answer: pointing right). The questions increase in complexity across the test and require medial parietal mediated mental imagery, rotation and egocentric processes, with no episodic memory demand. The test consists of 12 trials and takes 5-10 minutes to complete.

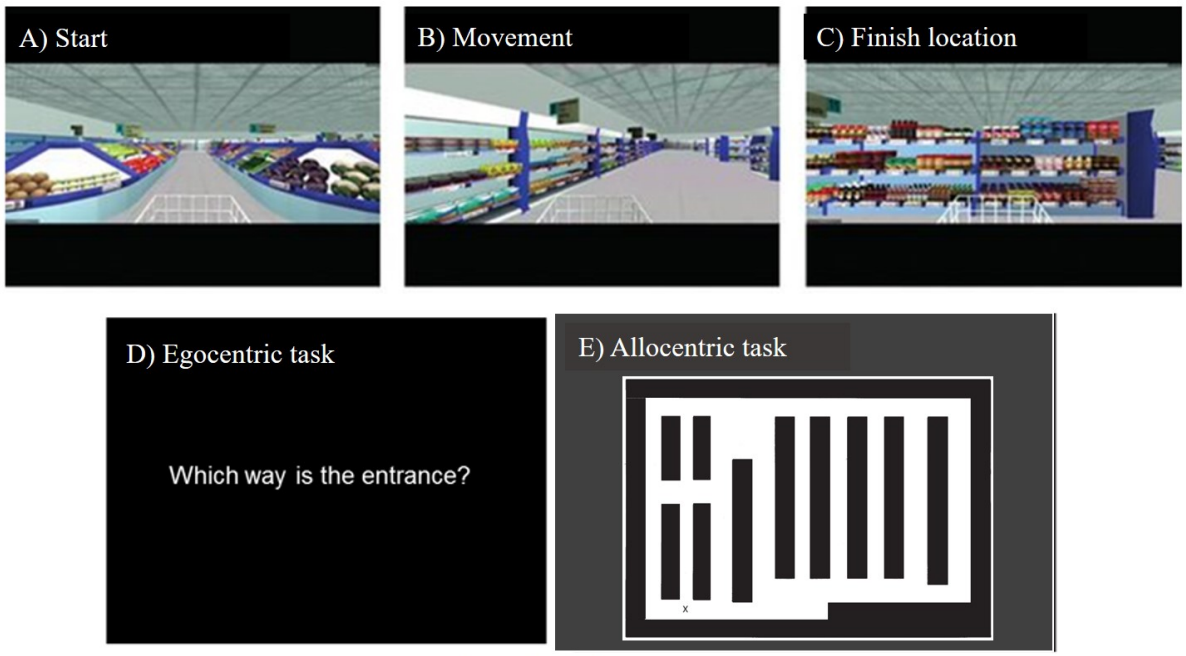
Procedure

Participants completed a battery of neuropsychological assessments at their home (see Table 4 for list of tasks). In a second session participants had a clinical interview held at the Norfolk and Suffolk Foundation Trust and undertook cognitive experimental tests (including the virtual Supermarket task and Clock Orientation test).

Statistical Analysis

Statistical analysis was performed using IBM SPSS (Version 25). Chi square and two tailed one-way univariate analysis of covariance (ANCOVA) with age and sex as covariates were

used to test the significance of any demographic or neuropsychological differences between the clinical groups. When quantifying group differences, partial eta-squared (n_p^2) was used as a measure of effect size ($\eta_p^2 = 0.01$ indicates a small effect, $\eta_p^2 = 0.06$ indicates a medium effect and $\eta_p^2 = 0.14$ indicates a large effect (Cohen, 1988)). The Virtual Supermarket task has 3 measures -specifically egocentric response, allocentric response and heading direction. Each outcome measure was individually entered into a one-way analysis of covariance (ANCOVA) with group as the independent variable and age and sex as covariates. Although groups were well matched for age and sex, these covariates were decided as evidence suggests they can affect navigational behaviour (Coutrot et al., 2018). The Clock Orientation test was also analysed using a one-way ANCOVA with group as the independent variable and age and sex as covariates. Post-hoc pairwise comparisons were conducted using Bonferroni adjustment for multiple comparisons. Sensitivity and specificity of the egocentric supermarket task and clock orientation test performance in VCI and AD were compared using logistic regression and ROC curve analysis. A Z-score of AD performance was computed for 7 missing values for one AD patient in the Virtual Supermarket task.



Tu et al (2015, 2017)

Figure 5. Screenshots from the Virtual Supermarket task, showing (A) starting viewpoint, (B) movement during the example video clip, (C) end location of an example video clip, (D) onscreen instructions prompting the participant to indicate the direction of their starting point, (E) the supermarket map participants use to indicate their finishing location and their heading direction when the video clip ends.

Results

Demographics and Neuropsychology

Participant groups were well matched and no significant differences in demographic measures were observed between the VCI, AD and control groups (all p-values > .1). ANOVA of participant groups showed both VCI and AD patients performed significantly lower on a general cognitive screening test (ACE-III) and the memory recall domain of RCFT compared to controls (all p-values < .01). Results showed no significant neuropsychological differences between the VCI and AD patients for the ACE-III, RCFT recall condition, VOSP dot counting and cube analysis sub-sets (all p-values > 0.1. However, VCI patients were significantly more impaired than AD patients in the RCFT copy condition,

FCSRT free recall condition and the VOSP position discrimination (all p-values < .1) (see table 4).

Table 4. Demographic characteristics and neuropsychological performance.

	VCI	AD	Control	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Sig post-hoc VCI vs. AD comparisons*
n	9	10	20	
Sex (F/M)	3/6	2/8	9/11	*ns*
Age	70.22 (4.57)	69.91 (7.7)	69.6 (6.45)	*ns*
Disease duration	3.13 (2.64)	2.81 (2.21)	n/a	*ns*
General cognition				
Total ACE-III	69.44 (12.9)	72.1 (22.41)	95.1 (3.13)	*ns*
ACE: Attention	13.5 (.72)	15.75 (.72)	17.6 (.45)	*ns*
ACE: Memory	13.5 (1.73)	17.13 (1.17)	24.3 (.74)	*ns*
ACE: Fluency	7.13 (.59)	8.12 (.59)	11.7 (.37)	*ns*
ACE: Language	21.77 (2.44)	22.33 (3.04)	25.6 (.61)	*ns*
ACE: Visuospatial	11.5 (1.19)	16.67 (1.12)	15.8 (.75)	*ns*
Visuospatial ability				
RCFT: Copy	22.1 (7.17)	28.4 (8.92)	32.72 (3.23)	*ns*
RCFT: Recall	7 (5.65)	11.8 (8.12)	17.55 (5.43)	*ns*
Dot Counting	9.5 (0.71)	9.8 (0.42)	10 (0)	*ns*
Position Discrim	18.87 (1.27)	19.7 (0.67)	19.85 (0.37)	*ns*
Cube Analysis	8.11 (2.62)	8.7 (1.88)	9.8 (0.52)	*ns*
Memory ability				
Total FCSRT	29.21 (2.84)	42.91 (2.63)	47.92 (2.01)	*
FCSRT: Free recall	8.83 (7.94)	17.14 (8.83)	26.83 (4.17)	*ns*
FCSRT:Cued recall	25.7 (4.94)	20.5 (7.2)	23.35 (4.87)	*ns*
Supermarket task				
Egocentric	3.44 (3.24)	9.4 (2.27)	8.1 (3.7)	*
Allocentric	69.1 (38.11)	48.41 (12.17)	30.2 (14.13)	*ns*
Head direction	4.8 (1.33)	5 (3.41)	7.1 (0.9)	*ns*
Clock test	5.43 (0.81)	10.1 (1.2)	10.1 (0.51)	**

*Significant group differences between VCI and AD patients. *$p < 0.01$, **$p < 0.001$, ns = non-significant. ACE-III = Addenbrooke's cognitive examination. RCFT: Copy = Rey-Osterrieth Complex Figure Task, copy condition. RCFT: Recall = Rey-Osterrieth Complex Figure Task, recall 3 min after copy. Dot Counting, Position Discrimination, and Cube Analysis = sub-sets from Visual Object and Space Perception Battery (VOSP). FCSRT: free recall = Free and Cued Selective Reminding Test, free recall Test condition, FCSRT: free recall = Cued and Cued Selective Reminding Test, cued condition.

Group differences in spatial navigation

Virtual Supermarket Test

An ANCOVA with age and sex as covariates revealed a significant differences between egocentric responses on the supermarket task, $F\ (2, 34) = 8.14, p < .001, n_p^2 = .32$. Post-hoc comparisons revealed significantly greater egocentric impairment in VCI (M= 3.5, SD= 3.24) compared to AD (M= 10.01, SE= 1.11), $p < .002$, 95% CI [-10, -2.1] and control groups (M= 8.1, SD= 3.7), $p < .009$, 95% CI [-7.95, -1.1]. No other significant group differences were observed ($p > .1$) (see figure 6A).

Allocentric responses showed a significance difference between groups, controlled for age and sex $F\ (2,34) = 10.1, p <.001, n_p^2 = .37$. Post-hoc comparisons showed significantly greater impairments in VCI patients (M = 68.33, SD= 38.1) compared to controls (M= 30.85, SD= 14.13), $p < .001$, 95% CI [16.02, 61.1] but impairments did not reach statistical significance in AD patients (M= 50.1, SD= 7), $p = 0.09$, 95% CI [-41.11, 2.1] compared to controls. However, there were no significant groups differences between VCI and AD (p>.1) (see figure 6B).

Heading direction (correct judgement of facing direction after travel period) did not reveal significant group differences when controlling for age and sex $F\ (2, 34) = 1.11, p > .1, n_p^2 = .06$ (see figure 6C).

Clock Orientation Test

An ANCOVA with age and sex as covariates revealed a significant difference between egocentric responses on the Clock Orientation task $F\ (2, 34) = 13.4, p < .001, n_p^2 = .44$. Post-

hoc comparisons showed significantly greater egocentric deficits in VCI patients (M= 5.42, SD= 3.16) compared to AD (M= 10.1, SD= 1.21), $p < .001$, 95% CI [-7.2, -2] and control groups (M= 9.65, SD= 2.06), $p < .001$, 95% CI [-6.56, -7.1]. No other significant group differences were observed ($p > .1$) (see figure 6D).

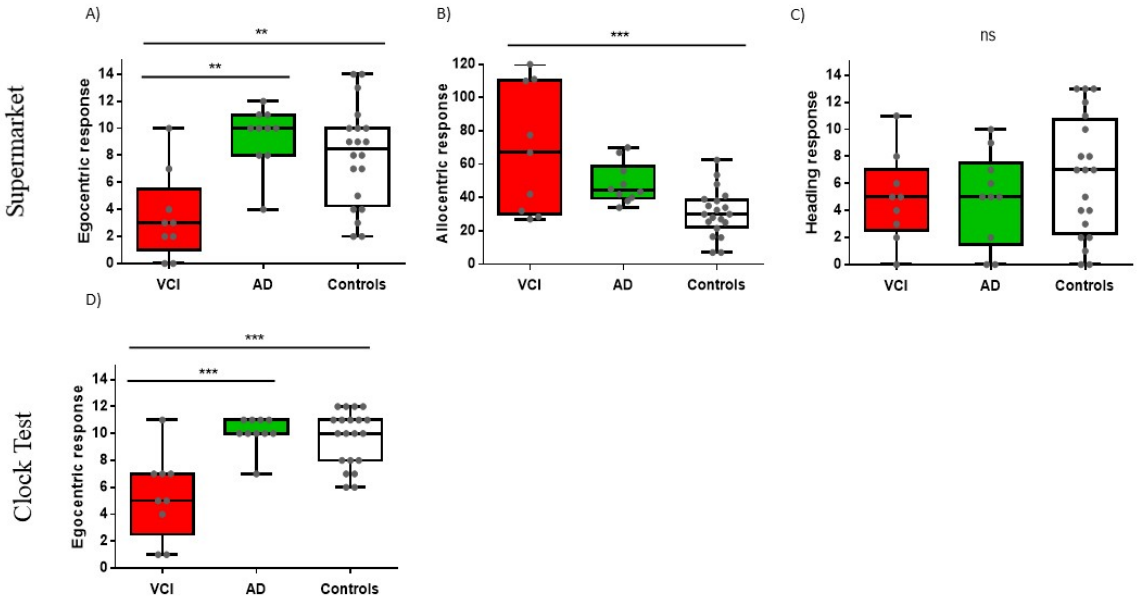


*Figure 6. Spatial orientation performance between vascular cognitive impairment (VCI), Alzheimer's disease (AD), and controls. **p < 0.01, ***p < 0.001, ns = non-significant. Figures (A–C) show The Virtual Supermarket task performance; (A) egocentric response (correct), (B) allocentric response (error in mm) and (C) heading response (correct). Figure (D) displays The Clock Orientation test egocentric response (correct).*

Sensitivity and Specificity

Sensitivity and specificity of egocentric Virtual Supermarket and Clock Orientation test performance in VCI and AD were explored using logistic regression and ROC curves. Logistic regression indicated that the regression model based on egocentric scores of

Supermarket and Clock Orientation predictors was statistically significant, $X^2(2) = 16.36$, $p < .001$. The model explained 77% (Nagelkerke R^2) of variance in VCI and AD patients and correctly classified 84% of patients (7 out of 9 VCI; 9 out of 10 AD) into their respective cohorts. ROC curves were computed for the supermarket and clock test predictors in discerning VCI from AD patients. Similarly, Area Under the Curve (AUC) values indicated that egocentric orientation in the Supermarket (AUC = .8, SE = .12; 95% CI [.56, 1]) and Clock test (AUC= .91, SE = .06, 95% CI [.8, 1]) had strong diagnostic accuracy in distinguishing VCI from AD patients (see, figure 7).

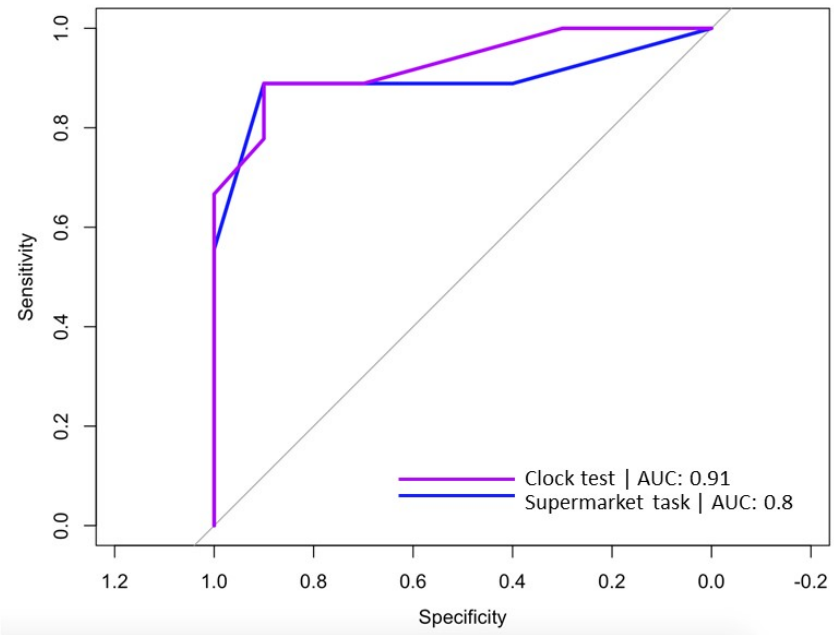


Figure 7. ROC curves for the Virtual Supermarket Test (blue line) and Clock Orientation test (purple line) predicting correct diagnosis (VCI or AD).

Discussion

Overall, our results indicate that medial parietal mediated egocentric path integration processes are a sensitive and specific cognitive marker selective for VCI. By contrast, allocentric orientation deficits were less sensitive, and not specific to distinguish between the underlying pathologies.

In more detail, the egocentric path integration measures of the Virtual Supermarket task and Clock Orientation test successfully detect vascular changes in patient populations. More importantly, the measures allowed to reliably distinguish vascular from AD pathophysiology in the patient populations. Notably, egocentric orientation was impaired in VCI, but relatively intact in AD patient groups when controlling for age and sex. This supports findings from our vascular patient case study (Coughlan et al., 2018a) and may suggest egocentric impairments indicate a more medial parietal focused change (Weniger et al., 2009) in VCI. Furthermore, the AD patient's egocentric ability remained intact which supports suggestions that MCI and earlier stage AD groups show an undisturbed egocentric orientation (Coughlan et al., 2019), which is consistent with our early stage AD patient population (see, total ACE-III score of 72.1). It would be interesting to explore whether more moderate to advanced AD patients might show problems using both allocentric and egocentric orientation, as it is known that medial parietal structures might be affected only later in the disease course (Braak & Del Tredici, 2015).

Medial parietal mediated egocentric deficits appear to characterise VCI patients. This is consistent with emerging evidence suggesting the earliest signs of dysfunction appear in medial frontal and anterior cingulate regions in at VCI-risk individuals (Haight et al., 2015; Papma et al., 2012), which is accompanied by a more typical vascular profile of reduced

integrity of white matter in the bilateral superior longitudinal fasciculus (Beason-Held et al., 2012). Since egocentric orientation does not deteriorate in healthy aging and early stage AD, compared to medial temporal based cognitive functions (for review, see Colombo et al., 2017) it emerges as a potential powerful cognitive marker to identify early vascular-related pathology. Given the prevalence of vascular related dementia it is surprising that investigation to isolate cognitive deficits unique to this pathology is so sparse. However, based on our findings, it appears that egocentric orientation may be a useful diagnostic tool to discriminate VCI from other neurodegenerative conditions.

Our study suggests allocentric orientation deficits were not statistically present in AD, only VCI showed significant impairments compared to healthy controls. This does not support our prediction that allocentric deficits would be more profound in AD. The literature suggests allocentric deficits are more prominent in preclinical AD(Coughlan et al., 2018b) with a loss in selectivity as the disease stage progresses and deficits become more widespread (Braak & Del Tredici, 2015). Yet, for the early-stage AD patients in our study results were not significant. A post-hoc power analysis was employed using G*Power3 (Faul et al., 2007) and results indicate power at Cohen's d= 0.32 would have been sufficient to yield significant results between AD and VCI allocentric performance. The actual power yielded between groups was reported at Cohen's d= 0.71. Therefore, a larger sample size would indeed, expect to report greater group differences for the allocentric measure. However, as evident from Figure 6, it is clear that AD patients perform differently from controls but this did not reach statistical significance.

One potential explanation for the results observed may be provided by the large range in allocentric scores across the VCI group (see, Table 4). VCI is a highly heterogeneous

disorder in terms of disease pathology and subsequent cognitive impairments which may account for this variation, compared to AD pathology and symptoms that are more uniform. As VCI patients revealed both egocentric and allocentric orientation problems this is likely to represent a disruption to translational and integration processes where both frames are combined to produce effective navigation. This view also explains the reduced visuospatial performance exhibited by the VCI patients during neuropsychological testing across RCFT copy and position discrimination tasks.

Despite these exciting findings, our study is not without limitations. First and foremost, replication in larger patient cohorts is important. Further, clinical characterisation of VCI subtypes (Skrobot et al., 2017) would help to better classify vascular pathology and determine accompanying cognitive symptoms, this may also help inform the variation of results seen in allocentric performance for the VCI patients. Future studies may also wish to examine the relationship between spatial navigation performance and the patient's perceived navigational abilities. Findings suggest perceived spatial ability assessed by the self-report Santa Barbara Sense of Direction Scale (Hegarty et al., 2002) are correlated with spatial accuracy and hippocampal volume (Burte et al., 2018). Therefore, assessment of perceived spatial abilities may help inform spatial navigation as a marker of pathological aging. Finally, as the study did not access the patient's clinical MRI scans, the confirmation of vascular lesions and their locations, as well as AD specific biomarkers would be important in future investigations to corroborate our cognitive findings.

Nevertheless, to our knowledge this in the first study to isolate a selective navigational deficit in VCI. This showcases the important role of virtual navigation and spatial tests in the future development of sensitive and specific diagnostic tests for VCI. Further investigation into the

cognitive symptoms selective to VCI as well as longitudinal cohort studies in at VCI-risk individuals is critical to identify the emergence of the disease and intervene with therapeutic strategies as early as possible.

In conclusion, our findings show a distinct egocentric orientation deficit that is specific for VCI relative to AD. This is critical given the lack of specificity in current diagnostic tests and the indistinct diagnostic criteria for cognitive symptoms in VCI. In turn, this will inform diagnostic work-ups and aid personalised treatment pathways to treat underlying vascular changes in patients.

Taking these findings discussed in chapter 2, it appears egocentric orientation is sensitive to VCI patients whilst, heading direction no longer shows such a strong effect as it did in the initial case study informed by the patient RK (Coughlan et al., 2018a). Interestingly, allocentric orientation was also shown to be impaired in the VCI patients, although it was anticipated this would remain intact as shown in RK's condition (Coughlan et al., 2018a). Perhaps because the disease stage was further progresses in the patients in chapter 2, with an average of three years disease duration compared to RK who was diagnosed just one year prior to testing. Given these findings, and that the examination of spatial abilities in VCI are in such early stages, I decided to follow up with the patient RK, to observe any changes to his condition and spatial navigational abilities and shed a light on if he too now had allocentric deficits, consistent with the patients in this study. Investigating RK's condition three years on, will help add to our knowledge concerning VCI and associated cognitive and spatial trajectories.

Chapter 3: Egocentric spatial orientation – a key cognitive marker for vascular cognitive impairment? A longitudinal case study.

Submitted manuscript

Lowry, E., Coughlan, G., Morrissey, S., Jeffs, S., Hornberger, M. (submitted). Egocentric spatial orientation – a key cognitive marker for vascular cognitive impairment?

Introduction

Vascular cognitive impairment (VCI) is thought to account for at least 20% of the clinical population affected by dementia (Gorelick et al., 2011), second in prevalence only to Alzheimer's disease (Plassman et al., 2007). Despite that, the cognitive features specific to VCI are still being explored, with currently subtle executive dysfunction mostly associated with the condition (Sachdev et al., 2014). This cognitive heterogeneity is likely due to the diverse nature of VCI, ranging from microinfarcts to white matter hyperintensities (WMH) (Dichgans & Leys, 2017; Iadecola, 2013; Prins & Scheltens, 2015). Microinfarcts in particular can affect several cortical and subcortical regions (Roman et al., 2002), accounting for the cognitive heterogeneity in VCI patients. By contrast, WMH are more consistent in their location and show a propensity to the superior longitudinal fasciculus (Chen et al., 2019; Liu et al., 2021; Veldsman et al., 2020).

The Superior longitudinal fasciculus (SLF) is a major white matter pathway in the brain, connecting mostly frontal and parietal brain regions. I have previously hypothesised that disruption of the SLF should not only result in subtle frontally-mediated executive change but also medial parietal-mediated, egocentric spatial orientation changes (Lowry et al., 2021). Indeed, a previous publication of ours shows that egocentric spatial navigation tests are highly sensitive to VCI and distinguish it reliably not only from healthy people but also

Alzheimer's disease (Lowry et al., 2020), though see (Moussavi et al., 2022). These egocentric spatial orientation measures might provide a promising cognitive diagnostic and treatment outcome measure for WMH in VCI, specifically.

However, at this stage it is not clear how those WMH changes co-exist with egocentric spatial orientation changes over time. This current study tries to address this outstanding question by testing a single VCI case over a three-year period. RK, the 67-year-old VCI patient first presented to our memory service in 2017. At that time RK presented with egocentric orientation deficits while his allocentric orientation remained intact (Coughlan et al., 2018a).

Aims and hypotheses

Here, I now present the follow-up assessment of RK, along with SLF neuroimaging, to determine if the egocentric spatial orientation changes in RK after a three-year period are present, and how they relate to his WMH in the SLF. This will inform how consistent egocentric spatial orientation changes are in VCI associated with WMH, and how they relate to the underlying brain integrity. It will inform future cognitive diagnostic and treatment outcome measures for VCI.

Methods

Participant

Our research group previously reported the case of RK, a now 67-year-old married man, with six years of secondary education. RK received a diagnosis of vascular dementia (aka VCI) in March 2017 at our dementia research clinic. His medical history included

hypercholesterolemia, stage 2 hypertension, an elevated BMI, life-long cigarette smoking, as well as a strong family history of hypercholesterolemia and heart disease. Since enrolling in the research study, RK now reports increased medical management for hypertension and an enlarged prostate. RK and his care-giver report advancing memory problems and an increased need for daily-living assistance from time one (t1) to time two (t2), although he remains independent in leaving the house to walk to the local shop daily. I have compared new case control participants (*N*=14) with a mean age of 67.79 (SD = 3.17), nine male, five female, who underwent the same cognitive and spatial testing, as follow up data was not available from the original control cohort used at t1. The research was approved by the UK National Research Ethics Service (NRES: 16/LO/1366) and written informed consent was obtained prior to research activities.

Table 5. Patient physical characteristics time 1 to time 2.

	Time 1	***Time 2***	***Patient change***
Age	65	67	+2
Height (cm)	175	175	0
Weight (kg)	91	90	-1
BMI	30	29	-1
BP SYS	165	162	-3
BP DIA	100	93	-7
Pulse	55	64	+9
Medical Management	Simvastatin 40mg, Bendroflumethiazide 2.5mg, Clopidogrel 75mg, Losartan 100mg	Simvastatin 40mg, Bendroflumethiazide 2.5mg, Bisoprolol 1.25mg, Clopidogrel 75mg, Losartan 100mg, Levothyroxine 100mg, Finasteride 5mg	+3

[*]*For patient change + represents increase and - represents decrease.*

Measures and Materials

Cognitive Screening

RK underwent neuropsychological screening, including; Addenbrooke's cognitive examination (ACE-III) (Hsieh et al., 2013) (version A at t1 and version C at t2 to minimise test re-test effects), Rey–Osterrieth Complex Figure Test (RCFT) copy and with 3-min delayed recall (Lazek, 1983), Cube Analysis, Dot Counting and Position Discrimination from the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991), Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984), INECO Frontal Screen Test (Torralva et al., 2009) and the Trail Making Test (TMT) part A and part B (Reitan, 1958) (see, Table. 5). Controls underwent neuropsychological screening using; ACE-III, RCFT and TMT.

The Virtual Supermarket Test

RK and controls underwent spatial testing using the Virtual Supermarket Test (VST). The VST has been developed by our group previously and used in symptomatic mild cognitive impairment (MCI), AD, frontotemporal dementia (FTD) and VCI patients (Coughlan et al., 2018a; Lowry et al., 2020; Tu et al., 2015, 2017). The VR task is an ecological test of spatial navigation abilities designed to simulate navigating through a real-world supermarket. While at t1, a paper version of the supermarket map (allocentric measure) was used, an alternative form of this measure was employed 3 years later at re-test (t2), to facilitate electronic and automatic recording of participant responses. VST trials (1-14) in both versions were identical (see, Figure. 8A-C). At t1 a paper version of the supermarket was used to record responses (identical to that shown in Figure. 8D-F), which has now been automated. The task consists of 14 trials and takes approximately 15 minutes to complete. An iPad 9.7 (Apple

Inc.,) was used to show participants 20-40 second video clips of a moving shopping trolley in the virtual supermarket. The task avoids the use of landmarks or salient features within the environment and limits the demand on episodic memory, reflecting similar tasks in the literature (Cushman et al., 2008; Morganti et al., 2013; Wolbers et al., 2007) and taps into path integration processes via three core spatial processes: i) egocentric self-reference navigation; ii) allocentric map-based navigation and iii) heading direction. Performance is calculated using the distance between this and the coordinates of the actual finishing location. This map-based component provides an assessment of geocentric encoding of the virtual environment.

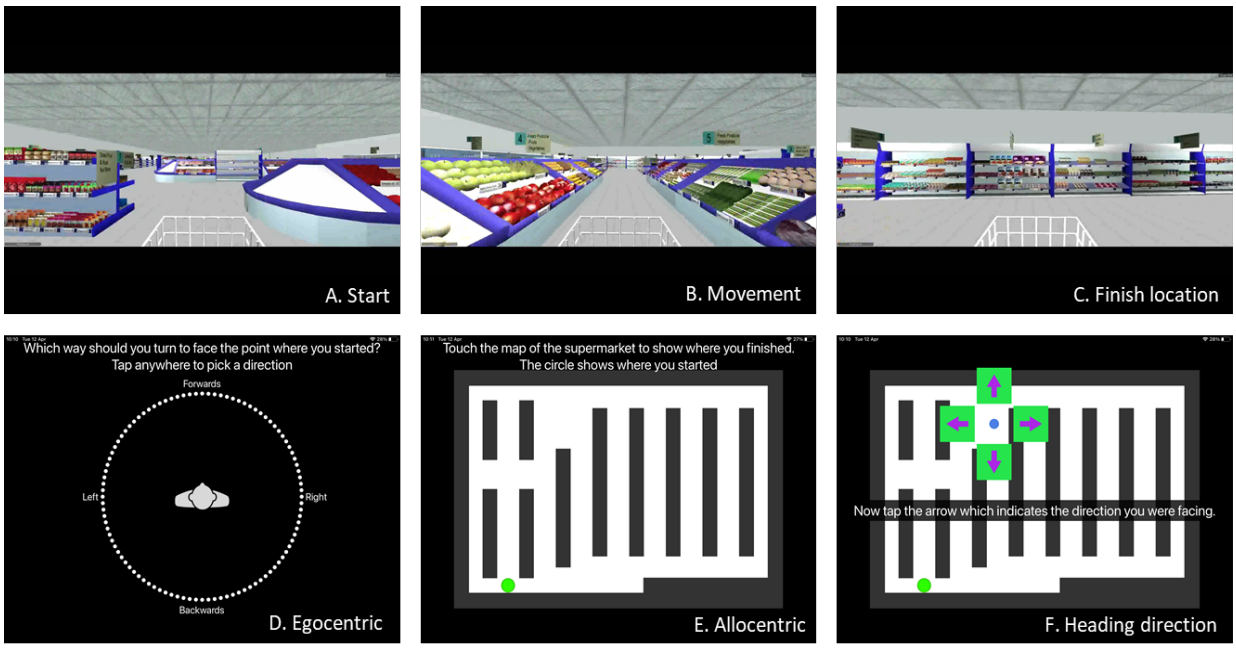


Figure 8. Virtual Supermarket Test.

Videos were presented in a first-person perspective and participants are provided with optic flow cues from the moving shopping trolley and changing scenery as it followed different routes to reach a different end point in each trial (A-C). Once the video clip stops, participants indicate in real-life the direction of their starting point (egocentric orientation; 7D). In a second step, participants indicate their finishing location on a birds-eye view map of the supermarket (allocentric orientation; 7E). Lastly, participants are asked to indicate which direction they were facing at the finishing location

(heading direction; 7F). Participants indicate their responses by taping their response location on the screen.

The Clock Orientation Test

RK and controls underwent spatial testing using the Clock Orientation Test (COT). The COT has also been developed by our lab (Coughlan et al., 2018a; Lowry et al., 2020) as a bedside clinical test for egocentric orientation. It requires participants to imagine they are standing in the centre of a large clock, facing a particular number, e.g., the number 3. Participants are then asked, "which number is directly behind you?" (Answer: number 9). Next participants are asked to point, in real-life, to the positions of different numbers on the clock face in relation to the number that they are currently facing. For example, "You are facing number 12, can you point to the number 3?" (Answer: pointing right). The questions increase in complexity across the test and require medial parietal mediated mental imagery, rotation and egocentric processes, with no episodic memory demand. The test consists of 12 trials and takes 5-10 minutes to complete.

Sea Hero Quest

RK and controls underwent spatial testing using Sea hero Quest (SHQ). SHQ is an app-based cognitive task that enables the collection of spatial navigation data and is used in large scale population based studies (Coutrot et al., 2018) and has been shown to differentiate egocentric and allocentric frames of reference, exhibiting selective 'wayfinding' allocentric deficits in prodromal Alzheimer's disease (Coughlan et al., 2019). SHQ goal-oriented wayfinding (allocentric) levels 6 , 8 and 11 were selected due to their previous sensitivity to identifying pre-clinical AD (Coughlan et al., 2019). Players initially see a map featuring a start location and several checkpoints to find in a set order. Participants study a map of the level for a recorded number of seconds. When participants exit the map view, they are asked

to immediately find the checkpoints in the order indicated on the map under timed conditions. As participants navigate the boat, they must keep track of their location using self-motion and environmental landscape cues such as water– land separation. If the participant takes more than a set time, an arrow appears pointing in the direction along the Euclidean line to the goal to aid navigation. In flare accuracy (egocentric) levels (here, levels 14, 19, 24, 34 and 44), participants are not provided with an allocentric map. Instead, they immediately navigated along a river to find a flare gun. Once they find the flare gun at the end of the river, the boat rotates by 180°, and participants are asked to choose one of three possible directions (right, front, and left) that they believe points to the starting point. This level requires participants to (i) form an accurate representation of the starting point relative to their position and (ii) integrate this representation with a representation of the direction they are facing after the rotation. Depending on their performance, players receive one, two, or three stars.

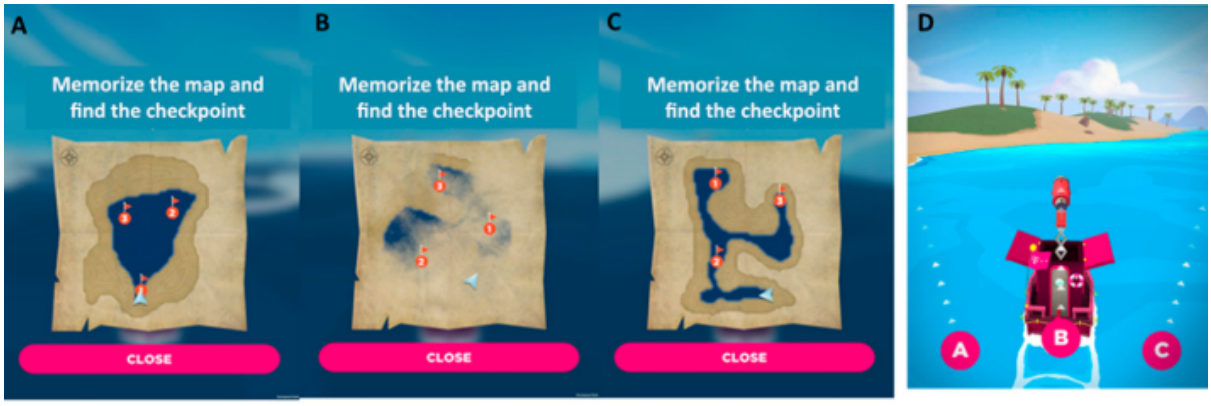


Figure 9. SHQ Wayfinding (allocentric) and Flare Accuracy (egocentric) levels.

MRI acquisition

MRI data was obtained from RK and controls using a 3 tesla Discovery 750w widebore system (GE Healthcare, Milwaukee, WI, USA) with a 12-channel phased-array head coil for signal reception. After localizers, the T1-weighted (T1w) structural data was acquired using a

whole-head 3D inversion-recovery fast spoiled gradient recalled echo sequence with the following parameters: repetition time ¼ 7.7 ms; echo time ¼ 3.1 ms; inversion time ¼ 400 ms; field-of view ¼ 256 mm; acquired matrix ¼ 256 256; 200 sagittal sections of 1mmthickness; flip angle ¼ 11 ; and an ASSET acceleration factor of 2 in the phase-encoding direction. Furthermore, a 3D T2- weighted fluid attenuated inversion recovery (T2w FLAIR) sequence was prescribed as follows: repetition time ¼ 4800 ms; echo time ¼ 129 ms; inversion time ¼ 1462 ms; field-of-view ¼ 256 mm; acquired matrix ¼ 256 256; 182 sagittal sections of 1mmthickness; flip angle ¼ 90; an ARC acceleration factor of 2 in the phase encoding direction; and a “HyperSense” compressed sensing subsampling factor of 2.

DTI (diffusion-weighted single shot spin-echo planar imaging sequence, TR = 6.7 s,TE = XX ms, 59 axial slices, resolution = 0.937 × 0.937 × 2.499 mm, no cardiac gating, 61 images with diffusion weighting, b = 2000 s/mm2, four images without diffusion-weighting, b = 0 s/mm2, subsequently referred to as b0 images) scans were acquired for all participants. MRIs were screened by a consultant neurologist and analysed using FSL (v6.0.0) and Freesurfer (v11.4.2) software.

White matter hyperintensities, infarcts and perivascular space

The Fazekas scale (Fazekas et al., 1987) was used to quantify the amount of white matter T2 hyperintense lesions in RK as it is a widely used system for describing white matter disease severity associated with cognitive decline (Benedictus et al., 2015; van Rooden et al., 2018). The scale divides the white matter in periventricular and deep white matter, and each region is given a grade depending on the size and confluence of lesions (periventricular hyperintensities (0-3), White matter hyperintensities (0-3), PV (periventricular hyperintensities)= 0 (absence), 1 ("caps" or pencil-thin lining), 2 (smooth "halo"), or 3

(irregular PV extending into the deep white matter), and WM (white matter hyperintensities) = 0 (absence), 1 (punctate foci), 2 (beginning confluence of loci), or 3 (large confluent areas)). Infarct, and perivascular space were quantified by visual inspection using FSL on T2-weighted fluid-attenuated inversion recovery (FLAIR) and on T1-weighted (T1w) structural MRI. Topographical location of each lesion was reported using atlases in FSL eyes. The rater was blinded to all cognitive and spatial navigational results.

TRActs Constrained by UnderLying Anatomy (TRACULA)

Tractography were performed within Freesurfer (TRACULA version 1.56), DTI data was processed using the ENIGMA DTI pre-processing steps (http://enigma.ini.usc.edu/protocols/dti-protocols/). In particular, we used the first b0image as a reference for co-registration of subsequent b0 images (FSL FLIRT(S. M. Smith et al., 2004)). The resulting co-registered b0 images were averaged and served as a reference image during motion correction on the diffusion-weighted images. The gradient table information was adjusted accordingly (Leemans & Jones, 2009). Subsequently the data was processed in order to account for geometric distortions, this was performed on the mean b0 image via the T1-w scan. In order to achieve distortion correction, the T1-w scan was rigidly aligned with the mean b0 image(S. M. Smith et al., 2004) and the mean b0 image was nonlinearly registered to this T1-w scan in diffusion space using Advanced Normalization Tools (http://stnava.github.io/ANTs/). The resulting nonlinear registration information was used to unwarp subsequent diffusion-weighted images in native diffusion space. TRACULA's default tensor fitting and tract reconstruction pipelines using the ball-and-stick model were applied to the pre-processed data. The DTI data images were assessed visually. We visually appraised TRACULA's performance in terms of tract reconstruction for temporal and parietal divisions of the superior longitudinal fasciculus as per standard TRACULA segmentation (using global

probabilistic tractography with anatomical prior information of predefined pathways). We investigated tract DTI-derived scalar metrics fractional anisotropy (FA) for the tract previously hypothesised to be affected in this patient.

Procedure

RK underwent initial cognitive assessment (including neuropsychology and spatial navigation) in March 2017. Findings from this assessment were previously published (Coughlan et al., 2018a). RK received an anatomical and diffusion weighted brain scan in August 2019 as part of a longitudinal follow up to identify the vascular abnormalities underlying RK's symptoms of reduced information processing and spatial disorientation and a follow-up physical, cognitive, and spatial orientation assessment was conducted in February 2020 to measure the change in symptoms over three years (from 2017 to 2020) (labelled as time 2 in Table.6). Controls The spatial orientation measures consisted of the Virtual Supermarket Test and the Clock Orientation Test, both of which were sensitive to RK's egocentric impairments at t1, and the addition of Sea Hero Quest was introduced at t2 as a further assessment of egocentric and allocentric spatial ability. The iPad tasks were completed with participants sitting approximately 30cms from the screen which was situated flat on a desk in front of them. MRI scanning took place by radiologists at the Norfolk and Norwich University Hospital. Tests were administered in the same order for each participant and breaks were given as requested. Testing sessions took approximately 1 hour to complete.

Statistical analysis

RK's spatial orientation ability and dMRI mean FA (fractional anisotropy) of the superior longitudinal fasciculus were contrasted against the controls (*N=14*) using a Crawford and

Howell's (1998) modified paired sample t-test (Crawford & Howell, 1998) resulting in a Z-case-control (Z_{cc}) score as an interval estimate of the effect size, comparable with Cohen's d 0.2 = small, 0.5 = medium, 0.8 = large effect sizes (Cohen. 1988).

Results

RK's Neuropsychological assessment

Follow up neuropsychological assessment from time 1 to time 2 suggest a slight increase in scores on the ACE in domains of memory and fluency. Copy and Recall domains of the Rey Complex Figure have also improved, along with a slight lift in INECO scores of executive function in domains of inference sensitivity, inhibitory control and verbal working memory. All other neuropsychological assessment seems relatively stable from time 1 to time 2 (see Table. 6).

Table 6. Patient v Control's Neuropsychological Assessments t1 to t2.

	Time 1		***Time 2***		
General cognition	***Patient Score***	***Control Score***	***Patient Score***	***Control Score***	***Patient Change***
ACE total	82	92 (4.7)	94	95.45 (4.37)	+12
ACE: Attention	18	17 (1.9)	17	17.54 (0.93)	-1
ACE: Memory	18	23 (2.7)	24	24.45 (2.66)	+6
ACE: Fluency	4	12 (2.0)	11	13.09 (1.45)	+7
ACE: Language	26	25 (0.9)	26	25.64 (0.5)	
ACE: Visuospatial	16	14 (1.0)	16	14.73 (1.1)	
Visuospatial function					
VOSP: Dot Counting	9		10		+1
VOSP: Position discrim	20		20		
VOSP: Cube analysis	10		10		
ROCF: Copy	25	33.7 (1.6)	29	33 (2.87)	+4
ROCF: Recall	9	19 (4.5)	12	22.1 (5.6)	+3
Episodic memory					
FCSRT: Free recall	15		14		-1
FCSRT: Cued recall	33		32		-1
FCSRT: Free delayed recall	6		4		-2
FCSRT: Cued delayed recall	10		10		
Executive function					
INECO total	16.5		20		+3.5
Motor series	3		3		
Interference sensitivity	2		3		+1
Inhibitory control	2		3		+1
Digit backwards	2		2		
Verbal working memory	1		2		+1
Spatial working memory	1		1		
Proverbs	0.5		0.5		
Hayling test	5		5		
Working memory index	3		3		
Trial Making Test	Part A	Part B	Part A	Part B	
Trial making test: Time	79	117	66	92	A: -13, B: -25
Trial making test: Errors	0	2	0	0	A: 0, B: -2

*ACE, Addenbrooke's cognitive examination; VOSP, Visual Object and Space Perception battery; FCSRT, Free and Cued Selective Reminding Test; INECO frontal screen

Spatial navigation assessment

Scores indicate an uplift in RK's spatial processing but remains to show significant deficits in egocentric measures of VST, COT and SHQ as well as allocentric measures of the VST compared to controls (see, Table. 7)

Table 7. Total scores, standard deviations (SD), Z-case control (Zcc) scores, confidence intervals from a modified paired samples t-test for patient and control group on the Spatial Battery at Time 2.

		Time 1	***Time 2***						
Measure	***Condition***	***Patient Score***	***Patient Score***	***Control mean (n=14)***	***SD***	***t-value***	***p value***	***size effects (Z_cc)***	***95% CI***	***Normal population falling below RK's score***
Virtual Supermarket Test (VST)	Egocentric	**4**	**5***	**7.8**	**1.2**	**2.31**	**0.021**	**-2.33**	**-3.35:1.29**	**2.10%**
	Allocentric	*1.5*	*4**	*13.82*	*5.46*	*-1.74*	*0.052*	*-1.72*	*2.64: -0.92*	5.29%
	Heading	**6**	11	10	3.01	0.32	0.37	0.33	0.21: 0.86	62.30%
The Clock Test	Cardinal	**1**	4	3.77	0.599	0.377	0.41	0.39	0.16:0.93	64.37%
	Right Angle	**1**	**1***	**3.09**	**0.76**	**-2.66**	**0.01**	**-2.75**	**3.9: -1.57**	**0.98%**
	Mixed	*1*	*1**	*2.77*	*1.09*	*-1.61*	*0.07*	*1.62*	*-2.42:0.8*	*7%*
	Total	**3**	**6***	**9.62**	**1.04**	**-3.41**	**0.002**	**-3.48**	**4.9:2.05**	**0.25%**
Sea Hero Quest	Flare Accuracy	**-**	**10***	**11.3**	**0.67**	**1.98**	**0.042**	**-1.94**	**2.83:1.02**	**4.17%**
	Flare Duration	-	41.1	43.15	12.89	0.15	0.44	-0.16	0.63:0.37	44.10%
	Flare Distance	-	361.7	374.92	112.7	-0.21	0.42	-0.22	0.73:0.32	41.85%
	Wayfinding Distance	-	520.5	800.23	227.4	-0.51	0.31	-0.53	-1.08:0.04	30.76%
	Wayfinding Duration	-	430	91.34	43.65	-0.78	0.23	-0.8	-1.4:-0.18	22.61%

**Significant differences for RK compared to controls are marked in bold. Trend towards significance are marked in italics. P value represents a two-tailed probability that case score differs from controls. RK's score s from time one in grey column.*

MRI Analysis

Visual rating of signal hyperintensities

Periventricular hyperintensities and white matter hyperintensities were observed with up to five lesions present, positioning RK as Fazekas grade 2 (see Figure. 10). The Fazekas scale was used to assess severity of WMH (Fazekas et al., 1987). Periventricular WMH and deep WMH were evaluated separately and totalled together as Fazekas scores. The degree of WMH severity was rated by Fazekas scores (mild: 0–2; moderate: 3–4; severe: 5–6).

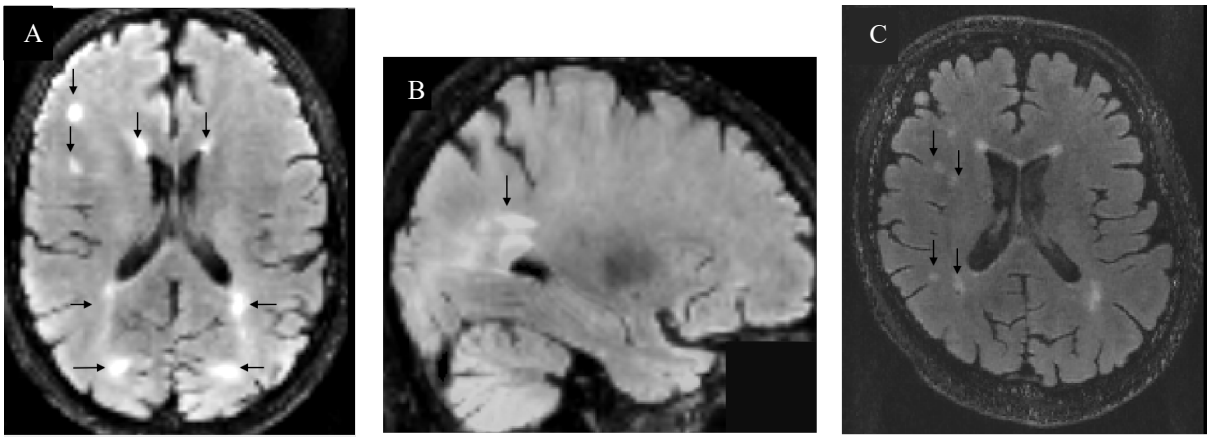


Figure 10. Visual rating of RK's FLAIR imaging.

A. White matter hyperintensities on FLAIR MRI (in MNI space) predominately in the right frontal lobe of the cerebral cortex and cerebral white matter. Periventricular white matter lesions are present near the left and right ventricles and close to the white matter collosal body and the lateral occipital cortex, superior division.

B. While matter hyperintensity in the occipital lobe.

C. Signs of punctuate deep white matter lesions beginning confluence.

White matter differences

The SLF diffusion properties were assessed using mean fractional anisotropy (FA) and divided into four parameters; right hemisphere superior longitudinal fasciculus parietal (rh SLFP); left hemisphere superior longitudinal fasciculus parietal (lh SLFP); right hemisphere superior longitudinal fasciculus temporal (rh SLFT); left hemisphere superior longitudinal

fasciculus temporal (lh SLFT). Mean FA was reduced in all tracts of the SLF for RK compared to case controls, although none of which reach statistical significance (see, Figure.11). FA was most reduced in the left hemisphere superior longitudinal fasciculus parietal (lh SLFP) for RK compared to the case controls, where this appeared to be approaching significance ($p = 0.059$).

Table 8. SLF Tracts of Interest Patient vs Controls.

	rh SLFP	lh SLFP	rh SLFT	lh SLFT	*Motion*
Patient RK	0.41	0.41	0.44	0.45	0.28
Controls	0.44 (0.02)	0.44 (0.03)	0.45 (0.02)	0.47 (0.02)	0.34 (0.07)
Significance	0.08	0.06	0.26	0.17	0.17
Size effects (Z_cc)	-1.65	-1.73	-0.63	-1.04	-1.01
Normal population falling below RK's score	*10.1%%*	*5.90%*	*26.04%*	*17.80%*	*17.26%*

***Standard deviation in parenthesis. Rh SLFP, right hemisphere superior longitudinal fasciculus parietal; lh SLFP, left hemisphere superior longitudinal fasciculus parietal; rh SLFT, right hemisphere superior longitudinal fasciculus temporal; lh SLFT, left hemisphere superior longitudinal fasciculus temporal.*

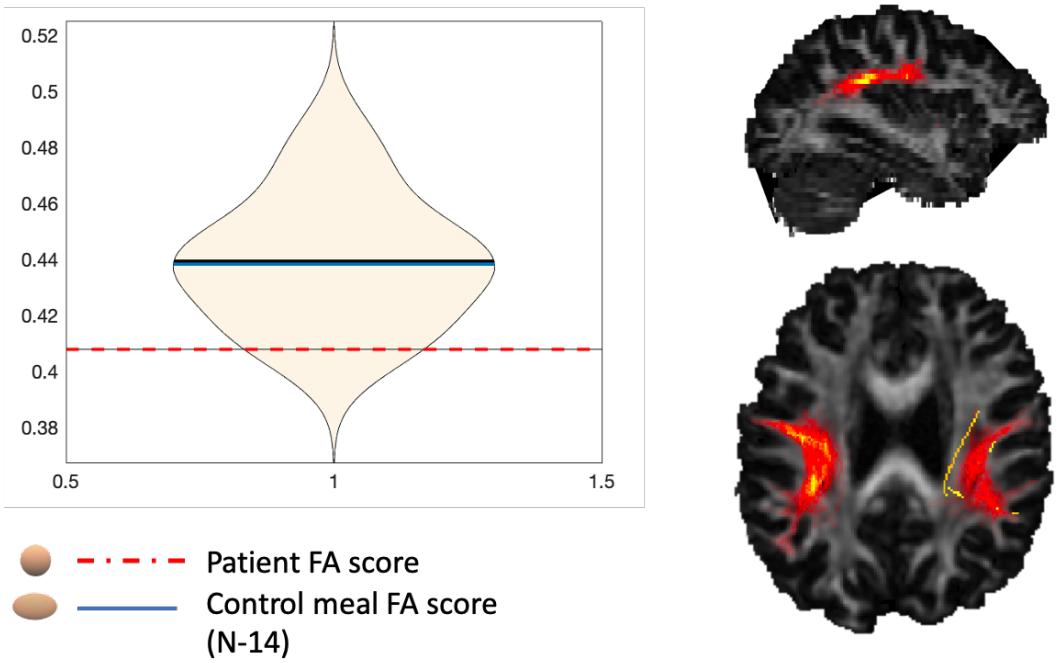


Figure 11. *SLF parietal division RK and controls FA mean score.*

Discussion

The current case report replicates our previous findings in showing egocentric spatial orientation deficits in VCI. More importantly, I demonstrate that egocentric spatial orientation deficits persist while other cognitive scores show no changes or even improvement over time. At the same time, we can associate the egocentric spatial orientation deficits with changes to the posterior SLF, making them highly specific to the WMH in VCI in that region. In particular, fractional anisotropy suggests potential reduced white matter integrity to the left and right SLF parietal sections appear linked to egocentric spatial orientation deficits in VCI.

Results suggest RK's general cognition improved from t1 to t2 in measures of the ACE-III, VOSP, INECO and TMT. The FCSRT remained stable from t1 to t2 for RK. Interestingly, RK's scores would only indicate a clinical cut-off for dementia on the INECO, ROCF-recall

and TMT-part B reaction time. Although, the uplift in scores is likely due to test re-test effects which are a common problem in neuropsychological assessment (Aldridge et al., 2017).

Despite some uplift in results, spatial tests suggest RK remains to have an egocentric deficit when assessed by the Virtual Supermarket Test, the Clock Orientation Test and Sea Hero Quest compared to healthy controls. However, RK now shows an allocentric deficit at follow-up testing compared to controls in the Virtual Supermarket Test, despite showing improvements from t1. This stands in contrast to RK's general cognition which remained stable or improved at follow-up when assessed by standard clinical neuropsychological assessment in domains of attention, fluency, language, and visuospatial processing (see Table. 2). Perhaps suggesting RK has consistently had both egocentric and allocentric deficits with instead inconsistencies occurring between the control groups. There are large standard variations in performance for the control groups at both t1 to t2 for allocentric ability on the VST, with the controls at t2 scoring worse on the spatial tasks than the controls at t1 (see, Appendix. A).

In sum, it appears RK's spatial impairments are now apparent in both spatial orientation frames (egocentric and allocentric). Critically, these changes were detected with novel spatial testing and were undetected on standard neuropsychological assessments specifically targeting spatial processing when comparing RK's scores from t1 to t2 (see, Table. 6). Perhaps due to the greater sensitivity than pen and paper testing, as well as strong test-retest reliability (Coughlan et al., 2020).

MRI analysis using FLAIR imaging indicates RK has white matter hyperintensities to the right hemisphere frontal lobe of the cerebral cortex and cerebral white matter, as well as periventricular white matter lesions near the lateral ventricles, close to the collosal body and the superior division of the lateral occipital cortex. Although WMH are also common in healthy aging (de Leeuw et al., 2001), the MRI profile is consistent with typical subcortical ischemic presentation of VCI (Dichgans & Leys, 2017). However, further DTI analysis was used to assess white matter integrity in SLF and results suggest FA was reduced in all four SLF tracts for RK compared to controls. Although differences did not reach statistical significance, a trend towards significance was strongest for the left and right SLF parietal sections (see, Table. 8). This findings is not conclusive, but supports the notion that reduced integrity to the posterior tracts of the SLF may be a potential hallmark of VCI (Lowry et al., 2021), and could manifest as this apparent egocentric orientation deficit.

This case report comes as further evidence to support the use of spatial navigation testing in clinical settings and serves as a sensitive diagnostic tool in the assessment of VCI. The continued sensitivity of The Virtual Supermarket test and the Clock Orientation Test to RK's condition, in light of improved scores on conventional cognitive assessments (ACE-III, VOSP, INECO, TMT), suggest these simple and quick to administer spatial tasks would also be a favourable sensitive cognitive measure for use in VCI intervention studies.

Despite these exciting findings, our study has limitations, RK's MRI scan took place three years after his initial diagnosis, therefore RK's brain imaging should be interpreted with caution when associating with his initial (t1) test scores. Although, reduced integrity to the posterior SLF is of interest concerning his egocentric spatial deficits, FLAIR MRI indicates multiple sites of white matter hyperintensities to suggest axonal loss more typical of a

subcortical ischemic VCI (Dichgans & Leys, 2017). Pre-existing healthy WMH load has also been shown to exhibit as reduced FA in the SLF (Svä rd et al., 2017). As such, we cannot be clear on the order of the pathogenesis of these injuries, thus, a link between egocentric deficits in VCI and posterior SLF integrity cannot conclusive.

Critically, these injuries observed in RK's MRI could be sensitive to novel spatial tests but go undetected on visuospatial measures of neuropsychological assessment. Future studies are needed to explore potential parietal-to-frontal network disruption in the pre-clinical stages of VCI to inform the pathogenesis of egocentric disruptions.

This case study illustrates the potential for the application of spatial orientation assessment in clinical settings. This is especially critical for disease monitoring, given that standard neuropsychological assessment has poor selectivity in discriminating dementia sub-types and lacks sensitivity for disease monitoring overtime. This is in contrast to spatial navigation tasks measuring egocentric or 'self-referential' processing. In sum, the Virtual Supermarket Test, the Clock Orientation Test and Sea Hero Quest appear to be sensitive to the detection of vascular cognitive impairment.

Chapter 4: Egocentric orientation and P300 as indexes of preclinical VCI

Lowry, E., Johnen, A., Hornberger, M., Renoult, L. (2022). Egocentric orientation and P300 as indexes of preclinical VCI. In preparation.

Introduction

Dementia is one of the greatest medical threats facing our aging population and has higher health and social care cost than cancer and chronic heart disease combined (Luengo-Fernandez et al., 2015). Major risk factors for cognitive impairment relate to the vascular system (hypertension, obesity, diabetes, high cholesterol and lack of physical exercise) which currently affect >30% of the global population (WHO, 2021). As such, evidence is accumulating to suggest cardiovascular risk factors in midlife predict the onset of vascular cognitive impairment (VCI) in later life (Tolppanen et al., 2015). Yet, due to the heterogenous profile of established VCI, there is a distinct lack of specificity for identifying the cognitive symptoms.

Less is known still, of the preclinical cognitive characteristics of VCI. Hypertension, high cholesterol, diabetes type 1 and obesity are thought to be the strongest risk factors besides age for predicting VCI (Kivipelto et al., 2018; Lowry et al., 2021), along with interacting genetic contributions and lifestyle factors. Composite risk scores assessing such factors are readily used in routine clinical practice to identify patients who could benefit from intervention. In the National Health Service QRisk®3-2018 (Hippisley-Cox et al., 2017) is used to calculate an individual's risk of cardiovascular disease in the next 10 years. Such cardiovascular risk prediction is vital for better patient outcomes, especially given that >35% of all dementia cases are attributed to modifiable risk factors (Livingston et al., 2020) . Yet,

there is a distinct lack of research exploring the cognitive correlates of these risk factors to identify and track those at greatest risk of developing VCI. This is likely due to the reduced sensitivity of typical standardised cognitive assessments towards preclinical features of VCI, which is surprising, given early identification and intervention has been shown to slow and even halt cognitive decline in VCI (Ngandu et al., 2015).

Electrophysiological approaches are sensitive to the early effects of AD (Paitel et al., 2021). Event-related potentials (ERPs), particularly the P300 component, appear to show sensitivity to VCI (Xu et al., 2012; Yamaguchi et al., 2000). The P300 component is thought to represent the neural responses of changing and updating the mental model of our environment in order to make an appropriate response (Polich, 2012). The P300 can be split into two subcomponents, the P3a and P3b. It is thought that stimulus evaluation engages focal attention (P3a) to facilitate context updating (P3b), which is associated with memory processes (Hartikainen & Knight, 2003).

The Target P300 (P3b), which exhibits a parietal maximal ERP response, is evoked when 'target' or nonfrequent stimuli are inserted into a sequence of 'standard' or frequent stimuli. Participants are asked to respond to the target and attentional mechanisms are required to 'update' the neural representation of the stimulus context and index the event in working memory (Fabiani et al., 1996; Johnson., 1995). The Novelty P300 (P3a) exhibits a frontal/central scalp distribution and is evoked when distractor or novel stimuli are inserted into a sequence of target and standard stimuli. The novelty processing interrupts the existing scheme of identifying targets among standard stimuli and evokes attentional 'switching' to the new novel stimuli (Comerchero & Polich, 1999; Polich & Comerchero, 2003). The neural regions generating these two P300 ERP components are thought to heavily overlap,

underpinned by a circuit pathway between frontal and temporal/parietal brain areas (Huang et al., 2015; Knight, 1990; Polich, 2003; Soltani & Knight, 2000). The P300 Target processing (P3b) is linked to temporal-parietal locations including the temporal-parietal junction (TPJ) and its integrity (Verleger et al., 1994; Yamaguchi & Knight, 1992) and thought to represent updating of our mental model. Whereas, Parietal-cingulate-frontal structures are linked with the P300 Novel response (P3a) (Halgren et al., 1995; Halgren & Marinkovic, 1995) and are thought to underpin the ability to respond to unexpected stimuli. As such, the Novelty P300 is thought to reflect a conscious, evaluative aspect of the orientating response (Cycowicz & Friedman, 1998; Näätänen, 1990), subserved by functional interactions within the frontoparietal attentional network (Ptak, 2012; Szczepanski et al., 2013; Vossel et al., 2014).

Studies using the three-stimuli 'Oddball' task, with standard, target and novel stimuli have been shown to dissociate different profiles of brain lesions. Patients with lateral parietal and prefrontal lesions have a diminished P300 novelty response (Knight, 1984), while the P300 target response is unaffected (Knight, 1997). This is in keeping with research that demonstrates reduced P300 response to novel stimuli in VCI patients compared to Alzheimer's disease (Yamaguchi et al., 2000) and reduced parietal-to-frontal and parietal-to-central connectivity, compared to healthy controls(Wang et al., 2014, 2016). The P300 component also shows potential as a promising biomarker for preclinical VCI, as increased P300 latencies are present in midlife type 2 diabetics (Hazari et al., 2015) and hypertensive older adults (Cicconetti et al., 2007), compared to healthy controls. Yet, the P300 response in VCI risk individuals has not been explored.

Along with the P300 response, there is some evidence to suggest egocentric (self-referential) spatial orientation appears sensitive to VCI (Coughlan et al., 2018a; Lowry et al., 2020).

Spatial navigation is a promising marker in the early detection of AD (Coughlan et al., 2018; Kunz et al., 2015; Allison et al., 2016) but is little explored in VCI. Studies from our group have shown egocentric spatial orientation has sensitivity and selectivity to VCI and can be used as a measure to differentiate between VCI and AD patients (Lowry et al., 2020). This is supported by an earlier case study suggesting egocentric orientation deficits, mediated by frontoparietal structures, may be a promising marker for the identification of neurovascular pathology (Coughlan et al., 2018a). These finding in the context of the existing literature on preclinical VCI (for a review see Lowry et al., 2021), may suggest early dysfunction between frontal-parietal networks, mainly the superior longitudinal fasciculus (SLF) (white matter tracts connecting parietal and temporal with prefrontal regions) and overlapping subcortical structures. Therefore, tasks that tap into these structures, such as the P300 response and egocentric orientation may also prove sensitive to structural brain changes in preclinical VCI.

Aims and hypothesis

The current study aims to examine if the P300 response and egocentric orientation could act as potential bio-cognitive markers for preclinical VCI indicative of potential frontoparietal dysfunction. I hypothesise that high cardiovascular risk individual's (CVR+), as determined by QRisk®3-2018 (Hippisley-Cox et al., 2017), will show a delayed P300 response as assessed by longer latencies as well as reduced amplitudes, and reduced egocentric performance in spatial orientation compared to healthy controls (HC). I will examine the P300 at midline electrodes and aim to combine the analysis of experimental methods with standard neuropsychological tests to provide insight into the sensitivity and selectivity of reliable measures to identify and track preclinical VCI.

Methods

Participants

Between November 2019 and September 2021, 62 people between 40 to 75 years of age were recruited from the community to participate in a research study at the University of East Anglia. All participants were pre-screened for a history of psychiatric or neurological disease, visual impairments, motor impairments or any significant relevant comorbidity. All participants had normal or corrected-to-normal vision. Diabetes, smoking and inherited lipid disorder status was determined, along with the use of regular medication. Family history of angina or heart attack was obtained. From these participants 50 met the study eligibility criteria (see, Figure. 15).

In total, 45 participants underwent cognitive testing, as during the testing period, a total of five participants withdrew from the study due to disruption from the COVID-19 pandemic. The final group sizes post-inclusion consisted of high cardiovascular risk, n = 25 and healthy controls, n = 20. Written consent was obtained from all participants and ethical approval was obtained from Faculty of Medicine and Health Sciences Ethical Committee at the University of East Anglia reference FMH 201819-052.

Measures and Materials

Cholesterol Testing

The ACON Mission™ Cholesterol test device 3-1 lipid panel (Mission Cholesterol - ACON LABS INC.) was used to measure lipid concentration in the whole blood, plasma and serum from 35uL fingertip capillary blood. This allowed to determine total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), Triglycerides (TRIG) and cholesterol ratio.

Blood Pressure Taking

The automatic upper arm Omron™ M7 Intelli IT Blood Pressure Monitor was used to determine systolic blood pressure, diastolic blood pressure and pulse. Two readings were taken approximately 5 minutes apart and mean values of these reading with standard deviations were computed, in line with the American Heart Association guidelines (Muntner et al., 2019).

Medical History

A pre-screening questionnaire containing questions on height (cm), weight (kg), medical history, current medication and demographic information was completed by the participants. Body Mass Index (BMI) was calculated using self-report data. History of familial hypercholesterolaemia, chronic kidney disease or diabetes was taken, as well as first-degree relative who had premature atherosclerotic cardiovascular disease or familial dyslipidaemia, regardless of their age.

VCI Risk Stratification

The QRisk®3-2018 (Hippisley-Cox et al., 2017) was used to calculate the participants cardiovascular disease risk (heart attack or stroke in the next 10 years). Cardiovascular risk factors are the main pathology in the development of VCI (van der Flier et al., 2018). I determined group allocation using thresholds specified in the NICE Guidelines (National Institute for Health and Care Excellence). Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease (NICE, 2014), QRISK3 score >10% stratified as high cardiovascular risk (CVR+), QRISK3 < 10% stratified as healthy control (HC).

Cognitive Tests

The CVR+ and HC groups underwent neuropsychological screening, including cognitive screening, executive functions and visuospatial tasks; Addenbrooke's cognitive examination (ACE-III) (Hsieh et al., 2013), Cube Analysis, Dot Counting and Position Discrimination from the Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991), Digit Symbol Substitution Test (Jaeger, 2018) and the Trail Making Test (TMT) part A and part B (Reitan, 1958).

Subjective Self-Report Measures

Cognitive Change Index (Rattanabannakit et al., 2016) was used to detect a decline in self-perceived memory, executive functions and language. International Physical Activity Questionnaire (IPAQ) short form(International Physical Activity Questionnaire., 2014) was used to measure sedentary hours per day. The Santa Barbra Sense of Direction Scale(Hegarty et al., 2002) was used to measure subjective navigational abilities. The Body Perception Questionnaire (Porges, 1993) was used to assess body awareness and autonomic

reactivity to form subjective awareness of the body, relevant to proprioception and the processing of egocentric spatial coordinates. Pittsburgh Sleep Quality Index (Buysse et al., 1989) was used to assess sleep quality as sleep deprivation can affect cognition and processing speed (Mantua & Simonelli, 2019). Measures for Assessing General Anxiety Disorder 7 (GAD-7)(Spitzer et al., 2006) and Patient Health Questionnaire-9 (PHQ-9) (Löwe et al., 2004) were used to assess mental health as this can impact cognition (Bauermeister & Bunce, 2014).

Oddball Task

An auditory 3-stimulus oddball (or novelty oddball) paradigm was presented using E-Prime and consisted of standard (75%), target (12.5%), and novel (12.5%) stimuli as used in (Tavakoli et al., 2021). The stimuli were presented in a pseudorandom order, in that target or novel stimuli could not be presented consecutively. The participants were instructed to respond only to the target stimuli using a mouse. Participants were seated with their hand on the mouse to minimise movement and asked to focus on a fixation cross presented in the centre of the computer screen. All stimuli had a duration of 200 ms and a rise-and-fall time of 5 ms. The standard stimulus was an 80 dB SPL 1000 Hz pure tone. The target stimulus was an 80 dB SPL 1500 Hz pure tone. The novel sounds had an average intensity of 80 dB SPL. A different novel sound (Fabiani et al., 1996) was presented on each trial so that none of the novel sounds were repeated. The novel sounds were unexpected environmental noises such as a dog barking, sweeping, whistle, etc and are described in detail by Fabiani (Fabiani et al., 1996). The first ten tones in the sequence consisted of only standards. The inter-stimulus interval was 1000 ms. A total of 400 stimuli were presented in a single sequence, consisting of 300 standards, 50 targets, and 50 novels. The test lasted approximately 8 minutes. A brief rest period was given within the sequence at approximately 4 minutes in.

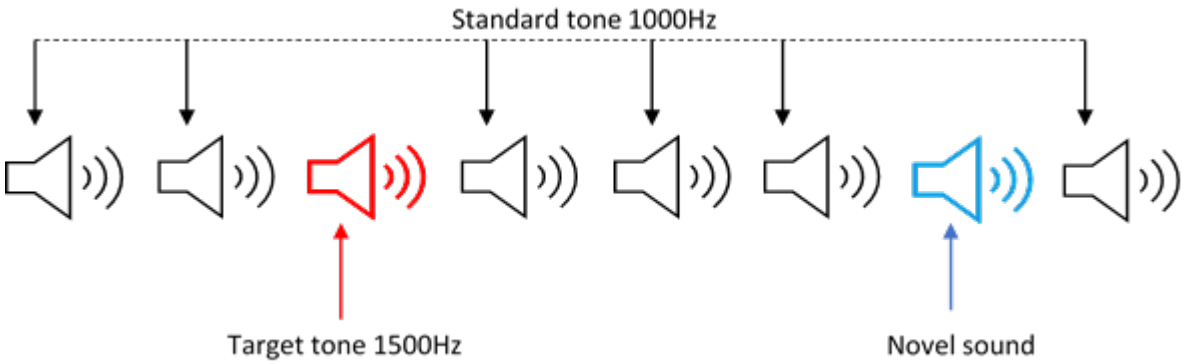


Figure 12. *Visual representation of the auditory oddball task. Novel sounds were unexpected environmental noises such as a dog barking, sweeping, whistle, etc.*

Sea Hero Quest

Sea hero Quest is an app- based cognitive task that enables the collection of spatial navigation data and is used in large scale population based studies (Coutrot et al., 2018). SHQ goal-oriented wayfinding (allocentric) levels are sensitivity to identifying pre-clinical AD(Coughlan et al., 2019). Flare (egocentric) levels 14, 19, 24, and 34 were selected (See Figure 13A-C) and for contrast of egocentric and allocentric abilities the Wayfinding (allocentric) levels 6, 8 and 11 were also selected. In the Wayfinding levels participants were shown locations to visit from a map. The map disappeared, and they had to navigate the boat through the virtual environment to find different checkpoints.

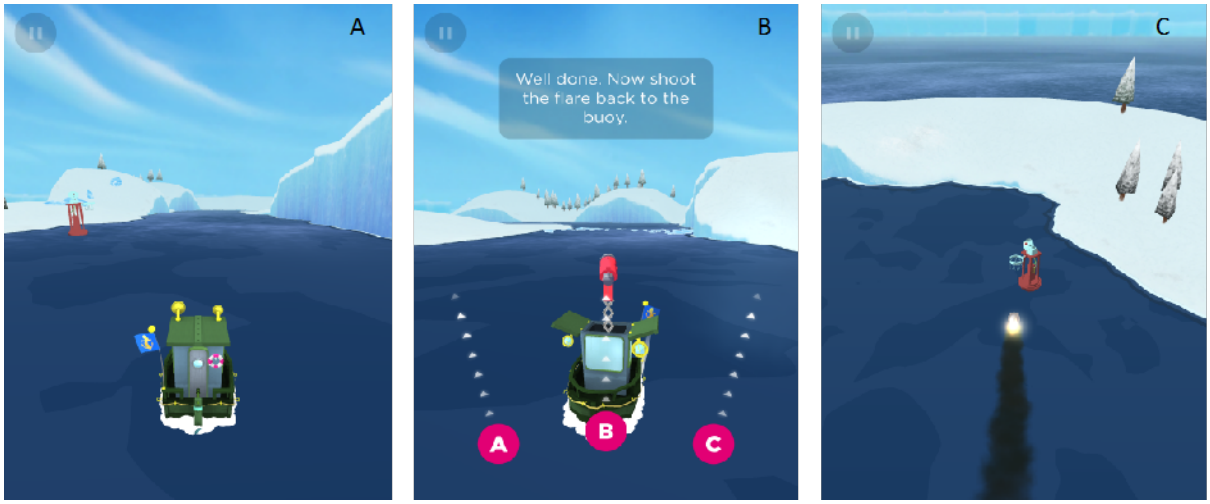


Figure 13. *SHQ Flare level 14.*

Participants start at a satellite buoy and are instructed to navigate a virtual boat along a river to find a flare gun (A). Once they find the flare gun at the end of the river, the boat rotates by 180°, and participants are asked to choose one of three possible directions (right, front, and left) that they believe points to the starting point (B). The flare is then fired in the direction of selected and participants (C). Outcome measures of distance travelled (pixels), task duration (sec) and Flare accuracy (0-3) are recorded. Flare (egocentric) levels require participants to (i) form an accurate representation of the starting point relative to their position and (ii) integrate this representation with a representation of the direction they are facing after the rotation.

The Virtual Supermarket Test

The Virtual Supermarket Test (VST) has been developed by our group previously and used in symptomatic mild cognitive impairment (MCI), AD, frontotemporal dementia (FTD) and VCI patients (Coughlan et al., 2018a; Lowry et al., 2020; Tu et al., 2015, 2017). The VR task is an ecological test of spatial navigation abilities designed to simulate navigating through a real-world supermarket. An iPad 9.7 (Apple Inc.,) was used to show participants 20-40 second video clips of a moving shopping trolley in the virtual supermarket (Figure 14A-E).

The task consists of 14 trials and takes approximately 15 minutes to complete. The task avoids the use of landmarks or salient features within the environment and limits the demand on episodic memory, reflecting similar tasks in the literature (Cushman et al., 2008; Morganti et al., 2013; Wolbers et al., 2007) and taps into path integration processes via three core spatial processes: i) egocentric self-reference navigation; ii) allocentric map-based navigation and iii) heading direction. Performance is calculated using the distance error (mm) between this and the coordinates of the actual finishing location. This map-based component provides an assessment of geocentric encoding of the virtual environment. The participant then indicates their heading direction at the finishing point, which determines the ability to which heading direction was encoded and updated throughout the task.

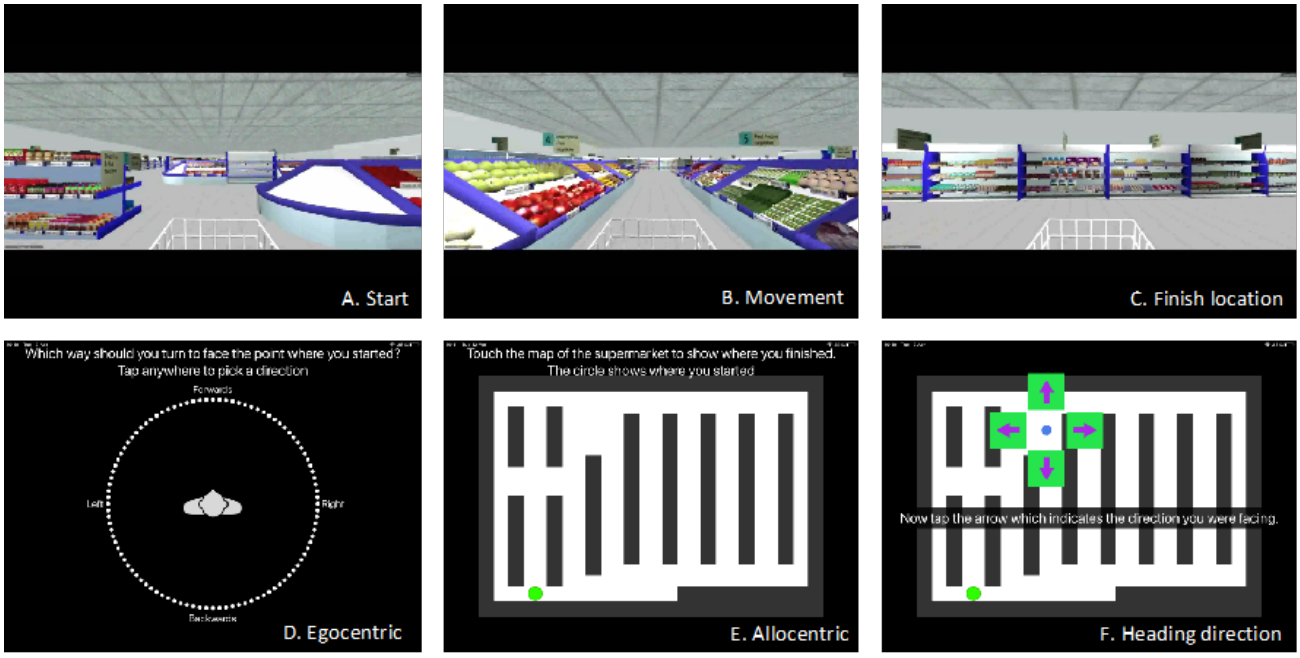


Figure 14. *Virtual Supermarket Test.*

Videos were presented in a first-person perspective and participants are provided with optic flow cues from the moving shopping trolley and changing scenery as it followed different routes to reach a different end point in each trial (Figure 14A-C). Once the video clip stops, participants indicate in real-life the direction of their starting point (egocentric orientation;

13D). In a second step, participants indicate their finishing location on a birds-eye view map of the supermarket (allocentric orientation; 13E). Lastly, participants are asked to indicate which direction they were facing at the finishing location (heading direction; 13F).

The Clock Orientation Test

The Clock Orientation test has also been developed by our group(Coughlan et al., 2018a; Lowry et al., 2020) as a bedside clinical test for egocentric orientation. It requires participants to imagine they are standing in the centre of a large clock, facing a particular number, e.g., the number 3. Participants are then asked, "which number is directly behind you?" (Answer: number 9). Next participants are asked to point, in real-life, to the positions of different numbers on the clock face in relation to the number that they are currently facing. For example, "You are facing number 12, can you point to the number 3?" (Answer: pointing right). The questions increase in complexity across the test and require medial parietal mediated mental imagery, rotation and egocentric processes, with no episodic memory demand. The test consists of 12 trials and takes 5-10 minutes to complete. Outcome measures of score (0-12) and reaction time for each question were recorded.

EEG acquisition

A 64-channel active electrode system (Brain Products GMbH) with a BrainAmp MR64 PLUS amplifier was used for EEG acquisition. Viewing distance was ~70 cm from eyes to a 61 cm monitor (resolution 1920 × 1080 px). Participants were positioned in a comfortable chair in front of a computer screen and two speakers ~70 cm from their face. Participants were presented with the task instructions on the computer screen and advised that the task involved listening out for a high-pitched (target) beep, and that they should press the left

button on the mouse when they heard these sounds. Accuracy and reaction time for the Oddball task were recorded for every trial.

EEG was recorded using a Brain Vision actiCAP system with 64 active electrodes. Participants wore an elastic nylon cap (10/10 system extended). One electrode was placed under the left eye to monitor vertical eye movements (lower EOG). The continuous EEG signal was recorded at a 500 Hz sampling rate using FCz as a reference electrode. All electrodes had connection impedance below 50 kΩ before recording commenced. Continuous EEG data were pre-processed and analysed offline using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014). High- and low-pass half-amplitude cut-offs were set at 0.1 and 40 Hz, respectively. Noisy channels were interpolated with the spherical interpolation function from EEGLAB. Continuous data were segmented into an epoch of -200 to 800 ms relative to stimulus onset and referenced to the mastoids, in line with previous studies examining P300 response (Lee et al., 2013). Trials containing excessive artefacts were rejected based on a step function (Luck, 2005; with the voltage threshold set to ± 100 μV in 200ms-wide moving windows, with a window step of 50ms).

A maximum of 10% of channels were interpolated per participant and the minimum number of accepted trials for each participant was 189 for the standard stimuli, 38 for the target stimuli and 39 for the novel stimuli. The P300 was defined as the largest positive peak 200-600ms after stimuli onset (Duncan et al., 2009; Polich, 2012) and analysed within these parameters. The peak latency of the P300 was measured in the same time window, relative to the pre-stimulus baseline. The P300 was examined at midline electrodes (Fz, Cz, CPz, Pz), in line with guidelines for measuring the P300 in clinical research (Duncan et al., 2009). I measured P300 elicited by the novel, target, and the standard tone.

Procedure

All participants underwent telephone pre-screening where they needed to meet our inclusion criteria in order to be invited for testing. Participants underwent a two-hour cognitive, neuropsychological and physical assessment at the first testing session which took place in their homes. Approximately seven days later participants underwent a further two-hour testing session where they completed EEG and spatial testing at the University of East Anglia EEG Laboratory.

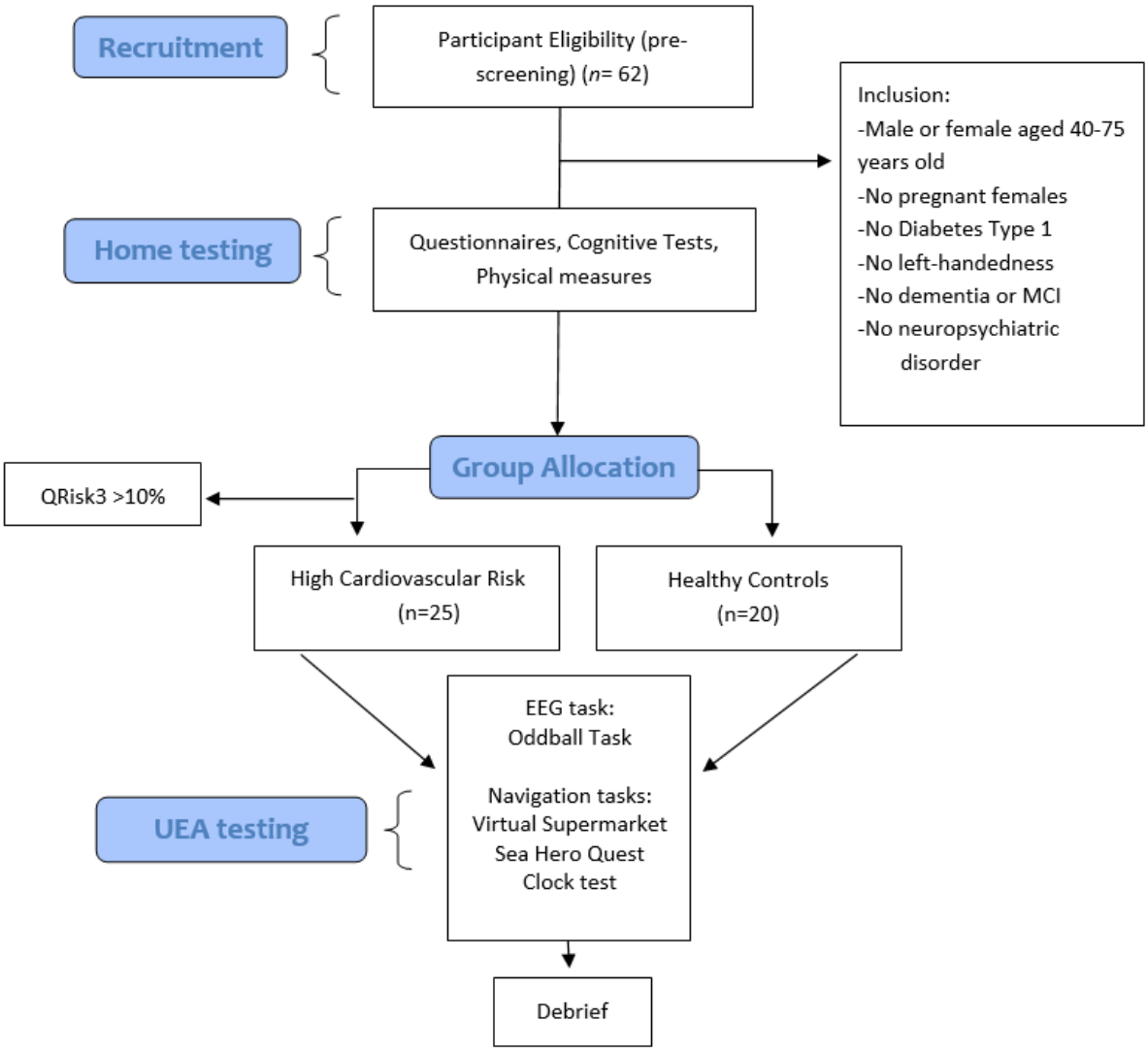


Figure 15. *Flow Diagram of Study Protocol.*

Statistical Analysis

The data was analysed using SPSS Statistics (version 26) and MATLAB (R2020b). Chi-square was used to test for independence between gender, education and risk group. One-way ANOVA was used to compare significant associations between Age, SBP, DBP, Total cholesterol, LDL cholesterol (see, Table 9). Group characteristics suggest the CVR+ were older and contained more males. Therefore, age and sex were entered as a covariate in all further analysis. These covariates were essential also given that sex has been shown to effect navigational performance (Driscoll et al., 2005) increased age has been associated with delayed P300 latencies and reduce amplitudes (Juckel et al., 2012). A one-way ANCOVA controlling for age and sex was used to determine group differences on cognitive measures (see, Table 10) and spatial measures (see, Table 11). Separate repeated mix measures analysis of covariance (ANCOVA) was employed for analysis of amplitude and latency P300 data, with group (CVR+ vs. HC) as a between subjects' factor and electrode (Fz, Cz, CPz, Pz) as the within subjects factor for each condition (novel, target, standard). Mauchley's test was used to evaluate the sphericity assumption. Post-hoc analysis was computed using one-way ANCOVA with age and sex as covariates. Effect sizes were computed using partial eta-squared and interpreted as; $\eta_p^2 = 0.01$ indicates a small effect, $\eta_p^2 = 0.06$ indicates a medium effect and $\eta_p^2 = 0.14$ indicates a large effect (Cohen, 1988). During data collect for Sea Hero Quest Two participants data were lost due to technical difficulties leaving a total of 43 participants for this analysis (23 CVR+, 20 HC). During EEG data collection seven participants were excluded from analysis due to noisy data (trial rejection > 30%), leaving a total of 38 participants (20 CVR+, 18 HC).

Results

Demographic Characteristics

Chi-square test for independence indicated no significant associations between gender and risk group, X^2 (1, n=45) = .291, p = .06 and education and risk group, X^2 (1, N=45) = -.1, P= .502. A one-way ANOVA was used to compare significant associations between Age, systolic blood pressure, diastolic blood pressure, cholesterol, LDL cholesterol and BMI between risk groups. A Significant difference between group was observed for age (p <.001) and systolic blood pressure (*p* <.001), see Table 9.

Table 9. Group characteristics of high cardiovascular risk (CVR+) and healthy control (HC) groups.

	Group		
	CVR+	HC	*p* value
N	25	20	
Sex (m/f)	12/13	4/16	0.06
Age	66.2 (4.45)	51.95 (5.40)	<.001*
Education (Secondary/HE)	10/15	10/10	0.5
Systolic BP (mmHg)	136.98 (14.85)	123.03 (11.07)	<.001*
Diastolic BP (mmHg)	84.14 (8.89)	82.25 (7.59)	0.45
BPM heart rate	66.22 (12.23)	67.87 (12.41)	0.66
Total Cholesterol (mmol/l)	5.11 (1.81)	4.75 (1.54)	0.51
LDL Cholesterol (mmol/l)	3.81 (1.49)	4.31 (1.34)	0.29
HDL Cholesterol (mmol/l)	1.31 (1.61)	1.55 (.44)	0.62
Triglycerides (mmol/l)	2.57 (1.3)	2.28 (.9)	0.41
BMI	27.27 (6.21)	27.51 (5.93)	0.9
Antihypertensive use	1	1	
Antidiabetic use	2	-	
Antihyperlipidemic use	4	-	
Family hist heart attack	4	-	

*Represents two tailed statistical significance at p<.05. Standard deviations in parenthesis. *Abbreviations*: BMP. Beats per minute; BMI. Body mass index; Family hist heart attack, Family history of heart attack or angina in first degree relative <60 years old.

Neuropsychology

A one-way ANCOVA controlling for age was used to compare associations between cognitive tests and risk groups, as age was significantly higher for the risk group and decline in general cognitive abilities is often reported in old age (Hartshorne & Germine, 2015). Cognitive scores indicate the CVR+ group had higher scores on the memory and fluency subscales of the ACE-III, as well as higher scores on the dot counting task from the VOSP compared to HC. No other comparisons were significant (see, Table. 10).

Table 10. General cognition scores from the test battery comparing high cardiovascular risk (CVR+) and healthy control (HC) groups controlling for age.

	Group				
	CVR+	HC	*F*	*p*	η_p^2
General cognition					
ACE total (/100)	96.5 (3.07)	96.6 (2.56)	2.25	.14	.05
ACE: attention	17.04 (1.53)	17.45 (1.23)	2.24	.14	.05
ACE: memory	25.29 (1.39)	24.6 (1.76)	5.5	.02*	.11
ACE: fluency	12.92 (1.56)	12.85 (1.31)	4.1	.05*	.1
ACE: language	25.48 (2)	25.70 (.57)	.38	.54	.009
ACE: visuospatial	15.32 (.95)	15.65 (.59)	1.14	.29	.03
Processing speed					
DSST: completed in 90 sec	49.32 (15.96)	59.6 (12.26)	1.85	.18	.04
Trial Making Test (part B): RT	68.38 (23.82)	69.03 (36.94)	1.67	.2	.04
Visuospatial ability					
Digit Symbol Substitution Test: errors	.08 (.4)	.1 (.45)	.18	.67	.004
Trial Making Test (part B): errors	.42 (.7)	.55 (1.23)	4.69	.04	.1
VOSP: Dot Counting (/10)	9.88 (.33)	9.75 (.55)	4.29	.05*	.09
VOSP: Cube analysis (/10)	9.4 (.76)	9.7 (.57)	.02	.88	.001
VOSP: Position Discrimination (/20)	19.64 (.76)	19.10 (3.34)	.02	.89	.001
Self-report measures					
Cognitive Change Index total (/100)	32.52 (14.21)	36.70 (14.15)	2.31	.14	.05
Cognitive Change Index: memory	20.82 (8.63)	23.2 (8.6)	1.48	.23	.03
Cognitive Change Index: executive function	6.92 (3.79)	8.7 (4.46)	3.11	.08	.07
Cognitive Change Index: language	4.76 (2.59)	4.8 (2.54)	2.19	.14	.05
IPAQ: Sedentary hours per day	7 (5.06)	5.17 (3.4)	2.84	.1	.11
Pittsburgh Sleep Quality Index	4.64 (2.94)	6.89 (4.31)	2.79	.1	.07
Santa Barbra Sense of Direction Index	56.24 (19.3)	60.95 (18.36)	2.3	.13	.05
Body Perception Questionnaire	29.92 (16.18)	27.65 (15.83)	.93	.34	.02
GAD-7	1.6 (1.63)	5.95 (3.79)	2.98	.09	.07
PHQ-9	1.56 (2.93)	6.25 (3.33)	3.68	.06	.08

*Represents statistical significance of ≤.05. Standard deviations in parenthesis. ACE, Addenbrookes Cognitive Examination; DSST, Digit symbol substitution test; VOSP, Visual Object and Space Perception Battery; IPAQ, International Physical Activity Questionnaire; GAD-7, General Anxiety Disorder questionnaire; PHQ-9, Patient Health Questionnaire.

Sea Hero Quest egocentric sensitivity to CVR+

A one-way mixed ANCOVA controlling for age and gender showed that performance for Flare (egocentric) level 14 differed between the groups. Flare accuracy scores showed a significant difference between the CVR+ and HC groups when controlling for age and sex F (1,43) = 5.22, p = .03, η_p^2 = .18. The CVR+ group had reduced accuracy (2.59 (.11)) compared to HC (3.11 (.14)). Flare level 14 duration also differed between groups, when controlling for age and sex, F (1, 43) = 6.25, p=.02, η_p^2 = .16. The CVR+ group took longer (40.88 (3.52) to complete the level than HC (23.12 (4.56)), see Table. 11. No other spatial tests reached statistical significance (p>.09), see supplementary material for more information.

Table 11. Indicates reduced accuracy and increased duration in Sea Hero Quest Flare level 14 for the high cardiovascular risk (CVR+) group compared to healthy controls. There were no differences in behavioural outcome of the Oddball task between groups.

	Group				
	CVR+	HC	*F*	*p*	η_p^2
SHQ Flare Accuracy	2.76 (.43)	3 (.0)	5.22	0.03*	0.21
SHQ Flare Duration (ms)	408.87 (35.26)	231.25 (45.67)	6.25	0.02*	0.2
Oddball % of correct hits	97.69% (3.3%)	98.7% (3.9%)	1.49	0.22	0.16
Oddball RT (ms)	432.04 (68.0)	422.24 (47)	0.9	0.59	0.61

*Represents statistical significance of ≤.05. Standard deviations in parenthesis.

EEG Analysis

There were no group differences between the oddball task performance (see, Table. 11). All participants had a minimum of 100 trials for the standard condition, 35 trials for the target and novel conditions.

Midline P300 Amplitude

Repeated measures ANCOVA with age and sex as covariates was performed for each condition. For the standard condition there was no interaction of electrode x group (Fz, Cz, CPz, Pz) or group (CVR+, HC) F (3, 144) = .3, p = .84, η_p^2 = .01 and no main effect of electrode F (3, 144) = .4, p = .8, η_p^2 = .01 or group F (1, 38) = 1.1, p =.7, η_p^2 = .03. For the target condition there was no interaction of electrode x group F (3, 144) = .21, p = .1, η_p^2 = .01 and no main effect of electrode F (3, 144) = 1.4, p =.24, η_p^2 =.05 or group F (1, 38) = 1.2, p = .4, η_p^2 = .03. For the novel condition there was no electrode x group interaction F (3, 144) = 1.1, p = .43, η_p^2 = .03 and no main effect of electrode F (3, 144) =.1, p = 1.1, η_p^2 = .002 or group F (1, 38) = .32, p = .6, η_p^2 = .01.

Midline P300 Latency

Repeated measures ANCOVA with age and sex as covariates was performed for each condition. For the standard condition there was no interaction of electrode x group (FZ, Cz, CPz, Pz) F (3, 144) = .08, p = 1.1, η_p^2 = .001, no main effect of electrode F (3, 144) = .1, p =.5, η_p^2 = .03 or group F (1, 38) = 3.1, p = .1, η_p^2 = .11. For the target condition there was no interaction of electrode x group F (3, 144) = 1.2, p = .43, η_p^2 = .03. There was a significant main effect of electrode F (3, 144) = 3.1, p = .04, η_p^2 = .12, planned pairwise comparisons suggests a longer latency for the Pz electrode to Fz for both groups (mean difference -58.95,

95% CI [-108.5 to -9.4]). But, critically there was no main effect of group F (1,38) = .1, p = .82, η_p^2 = .002. For the novel condition there was no electrode x group interaction F (3, 144) = 1.8, p = .16, η_p^2 = .1 and no main effect of electrode F (3, 144) = 1.02, p = .4, η_p^2 = .03. There was, however, a significant main effect of group F (1,38) = 6.2, p = .02, η_p^2 = .14, with the CVR+ group reporting significantly longer latencies (408.25ms + 46.9) compared to HC (329.8MS + 48.65). Planned post-hoc analysis using one-way ANCOVA at the electrode level showed significantly longer latencies at the Pz electrode for the CVR+ group (408.3MS + 46.9) compared to HC (329.87+48.6), F (1,38) = 24, p = .001, η_p^2 = .41. No other comparisons reached significance.

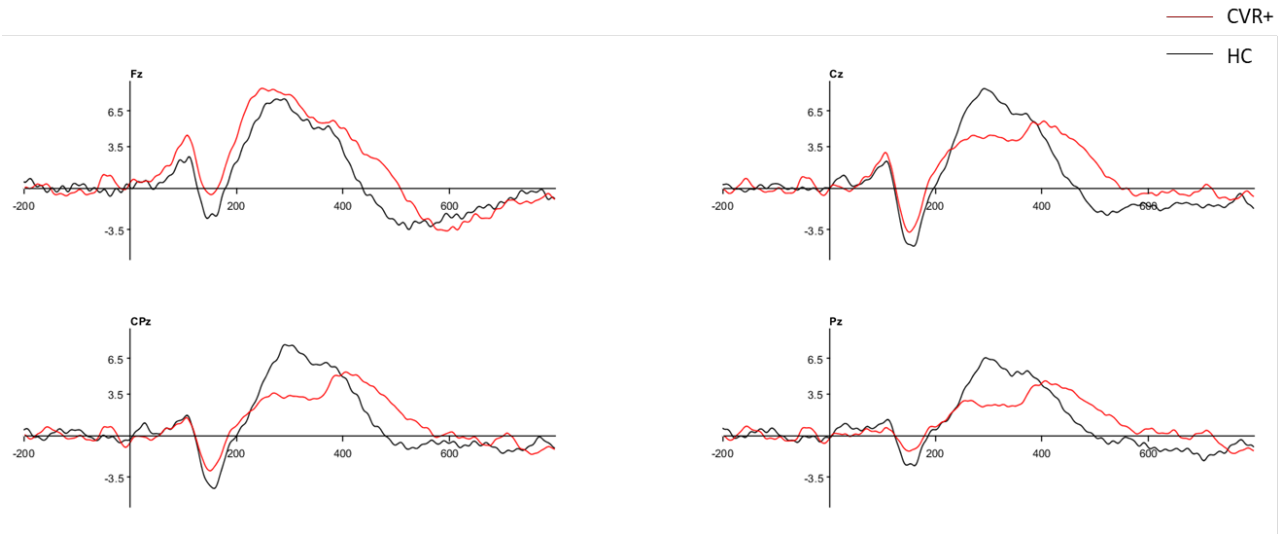


Figure 16. Waveforms for the midline P300 latencies in the novelty condition for the cardiovascular risk (CVR+ red line) and healthy control (HC black line) groups.

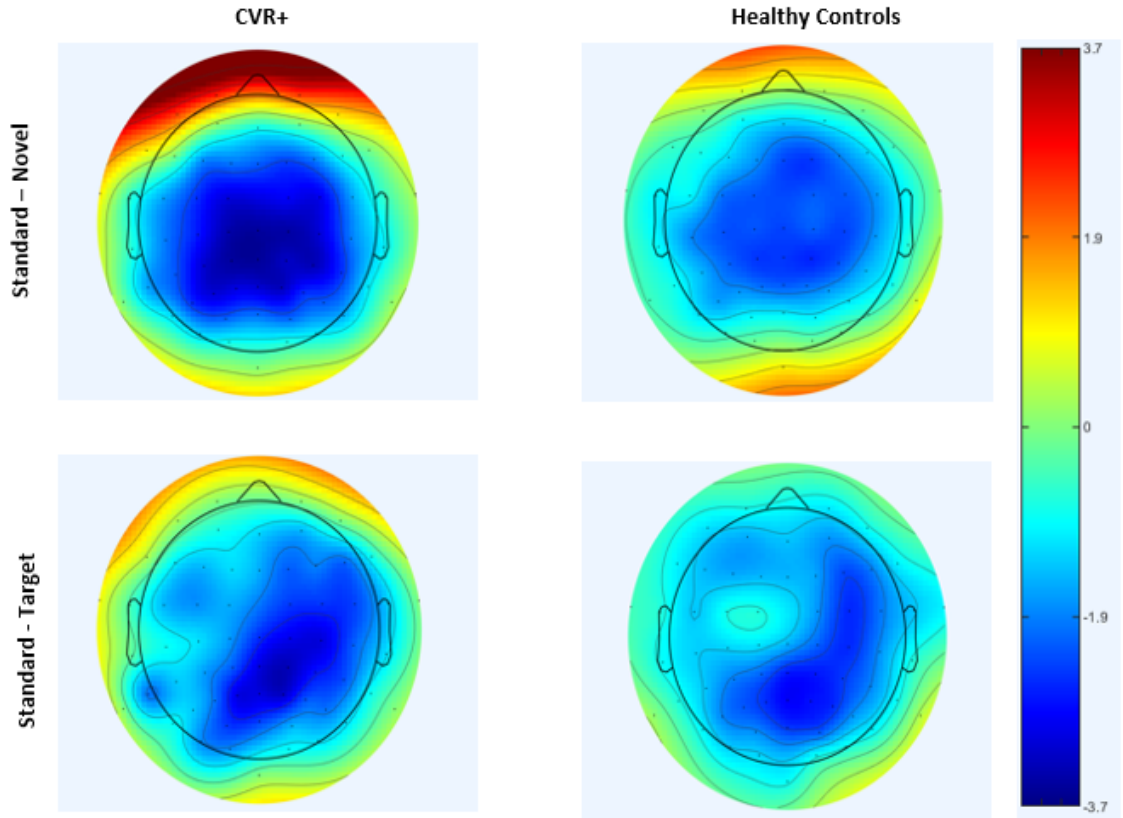


Figure 17. *P300 scalp maps showing amplitude distribution from 200 to 600ms after stimulus onset for the standard minus the novel condition (top row) and for the standard minus the target condition (bottom row).*

Relationships between sensitive measures and behavioural data

Pearson's correlation was used to identify significant associations between the measures which showed sensitivity to the high cardiovascular risk group (P300 latency at Pz electrode for the novel condition, Flare accuracy and Flare duration) and the behavioural data (see Table.12).

Table 12. Significant relationships between sensitive measures and behavioural data for the CVR+ group.

	r	*p*
Pz novel latency + Dot counting	-0.479	0.033*
Pz novel latency + DSST errors	-0.477	0.033*
Pz novel latency + Attention	0.445	0.049*
Flare duration + Visuospatial	0.477	0.029*
Flare duration + SBSDS	-0.458	0.037*
Flare duration + VST egocentric	0.52	0.016*

*Represents statistical significance of ≤.05.

Correlational analysis suggests that, as P300 latency at Pz electrode in the novel condition increases in the CVR+ group, dot counting ability is reduced. Increases in P300 latency is also associated with reduced DSST errors and higher scores in attention. Longer flare duration for the high risk group is associated with reduced self-report measures of sense of direction (SBSDS), higher visuospatial and VST egocentric scores.

Sensitivity and Specificity

The sensitivity and specificity of the P300 latency in the novel condition, Flare accuracy and Flare duration for level 14 data were explored using logistic regression and ROC curves. The Logistic regression model was significant $X^2 = 18.66$, $p = < .001$. The model explained 62% (Nagelkerke R^2) of variance in Risk and control groups and correctly classified 83.3% of participants. ROC curves were computed for the P300 latency in the novel condition, Flare accuracy and Flare duration for level 14 predictors in discerning CVR+ individuals from HC. Area Under the Curve (AUC) values indicated that the P300 latency in the novel condition had the strongest diagnostic accuracy in the model at predicting group membership [AUC = 0.87, SE = .07, 95% CI (.73, .99)]. Flare duration also had some diagnostic accuracy [AUC = .66, SE = .09, 95% CI (.13, .46)]. Flare accuracy was not effective at classifying risk and control groups [AUC = .38, SE = .1, 95% CI (.18, .58)], see Figure. 18.

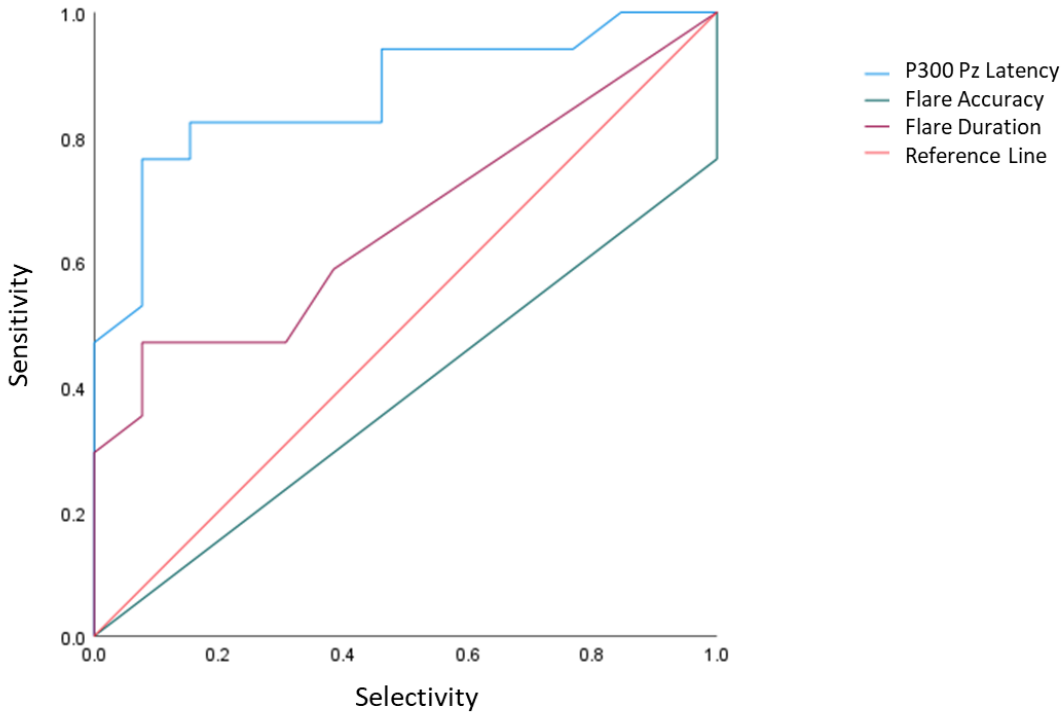


Figure 18. *ROC curves for P300 latency at Pz electrode (blue line). Flare accuracy (green line), Flare duration (purple line) and reference (orange line) predicting correct diagnosis (high risk or control group).*

Discussion

In the present study we aimed to detect dysfunction to the P300 response and egocentric spatial orientation in CVR+ individuals compared to HC, indicating potential cerebrovascular dysfunction to frontoparietal structures (Lowry et al., 2021). Baseline characteristics suggest the CVR+ group were older and had higher systolic blood pressure than heathy controls, consistent with validated cardiovascular risk predictors (Hippisley-Cox et al., 2008). Interestingly, the risk group scored slightly higher on memory and fluency subsections of the ACE and in the dot counting subsection of the VOSP, though size effects were medium (Cohen, 1988).

Our results indicate P300 latency in the novel condition at posterior ERP generators are a sensitive and specific marker selective for identifying CVR+ individuals. The present study confirmed a greater P300 latency at the Pz electrode for novel stimuli in CVR+ individuals compared to HC. However, there were no significant differences in the P300 amplitude between the CVR+ and HC groups. Our finding is consistent with previous studies, which shows increases in the P300 latency is a more sensitive marker of cognitive decline in preclinical VCI compared to the P300 amplitude response (Cicconetti et al., 2007; Hazari et al., 2015).

The results reported in this study, show group differences appear over the more posterior parietal-based electrode generator site of Pz. Subregions of the posterior parietal cortex (which are thought to overlap P300 generators (Johnson, 1993) and prefrontal cortex (Kravitz et al., 2011; Szczepanski et al., 2013) are involved in encoding context dependent and trial-by-trial modulation of attention and response inhibition (Cieslik et al., 2011; Corbetta et al., 2008; Sestieri et al., 2017). Our results could be interpreted using 'context-updating theory' (Donchin, 1986), which suggests the P300 and both subcomponents (P3a and P3b) are on a continuum, with P3a 'identifying change' and the P3b 'updating the model'. Therefore, slowed response at Pz indicated in this study may indicate disruptions to the identifying and updating function (Fabiani et al., 1996) of the mental representations of the disrupted oddball sequence . Which indeed, is consistent with findings from patient lesion studies that indicate the novelty and target P300 are produced by a neural pathway between frontal and temporal/parietal regions (Polich, 2003), instead of localised neural processes.

Results also indicate egocentric (self-referential) spatial orientation differences between the CVR+ and HC groups using Sea Hero Quest. At risk individuals showed reduced accuracy

and increase duration to complete the Flare (egocentric) level 14 compared to healthy controls. Egocentric orientation provides a sensorimotor mental spatial representation which relate to the body in order to effectively orientate and navigate. Prefrontal and parietal cortex are thought to localise the position of objects relative to the body (Arnold et al., 2014; Goodale & Milner, 1992) and the precuneus integrates location cues and egocentric representation from the surrounding space (Wolbers & Wiener, 2014). The SHQ Flare levels require the player to access path integration and metal rotation mechanisms in order to locate their starting position, processes typically associated with functions of the medial parietal cortex (Galati et al., 2000; Goodale & Milner, 1992; Zaehle, Jordan, Wustenberg, et al., 2007) and prefrontal cortex (Spiers, 2008; Spiers & Barry, 2015). This dysfunction in egocentric processes is consistent with studies examining spatial orientation in VCI (Coughlan et al., 2018a; Lowry et al., 2020). This result in particular, is supported by findings from VCI case study RK, in Chapter three (Lowry et al., submitted) which suggests reduced white matter integrity to the left and right SLF parietal sections could be linked to egocentric spatial orientation deficits in VCI. Potential disruption to egocentric networks supports our overarching hypothesis and may represent dysfunction to frontoparietal networks via integrity changes to the SLF (Lowry et al., 2021).

When modelling sensitivity and specificity, results suggest the P300 latency for novel stimuli from the auditory oddball task has the strongest diagnostic accuracy at predicting CVR+ individuals compared to egocentric accuracy and duration of SHQ. Our results are consistent with research suggesting increased P300 latencies can be used to indicate cognitive decline (Polich & Criado, 2006). Superior regions of the posterior parietal lobe, including the intraparietal sulcus, somatosensory motor area, as well as the fusiform face area are involved in egocentric processing (Breveglieri et al., 2013; Galletti et al., 2001; Kravitz et al., 2011)

and the intraparietal sulcus is involved in attention (Derbie et al., 2021; Ptak, 2012) Medial regions of parietal cortex including the precuneus update spatial referencing (Kravitz et al., 2013) as well as shifting spatial attention (Kravitz et al., 2011). These functions also overlap with superior fibres of the SLF (SLF I) which project from the superior parietal lobe terminating at the supplementary motor and pre motor areas of the frontal lobe and are thought to be implicated in functions of proprioception (Chang et al., 2015). Lesion studies indicate disruptions to the SLF, inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus disrupt neural activities in during egocentric spatial coding (Ptak, 2012; Serrao et al., 2021) . Changes in orientating attention are associated with reduced WM integrity to the SLF and ILF (De Schotten et al., 2011) and are associated with slowed reaction times among older adults (Bennett et al., 2012). Taken together, our findings indicate dysfunction to the frontoparietal networks involved in novelty processing and egocentric orientation and point towards potential cerebrovascular change with parietal origins in CVR+ individuals.

Associations between cognitive tests and the experimental measures sensitive to detecting the CVR+ group revealed as the P300 novelty latency at the Pz electrode increased, dot counting ability is reduced. This finding is in keeping with literature suggesting the P300 latency indicates how long it takes to process information before making a response and has been associated with the neural activity underlying processes of attention allocation and immediate memory (Polich, 2007) required to successfully dot count. Correlations also suggest longer flare duration for the CVR+ group is associated with reduced self-report measures of sense of direction (assessed by SBSDS). Given that subjective spatial abilities are highly correlated with directional knowledge and thought to represent our ability to orient ourselves in an environment (Weisberg et al., 2014), it is unsurprising individuals who took longer to

orientate themselves and find the flare gun during SHQ also reported lower sense of direction abilities. Associations between Pz novelty latency and reduced digit symbol substitution errors and higher scores in attention were shown for the CVR+ group, as well as associations between flare duration and higher visuospatial and VST egocentric scores for the CVR+ group. This perhaps reflects longer processing speed to orientate to the task environment and achieve the correct response.

The study reveals an exciting finding of P300 latency and SHQ egocentric flare accuracy and duration as a potential marker of preclinical vascular cognitive impairment. However, there are some limitations. Egocentric measures of the Virtual Supermarket Test and the Clock Orientation Test have previously demonstrated selectivity and specificity to VCI (Lowry et al., 2020; Coughlan et al., 2018a) were not sensitive to CVR+ individuals in this study. The Clock Orientation Test is a simple pen and paper task which requires the participants to state the answer whilst the interviewer notes their response and reaction time. Whilst during the virtual supermarket test, duration data was not collected. Therefore, perhaps these measures lack the sensitivity to detect these subtle yet insidious changes in preclinical populations compared to SHQ (see Coughlan et al., 2019). Ceiling effects were also observed for the HC group potentially confounding statistical analysis. The control group contained fewer males than females, although sex was a covariate in the analysis, future studies may wish to consider a more even representation of males to correct any potential confounds. In addition, EEG provides great insights, but diffusion tensor imaging MRI is required to examine fractional atrophy in the frontoparietal connecting networks to substantiate our hypothesis.

In conclusion, midlife high cardiovascular risk individual's indicative of preclinical VCI, appear to have greater P300 novelty latencies compared to healthy controls. Egocentric

orientation is also disrupted with reduced accuracy and increased processing speed during SHQ for high cardiovascular risk individuals. Findings indicate potential dysfunction to functions at parietal brain sites associated with 'updating' our mental representations of the environment. The study is the first step towards exploring the clinical utility of experimental measures alongside existing clinical tools (QRISK3) to identify and track cognitive decline in cardiovascular risk individuals. More research is needed to replicate this finding across a larger sample and more diverse population, but findings indicate a promising neurocognitive marker of preclinical VCI.

Chapter 5: General Discussion

Summary

The primary goal of this thesis was to establish if spatial orientation deficits were a sensitive and selective marker of vascular cognitive impairment (VCI) and if it could be used to identify at VCI-risk individuals at the preclinical stage. The secondary goal was to examine the neural correlates of VCI at the symptomatic stage using the case study RK, to observe if neural degeneration was consistent with the brain regions associated with spatial orientation. Finally, we examined the electrophysiological response in at VCI-Risk individuals to explore if differences existed between cardiovascular risk individuals and healthy controls. Chapter one synthesised the existing literature on the midlife risk factors of VCI and their cognitive and neural correlates and proposes a model of dysconnectivity to frontoparietal networks which may be identified using novel techniques including spatial navigation and the P300 electrophysiological response. Chapter two showed that VCI patients have egocentric and allocentric deficits when navigating the Virtual Supermarket Test and the Clock Orientation Test, critically egocentric deficits were not present in Alzheimer's disease (AD) patients. In Chapter three, a follow-up with the VCI case study, RK, showed a continued egocentric deficit with new allocentric impairment, both of which went undetected using conventional neuropsychological assessment. RK's brain imaging indicated a potential loss of structural integrity to the parietal segments of the longitudinal superior fasciculus (SLF), perhaps reflecting reduced network connectivity in regions underpinning spatial orientation. The final experimental chapter, Chapter four, suggests that VCI-risk individuals in midlife can be detected using egocentric spatial orientation and the P300 novelty latency response. Figure 19 provides a conceptual overview of the key findings.

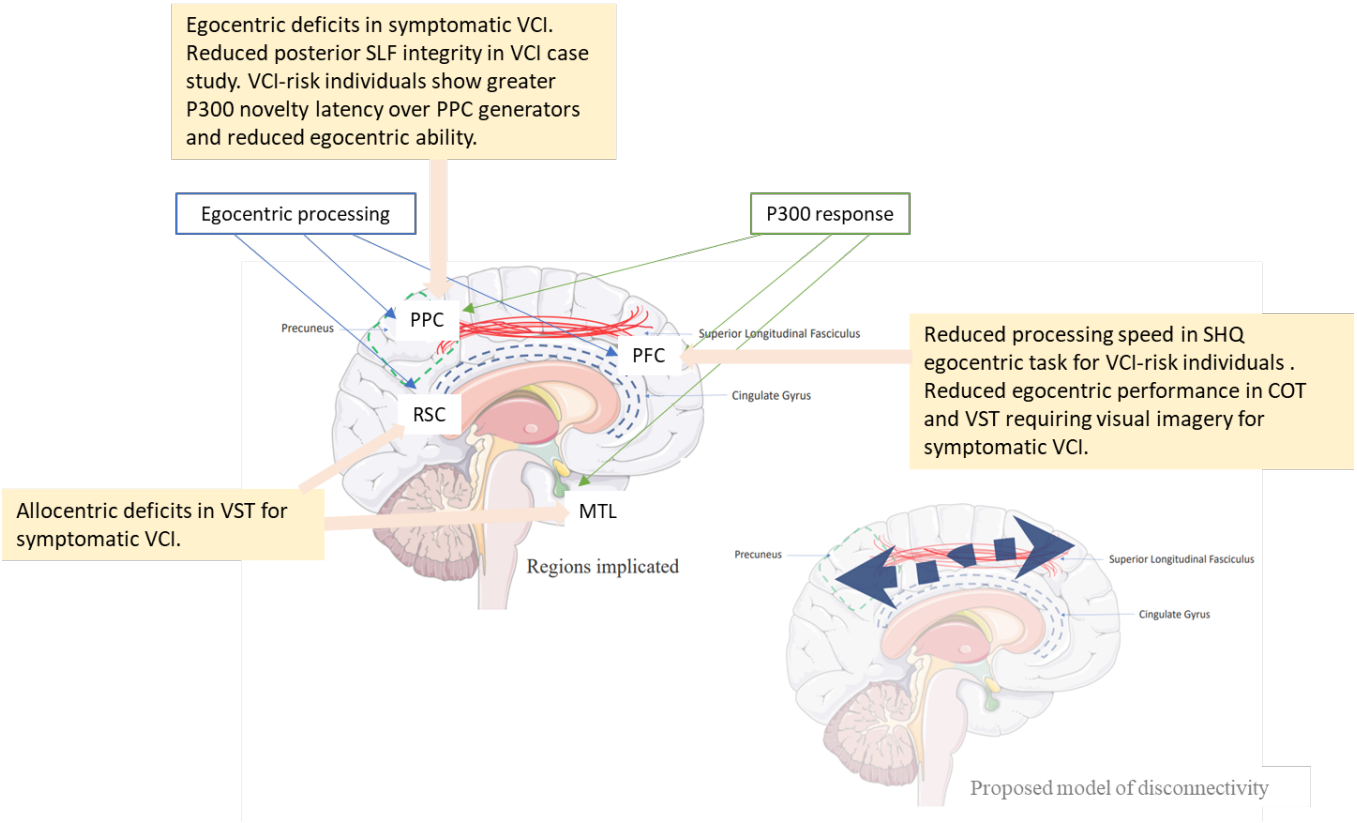


Figure 19. *The neurocognitive profile of symptomatic VCI and VCI-risk individuals from this thesis. Featuring the neural anatomy of egocentric orientation (blue arrows) and the P300 response neural generators (green arrows), results from the studies (orange boxes) and our proposed model of dysconnectivity from Chapter 1. Figure adapted from* (Lowry et al., 2021). *VCI, vascular cognitive impairment; VST, virtual supermarket test; SHQ, sea hero quest, PPC; posterior parietal cortex, RSC; retrosplenial cortex, PFC; prefrontal cortex, MTL; medial temporal lobe.*

Egocentric orientation a marker of symptomatic VCI

The initial goal of this thesis was to establish if spatial navigation deficits could be used as a sensitive and selective cognitive screening tool for the detection of VCI and provide a clear distinction between VCI and AD. Findings from Chapter two indicate that egocentric

orientation processes were impaired in VCI and not AD, reliably distinguishing vascular from AD pathophysiology. This supported findings from the VCI case study RK (Coughlan et al., 2018a), who had egocentric path integration deficits. While allocentric orientation was impaired in both VCI and AD. Suggesting dysfunction to path integration processes which combine egocentric and allocentric information.

Disruptions to spatial orientation was measured using the novel virtual reality (VR) Virtual Supermarket Test (VST) and the bed-side assessment Clock Orientation Test (COT) and presented as reduced scores in egocentric orientation. Potentially representing pathological change to the inferior and superior parietal cortices. This picture seems consistent with previous evidence examining patients with unilateral parietal cortex lesions due to infarction or intracerebral haemorrhage using a virtual reality maze (Weniger et al., 2009). Findings suggest that only egocentric impairments were present in the patients and performance correlated with reduced volumes of the right-sides precuneus. While allocentric performance was unaffected in the parietal lesion patients, memory problems were apparent (Weniger et al., 2009). Perhaps this finding, along with our own results may represent the role of the parietal cortex in spatial memory as seen in rodent studies (Save et al., 2005), therefore somewhat explaining potential mechanism for the allocentric deficits. Disruptions to spatial memory may also contribute to reduced performance in the visuospatial domain of the ACE-III, RCFT copy condition for the VCI patients. Free recall of the FCSRT was also impaired potentially representing dysfunction to the retrieval demands on prefrontal and parietal structures (Staresina & Davachi, 2006), rather than hippocampal-memory based problems per sue. As when VCI patients were cued in the FCSRT they outperformed AD patients. Reduced volumes to the right sided precuneus have also been associated with egocentric deficits in amnesic mild cognitive impairment (MCI) patients, while reduced hippocampal volume

corresponded with diminished allocentric abilities (Weniger et al., 2011), consistent with the neuroanatomy of spatial navigational processes.

The egocentric demand in the virtual Supermarket requires the individual to form an accurate representation of the starting point by integrating virtual self-motion with heading direction to reach their end destination. Path integration plays an important role in updating spatial orientation during self-motion but this process is accumulative, therefore can be liable to directional errors with respect to the original starting position (McNaughton et al., 2006), which may be responsible for problems observed across both egocentric tasks. Whereas the Clock Orientation test demands egocentric processes to configure the position of numbers on a clock face relative to the individual's current position. Both tasks rely on accessing scene construction, mental rotation and imagery translated from an egocentric orientation (Byrne et al., 2007; Dhindsa et al., 2014; Irish et al., 2015). At the neural level, translation of these egocentric processes depend mainly on medial parietal cortex (Galati et al., 2000; Goodale & Milner, 1992; Zaehle et al., 2007) as well as prefrontal cortex (Spiers, 2008; Spiers & Barry, 2015) indicating potential disruptions in fronto-parietal structures typically seen in vascular patients (Beason-Held et al., 2012; Heiss et al., 2016; Van Der Flier et al., 2018; Vipin et al., 2018).

It is also important to consider the domain of memory when interpreting our findings from Chapter two. Results from the FCSRT suggest VCI patients had significantly worse memory than the AD and control groups, sub-score results indicate this is driven by reduced performance during free recall. This is likely due to the retrieval demands on pre-frontal and parietal structures (Staresina & Davachi, 2006) which are typically disrupted in VCI opposed to hippocampal-memory based problems. As when cued VCI patients outperform AD

patients. This finding is consistent with evidence that suggests providing a cue has little bearing on improved memory recall in AD (Sarazin et al., 2007; Wagner et al., 2012). This finding may be relevant to the poor allocentric results observed for VCI patients, as reduced retrieval mechanisms may have disrupted their task performance opposed to pure allocentric (medial temporal) mapping problems, which we would expect to see in the AD patients.

However, the virtual supermarket test is not a pure egocentric or allocentric task. Therefore, combined usage of egocentric and allocentric processes in order to navigate the task is likely (Burgess, 2006). Precuneus-modulated egocentric information such as gathering an imaginable representation of the environment relative to the person (Gusnard & Raichle, 2001) could be translated to the map-based allocentric assessment and therefore, disrupt allocentric performance. Though, translations of egocentric and allocentric information are thought to integrate in the retrosplenial cortex (RSC). This is supported by research examining AD patients using the virtual supermarket test as egocentric performance was thought to partly rely on the volumetric integrity of the RSC (Tu et al., 2015).

Egocentric orientation deficits were also observed in VCI patients in Chapter two when assessed using the clock orientation test. Unlike the VST, the COT is a non-VR bedside task that requires the patient to imagine they were in the centre of a clock face and either verbally respond or point to a series of orientation-based questions based on cardinal, right angled points and free angle positions. Tapping into mental imagery, rotation and egocentric abilities by asking questions such as “imagine you are facing number ‘3’, which number is directly behind you?”. This task bares likeness to the judgements of relative direction (JRD) task, frequently used to assess egocentric and allocentric abilities (Dhindsa et al., 2014). The JDR necessitates knowledge of the persons imagined position in the environment as they are

required to imagine they are standing in one position facing an object and then asked to indicate the direction of a further object (Carpenter & Kelly, 2012). Both the JRD and COT involve transforming between different coordinates and transferring different viewpoints, which indeed is associated with recruiting of the RSC (Dhindsa et al., 2014), potentially indicating the involvement of disruption to path integration processes in the VCI patients in this study.

Though, an alternative perspective in the context of our findings is that of the so called 'BBB' model (Byrne et al., 2007). It proposes that neurons within the posterior parietal cortex (PPC) maintain a head-centred egocentric map of space that is driven from either sensory input or by long-term memory to represent the locations of landmarks and objects that are visible from the navigator's viewpoint recalled from their previous experience. The precuneus is thought to compute this information based on a combination of sensory information and the manipulation of this spatial information for the purposes of navigating and spatial updating occurs with this 'parietal window'. Authors posit that for spatial updating circuitry within the precuneus is activated by proprioceptive cues signalling a change in direction or location. Whereas for mental imagery, the circuit is activated by imagined rotations and translations of route planning. Allowing for an internal representation of the environment without sensory input. Both egocentric tests of the COT and VST require a person-centred mental image of either the clock face or supermarket to successfully provide the coordinates of a secondary position when it is out of sight. Given that the 'BBB' model assumes egocentric representations are transformed to allocentric representations by combining head direction with egocentric input from the 'parietal window'. It is assumed that allocentric representations also rely on egocentric input. If indeed, this is true it may explain egocentric and allocentric deficits observed in the VCI patients in this thesis. As allocentric

as well as egocentric orientation deficits were observed in the VCI patients discussed in Chapter 2. As well as the in the VCI case study. RK, in Chapter 3. RK also appeared to have reduced integrity to the parietal component of the SLF, potentially indicating dysfunction in PPC circulatory in line with the 'BBB' hypothesis.

However, without the accompaniment of MRI analysis for the patients in Chapter two it is unclear if the apparent egocentric deficits in VCI are due to a 'pure' parietal-modulate egocentric deficit or in fact represent dysfunction to path integration processes associated with the RSC. The findings of this chapter need to be replicated in a larger patient cohort study with greater clinical characterisation of the neural profile of VCI, given that VCI has multiple pathological profiles (Skrobot et al., 2016). Though the neural underpinnings of this apparent egocentric deficit in VCI patients is not fully understood, the novel spatial orientation tasks mentioned above in this thesis, may be a useful tool for the detection of VCI. Their role in the future diagnostic criteria for VCI and at its preclinical stages will be discussed in more detail in the upcoming sections.

Egocentric abilities overtime and the neural profile for patient RK

VCI is the second most prevalent form of dementia, but little is known about the early cognitive and neuroimaging markers. Spatial navigation deficits are an emerging marker for AD, yet less is known about spatial orientation deficits sensitive to VCI. The case report outlined in Chapter three follows up on the first VCI patient identified to have an egocentric orientation deficit (Coughlan et al., 2018a). The study aimed to examine the change in the patient's egocentric deficit three years on and gain insights from the addition of the patient's MRI brain scan. A battery of spatial navigation tasks were administered following a comprehensive neuropsychological assessment. Results show improvements across cognitive

domains but egocentric performance continues to be poorer than controls. RK's allocentric scores are now also inferior to controls, which was not previously observed. Critically, RK's functional decline and brain injury are sensitive to novel spatial tests but go undetected on visuospatial measures of neuropsychological assessment. MRI analysis suggest a profile of mild stage subcortical ischemic VCI. More sensitive MRI DTI also indicates a potential loss of structural integrity to the posterior tracts of the longitudinal superior fasciculus (SLF). This may reflect potential reduced network connectivity in posterior to anterior tracts associated with spatial orientation deficits. Findings have clinical utility and show spatial orientation as a potential sensitive cognitive marker for VCI. Especially, given that reduced WM volumes negatively impact cognition and predict VCI onset (Egle et al., 2022).

Interestingly, the deficits observed in RK's allocentric performance may shed some light on the findings observed in VCI patients outlined Chapter two. RK was first diagnosed with VCI in March 2017 and spatial testing occurred shortly thereafter. The follow up case study outlined in Chapter three took place approximately three years later, which reflects the mean disease duration for the VCI patients in Chapter two (three years). This apparent new allocentric impairment may represent the overall disease trajectory for VCI, with egocentric deficits initially affected and allocentric abilities presenting later, perhaps attributed to an overall cognitive decline as the disease progresses. Although, scores on standard neuropsychological assessments suggest an overall uplift in RK's general cognition, his primary caregiver reports advancing memory problems and an increased need for daily-living assistance. In Chapter three I discuss potential test-retest effects which may mask the true profile of RK's cognitive decline (Aldridge et al., 2017).

It is commonly recognised that egocentric and allocentric reference frames use separate neurocognitive pathways mediated by different neural structures (Ekstrom & Isham, 2017; Hartley et al., 2003; Ladyka-Wojcik & Barense, 2021; Wolbers et al., 2004), but these frames can work in parallel with one another (Burgess, 2006). While, egocentric frames can be used alone, there is evidence to suggest allocentric representations require the translation of sensory and imagery input from transient egocentric representations (Burgess et al., 2001). This may explain both egocentric and allocentric deficits observed in RK when using the Virtual Supermarket test. In support of this, rodent models of spatial processing suggest egocentric sensory information travels through parietal cortex in order to elicit 'place cell' firing in the hippocampus, which is key to the translation of map based allocentric representations (Save et al., 2005), it is also suggested human allocentric map based hippocampal representations are driven from inputs from dorsal and ventral visual pathways overlapping posterior parietal regions (Byrne et al., 2007).

As such, our results could be viewed in the context of this integrated model of allocentric representations, which may explain reduced allocentric performance due to egocentric posterior parietal damage in patient RK. In support of this, the demands of allocentric metric of the Virtual Supermarket Test require the participant to view a map of the supermarket and indicate their current position. As well as medial temporal map-based processing, this may also call on visual imagery and short-term spatial memory mediated by medial parietal structures (Fletcher et al., 1996; Wallentin et al., 2006) to reconstruct their 'steps' taken to arrive at the end location. Although, allocentric deficits were not observed when tested using SHQ, RK took considerably longer to complete the Wayfinding (allocentric) levels compared to controls. As such, the egocentric mechanisms affected in RK could be interfering with the

formation of allocentric representations. Future studies in a larger sample of mild to moderate VCI patients are required to explore this potential explanation further.

The pathological trajectory for symptomatic VCI is variable (Roman et al., 1993; Skrobot et al., 2016; van der Flier et al., 2018). Though the neural profile of RK was assessed using FLAIR imaging and visually rated using the Fazekas scale (Fazekas et al., 1987) suggests white matter hyperintensities were present to the right hemisphere frontal lobe of the cerebral cortex and cerebral white matter, as well as periventricular white matter lesions near the lateral ventricles, close to the collosal body and the superior division of the lateral occipital cortex, consistent with subcortical ischemic VCI (Dichgans & Leys, 2017). DTI analysis using fractional anisotropy (FA) was employed to infer white matter integrity to the SLF, as based on our findings in Chapters one and two I hypothesised egocentric deficits may be in part due to injury and subsequent of the SLF connectivity (Lowry et al., 2021). Although differences did not reach significance, a trend towards significance was strongest for the left and right SLF parietal sections.

Neuroimaging studies emphasise the role of medial and posterior partial regions in computing egocentric spatial representations (Burgess et al., 2001; Neggers et al., 2006) and research examining the application of virtual reality assessing early neurodegeneration suggest reduced right hemisphere precuneus volumes are associated with poorer egocentric performance (Weniger et al., 2011). These findings are paralleled by our present results and may suggest posterior regions of the SLF connecting the parietal-to-frontal structures may be implicated in this apparent egocentric decline in spatial orientation observed in RK and our previous VCI patient group study (Lowry et al., 2020)

The SLF is thought to underlie many cognitive process including processes that exhibit control of inhibition processes. The SLF is implicated in visuospatial cognition, attention and working memory all of which vital in spatial processing. Critically, the posterior segment connects temporal and parietal lobes, specifically the middle and superior temporal gyrus to the posteroventral portion of the inferior and superior parietal lobe (Nakajima et al., 2019). Thought to specialise in visuospatial and auditory function, as well as auditory comprehension, reading and lexical access (Nakajima et al., 2019). Findings from this case study suggest RK indeed presents with spatial orientation problems yet, conventional neuropsychological assessments (ACE-III, VOSP and ROCF-copy condition) did not detect his deficits. Only when RK was required to freely recall the ROCF did he display difficulties. This apparent retrieval dysfunction was also apparent of the free recall components of the FCRT. Suggesting potential dysfunction between parietal and temporal cortices implicated in the translation of sensory (egocentric) to map-based (allocentric) representations(Save et al., 2005). If indeed the 'BBB' hypothesis (Byrne et al., 2007) is correct, dysfunction in the circuitry of parietal structures may be responsible for disruptions of the translation of mental imagery and spatial updating from egocentric-parietal to allocentric-temporal frames. As the 'BBB' model suggests visual and sensory stimulus has to be transformed from egocentric to allocentric coded frames, in order to match against or store spatial input within spatial long-term memory. Therefore, supporting the notion that parietal divisions of the SLF responsible for the translation of egocentric spatial may be associated with the presentation of RK's symptoms in not only egocentric frames but spatial memory and free recall process of allocentric memory storage.

Executive processes continue to be apparent in RK measured by INECO, and reaction time speed is slower on the TMT-part B reflecting more conventional symptomology of VCI

(Sachdev et al., 2014) and consistent with FLAIR imaging suggesting RK has white matter hyperintensities to the right frontal lobe cortex and cerebral white matter. Though, slowed reaction times and processes involved in orientating attention are thought to be underpinned by the long-range white matter tracts the SLF and the inferior longitudinal fasciculus (ILF) (De Schotten et al., 2011). The IFL connects the occipital and temporal-occipital to anterior temporal regions of the brain and is implicated in the transfer of visual perception including object and place processing and visual memory (Justen & Herbert, 2018). Perhaps indicating network disruptions to frontoparietal and temporal connectivity as executive function, spatial orientation and memory are all affected in RK. Especially plausible, since white matter hyperintensity (WMH) burden is greatest in the frontal lobe in healthy aging (Hirsiger et al., 2017), yet processing speed measured by the TMT is most associated with WMH burden to parietal regions and white matter volumes of parietal and temporal lobes. Whereas the process of task switching is more associated with reduced white matter volumes and WMH burden to frontal and parietal regions (Hirsiger et al., 2017).

Most of what we know of brain function derives from patient lesion studies, therefore Chapter three's findings hold useful insight, but the results observed from RK need to be replicated in a larger VCI patient cohort study. Egocentric and subsequent allocentric impairments in the patient are clear but the associated neural mechanisms still need to be understood. As SLF integrity to the right and left parietal portion did not meet the statistically significant threshold of $p = <.05$. Further to this, the control participants for the follow up study are different to those at the time one assessment. Although control participants were well matched to RK, for consistently and improved validity the original control participants would have been preferential. This was unable to occur as I did not have longitudinal data for those participants.

Theoretically, RK's cognitive deficits measured by standard neuropsychological assessments and novel spatial test support potential for dysfunction to parietal involvement in processing speed and spatial mechanism, namely the translation of egocentric to allocentric computations as described by the 'BBB' model with potential dysfunction to the 'parietal window' mechanisms (Byrne et al., 2007), which is also supported by reduced integrity to the parietal portion of the SLF. Clinically, our findings come as further support for the use of spatial navigation testing in clinical settings, given its sensitivity to WM changes compared to traditional neuropsychological assessments (ACE-III and VOSP) which did not detect visuospatial impairments or place RK at the clinical thresholds for dementia. Spatial navigation may also be useful tool to track VCI trajectories. The exploration of the use of spatial navigation as a tool to detect preclinical VCI individuals is discussed below.

The latency of the P300 component is sensitive to preclinical VCI

Our findings discussed in Chapter four show the P300 novelty latency as a potential marker of preclinical VCI. As the novelty P300 is thought to reflect a conscious, evaluative aspect of the orientating response (Cycowicz & Friedman, 1998; Näätänen, 1990), underpinned by functional interactions within the frontoparietal attentional network (Ptak, 2012; Szczepanski et al., 2013; Vossel et al., 2014),these findings build support for the notion proposed in Chapter one that frontoparietal dysfunction may be at play in VCI pathology.

According to 'context updating theory' (Polich, 2003), the subcomponent P3a is an earlier 'novelty' response that occurs when the stimulus is nonrepeating and unexpected which is generated from frontal regions, whereas the P3b is a later 'updating response' that occurs when stimulus is repeating and occurs over parietal generators (see, Figure 20).

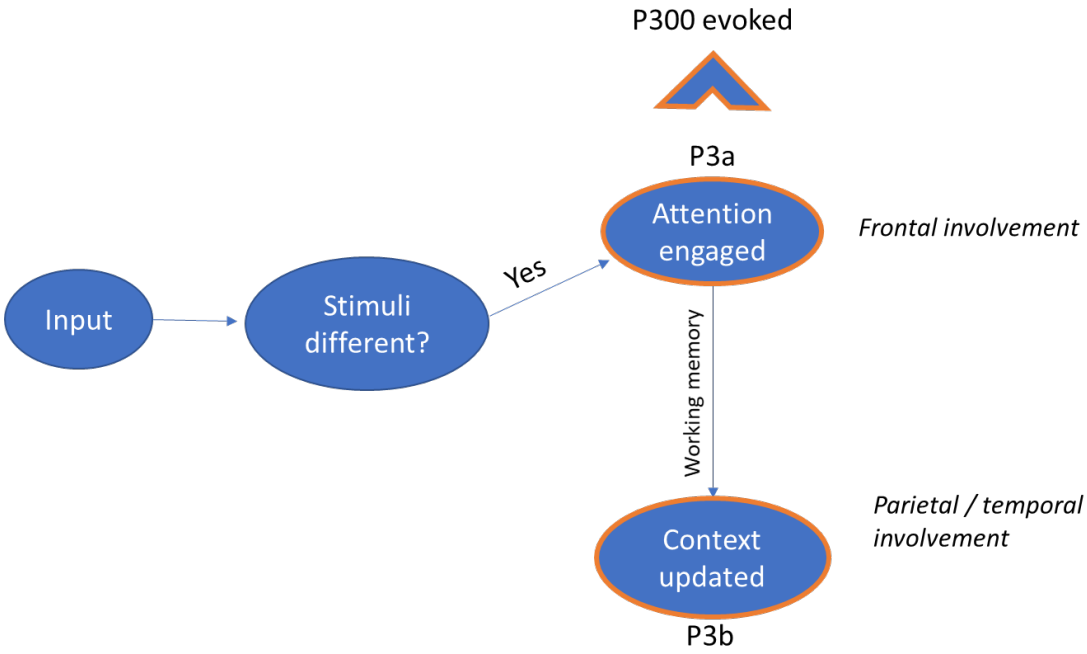


Figure 20. P300 Context Updating Theory modified version of Polich (2007).

As such, the use of the oddball paradigm and subsequent P300 response appears to be a strong proxy for the measurement of frontal-to-parietal interactions. Frontal lobe activations (P3a) are thought to reflect the attentional focus required by task performance, which is required to engage for the detection of rare or novel stimuli. This novelty P300 response is related to changes in anterior cingulate when incoming stimuli replace the contents of working memory (Desimone et al., 1995). When a novel stimulus evokes frontal lobe attention then attentional resources are allocated for subsequent memory updating after this initial evaluative process. Then parietal/ temporal regions are evoked to relay the change and update our working model of the task (P3b). The model suggests neuroelectric events that underlie the P300 stem from the interaction of frontal lobe and hippocampal/ temporal – parietal function. This suggests that after initial sensory processing, an attention driven comparison takes place in working memory to compare previous and current stimulus, only if change is detected (either target or novel stimulus) a P300 occurs.

ERP Latency is thought to index the classification speed which reflects the time required to detect and process a target item (Kutas et al., 1977). As such, the P300 latency is thought to be linked to mental speed and act as a proxy for cognitive abilities, with fast response related to superior abilities (Pelosi et al., 1992). Peak latency increases with healthy aging (Fjell & Walhovd, 2001). Cognitive decline in dementia has also been shown to prolong the P300 latency (Rossini et al., 2007). Evidence from a meta-analysis exploring the utility of the auditory P300 latency component in MCI indicates latencies from approximately 337ms to 423ms (see, Howe et al., 2014). Results from Chapter four for the CVR+ group indicate a latency of 408.3ms which is consistent with this. Interestingly and consistent with our findings for CVR+ individuals, Howe et al (2014) also found the largest size effects occurred at the Pz electrode for MCI and AD individuals, leading authors to suggest future studies comparing patient groups and healthy controls may want to solely focus on this electrode for greater differentiation (Howe et al., 2014).

P300 latency response and egocentric decline in preclinical VCI

The findings discussed in Chapter four also suggest an egocentric deficit in VCI risk individuals detected by Sea Hero Quest. Taking these findings along with the slowing of the P300 latency, there are some explanations which point towards shared underling dysfunction to cognitive and neural mechanisms. First, focal attention is required for effective stimulus evaluation during both Sea Hero Quest and the Oddball task. Stimulus evaluation is also crucial in the guidance of spatial attention (to focus in on and evaluate the given environment) and both of these processes are thought to be underpinned by a prefrontal-parietal network (Corbetta et al., 2008) and are important for working memory processing. The ability to hold information in mind for the future is critical for goal directed behaviour such as spatial orientation. For visual imagery to support route planning and subsequent

navigation, working memory is used to temporality hold and manipulate spatial information. We know egocentric processing is mediated by a network that includes frontal structures (Arnold et al., 2014; Goodale & Milner, 1992) associated with working memory processes. Prefrontal lesions have also shown fragility to egocentric processing when allocentric performance goes unaffected (Semmes et al., 1963). Medial frontal cortex also subserves egocentric processes such as 'value' judgements (Seitz et al., 2009) critical for the self-control of action. These inhibitory processes are clearly associated with attentional mechanisms involved in the processing of task relevant information in the P300 oddball task and needed for the working memory processes involved in egocentric orientation. Therefore, as our results indicate, egocentric orientation and the novelty P300 response may overlap some cognitive domains as well as neural components.

Second, according to 'context updating theory' (Polich, 2007) the P300 response is heavily dependent on working memory which is underpinned by right frontal regions (Geula et al., 2017). Some accounts also suggest working memory is a vital component in egocentric orientation (Mallot & Basten, 2009), acting as a tool to temporarily store sensory information and integrate these with spatial and route memories retrieved from longer-term representations. There is some evidence from animal studies which suggests working memory is thought to be implicated in simple path integration, route planning and object permeance processes from an egocentric perspective (Mallot & Basten, 2009). Hierarchical theories of spatial representations (Wiener & Mallot, 2003) suggest spatial memory consists of many different structures according to one's subjective perception and the physical properties of the environment which form together and create superordinate entities in graph-like representants of the space. As such, to effectively navigate tight integration between spatial referencing and working memory is required (Wiener & Mallot, 2003). The results

shown in Chapter four indicate dysfunction to the neural mechanisms involved in attention and stimulus evaluation as well as working memory and context updating which appear to be implicated in the disruption of P300 and egocentric performance for at VCI risk individuals.

Limitations

Limitations are discussed in each chapter, however what follows is the methodological shortfalls across the thesis and recommended improvements for future testing.

Effect size

When considering the implications of the findings from the thesis the sensitivity and selectivity of spatial navigation in detecting VCI pathology, it is important to consider the effect sizes associated with these findings. For clarity, in Chapter two and four effect sizes were computed using partial eta-squared and interpreted as; $\eta_p^2 = 0.01$ indicates a small effect, $\eta_p^2 = 0.06$ indicates a medium effect and $\eta_p^2 = 0.14$ indicates a large effect (Cohen, 1988). In Chapter three, effect size was calculated using Crawford and Howell's (1998) modified paired sample t-test resulting in a Z-case-control (Z_{cc}) score as an interval estimate of the effect size, comparable with Cohen's d; 0.2 = small, 0.5 = medium, 0.8 = large effect sizes (Cohen. 1988).

Findings from Chapter two and three indicate egocentric deficits in VCI patients appear to be most sensitive to the clock orientation test (COT) (Chapter two; effect size; $\eta_p^2 = .44$, Chapter three $Z_{cc} = -3.48$), compared to the VST (effect size; Chapter two $\eta_p^2 = 1.48$, Chapter three $Z_{cc} = 2.33$), and hence should be preferential when designing future studies to assess egocentric abilities in VCI patients. Whereas results from Chapter four indicate that the P300 latency for novelty stimulus showed the greatest effect size for identifying cardiovascular risk

individuals (CVR+) (η_p^2 = .41). Sea Hero Quest transpired to be the only test of spatial navigation able to detect CVR+ individuals although these effect sizes were smaller (accuracy, η_p^2 = .21, duration η_p^2 =.2), which is indeed supported by ROC analysis indicating the P300 latency as the strongest predictor of correct group allocation between CVR+ and healthy controls. Our results suggest that the fine-tuned parameters of the electrophysiological response and SHQ tasks is sensitive to the prodromal stages VCI. However, the efficacy of SHQ to detect symptomatic VCI requires further investigation in larger patient cohort studies as SHQ was not used as an outcome measure in Chapter two. Therefore, further studies are required to validate SHQ as a sensitive tool to detect established VCI. Chapter three highlights the usefulness of SHQ to detect egocentric deficits in case study RK (Z_{cc} = -1.94), but effect sizes remain strongest for the Clock Orientation test (Z_{cc} = 3.48). Future studies with larger patient cohort sizes need to validate sensitivity and selectivity of SHQ in VCI patients.

For the DTI MRI results in Chapter three, the extent to which reduced FA to the SLF informs egocentric deficits in VCI is unclear. Reduced FA volumes to the left and right hemisphere SLF-parietal had strong effect sizes (Z_{cc} = -1.73 and Z_{cc} = -1.65 respectively), yet results did not reach significance. Therefore, it is important to substantiate this in a larger sample of VCI patients before links can be established.

Baseline group differences

In Chapter three, it is also important to consider the implications of having different control participants from time one to time two. There are large variations in performance for the control groups, with the controls at time two scoring worse on the spatial tasks than the controls at time one (see, Appendix A). This confound is difficult to explain, although we

know as age increases spatial abilities become poorer (Gazova et al., 2013; Li & King, 2019). The mean age at time one was 63 years old (SD = 4.8), compared to the mean age of 67.79 years old (SD = 3.17) at time two. Suggesting the controls at time two were better matched to RK's age and therefore may show greater integrity for comparison of RK's performance than scores at time one. Yet, this shortcoming remains to reduce consistency overall when comparing time one to time two experiments.

In Chapter four, although not significant at the p <.05 threshold, the CVR+ group had higher educational attainment than the control group, potentially masking any changes to cognitive abilities, given that educational attainment is widely considered protective against cognitive decline (Vanenzuela & Sachdev, 2006), though some accounts now suggest the impact of education on later life cognition is negligible (Seblova et al., 2020). A larger sample for each cohort would reduce potential confounds. In addition, the control group contained fewer males than females, although sex was a covariate in the analysis, future studies may wish to consider a more even representation of males to correct any potential confounds. This would also allow for sex disaggregated data, which is important given gender specific differences in cardiovascular diseases (Jochmann et al., 2005).

Test re-test effects

In Chapter three, the variability in RK's cognition from time one to time two appears to demonstrate a level of recovery in his cognitive and spatial abilities. This may represent the test re-test effects of the methods used. The reliability of the VST has been validated (see, Coughlan et al., 2020), however the reliability of COT and SHQ have not. Future studies may wish to consider adding a broader battery of cognitive and spatial assessments to counter practice effects.

Study design

The cross-sectional nature of the research discussed in chapters two and four are methodological limitations of this thesis. Much of the research in the field of identifying early cognitive and biological markers of dementia is focused on large scale longitudinal cohort studies (see, Chapter one, Table 2). The advantage of this design allows participant follow-up over time to track changes in cognition and associated risk factors over the life course. Due to the extenuating circumstances of the pandemic, the study outlined in Chapter four was unable offer a later follow-up session, as previously set out in our protocol approved by the UEA ethics committee. Future research examining spatial navigation, cognition and cardiovascular risk would benefit from a longitudinal design.

In terms of the methods used in this thesis, evidence suggests virtual reality by way of immersive and screen-based tools offers many advantages in for testing spatial navigation abilities. Virtual reality tasked used to assess spatial navigation are shown to have ecological validity and is more cost effective, quicker and safer to administer than real-world navigation. Coutrot et al., (2019) reports strong correlations between SHQ and real-world spatial abilities. However, it is unclear how the results from VST and COT translate to real-world navigation in terms of likelihood of getting lost. The accompaniment of real-world techniques such as GPS tracking of navigational patterns (see, Pot et al., 2012; Puthusseryppady et al., 2022), would enhance our understanding of the applied nature of this line of enquiry.

Recruitment

The patient's described in Chapter's two and three were recruited from an existing database and actively wished to participate in dementia studies. This could present a self-selection bias

(Heckmen, 2010), given that this sample is able to complete the experimental task, give informed consent and demonstrate a reasonable degree of functioning. This may distort the inferability of the sample in these studies to the population. To improve the sampling strategy the study described in Chapter four, recruited entirely new participants from outside of our existing databases using local groups on Facebook. Most of these participants reported never having been involved in research prior, enhancing the overall representation of the sample to reflect the population. An increased sample size in Chapter four would have also been preferential to allow more detailed statistical analysis. The use of multi-level modelling would have been insightful to demonstrate the VCI risk factors most sensitive to the experimental measures. Given that elevated blood pressure in midlife is consistently linked to changes in brain structure, specifically white matter hyperintensities (Wartolowska et al., 2021; Jiang et al., 2022). Whereas other risk factors such has high cholesterol have a less substantive evidence base.

Implications

From a theoretical perspective, the work in this thesis addresses current limitations and gaps in the VCI literature. Major risk factors for VCI relate to modifiable factors that affect the vascular and metabolic system. Hypertension, obesity, diabetes, high cholesterol and a lack of physical exercise contribute to an increased risk of developing dementia (Van Der Flier et al., 2018). Evidence from longitudinal observational studies suggest that the effect of the specific risk factors largely depend on age, with hypertension, obesity and hypercholesterolaemia having the most destructive impact in mid-life (<65yrs) (Solomon et al., 2014). Yet, it is highlighted in Chapter one that very little is known about the specific cognitive correlates of the disease and even less of the preclinical cognitive and neuroimaging profile of VCI.

The findings from our literature review (Lowry et al., 2021) outlined in Chapter one suggest that midlife risk factors are associated with insidious changes to cognition and neuroanatomical function. In Chapter two the work here begins to explore this further. Findings highlighted that indeed, egocentric deficits were able to distinguish VCI from AD patients. Showing the usefulness of spatial testing compared to many standardised cognitive assessments to distinguish between pathologies. To our knowledge, this is the first study to demonstrate this in VCI patients, which aids the overall diagnostic accuracy of VCI. An additional strength of this research is that spatial navigation is a human process used in everyday life compared to conventional cognitive assessments which can be influenced by culture, language and literacy (Ardila, 2005). The use of VR tasks set in ecological environments, such as a supermarket, may have great implications for overcoming educational barriers in the detection of cognitive decline. This is particularly relevant, given the estimated growth of dementia incidence in developing countries (Prince et al., 2013) and may compliment the emerging literature employing novel techniques to address this barrier and provide greater specificity in diagnostic testing in these populations (see, Crombie et al., 2022).

Chapter three provides an in-depth study of the VCI patient RK. Adding to our understanding of symptomatic VCI and the variability of symptoms throughout the disease course. Findings may indicate the utility of spatial navigation for disease monitoring and could be of benefit to track rehabilitation in brain injury with a level of recovery, such as stroke. Importantly, spatial navigation may help inform disease state in VCI, particularly WM volumes in fronto-parietal pathways. The link between egocentric orientation and the SLF requires further

inquiry, but this study lays the foundation for potential theoretical and clinical advancements in understanding white matter degeneration and the cognitive impact.

Finally, Chapter four built on the knowledge gained in previous chapters and demonstrated that midlife high cardiovascular risk individuals had reduced egocentric accuracy and increased processing speed measured by SHQ. High risk individuals also had greater P300 novelty latencies over parietal neural generators compared to healthy controls. To our knowledge this is the first study to demonstrate egocentric orientation as a potential marker of preclinical VCI. Implications of which are discussed in the terms of future directions below.

Given our findings, it is critical that tests assessing spatial navigation and associated neural anatomy are included in future cardiovascular risk diagnostic and treatment studies. The majority of this research area is dominated by large scale multidomain trial longitudinal studies (Ngandu et al., 2015; Rosenberg et al., 2020; van Charante et al., 2016), but, as this thesis highlights, the benefit of more detailed patient cohort studies is apparent and much is yet to be learned from clinical case studies. The introduction of novel spatial testing is emerging in Alzheimer's disease research (Ritchie et al., 2016; K. Ritchie et al., 2010) and findings from this thesis suggests it would be beneficial to adopt a similar approach in VCI and cardiovascular risk studies. It would be prudent to use these novel tests in tandem with standardised neuropsychological tests recommended for the screening of VCI (see, Sachdev et al., 2014), until evidence amasses to suggest spatial navigation tools detect VCI pathology earlier than tests of executive function and processing speed.

The neurocognitive processes involved in spatial navigation and specifically the spatial tasks used throughout this thesis have been discussed at length in each chapter and above when

considering spatial navigation and symptomatic VCI. Indicating parietal involvement acts as a ’hub’ for the integration of egocentric information (Byrne et al., 2007; Cavina-Pratesi et al., 2018; Desmurget et al., 1999; Meek et al., 2013). The results from chapter four suggest indeed, egocentric processing when measured using SHQ is impaired and risk individuals took longer to orientate themselves throughout the egocentric task compared to healthy controls. The electrophysiological response measured by the P300 component dovetails with this finding and suggests longer latencies over the parietal neural generator. To synthesise these findings theoretical models of ‘context updating’ are discussed along with the P300 novelty response reflecting an evaluative aspect of the orientating response, particularly relevant to spatial cognition.

Future Directions

This thesis offers a rationale for the further investigation into how spatial navigation, P300 response, symptomatic VCI and preclinical VCI relate. Spatial orientation and the neural correlates seem to suggest a network model of frontoparietal processing with some involvement from RSC and medial temporal structures in VCI. Attentional processes also seem to be implicated demonstrated by dysfunction to P300 latencies for novel stimulus. These results taken in the context of findings from the above Chapters appear to present a profile of frontoparietal disruptions with some RSC medial temporal interaction in symptomatic and preclinical VCI. Therefore, tests that tap into these structures like that of SHQ, Virtual Supermarket, Clock Orientation Test and the oddball task may pose clinical utility for the identification and tracking of VCI pathology.

Although, more research is required in both symptomatic and preclinical VCI, novel spatial testing may prove to be a valuable tool for the screening of cognitive decline. If the findings

of this thesis are substantiated by a further body of evidence, the use of novel app-based spatial orientation tools may be beneficial in clinical practice. Especially given, that VCI risk factors are largely modifiable (van der Flier et al., 2018). Cognitive screening using the spatial tasks could take place at routine 'NHS Health Check's' for those with high cardiovascular risk factors. As cardiovascular risks in midlife are most damaging to cognition in later life, tracking cognition using tools sensitive to the preclinical symptoms of cognitive decline alongside precautionary health checks is critical. The use of novel spatial orientation testing could help to identify and track symptoms or act as a motivation to change health behaviours, pursue healthier lifestyle options and enhance compliance to medical management. Particularly as the link between modifiable risk factors, midlife health and dementia is clear.

The clinical utility of EEG and the P300 response is less accessible, due to the equipment cost and training and needed to operationalise this method of neuroimaging. However, promising developments are being made to establish event related potentials as biomarkers of cognitive performance in individuals with cardiovascular risk factors in large scale cohort studies (Marin et al., 2022). Though EEG is a tool employed for the evaluation of people with epilepsy and is used in both hospital and clinical settings, the low spatial resolution and diagnostic yield in detecting dysfunction in more medial brain regions is less effective (Tatum et al., 2018). The use of source localisation in EEG is thought to enhance this detection. However, MRI DTI analysis as used in Chapter three would be preferential to substantiate dysfunction to the SLF and frontoparietal networks in symptomatic and preclinical VCI. Especially since microstructural changes in WM volumes are associated with executive function and general cognitive abilities (Williams et al., 2019) and are highly

related to processing speed (Lawrence et al., 2014) – cognitive attributes associated with Oddball and spatial paradigms.

Future questions motivated from this thesis include 1) Can egocentric orientation be used to discriminate VCI from other dementias such as; Posterior Cortical Atrophy, Lewy Body Dementia...? 2) Can egocentric orientation tasks detect white matter volume loss and is this focused to the parietal segments of the SLF? 3) Are there specific VCI risk factors that are more sensitive to the P300 latency and egocentric orientation?

Conclusions

The key finding from this research suggest that egocentric spatial navigation appears to be sensitive and selective to symptomatic VCI. These apparent egocentric deficits also appear in cardiovascular risk individuals in midlife. These findings require replication in larger cohort studies, but provide a platform, for future studies to investigate spatial navigation in symptomatic and preclinical VCI. The model proposed in Chapter one and reiterated at the start of this discussion concerning dysfunction between frontoparietal pathways as an early marker of VCI will provide further theoretical insight into the problem of profiling such a heterogenous disease at its symptomatic stages and potentially help build a profile of cognitive and neuroimaging factors of high-risk individuals.

References

Aguirre, G. K., Detre, J. A., Alsop, D. C., & D'Esposito, M. (1996). The Parahippocampus Subserves Topographical Learning in Man. *Cerebral Cortex*, *6*(6), 823–829. https://doi.org/10.1093/CERCOR/6.6.823

Aldridge, V. K., Dovey, T. M., & Wade, A. (2017). Assessing Test-Retest Reliability of Psychological Measures. *European Psychologist*, *22*(4), 207–218. https://doi.org/10.1027/1016-9040/A000298

Alexander, A. S., & Nitz, D. A. (2015). Retrosplenial cortex maps the conjunction of internal and external spaces. *Nature Neuroscience 2015 18:8*, *18*(8), 1143–1151. https://doi.org/10.1038/nn.4058

Allison, S.L., Fagen, A., Morris, J.C., , Head, D. (2016). Spatial Navigation in Preclinical Alzheimer's Disease. *Journal of Alzheimer's Disease*, *52*(1), 77–90. https://doi.org/10.3233/JAD-150855.

Anstey, K. J., Cherbuin, N., Budge, M., & 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*(5), e426-37. https://doi.org/10.1111/j.1467-789X.2010.00825.x

Ardila, A. (2005). Cultural values underlying psychometric cognitive testing. *Neuropsychology review*, *15*(4), 185-195.

Arnold, A. E. G. F., Burles, F., Bray, S., Levy, R. M., & Iaria, G. (2014). Differential neural network configuration during human path integration. *Frontiers in Human Neuroscience*, *8*(1 APR). https://doi.org/10.3389/fnhum.2014.00263

Attems, J., & Jellinger, K. A. (2014). The overlap between vascular disease and Alzheimer's disease - lessons from pathology. *BMC Medicine*, *12*(1), 1–12. https://doi.org/10.1186/s12916-014-0206-2

Au, R., Massaro, J. M., Wolf, P. A., Young, M. E., Beiser, A., Seshadri, S., D'Agostino, R. B., & DeCarli, C. (2006). Association of white matter hyperintensity volume with decreased cognitive functioning: The Framingham Heart Study. *Archives of Neurology*, *63*(2), 246–250. https://doi.org/10.1001/archneur.63.2.246

Awad, N., Gagnon, M., & Messier, C. (2004). The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. In *Journal of Clinical and Experimental Neuropsychology* (Vol. 26, Issue 8). https://doi.org/10.1080/13803390490514875

Bauermeister, S., & Bunce, D. (2014). Poorer mental health is associated with cognitive deficits in old age. *Http://Dx.Doi.Org/10.1080/13825585.2014.893554*, *22*(1), 95–105. https://doi.org/10.1080/13825585.2014.893554

Beason-Held, L. L., Thambisetty, M., Deib, G., Sojkova, J., Landman, B. A., Zonderman, A. B., Ferrucci, L., Kraut, M. A., & Resnick, S. M. (2012). Baseline cardiovascular risk predicts subsequent changes in resting brain function. *Stroke*, *43*(6), 1542–1547. https://doi.org/10.1161/STROKEAHA.111.638437

Benedictus, M. R., van Harten, A. C., Leeuwis, A. E., Koene, T., Scheltens, P., Barkhof, F., ... &

van der Flier, W. M. (2015). White matter hyperintensities relate to clinical progression in subjective cognitive decline. *Stroke*, *46*(9), 2661-2664.

Bennett, I. J., Motes, M. A., Rao, N. K., & Rypma, B. (2012). White matter tract integrity predicts visual search performance in young and older adults. *Neurobiology of Aging*, *33*(2), 433.e21-433.e31. https://doi.org/10.1016/J.NEUROBIOLAGING.2011.02.001

Braak, H., & Del Tredici, K. (2015). The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. *Brain*, *138*(Pt 10), 2814–2833. https://doi.org/10.1093/brain/awv236

Breveglieri, R., Galletti, C., Dal Bo, G., Hadjidimitrakis, K., & Fattori, P. (2013). Multiple Aspects of Neural Activity during Reaching Preparation in the V6A. *Journal of Cognitive Neuroscience*, *25*(2), 1–10. https://doi.org/10.1162/jocn

Brookes, R. L., Hollocks, M. J., Khan, U., Morris, R. G., & Markus, H. S. (2015). The Brief Memory and Executive Test (BMET) for detecting vascular cognitive impairment in small vessel disease: a validation study. *BMC Med*, *13*, 51. https://doi.org/10.1186/s12916-015-0290-y

Burgess, N. (2006). Spatial memory: how egocentric and allocentric combine. *Trends in Cognitive Sciences*, *10*(12), 551–557. https://doi.org/10.1016/j.tics.2006.10.005

Burgess, N. (2008). Spatial Cognition and the Brain. *Annals of the New York Academy of Sciences*, *1124*(1), 77–97. https://doi.org/10.1196/ANNALS.1440.002

Burgess, N., Becker, S., king, john, & O'Keefe, J. (2001). Memory for events and their spatial context: models abd experiments. *Philos Trans R Soc Lond B Biol Sci*, *356*(1413), 1493–1503. https://doi.org/10.1098/rstb.2001.0948

Burles, F., Slone, E., & Iaria, G. (2017). Dorso-medial and ventro-lateral functional specialization of the human retrosplenial complex in spatial updating and orienting. *Brain Structure and Function*, *222*(3), 1481–1493. https://doi.org/10.1007/s00429-016-

1288-8

Burte, H., Turner, B. O., Miller, M. B., & Hegarty, M. (2018). The neural basis of individual differences in directional sense. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00410

Buschke, H. (1984). Cued recall in amnesia. *Journal of Clinical and Experimental Neuropsychology*, *6*(4), 433–440.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213. https://doi.org/10.1016/0165-1781(89)90047-4

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: a neural model of spatial memory and imagery. *Psychol Rev*, *114*(2), 340–375. https://doi.org/10.1037/0033-295X.114.2.340

Carpenter, S. K., & Kelly, J. W. (2012). Tests enhance retention and transfer of spatial learning. *Psychonomic Bulletin and Review*, *19*(3), 443–448. https://doi.org/10.3758/S13423-012-0221-2/FIGURES/3

Cavina-Pratesi, C., Connolly, J. D., Monaco, S., Figley, T. D., Milner, A. D., Schenk, T., & Culham, J. C. (2018). Human neuroimaging reveals the subcomponents of grasping, reaching and pointing actions. *Cortex*, *98*, 128–148. https://doi.org/10.1016/j.cortex.2017.05.018

Chand, G. B., Wu, J., Hajjar, I., & Qiu, D. (2017). Interactions of the Salience Network and Its Subsystems with the Default-Mode and the Central-Executive Networks in Normal Aging and Mild Cognitive Impairment. *Brain Connectivity*, *7*(7), 401–412. https://doi.org/10.1089/brain.2017.0509

Chang, E. F., Raygor, K. P., & Berger, M. S. (2015). Contemporary model of language organization: an overview for neurosurgeons. *Journal of Neurosurgery*, *122*(2), 250–261. https://doi.org/10.3171/2014.10.JNS132647

Chen, H.-F., Huang, L.-L., Li, H.-Y., Qian, Y., Yang, D., Qing, Z., Luo, C.-M., Li, M.-C., Zhang, B., & Xu, Y. (2019). *Microstructural disruption of the right inferior fronto-occipital and inferior longitudinal fasciculus contributes to WMH-related cognitive impairment*. https://doi.org/10.1111/cns.13283

Chuang, Y. F., Eldreth, D., Erickson, K. I., Varma, V., Harris, G., Fried, L. P., Rebok, G. W., Tanner, E. K., & Carlson, M. C. (2014). Cardiovascular risks and brain function: A functional magnetic resonance imaging study of executive function in older adults. *Neurobiology of Aging*, *35*(6), 1396–1403.

https://doi.org/10.1016/j.neurobiolaging.2013.12.008

Chui, H. (1992). *Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers*.

Cicconetti, P., Priami, C., Sagrafoli, C., Tafaro, L., Ettorre, E., Donadio, C., Cacciafesta, M., & Marigliano, V. (2007). Cognitive function by brain event-related potentials (ERP) in elderly with borderline isolated systolic hypertension (BISH). *Arch Gerontol Geriatr*, *44 Suppl 1*, 105–111. https://doi.org/10.1016/j.archger.2007.01.016

Cieslik, E. C., Zilles, K., Grefkes, C., & Eickhoff, S. B. (2011). Dynamic interactions in the fronto-parietal network during a manual stimulus-response compatibility task. *Neuroimage*, *58*(3), 860–869. https://doi.org/10.1016/J.NEUROIMAGE.2011.05.089

Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Routledge. https://doi.org/10.4324/9780203771587

Colombo, D., Serino, S., Tuena, C., Pedroli, E., Dakanalis, A., Cipresso, P., & Riva, G. (2017). Egocentric and allocentric spatial reference frames in aging: A systematic review. *Neuroscience and Biobehavioral Reviews*, *80*(June), 605–621. https://doi.org/10.1016/j.neubiorev.2017.07.012

Comerchero, M., & Polich, J. (1999). P3a and P3b from typical auditory and visual stimuli. *Clinical Neurophysiology*.

Cook, D., & Kesner, R. P. (1988). Caudate nucleus and memory for egocentric localization. *Behavioral and Neural Biology*, *49*(3), 332–343. https://doi.org/10.1016/S0163-1047(88)90338-X

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, *58*(3), 306–324. https://doi.org/10.1016/J.NEURON.2008.04.017

Coutrot, A., Schmidt, S., Coutrot, L., Pittman, J., Hong, L., Wiener, J. M., ... & Spiers, H. J. (2019). Virtual navigation tested on a mobile app is predictive of real-world wayfinding navigation performance. *PloS one*, *14*(3), e0213272.

Coughlan, G., Coutrot, A., Khondoker, M., Minihane, A. M., Spiers, H., & Hornberger, M. (2019). Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. *Proc Natl Acad Sci U S A*, *116*(19), 9285–9292. https://doi.org/10.1073/pnas.1901600116

Coughlan, G., Flanagan, E., Jeffs, S., Bertoux, M., Spiers, H., Mioshi, E., & Hornberger, M. (2018a). Diagnostic relevance of spatial orientation for vascular dementia: A case study. *Dement Neuropsychol*, *12*(1), 85–91. https://doi.org/10.1590/1980-57642018dn12-

010013

Coughlan, G., Laczo, J., Hort, J., Minihane, A. M., & Hornberger, M. (2018b). Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol*, *14*(8), 496–506. https://doi.org/10.1038/s41582-018-0031-x

Coughlan, G., Puthusseryppady, V., Lowry, E., Gillings, R., Spiers, H., Minihane, A. M., & Hornberger, M. (2020). Test-retest reliability of spatial navigation in adults at-risk of Alzheimer's disease. *PLoS ONE*, *15*(9 September). https://doi.org/10.1371/JOURNAL.PONE.0239077

Coutrot, A., Silva, R., Manley, E., de Cothi, W., Sami, S., Bohbot, V. D., Wiener, J. M., Hölscher, C., Dalton, R. C., Hornberger, M., & Spiers, H. J. (2018). Global Determinants of Navigation Ability. *Current Biology*, *28*(17), 2861-2866.e4. https://doi.org/10.1016/j.cub.2018.06.009

Crawford, J. R., & Howell, D. C. (1998). Comparing an individual's test score against norms derived from small samples. *Clinical Neuropsychologist*, *12*(4), 482–486. https://doi.org/10.1076/clin.12.4.482.7241

Cushman, L. A., Stein, K., & Duffy, C. J. (2008). *Detecting navigational deficits in cognitive aging and Alzheimer disease using virtual reality*.

Cycowicz, Y. M., & Friedman, D. (1998). Effect of Sound Familiarity on the Event-Related Potentials Elicited by Novel Environmental Sounds. *Brain and Cognition*, *36*(1), 30–51. https://doi.org/10.1006/BRCG.1997.0955

de Leeuw, F. E., de Groot, J. C., Oudkerk, M., Ramos, L. M. P., Heijboer, R., Hofman, A., Jolles, J., van Gijn, J., & Breteler, M. M. B. (2001). Prevalence of cerebral white matter lesions in elderly people: A population based magnetic resonance imaging study: The Rotterdam Scan Study. *Journal of Neurology Neurosurgery and Psychiatry*, *70*(1), 2–3. https://doi.org/10.1136/jnnp.70.1.9

De Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience*, *14*(10), 1245–1246. https://doi.org/10.1038/nn.2905

Debener, S., Kranczioch, C., Herrmann, C. S., & Engel, A. K. (2002). Auditory novelty oddball allows reliable distinction of top–down and bottom–up processes of attention. *International Journal of Psychophysiology*, *46*(1), 77–84. https://doi.org/10.1016/S0167-8760(02)00072-7

Degen, C., Toro, P., Schonknecht, P., Sattler, C., & Schroder, J. (2016). Diabetes mellitus Type II and cognitive capacity in healthy aging, mild cognitive impairment and

Alzheimer's disease. *Psychiatry Res*, *240*, 42–46. https://doi.org/10.1016/j.psychres.2016.04.009

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. https://doi.org/10.1016/J.JNEUMETH.2003.10.009

Demeyere Riddoch, M. J., Slavkova, E. D., Bickerton, W. L., & Humphreys, G. W., N. (2015). The Oxford Cognitive Screen (OCS): Validation of a stroke-specific short cognitive screening tool. *Psychological Assessment*, *27(3)*, 883.

Derbie, A. Y., Chau, B. K. H., Wong, C. H. Y., Chen, L. D., Ting, K. hung, Lam, B. Y. H., Lee, T. M. C., Chan, C. C. H., & Smith, Y. (2021). Common and distinct neural trends of allocentric and egocentric spatial coding: An ALE meta-analysis. *European Journal of Neuroscience*, *53*(11), 3672–3687. https://doi.org/10.1111/EJN.15240

Desimone, R., Miller, E. K., Chelazzi, L., & Lueschow, A. (1995). *Multiple memory systems in the visual cortex. In M. S. Gazzaniga (Ed.), The cognitive neurosciences.* Cambridge, MA MIT Press. https://www.scirp.org/(S(351jmbntv-nsjt1aadkposzje))/reference/referencespapers.aspx?referenceid=557899

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, *2*(6), 563–567. https://doi.org/10.1038/9219

Dhindsa, K., Drobinin, V., King, J., Hall, G. B., Burgess, N., & Becker, S. (2014). Examining the role of the temporo-parietal network in memory, imagery, and viewpoint transformations. *Frontiers in Human Neuroscience*, *8*, 1–13. https://doi.org/10.3389/FNHUM.2014.00709/BIBTEX

Dichgans, M., & Leys, D. (2017). Vascular Cognitive Impairment. *Circulation Research*, *120*(3), 573–591. https://doi.org/10.1161/CIRCRESAHA.116.308426

Diwadkar, V. A., & McNamara, T. P. (2016). Viewpoint Dependence in Scene Recognition: *Https://Doi.Org/10.1111/j.1467-9280.1997.Tb00442.X*, *8*(4), 302–307. https://doi.org/10.1111/J.1467-9280.1997.TB00442.X

Donchin, E. (1986). Cognitive psychophysiology and human information processing. *Psychophysiology: Systems, Processes and Applications.*, 244–267.

Driscoll, I., Hamilton, D. A., Yeo, R. A., Brooks, W. M., & Sutherland, R. J. (2005). Virtual navigation in humans: the impact of age, sex, and hormones on place learning. *Hormones and Behavior*, *47*(3), 326–335. https://doi.org/10.1016/J.YHBEH.2004.11.013

Dubois, B., Feldman, H. H., Jacova, C., DeKosky, S. T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P. J., & Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *The Lancet. Neurology*, *6*(8), 734–746. https://doi.org/10.1016/S1474-4422(07)70178-3

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., Polich, J., Reinvang, I., & Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical Neurophysiology*, *120*(11), 1883–1908. https://doi.org/10.1016/j.clinph.2009.07.045

Egle, M., Hilal, S., Tuladhar, A. M., Pirpamer, L., Hofer, E., Duering, M., ... & Markus, H. S. (2022). Prediction of dementia using diffusion tensor MRI measures: the OPTIMAL collaboration. *Journal of Neurology, Neurosurgery & Psychiatry*, *93*(1), 14-23.

Ekstrom, A. D., Huffman, D. J., & Starrett, M. (2017). Interacting networks of brain regions underlie human spatial navigation: a review and novel synthesis of the literature. *Journal of Neurophysiology*, *118*(6), 3328–3344. https://doi.org/10.1152/JN.00531.2017

Ekstrom, A. D., & Isham, E. A. (2017). Human spatial navigation: representations across dimensions and scales. *Current Opinion in Behavioral Sciences*, *17*, 84–89. https://doi.org/10.1016/J.COBEHA.2017.06.005

Etienne, A. S., & Jeffery, K. J. (2004). Path integration in mammals. In *Hippocampus* (Vol. 14, Issue 2, pp. 180–192). https://doi.org/10.1002/hipo.10173

Exalto, L. G., Quesenberry, C. P., Barnes, D., Kivipelto, M., Biessels, G. J., & Whitmer, R. A. (2014). Midlife risk score for the prediction of dementia four decades later. *Alzheimers Dement*, *10*(5), 562–570. https://doi.org/10.1016/j.jalz.2013.05.1772

Fabiani, M., Kazmerski, V. A., Cycowicz, Y. M., & Friedman, D. (1996). Naming norms for brief environmental sounds: Effects of age and dementia. *Psychophysiology*, *33*(4), 462–475. https://doi.org/10.1111/J.1469-8986.1996.TB01072.X

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146

Fazekas, F., Chawluk, J. B., & Alavi, A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *American Journal of Neuroradiology*, *8*(3), 421–426.

Fjell, A. M., & Walhovd, K. B. (2001). P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes. *Brain Topography*, *14*(1), 25–40. https://doi.org/10.1023/A:1012563605837

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1996). Brain activity during memory retrieval The influence of imagery and semantic cueing. *Brain*, *119*, 1587–1596. https://academic.oup.com/brain/article/119/5/1587/369207

Fuentes-Claramonte, P., Santo-Angles, A., Argila-Plaza, I., Lechón, M., Guardiola-Ripoll, M., Almodóvar-Payá, C., ... & Salvador, R. (2021). Brain imaging of executive function with the computerised multiple elements test. *Brain Imaging and Behavior*, *15*(5), 2317-2329.

Galati, G., Lobel, E., Vallar, G., Berthoz, A., Pizzamiglio, L., & Bihan, D. Le. (2000). The neural basis of egocentric and allocentric coding of space in humans: A functional magnetic resonance study. *Experimental Brain Research*, *133*(2), 156–164. https://doi.org/10.1007/S002210000375

Galletti, C., Gamberini, M., Kutz, D. F., Fattori, P., Luppino, G., & Matelli, M. (2001). The cortical connections of area V6: An occipito-parietal network processing visual information. *European Journal of Neuroscience*, *13*(8), 1572–1588. https://doi.org/10.1046/J.0953-816X.2001.01538.X

Gazova, I., Laczó, J., Rubinova, E., Mokrisova, I., Hyncicova, E., Andel, R., Vyhnalek, M., Sheardova, K., Coulson, E. J., & Hort, J. (2013). Spatial navigation in young versus older adults. *Frontiers in Aging Neuroscience*, *5*(DEC), 94. https://doi.org/10.3389/FNAGI.2013.00094/BIBTEX

Geula, C., Sehgal, N., Wright, C. B., Woods, A. J., Nissim, N. R., O'shea, A. M., Bryant, V., Porges, E. C., & Cohen, R. (2017). *Frontal Structural Neural Correlates of Working Memory Performance in Older Adults*. https://doi.org/10.3389/fnagi.2016.00328

Gianaros, P. J., Greer, P. J., Ryan, C. M., & Jennings, J. R. (2006). Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage*, *31*(2), 754–765.

Gonzalez, H. M., Tarraf, W., Harrison, K., Windham, B. G., Tingle, J., Alonso, A., Griswold, M., Heiss, G., Knopman, D., & Mosley, T. H. (2018). Midlife cardiovascular health and 20-year cognitive decline: Atherosclerosis Risk in Communities Study results. *Alzheimers Dement*, *14*(5), 579–589. https://doi.org/10.1016/j.jalz.2017.11.002

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*(1), 20–25.

Goodman, R. A., Lochner, K. A., Thambisetty, M., Wingo, T. S., Posner, S. F., & Ling, S. M. (2017). Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement*, *13*(1), 28–37. https://doi.org/10.1016/j.jalz.2016.04.002

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., Launer, L. J., Laurent, S., Lopez, O. L., Nyenhuis, D., Petersen, R. C., Schneider, J. A., Tzourio, C., Arnett, D. K., Bennett, D. A., Chui, H. C., Higashida, R. T., Lindquist, R., Nilsson, P. M., … Anesthesia. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke*, *42*(9), 2672–2713. https://doi.org/10.1161/STR.0b013e3182299496

Gottesman, R. F., Schneider, A. L., Albert, M., Alonso, A., Bandeen-Roche, K., Coker, L., Coresh, J., Knopman, D., Power, M. C., Rawlings, A., Sharrett, A. R., Wruck, L. M., & Mosley, T. H. (2014). Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol*, *71*(10), 1218–1227. https://doi.org/10.1001/jamaneurol.2014.1646

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(13), 4637–4642. https://doi.org/10.1073/pnas.0308627101

Guarino, A., Favieri, F., Boncompagni, I., Agostini, F., Cantone, M., & Casagrande, M. (2019). Executive Functions in Alzheimer Disease: A Systematic Review. *Frontiers in Aging Neuroscience*, *10*. https://doi.org/10.3389/FNAGI.2018.00437

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews. Neuroscience*, *2*(10), 685–694. https://doi.org/10.1038/35094500

Hachinski, V., Iadecola, C., Petersen, R. C., Breteler, M. M., Nyenhuis, D. L., Black, S. E., Powers, W. J., DeCarli, C., Merino, J. G., Kalaria, R. N., Vinters, H. V., Holtzman, D. M., Rosenberg, G. A., Dichgans, M., Marler, J. R., & Leblanc, G. G. (2006). National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke*, *37*(9), 2220–2241. https://doi.org/10.1161/01.STR.0000237236.88823.47

Haight, T. J., Bryan, R. N., Erus, G., Davatzikos, C., Jacobs, D. R., D'Esposito, M., Lewis, C. E., & Launer, L. J. (2015). Vascular risk factors, cerebrovascular reactivity, and the

default-mode brain network. *Neuroimage*, *115*, 7–16. https://doi.org/10.1016/j.neuroimage.2015.04.039

Haijar, I., Sorond, F., & Lipsitz, L. A. (2015). Apolipoprotein E, carbon dioxide vasoreactivity, and cognition in older adults: effect of hypertension. *J Am Geriatr Soc*, *63*(2), 276–281.

Hajjar, I., Yang, F., Sorond, F., Jones, R. N., Milberg, W., Cupples, L. A., & Lipsitz, L. A. (2009). A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: Relationship to blood pressure and other cardiovascular risks. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *64*(9), 994–1001. https://doi.org/10.1093/gerona/glp075

Haley, A. P., Gunstad, J., Cohen, R. A., Jerskey, B. A., Mulligan, R. C., & Sweet, L. H. (2008). Neural correlates of visuospatial working memory in healthy young adults at risk for hypertension. *Brain Imaging and Behavior*, *2*(3), 192–199. https://doi.org/10.1007/s11682-008-9025-4

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Liégeois, C., Chauvel, P., & Musolino, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography and Clinical Neurophysiology*, *94*(3), 191–220. https://doi.org/10.1016/0013-4694(94)00259-N

Halgren, E., & Marinkovic, K. (1995). Neurophysiological networks integrating human emotions. In M.S. Gazzaniga (Ed.). In M. S. Gazzaniga (Ed.), *The Cognitive Neurosciences* (pp. 1137–1151). The MIT Press.

Hartikainen, K. M., & Knight, R. T. (2003). Lateral and Orbital Prefrontal Cortex Contributions to Attention. *Detection of Change*, 99–116. https://doi.org/10.1007/978-1-4615-0294-4_6

Hartley, T., Maguire, E. A., Spiers, H. J., & Burgess, N. (2003). The well-worn route and the path less traveled: Distinct neural bases of route following and wayfinding in humans. *Neuron*, *37*(5), 877–888. https://doi.org/10.1016/S0896-6273(03)00095-3

Hartshorne, J. K., & Germine, L. T. (2015). When Does Cognitive Functioning Peak? The Asynchronous Rise and Fall of Different Cognitive Abilities Across the Life Span. *Psychological Science*, *26*(4), 433–443. https://doi.org/10.1177/0956797614567339

Hazari, M. A. H., Ram Reddy, B., Uzma, N., & Santhosh Kumar, B. (2015). Cognitive impairment in type 2 diabetes mellitus. *International Journal of Diabetes Mellitus*, *3*(1), 19–24. https://doi.org/10.1016/j.ijdm.2011.01.001

Heckman, J.J. (2010). Selection Bias and Self-Selection. In: Durlauf, S.N., Blume, L.E. (eds)

Microeconometrics. The New Palgrave Economics Collection. Palgrave Macmillan, London. https://doi.org/10.1057/9780230280816_29

Hegarty, M., Richardson, A. E., Montello, D. R., Lovelace, K., & Subbiah, I. (2002). Development of a self-report measure of environmental spatial ability. *Intelligence*, *30*(5), 425–447. https://doi.org/10.1016/S0160-2896(02)00116-2

Heiss, W. D., Rosenberg, G. A., Thiel, A., Berlot, R., & de Reuck, J. (2016). Neuroimaging in vascular cognitive impairment: a state-of-the-art review. *BMC Med*, *14*(1), 174. https://doi.org/10.1186/s12916-016-0725-0

Hippisley-Cox, J., Coupland, C., & Brindle, P. (2017). Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*, *357*, j2099. https://doi.org/10.1136/bmj.j2099

Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., Minhas, R., Sheikh, A., & Brindle, P. (2008). Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ (Clinical Research Ed.)*, *336*(7659), 1475–1482. https://doi.org/10.1136/BMJ.39609.449676.25

Hirsiger, S., Koppelmans, V., Mérillat, S., Erdin, C., Narkhede, A., Brickman, A. M., & Jäncke, L. (2017). Executive functions in healthy older adults are differentially related to macro- and microstructural white matter characteristics of the cerebral lobes. *Frontiers in Aging Neuroscience*, *9*(NOV). https://doi.org/10.3389/FNAGI.2017.00373/FULL

Howe, A. S., Bani-Fatemi, A., & De Luca, V. (2014). The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. *Brain and Cognition*, *86*(1), 64–74. https://doi.org/10.1016/j.bandc.2014.01.015

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*, *36*(3–4), 242–250. https://doi.org/10.1159/000351671

Hsu, C. C., Wahlqvist, M. L., Lee, M. S., & Tsai, H. N. (2011). Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis*, *24*(3), 485–493. https://doi.org/10.3233/JAD-2011-101524

Hsu, J. L., Chen, Y. L., Leu, J. G., Jaw, F. S., Lee, C. H., Tsai, Y. F., Hsu, C. Y., Bai, C. H., & Leemans, A. (2012). Microstructural white matter abnormalities in type 2 diabetes mellitus: a diffusion tensor imaging study. *Neuroimage*, *59*(2), 1098–1105. https://doi.org/10.1016/j.neuroimage.2011.09.041

Huang, W.-J., Chen, W.-W., & Zhang, X. (2015). The neurophysiology of P 300-an integrated review. *European Review for Medical and Pharmacological Sciences*, *19*, 1480–1488.

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron*, *80*(4), 844–866. https://doi.org/10.1016/j.neuron.2013.10.008

Iadecola, C., & Gottesman, R. F. (2019). Neurovascular and Cognitive Dysfunction in Hypertension: Epidemiology, Pathobiology, and Treatment. *Circulation Research*, *124*(7), 1025–1044. https://doi.org/10.1161/CIRCRESAHA.118.313260

Iaria, G., Bogod, N., Fox, C. J., & Barton, J. J. S. (2009). Developmental topographical disorientation: case one. *Neuropsychologia*, *47*(1), 30–40. https://doi.org/10.1016/J.neuropsychologia.2008.08.021

International Physical Activity Questionnaire. (2014). Short version (self-administered). *IPAQ Group,*. https://doi.org/10.2165/11531930-000000000

Irish, M., Halena, S., Kamminga, J., Tu, S., Hornberger, M., & Hodges, J. R. (2015). Scene construction impairments in Alzheimer's disease - A unique role for the posterior cingulate cortex. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *73*, 10–23. https://doi.org/10.1016/J.CORTEX.2015.08.004

Jaeger, J. (2018). Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. *J Clin Psychopharmacol*, *38*(5), 513–519. https://doi.org/10.1097/JCP.0000000000000941

Jheng, S. S., & Pai, M. C. (2009). Cognitive map in patients with mild Alzheimer's disease: A computer-generated arena study. *Behavioural Brain Research*. https://doi.org/10.1016/j.bbr.2008.12.029

Jiang, R., Calhoun, V. D., Noble, S., Sui, J., Liang, Q., Qi, S., & Scheinost, D. (2022). A functional connectome signature of blood pressure in> 30,000 participants from the UK Biobank. *Cardiovascular Research*.

Jochmann, N., Stangl, K., Garbe, E., Baumann, G., & Stangl, V. (2005). Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *European heart journal*, *26*(16), 1585-1595.

Johnson Jr., R. (1995). Event-related potential insights into the neurobiology of memory systems. In *Handbook of neuropsychology* (Vol. 10, Issue June, pp. 135–163). Elsevier B.V.

Johnson, R. (1993). On the neural generators of the P300 component of the event-related potential. *Psychophysiology*, *30*(1), 90–97. https://doi.org/10.1111/J.1469-

8986.1993.TB03208.X

Juckel, G., Karch, S., Kawohl, W., Kirsch, V., Jäger, L., Leicht, G., Lutz, J., Stammel, A., Pogarell, O., Ertl, M., Reiser, M., Hegerl, U., Möller, H. J., & Mulert, C. (2012). Age effects on the P300 potential and the corresponding fMRI BOLD-signal. *NeuroImage*, *60*(4), 2027–2034. https://doi.org/10.1016/J.NEUROIMAGE.2012.02.019

Justen, C., & Herbert, C. (2018). The spatio-temporal dynamics of deviance and target detection in the passive and active auditory oddball paradigm: a sLORETA study. *BMC Neurosci*, *19*(1), 25. https://doi.org/10.1186/s12868-018-0422-3

Kalaria, R. N. (2012). Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. *Stroke*, *43*(9), 2526–2534. https://doi.org/10.1161/STROKEAHA.112.655803

Kalaria, R. N. (2016). Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. *Acta Neuropathol*, *131*(5), 659–685. https://doi.org/10.1007/s00401-016-1571-z

Kivipelto, M., Mangialasche, F., & Ngandu, T. (2018). Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. In *Nature Reviews Neurology* (Vol. 14, Issue 11, pp. 653–666). Nature Publishing Group. https://doi.org/10.1038/s41582-018-0070-3

Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H., & Tuomilehto, J. (2006). Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurology*, *5*(9), 735–741. https://doi.org/10.1016/S1474-4422(06)70537-3

Knierim, J. J., Neunuebel, J. P., & Deshmukh, S. S. (2014). Functional correlates of the lateral and medial entorhinal cortex: Objects, path integration and local - Global reference frames. In *Philosophical Transactions of the Royal Society B: Biological Sciences* (Vol. 369, Issue 1635). Royal Society. https://doi.org/10.1098/rstb.2013.0369

Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *59*(1), 9–20. https://doi.org/10.1016/0168-5597(84)90016-9

Knight, R. T. (1990). *Neural mechanisms of event-related potentials from human lesion studies. In: Rohbraugh J, Parasuraman R, Johnson R, editors. Event-related brain potentials: basic issues and applications.* Oxford University Press.

Knight, R. T. (1997). Distributed cortical network for visual attention. *Journal of Cognitive Neuroscience*, *9*(1), 75–91. https://doi.org/10.1162/JOCN.1997.9.1.75

Knopman, D., Boland, L. L., Mosley, T., Howard, G., Liao, D., Szklo, M., McGovern, P., & Folsom, A. R. (2001). Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology*, *56*(1), 42–48. https://doi.org/10.1212/WNL.56.1.42

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nat Rev Neurosci*, *12*(4), 217–230. https://doi.org/10.1038/nrn3008

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: An expanded neural framework for the processing of object quality. *Trends in Cognitive Sciences*, *17*(1), 26. https://doi.org/10.1016/J.TICS.2012.10.011

Kunz, L., Schröder, T. N., Lee, H., Montag, C., Lachmann, B., Sariyska, R., Reuter, M., Stirnberg, R., Stöcker, T., Messing-Floeter, P. C., Fell, J., Doeller, C. F., & Axmacher, N. (2015). Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease. *Science*, *350*(6259), 430–433. https://doi.org/10.1126/science.aac8128

Kutas, M., Mccarthy, G., & Donchin, E. (1977). Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time. *Science (New York, N.Y.)*, *197*(4305), 792–795. https://doi.org/10.1126/SCIENCE.887923

Ladyka-Wojcik, N., & Barense, M. D. (2021). Reframing spatial frames of reference: What can aging tell us about egocentric and allocentric navigation? *Wiley Interdisciplinary Reviews: Cognitive Science*, *12*(3), e1549. https://doi.org/10.1002/WCS.1549

Lai, C. L., Lin, R. T., Liou, L. M., & Liu, C. K. (2010). The role of event-related potentials in cognitive decline in Alzheimer's disease. *Clin Neurophysiol*, *121*(2), 194–199. https://doi.org/10.1016/j.clinph.2009.11.001

Lawrence, A. J., Chung, A. W., Morris, R. G., Markus, H. S., & Barrick, T. R. (2014). Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology*, *83*(4), 304-311.

Lazek, N. (1983). *Neuropsychological Assessment.* (2nd.). Oxford University Press.

Lee, M. S., Lee, S. H., Moon, E. O., Moon, Y. J., Kim, S., Kim, S. H., & Jung, I. K. (2013). Neuropsychological correlates of the P300 in patients with Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry*, *40*, 62–69. https://doi.org/10.1016/j.pnpbp.2012.08.009

Leemans, A., & Jones, D. K. (2009). The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*, *61*(6), 1336–1349.

https://doi.org/10.1002/MRM.21890

Lester, A. W., Moffat, S. D., Wiener, J. M., Barnes, C. A., & Wolbers, T. (2017). The Aging Navigational System. In *Neuron* (Vol. 95, Issue 5). https://doi.org/10.1016/j.neuron.2017.06.037

Li, A. W. Y., & King, J. (2019). Spatial memory and navigation in ageing: A systematic review of MRI and fMRI studies in healthy participants. *Neuroscience & Biobehavioral Reviews*, *103*, 33–49. https://doi.org/10.1016/J.NEUBIOREV.2019.05.005

Li, X., Liang, Y., Chen, Y., Zhang, J., Wei, D., Chen, K., Shu, N., Reiman, E. M., & Zhang, Z. (2015). Disrupted Frontoparietal Network Mediates White Matter Structure Dysfunction Associated with Cognitive Decline in Hypertension Patients. *J Neurosci*, *35*(27), 10015–10024. https://doi.org/10.1523/JNEUROSCI.5113-14.2015

Linden, D. E. J. (2005). The P300: Where in the brain is it produced and what does it tell us? *Neuroscientist*, *11*(6), 563–576. https://doi.org/10.1177/1073858405280524

Littlejohns, T. J., Sudlow, C., Allen, N. E., & Collins, R. (2019). UK Biobank: opportunities for cardiovascular research. *European heart journal*, *40*(14), 1158-1166.

Liu, Y., Xia, Y., Wang, | Xiaoxiao, Wang, Y., Zhang, D., Benedictor, |, Nguchu, A., Jiajie He, |, Wang, Y., Yang, | Lumeng, Wang, Y., Ying, Y., Liang, | Xiaoniu, Zhao, Q., Wu, J., Liang, Z., Ding, D., Dong, Q., Bensheng Qiu, |, … Wang, X. (2021). *White matter hyperintensities induce distal deficits in the connected fibers The effect of WMH on the microstructural integrity of WM*. https://doi.org/10.1002/hbm.25338

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

Lockhart, S. N., Mayda, A. B. V., Roach, A. E., Fletcher, E., Carmichael, O., Maillard, P., Schwarz, C. G., Yonelinas, A. P., Ranganath, C., & DeCarli, C. (2012). Episodic memory function is associated with multiple measures of white matter integrity in cognitive aging. *Frontiers in Human Neuroscience*, *6*(MARCH 2012), 1–12. https://doi.org/10.3389/fnhum.2012.00056

Lopez-Calderon, J., & Luck, S. J. (2014). ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Front Hum Neurosci*, *8*, 213.

Löwe, B., Unützer, J., Callahan, C. M., Perkins, A. J., & Kroenke, K. (2004). Monitoring

depression treatment outcomes with the patient health questionnaire-9. *Medical Care*, *42*(12), 1194–1201. https://doi.org/10.1097/00005650-200412000-00006

Lowry, E., Puthusseryppady, V., Coughlan, G., Jeffs, S., & Hornberger, M. (2020). Path Integration Changes as a Cognitive Marker for Vascular Cognitive Impairment?—A Pilot Study. *Frontiers in Human Neuroscience*, *14*(April), 1–9. https://doi.org/10.3389/fnhum.2020.00131

Lowry, E., Puthusseryppady, V., Johnen, A.-K., Renoult, L., & Hornberger, M. (2021). Cognitive and neuroimaging markers for preclinical vascular cognitive impairment. *Cerebral Circulation - Cognition and Behavior*, *2*(October), 100029. https://doi.org/10.1016/j.cccb.2021.100029

Luengo-Fernandez, R., Leal, J., & Gray, A. (2015). UK research spend in 2008 and 2012: Comparing stroke, cancer, coronary heart disease and dementia. *BMJ Open*, *5*(4), 2008–2014. https://doi.org/10.1136/bmjopen-2014-006648

Maguire, E. A., Frith, C. D., Burgess, N., Donnett, J. G., & O'Keefe, J. (1998). Knowing where things are: Parahippocampal involvement in encoding object locations in virtual large-scale space. *Journal of Cognitive Neuroscience*, *10*(1), 61–76. https://doi.org/10.1162/089892998563789

Mallot, H. A., & Basten, K. (2009). Embodied spatial cognition: Biological and artificial systems. *Image and Vision Computing*, *27*(11), 1658–1670. https://doi.org/10.1016/J.IMAVIS.2008.09.001

Mantua, J., & Simonelli, G. (2019). Sleep duration and cognition: is there an ideal amount? *Sleep*, *42*(3), 1–3. https://doi.org/10.1093/SLEEP/ZSZ010

Marin, A., Schiloski, K., Vives-Rodriguez, A., DeCaro, R., Budson, A., & Turk, K. (2022). Event-related potentials as biomarkers of cognitive performance in Alzheimer's disease patients with cardiovascular risk factors (P1-1.Virtual). *Neurology*, *98*(18 Supplement).

Marseglia, A., Fratiglioni, L., Kalpouzos, G., Wang, R., Backman, L., & Xu, W. (2019). Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study. *Alzheimers Dement*, *15*(1), 25–33. https://doi.org/10.1016/j.jalz.2018.06.3060

Masi, S., Georgiopoulos, G., Khan, T., Johnson, W., Wong, A., Charakida, M., Whincup, P., Hughes, A. D., Richards, M., Hardy, R., & Deanfield, J. (2018). Patterns of adiposity, vascular phenotypes and cognitive function in the 1946 British Birth Cohort. *BMC Medicine*, *16*(1). https://doi.org/10.1186/s12916-018-1059-x

McCrimmon, R. J., Ryan, C. M., & Frier, B. M. (2012). Diabetes and cognitive dysfunction.

The Lancet, *379*(9833), 2291–2299. https://doi.org/10.1016/S0140-6736(12)60360-2

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M. B. (2006). Path integration and the neural basis of the "cognitive map." *Nat Rev Neurosci*, *7*(8), 663–678. https://doi.org/10.1038/nrn1932

Meek, B. P., Shelton, P., & Marotta, J. J. (2013). Posterior cortical atrophy: visuomotor deficits in reaching and grasping. *Front Hum Neurosci*, *7*, 294. https://doi.org/10.3389/fnhum.2013.00294

Mitolo, M., Gardini, S., Caffarra, P., Ronconi, L., Venneri, A., & Pazzaglia, F. (2015). Relationship between spatial ability, visuospatial working memory and self-assessed spatial orientation ability: a study in older adults. *Cognitive Processing*, *16*(2), 165–176. https://doi.org/10.1007/S10339-015-0647-3/FIGURES/3

Moran, C., Phan, T. G., Chen, J., Blizzard, L., Beare, R., Venn, A., Münch, G., Wood, A. G., Forbes, J., Greenaway, T. M., Pearson, S., & Srikanth, V. (2013). Brain atrophy in type 2 diabetes: Regional distribution and influence on cognition. *Diabetes Care*, *36*(12), 4036–4042. https://doi.org/10.2337/dc13-0143

Morganti, F., Stefanini, S., & Riva, G. (2013). From allo- to egocentric spatial ability in early Alzheimer's disease: A study with virtual reality spatial tasks. *Https://Doi-Org.Uea.Idm.Oclc.Org/10.1080/17588928.2013.854762*, *4*(3–4), 171–180. https://doi.org/10.1080/17588928.2013.854762

Moussavi, Z., Kimura, K., & Lithgow, B. (2022). Egocentric spatial orientation differences between Alzheimer's disease at early stages and mild cognitive impairment: a diagnostic aid. *Medical and Biological Engineering and Computing*, *60*(2), 501–509. https://doi.org/10.1007/S11517-021-02478-9/TABLES/3

Muntner, P., Shimbo, D., Carey, R. M., Charleston, J. B., Gaillard, T., Misra, S., Myers, M. G., Ogedegbe, G., Schwartz, J. E., Townsend, R. R., Urbina, E. M., Viera, A. J., White, W. B., & Wright, J. T. (2019). Measurement of Blood Pressure in Humans: A Scientific Statement From the American Heart Association. *Hypertension*, *73*(5), E35–E66. https://doi.org/10.1161/HYP.0000000000000087

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behavioral and Brain Sciences*, *13*(2), 201–233. https://doi.org/10.1017/S0140525X00078407

Nakajima, R., Kinoshita, M., Shinohara, H., & Nakada, M. (2019). The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging and Behavior 2019 14:6*, *14*(6), 2817–2830.

https://doi.org/10.1007/S11682-019-00187-4

Nannoni, S., Ohlmeier, L., Brown, R. B., Morris, R. G., MacKinnon, A. D., Markus, H. S., & DNA Lacunar 2 investigators. (2022). Cognitive impact of cerebral microbleeds in patients with symptomatic small vessel disease. *International Journal of Stroke*, *17*(4), 415-424.

National Institute for Health and Care Excellence. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. London, UK: NICE; Jul 2014. Retrieved April 13, 2022, from https://www.nice.org.uk/guidance/cg181/chapter/1-Recommendations#identifying-and-assessing-cardiovascular-disease-cvd-risk-2

Neggers, S. F., Van der Lubbe, R. H., Ramsey, N. F., & Postma, A. (2006). Interactions between ego- and allocentric neuronal representations of space. *Neuroimage*, *31*(1), 320–331. https://doi.org/10.1016/j.neuroimage.2005.12.028

Neufang, S., Akhrif, A., Riedl, V., Forstl, H., Kurz, A., Zimmer, C., Sorg, C., & Wohlschlager, A. M. (2011). Disconnection of frontal and parietal areas contributes to impaired attention in very early Alzheimer's disease. *J Alzheimers Dis*, *25*(2), 309–321. https://doi.org/10.3233/JAD-2011-102154

Newsome, R. N., Pun, C., Smith, V. M., Ferber, S., & Barense, M. D. (2013). Neural correlates of cognitive decline in older adults at-risk for developing MCI: Evidence from the CDA and P300. *Cognitive Neuroscience*, *4*(3–4), 152–162. https://doi.org/10.1080/17588928.2013.853658

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., … Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet*, *385*(9984), 2255–2263. https://doi.org/10.1016/S0140-6736(15)60461-5

Nordahl, C. W., Ranganath, C., Yonelinas, A. P., DeCarli, C., Reed, B., & Jagust, W. J. (2005). Different mechanisms of episodic memory failure in mild cognitive impairment. *Neuropsychologia*, *43*(11), 1688–1697. https://doi.org/10.1016/j.neuropsychologia.2005.01.003. Different

WHO. (2021). *Cardiovascular diseases (CVDs)*. World Health Organisation, News Room. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

Paitel, E. R., Samii, M. R., & Nielson, K. A. (2021). A systematic review of cognitive event-related potentials in mild cognitive impairment and Alzheimer's disease. *Behavioural Brain Research*, *396*, 112904. https://doi.org/10.1016/J.BBR.2020.112904

Papma, J. M., den Heijer, T., de Koning, I., Mattace-Raso, F. U., van der Lugt, A., van der Lijn, F., van Swieten, J. C., Koudstaal, P. J., Smits, M., & Prins, N. D. (2012). The influence of cerebral small vessel disease on default mode network deactivation in mild cognitive impairment. *Neuroimage Clin*, *2*, 33–42. https://doi.org/10.1016/j.nicl.2012.11.005

Papma, J. M., Den Heijer, T., De Koning, I., Mattace-Raso, F. U., Van Der Lugt, A., Van Der Lijn, F., Van Swieten, J. C., Koudstaal, P. J., Smits, M., & Prins, N. D. (2013). The influence of cerebral small vessel disease on default mode network deactivation in mild cognitive impairment. *NeuroImage: Clinical*, *2*(1), 33–42. https://doi.org/10.1016/j.nicl.2012.11.005

Parizkova, M., Lerch, O., Moffat, S. D., Andel, R., Mazancova, A. F., Nedelska, Z., Vyhnalek, M., Hort, J., & Laczó, J. (2018). The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiology of Aging*, *64*, 107–115. https://doi.org/10.1016/j.neurobiolaging.2017.12.019

Pedroso, R. V., Fraga, F. J., Corazza, D. I., Andreatto, C. A. A., Coelho, F. G. de M., Costa, J. L. R., & Santos-Galduróz, R. F. (2012). P300 latency and amplitude in Alzheimer's disease: A systematic review. *Brazilian Journal of Otorhinolaryngology*, *78*(4), 126–132. https://doi.org/10.1590/S1808-86942012000400023

Pelosi, L., Holly, M., Slade, T., Hayward, M., Barrett, G., & Blumhardt, L. D. (1992). Event-related potential (ERP) correlates of performance of intelligence tests. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *84*(6), 515–520. https://doi.org/10.1016/0168-5597(92)90040-I

Pengas, G., Hodges, J. R., Watson, P., & Nestor, P. J. (2010). Focal posterior cingulate atrophy in incipient Alzheimer's disease. *Neurobiol Aging*, *31*(1), 25–33. https://doi.org/10.1016/j.neurobiolaging.2008.03.014

Plancher, G., Tirard, A., Gyselinck, V., Nicolas, S., & Piolino, P. (2012). Using virtual reality to characterize episodic memory profiles in amnestic mild cognitive impairment and Alzheimer's disease: influence of active and passive encoding. *Neuropsychologia*, *50*(5), 592–602. https://doi.org/10.1016/j.neuropsychologia.2011.12.013

Plassman, B. L., Langa, K. M., Fisher, G. G., Heeringa, S. G., Weir, D. R., Ofstedal, M. B., Burke, J. R., Hurd, M. D., Potter, G. G., Rodgers, W. L., Steffens, D. C., Willis, R. J., &

Wallace, R. B. (2007). Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*, *29*(1–2), 125–132. https://doi.org/10.1159/000109998

Polich, J. (2003). *Detection of Change: Event-related potential and ERP findings*. Kluwer Academic Publishers. https://doi.org/10.1007/978-1-4615-0294-4

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol*, *118*(10), 2128–2148. https://doi.org/10.1016/j.clinph.2007.04.019

Polich, J. (2012). Neuropsychology of P300. In *The Oxford Handbook of Event-Related Potential Components*. https://doi.org/10.1093/oxfordhb/9780195374148.013.0089

Polich, J., & Comerchero, M. D. (2003). P3a from visual stimuli: Typicality, task, and topography. *Brain Topography*, *15*(3), 141–152. https://doi.org/10.1023/A:1022637732495

Polich, J., & Criado, J. R. (2006). Neuropsychology and neuropharmacology of P3a and P3b. *International Journal of Psychophysiology*, *60*(2), 172–185. https://doi.org/10.1016/J.IJPSYCHO.2005.12.012

Polich, J., & Margala, C. (1997). P300 and probability: comparison of oddball and single-stimulus paradigms. *International Journal of Psychophysiology*, *25*(2), 169–176. https://doi.org/10.1016/S0167-8760(96)00742-8

Porges, S. W. (1993). *Body Perception Questionnaire. Laboryory of Developmental Assessment: University of Maryland.*

Pot, A. M., Willemse, B. M., & Horjus, S. (2012). A pilot study on the use of tracking technology: feasibility, acceptability, and benefits for people in early stages of dementia and their informal caregivers. *Aging & mental health*, *16*(1), 127-134.

Power, M. C., Rawlings, A., Sharrett, A. R., Bandeen-Roche, K., Coresh, J., Ballantyne, C. M., Pokharel, Y., Michos, E. D., Penman, A., Alonso, A., Knopman, D., Mosley, T. H., & Gottesman, R. F. (2018). Association of midlife lipids with 20-year cognitive change: A cohort study. *Alzheimers Dement*, *14*(2), 167–177. https://doi.org/10.1016/j.jalz.2017.07.757

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & dementia*, *9*(1), 63-75.

Prins, N. D., & Scheltens, P. (2015). White matter hyperintensities, cognitive impairment and dementia: An update. *Nature Reviews Neurology*, *11*(3), 157–165. https://doi.org/10.1038/nrneurol.2015.10

Ptak, R. (2012). The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *18*(5), 502–515. https://doi.org/10.1177/1073858411409051

Puthusseryppady, V., Morrissey, S., Aung, M. H., Coughlan, G., Patel, M., & Hornberger, M. (2022). Using GPS Tracking to Investigate Outdoor Navigation Patterns in Patients With Alzheimer Disease: Cross-sectional Study. *JMIR aging*, *5*(2), e28222.

Raichle, M. E. (2015). The Brain's Default Mode Network. *Annual Review of Neuroscience*, *38*(1), 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Rattanabannakit, C., Risacher, S. L., Gao, S., Lane, K. A., Brown, S. A., McDonald, B. C., Unverzagt, F. W., Apostolova, L. G., Saykin, A. J., & Farlow, M. R. (2016). The Cognitive Change Index as a Measure of Self and Informant Perception of Cognitive Decline: Relation to Neuropsychological Tests. *J Alzheimers Dis*, *51*(4), 1145–1155. https://doi.org/10.3233/JAD-150729

Rawlings, A., Sharrett, A. R., Schneider, A. L. C., Coresh, J., Albert, M., Couper, D., Gottesman, R. F., Wagenknecht, L. E., Mph, D., Windham, G., & Selvin, E. (2014). Diabetes in midlife and cognitive change over 20 years: the Atherosclerosis Risk in Communities Neurocognitive Study. *Annals of Internal Medicine*, *161*(11), 785–793. https://doi.org/10.7326/M14-0737.Diabetes

Reijmer, Y. D., Brundel, M., De Bresser, J., Kappelle, L. J., Leemans, A., & Biessels, G. J. (2013). Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: A diffusion tensor imaging study. *Diabetes Care*, *36*(1), 137–144. https://doi.org/10.2337/dc12-0493

Reitan, R. M. (1958). Validity Of The Trail Making Test As An Indicator of organic brain damage. *Perceptual and Motor Skills*, *8*, 271–276.

Rieser, J. J. (1989). Access to knowledge of spatial structure at novel points of observation. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *15*(6), 1157–1165. https://doi.org/10.1037/0278-7393.15.6.1157

Ritchie Carrière, I., Howett, D., Su, l., Hornberger, M., K. (2018). Allocentric and egocentric spatial processing in middle-aged adults at high risk of late-onset Alzheimer's disease : the PREVENT Dementia study. *Journal of Alzheimer's Disease*, *65*(3), 885.

Ritchie, C. W., Molinuevo, J. L., Truyen, L., Satlin, A., Van der Geyten, S., & Lovestone, S. (2016). Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *The*

Lancet. Psychiatry, *3*(2), 179–186. https://doi.org/10.1016/S2215-0366(15)00454-X

Ritchie, K., Carrière, I., Ritchie, C. W., Berr, C., Artero, S., & Ancelin, M. L. (2010). Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ (Clinical Research Ed.)*, *341*(7768), 336. https://doi.org/10.1136/BMJ.C3885

Roman, G. (1993). *Vascular dementia: Diagnostic criteria for research studies Report of the NINDS-AIREN International Workshop*.

Roman, G. C., Erkinjuntti, T., Wallin, A., Pantoni, L., & Chui, H. C. (2002). Subcortical Ischemic Vascular Dementia. *Lancet Neurology*, *1*(7), 426–436. https://doi.org/10.1016/s1474-4422(02)00190-4.

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., Amaducci, L., Orgogozo, J. M., Brun, A., Hofman, A., Moody, D. M., O'Brien, M. D., Yamaguchi, T., Grafman, J., Drayer, B. P., Bennett, D. A., Fisher, M., Ogata, J., Kokmen, E., … Scheinberg, P. (1993). Vascular dementia: Diagnostic criteria for research studies: Report of the ninds-airen international workshop*. *Neurology*, *43*(2), 250–260. https://doi.org/10.1212/wnl.43.2.250

Rosano, C., Perera, S., Inzitari, M., Newman, A. B., Longstreth, W. T., & Studenski, S. (2016). Digit symbol substitution test and future clinical and subclinical disorders of cognition, mobility and mood in older adults. *Age and Ageing*, *45*(5), 687–694. https://doi.org/10.1093/ageing/afw116

Rosenberg, A., Mangialasche, F., Ngandu, T., Solomon, A., & Kivipelto, M. (2020). Multidomain Interventions to Prevent Cognitive Impairment, Alzheimer's Disease, and Dementia: From FINGER to World-Wide FINGERS. *Journal of Prevention of Alzheimer's Disease*, *7*(1), 29–36. https://doi.org/10.14283/JPAD.2019.41/FIGURES/1

Rossini, P. M., Rossi, S., Babiloni, C., & Polich, J. (2007). Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology*, *83*(6), 375–400. https://doi.org/10.1016/J.PNEUROBIO.2007.07.010

Roth, G. A., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., ... & Borschmann, R. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1736-1788.

Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S. E., Blacker, D., Blazer, D. G., Chen, C., Chui, H., Ganguli, M., Jellinger, K., Jeste, D. V, Pasquier, F., Paulsen, J., Prins, N., Rockwood, K., Roman, G., Scheltens, P., … Cognitive, D. (2014).

Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord*, *28*(3), 206–218. https://doi.org/10.1097/WAD.0000000000000034

Sachdev, P. S., Kalaria, R. N., O'Brien, J., Skoog, I., Alladi, S., Black, S. E., Blacker, D., Blazer, D., & Chen, C. L. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOGstatement. *Alzheimer Dis Assoc Disord*, *28*(3), 206–218.

Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., Michel, B., Puel, M., Volteau, M., Touchon, J., Verny, M., & Dubois, B. (2007). Amnestic syndrome of the medial temporal type identifies prodromal AD. *Neurology*, *69*(19), 1859–1867. https://doi.org/10.1212/01.WNL.0000279336.36610.F7

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function*, *217*(2), 503–515. https://doi.org/10.1007/s00429-011-0344-7

Save, E., Paz-Villagran, V., Alexinsky, T., & Poucet, B. (2005). Functional interaction between the associative parietal cortex and hippocampal place cell firing in the rat. *European Journal of Neuroscience*, *21*(2), 522–530. https://doi.org/10.1111/J.1460-9568.2005.03882.X

Schinazi, V. R., Nardi, D., Newcombe, N. S., Shipley, T. F., & Epstein, R. A. (2013). Hippocampal size predicts rapid learning of a cognitive map in humans. *Hippocampus*, *23*(6), 515–528. https://doi.org/10.1002/HIPO.22111

Seblova, D., Berggren, R., & Lövdén, M. (2020). Education and age-related decline in cognitive performance: Systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *58*, 101005.

Seitz, R. J., Franz, M., & Azari, N. P. (2009). Value judgments and self-control of action: The role of the medial frontal cortex. *Brain Research Reviews*, *60*(2), 368–378. https://doi.org/10.1016/J.BRAINRESREV.2009.02.003

Semmes, J., Weinstein, S., Ghent, G., Meyer, J. S., & Teuber, H. L. (1963). Correlates Of Impaired Orientation In Personal And Extrapersonal Space. *Brain*, *86*(4), 747–772. https://doi.org/10.1093/BRAIN/86.4.747

Serino, S., Cipresso, P., Morganti, F., & Riva, G. (2014). The role of egocentric and allocentric abilities in Alzheimer's disease: A systematic review. In *Ageing Research Reviews* (Vol. 16, Issue 1, pp. 32–44). Elsevier Ireland Ltd. https://doi.org/10.1016/j.arr.2014.04.004

Serino, S., Morganti, F., Di Stefano, F., & Riva, G. (2015). Detecting early egocentric and allocentric impairments deficits in Alzheimer's disease: An experimental study with

virtual reality. *Frontiers in Aging Neuroscience*, *7*(MAY). https://doi.org/10.3389/fnagi.2015.00088

Serino, S., & Riva, G. (2013). Getting lost in Alzheimer's disease: a break in the mental frame syncing. *Medical Hypotheses*, *80*(4), 416–421. https://doi.org/10.1016/J.MEHY.2012.12.031

Serrao, G., Xu, P., Aquino, D., Derbie, A. Y., Chau, B. K. H., & Chan, C. C. H. (2021). Functional and Structural Architectures of Allocentric and Egocentric Spatial Coding in Aging: A Combined DTI and fMRI Study. *Frontiers in Neurology*, *12*, 802975–802975. https://doi.org/10.3389/FNEUR.2021.802975

Sestieri, C., Shulman, G. L., & Corbetta, M. (2017). The contribution of the human posterior parietal cortex to episodic memory. *Nat Rev Neurosci*, *18*(3), 183–192. https://doi.org/10.1038/nrn.2017.6

Shin, M. S., Park, S. Y., Park, S. R., Seol, S. H., & Kwon, J. S. (2006). Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. *Nature Protocols*, *1*(2), 892–899. https://doi.org/10.1038/NPROT.2006.115

Skrobot, O. . A., O'Brien, J., Black, S., Chen, C., DeCarli, C., Erkinjuntti, T., Ford, G. A., Kalaria, R. N., Pantoni, L., Pasquier, F., Roman, G. C., Wallin, A., Sachdev, P., Skoog, I., Group, V., Ben-Shlomo, Y., Passmore, A. P., Love, S., & Kehoe, P. G. (2017). The Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement*, *13*(6), 624–633. https://doi.org/10.1016/j.jalz.2016.10.007

Skrobot, O. A., Attems, J., Esiri, M., Hortobagyi, T., Ironside, J. W., Kalaria, R. N., King, A., Lammie, G. A., Mann, D., Neal, J., Ben-Shlomo, Y., Kehoe, P. G., & Love, S. (2016). Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. *Brain*, *139*(11), 2957–2969. https://doi.org/10.1093/brain/aww214

Skrobot, O. A., Attems, J., Esiri, M., Hortobágyi, T., Ironside, J. W., Kalaria, R. N., King, A., Lammie, G. A., Mann, D., Neal, J., Ben-Shlomo, Y., Kehoe, P. G., & Love, S. (2016). Vascular cognitive impairment neuropathology guidelines (VCING): the contribution of cerebrovascular pathology to cognitive impairment. *Brain*, *139*(11), 2957–2969. https://doi.org/10.1093/brain/aww214

Skrobot, O. A., Black, S. E., Chen, C., DeCarli, C., Erkinjuntti, T., Ford, G. A., Kalaria, R. N., O'Brien, J., Pantoni, L., Pasquier, F., Roman, G. C., Wallin, A., Sachdev, P., Skoog, I., Taragano, F. E., Kril, J., Cavalieri, M., Jellinger, K. A., Kovacs, G. G., … Kehoe, P. G. (2018). Progress toward standardized diagnosis of vascular cognitive impairment:

Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimer's and Dementia*, *14*(3), 280–292. https://doi.org/10.1016/j.jalz.2017.09.007

Smith, E. E., Salat, D. H., Jeng, J., McCreary, C. R., Fischl, B., Schmahmann, J. D., Dickerson, B. C., Viswanathan, A., Albert, M. S., Blacker, D., & Greenberg, S. M. (2011). Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology*, *76*(17), 1492–1499. https://doi.org/10.1212/WNL.0b013e318217e7c8

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(SUPPL. 1), 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Solomon, A., Kivipelto, M., Wolozin, B., Zhou, J., & Whitmer, R. A. (2009). Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. *Dement Geriatr Cogn Disord*, *28*(1), 75–80. https://doi.org/10.1159/000231980

Solomon, A., Mangialasche, F., Richard, E., Andrieu, S., Bennett, D. A., Breteler, M., Fratiglioni, L., Hooshmand, B., Khachaturian, A. S., Schneider, L. S., Skoog, I., & Kivipelto, M. (2014). Advances in the prevention of Alzheimer's disease and dementia. *Journal of Internal Medicine*, *275*(3), 229–250. https://doi.org/10.1111/JOIM.12178

Soltani, M., & Knight, R. T. (2000). Neural Origins of the P300. *Critical Reviews™ in Neurobiology*, *14*(3–4), 199–224. https://doi.org/10.1615/CRITREVNEUROBIOL.V14.I3-4.20

Song, R., Xu, H., Dintica, C. S., Pan, K. Y., Qi, X., Buchman, A. S., Bennett, D. A., & Xu, W. (2020). Associations Between Cardiovascular Risk, Structural Brain Changes, and Cognitive Decline. *Journal of the American College of Cardiology*, *75*(20), 2525–2534. https://doi.org/10.1016/j.jacc.2020.03.053

Spiers, H. J. (2008). Keeping the goal in mind: prefrontal contributions to spatial navigation. *Neuropsychologia*, *46*(7), 2106–2108. https://doi.org/10.1016/j.neuropsychologia.2008.01.028

Spiers, H. J., & Barry, C. (2015). Neural systems supporting navigation. *Current Opinion in Behavioral Sciences*, *1*, 47–55. https://doi.org/10.1016/j.cobeha.2014.08.005

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine*,

166(10), 1092–1097. https://doi.org/10.1001/ARCHINTE.166.10.1092

Staresina, B. P., & Davachi, L. (2006). Differential Encoding Mechanisms for Subsequent Associative Recognition and Free Recall. *Journal of Neuroscience*, *26*(36), 9162–9172. https://doi.org/10.1523/JNEUROSCI.2877-06.2006

Svä rd, D., Nilsson, M., rn Lampinen, B., Lätt, J., Sundgren, P. C., Stomrud, E., Minthon, L., Hansson, O., & van Westen, D. (2017). *The effect of white matter hyperintensities on statistical analysis of diffusion tensor imaging in cognitively healthy elderly and prodromal Alzheimer's disease*. https://doi.org/10.1371/journal.pone.0185239

Sweeney, M. D., Kisler, K., Montagne, A., Toga, A. W., & Zlokovic, B. V. (2018). The role of brain vasculature in neurodegenerative disorders. *Nature neuroscience*, *21*(10), 1318-1331.

Szczepanski, S. M., Pinsk, M. A., Douglas, M. M., Kastner, S., & Saalmann, Y. B. (2013). Functional and structural architecture of the human dorsal frontoparietal attention network. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(39), 15806–15811. https://doi.org/10.1073/PNAS.1313903110

Takahashi, N., Kawamura, M., Shiota, J., Kasahata, N., & Hirayama, K. (1997). Pure topographic disorientation due to right retrosplenial lesion. *Neurology*, *49*(2), 464–469. https://doi.org/10.1212/WNL.49.2.464

Tatum, W. O., Rubboli, G., Kaplan, P. W., Mirsatari, S. M., Radhakrishnan, K., Gloss, D., Caboclo, L. O., Drislane, F. W., Koutroumanidis, M., Schomer, D. L., Kastelijn-Nolst Trenite, D., Cook, M., & Beniczky, S. (2018). Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. *Clinical Neurophysiology*, *129*(5), 1056–1082. https://doi.org/10.1016/J.CLINPH.2018.01.019

Tavakoli, P., Boafo, A., Jerome, E., & Campbell, K. (2021). Active and Passive Attentional Processing in Adolescent Suicide Attempters: An Event-Related Potential Study. *Clinical EEG and Neuroscience*, *52*(1), 29–37. https://doi.org/10.1177/1550059420933086

Toledo, J. B., Arnold, S. E., Raible, K., Brettschneider, J., Xie, S. X., Grossman, M., Monsell, S. E., Kukull, W. A., & Trojanowski, J. Q. (2013). Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*, *136*(9), 2697–2706. https://doi.org/10.1093/brain/awt188

Tolppanen, A. M., Solomon, A., Kulmala, J., Kareholt, I., Ngandu, T., Rusanen, M., Laatikainen, T., Soininen, H., & Kivipelto, M. (2015). Leisure-time physical activity

from mid- to late life, body mass index, and risk of dementia. *Alzheimers Dement*, *11*(4), 434-443 e6. https://doi.org/10.1016/j.jalz.2014.01.008

Torralva, T., Roca, M., Gleichgerrcht, E., López, P., & Manes, F. (2009). INECO Frontal Screening (IFS): A brief, sensitive, and specific tool to assess executive functions in dementia. *Journal of the International Neuropsychological Society*, *15*(5), 777–786. https://doi.org/10.1017/S1355617709990415

Tsolaki, A. C., Kosmidou, V., Kompatsiaris, I. Y., Papadaniil, C., Hadjileontiadis, L., Adam, A., & Tsolaki, M. (2017). Brain source localization of MMN and P300 ERPs in mild cognitive impairment and Alzheimer's disease: a high-density EEG approach. *Neurobiol Aging*, *55*, 190–201. https://doi.org/10.1016/j.neurobiolaging.2017.03.025

Tu, S., Spiers, H. J., Hodges, J. R., Piguet, O., & Hornberger, M. (2017). Egocentric versus Allocentric Spatial Memory in Behavioral Variant Frontotemporal Dementia and Alzheimer's Disease. *Journal of Alzheimer's Disease*, *59*(3), 883–892. https://doi.org/10.3233/JAD-160592

Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial translation - A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex*, *67*, 83–94. https://doi.org/10.1016/j.cortex.2015.03.016

Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015c). Lost in spatial translation - A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex*. https://doi.org/10.1016/j.cortex.2015.03.016

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and cognitive decline: a non-parametric systematic review. *Psychological medicine*, *36*(8), 1065-1073.

Vallar, G., Lobel, E., Galati, G., Berthoz, A., Pizzamiglio, L., & Le Bihan, D. (1999). A fronto-parietal system for computing the egocentric spatial frame of reference in humans. *Experimental Brain Research*, *124*(3), 281–286. https://doi.org/10.1007/S002210050624

van Charante, E. P. M., Richard, E., Eurelings, L. S., van Dalen, J. W., Ligthart, S. A., van Bussel, E. F., Hoevenaar-Blom, M. P., Vermeulen, M., & van Gool, W. A. (2016). Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet (London, England)*, *388*(10046), 797–805. https://doi.org/10.1016/S0140-6736(16)30950-3

Van Der Flier, W. M., Skoog, I., Schneider, J. A., Pantoni, L., Mok, V., Chen, C. L. H., &

Scheltens, P. (2018). Vascular cognitive impairment. *Nature Reviews Disease Primers*, *4*(Vci), 1–16. https://doi.org/10.1038/nrdp.2018.3

Van Rooden, S., van den Berg-Huysmans, A. A., Croll, P. H., Labadie, G., Hayes, J. M., Viviano, R., ... & Damoiseaux, J. S. (2018). Subjective cognitive decline is associated with greater white matter hyperintensity volume. *Journal of Alzheimer's Disease*, *66*(3), 1283-1294.

Veldsman, M., Tai, X. Y., Nichols, T., Smith, S., Peixoto, J., Manohar, S., & Husain, M. (2020). Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nature Communications 2020 11:1*, *11*(1), 1–10. https://doi.org/10.1038/s41467-020-18201-5

Veldsman, M., Werden, E., Egorova, N., Khlif, M. S., & Brodtmann, A. (2020). Microstructural degeneration and cerebrovascular risk burden underlying executive dysfunction after stroke. *Scientific Reports*, *10*, 17911. https://doi.org/10.1038/s41598-020-75074-w

Verleger, R., Heide, W., Butt, C., & Kömpf, D. (1994). Reduction of P3b in patients with temporo-parietal lesions. *Cognitive Brain Research*, *2*(2), 103–116. https://doi.org/10.1016/0926-6410(94)90007-8

Vipin, A., Loke, Y. M., Liu, S., Hilal, S., Shim, H. Y., Xu, X., Tan, B. Y., Venketasubramanian, N., Chen, C. L. H., & Zhou, J. (2018). Cerebrovascular disease influences functional and structural network connectivity in patients with amnestic mild cognitive impairment and Alzheimer's disease. *Alzheimer's Research and Therapy*, *10*(1), 1–15. https://doi.org/10.1186/s13195-018-0413-8

Vlček, K., & Laczó, J. (2014). Neural correlates of spatial navigation changes in mild cognitive impairment and Alzheimer's disease. *Frontiers in Behavioral Neuroscience*, *8*(MAR), 1–6. https://doi.org/10.3389/fnbeh.2014.00089

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *Neuroscientist*, *20*(2), 150–159. https://doi.org/10.1177/1073858413494269

Wagner, M., Wolf, S., Reischies, F. M., Daerr, M., Wolfsgruber, S., Jessen, F., Popp, J., Maier, W., Hüll, M., Frölich, L., Hampel, H., Perneczky, R., Peters, O., Jahn, H., Luckhaus, C., Gertz, H. J., Schröder, J., Pantel, J., Lewczuk, P., … Wiltfang, J. (2012). Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology*, *78*(6), 379–386. https://doi.org/10.1212/WNL.0B013E318245F447

Wallentin, M., Roepstorff, A., Glover, R., & Burgess, N. (2006). Parallel memory systems

for talking about location and age in precuneus, caudate and Broca's region. *NeuroImage*, *32*(4), 1850–1864. https://doi.org/10.1016/J.NEUROIMAGE.2006.05.002

Waller, D., & Hodgson, E. (2006). Transient and enduring spatial representations under disorientation and self-rotation. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *32*(4), 867. https://doi.org/10.1037/0278-7393.32.4.867

Wang, C., Xu, J., Lou, W., & Zhao, S. (2014). Dynamic information flow analysis in Vascular Dementia patients during the performance of a visual oddball task. *Neuroscience Letters*, *580*, 108–113. https://doi.org/10.1016/j.neulet.2014.07.056

Wang, C., Xu, J., Zhao, S., & Lou, W. (2016). Graph theoretical analysis of EEG effective connectivity in vascular dementia patients during a visual oddball task. *Clinical Neurophysiology*, *127*(1), 324–334. https://doi.org/10.1016/j.clinph.2015.04.063

Wang, R. F., & Spelke, E. S. (2000). Updating egocentric representations in human navigation. *Cognition*, *77*(3), 215–250. https://doi.org/10.1016/S0010-0277(00)00105-0

Wardlaw, J., Eric E Smith, Geert J Biessels, Charlotte Cordonnier, Franz Fazekas, Richard Frayne, Richard I Lindley, John T O'Brien, Frederik Barkhof, Oscar R Benavente, S., andra E Black, Carol Brayne, Monique Breteler, Hugues Chabriat, Charles DeCarli, Frank-Erik de Leeuw, Fergus Doubal, Marco Duering, Nick C Fox, … Dichgans, M. (2013). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*, *12*(38). https://doi.org/10.1016/S1474-4422(13)70124-8

Warrington, E. K., & James, M. (1991). *The Visual Object and Space Battery Perception.* Thames Valley Company.

Wartolowska, K. A., & Webb, A. J. S. (2021). Midlife blood pressure is associated with the severity of white matter hyperintensities: analysis of the UK Biobank cohort study. *European heart journal*, *42*(7), 750-757.

Weisberg, S. M., Schinazi, V. R., Newcombe, N. S., Shipley, T. F., & Epstein, R. A. (2014). Variations in cognitive maps: Understanding individual differences in navigation. *Journal of Experimental Psychology: Learning Memory and Cognition*, *40*(3), 669–682. https://doi.org/10.1037/a0035261

Weniger, G., Ruhleder, M., Lange, C., Wolf, S., & Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia*, *49*(3), 518–527. https://doi.org/10.1016/j.neuropsychologia.2010.12.031

https://doi.org/10.1016/j.neuropsychologia.2010.12.031

Weniger, G., Ruhleder, M., Wolf, S., Lange, C., & Irle, E. (2009). Egocentric memory impaired and allocentric memory intact as assessed by virtual reality in subjects with unilateral parietal cortex lesions. *Neuropsychologia*, *47*(1), 59–69. https://doi.org/10.1016/j.neuropsychologia.2008.08.018

Whitwell, R. L., Milner, A. D., & Goodale, M. A. (2014). The Two Visual Systems Hypothesis: New Challenges and Insights from Visual form Agnosic Patient DF. *Front Neurol*, *5*, 255. https://doi.org/10.3389/fneur.2014.00255

Wiener, J. M., & Mallot, H. A. (2003). "Fine-to-Coarse" Route Planning and Navigation in Regionalized Environments. *Spatial Cognition and Computation*, *April*, 331–358. https://doi.org/10.1207/s15427633scc0304

Williams, O. A., Zeestraten, E. A., Benjamin, P., Lambert, C., Lawrence, A. J., Mackinnon, A. D., ... & Charlton, R. A. (2019). Predicting dementia in cerebral small vessel disease using an automatic diffusion tensor image segmentation technique. *Stroke*, *50*(10), 2775-2782.

Wolbers, T., Weiller, C., & Buchel, C. (2004). Neural foundations of emerging route knowledge in complex spatial environments. *Brain Res Cogn Brain Res*, *21*(3), 401–411. https://doi.org/10.1016/j.cogbrainres.2004.06.013

Wolbers, T., & Wiener, J. M. (2014). Challenges for identifying the neural mechanisms that support spatial navigation: The impact of spatial scale. In *Frontiers in Human Neuroscience* (Vol. 8, Issue AUG). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2014.00571

Wolbers, T., Wiener, J. M., Mallot, A., & Buchel, C. (2007). Differential recruitment of the hippocampus, medial prefrontal cortex and the human motion complex during path integration in Humans. *The Journal of Neuroscience*, *27*(35), 9408–9416. https://doi.org/10.1523/JNEUROSCI.2146-07.2007

Xu, J., Sheng, H., Lou, W., & Zhao, S. (2012). Approximate entropy analysis of event-related potentials in patients with early vascular dementia. *Journal of Clinical Neurophysiology*, *29*(3), 230–236. https://doi.org/10.1097/WNP.0B013E318257CA9D

Yamaguchi, S., & Knight, R. T. (1992). Effects of temporal-parietal lesions on the somatosensory P3 to lower limb stimulation. *Electroencephalography and Clinical Neurophysiology*, *84*(2), 139–148. https://doi.org/10.1016/0168-5597(92)90018-7

Yamaguchi, S., Tsuchiya, H., Yamagata, S., Toyoda, G., & Kobayashi, S. (2000). Event-related brain potentials in response to novel sounds in dementia. *Clinical Neurophysiology*, *111*(2), 195–203. https://doi.org/10.1016/S1388-2457(99)00228-X

Yano, Y., Ning, H., Allen, N., Reis, J. P., Launer, L. J., Liu, K., Yaffe, K., Greenland, P., & Lloyd-Jones, D. M. (2014). Long-Term Blood Pressure Variability Throughout Young Adulthood and Cognitive Function in Midlife. *Hypertension*, *64*(5), 983–988. https://doi.org/10.1161/hypertensionaha.114.03978
https://doi.org/10.1161/HYPERTENSIONAHA.114.03978

Yau, P. L., Javier, D., Tsui, W., Sweat, V., Bruehl, H., Borod, J. C., & Convit, A. (2009). Emotional and neutral declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes. *Psychiatry Res*, *174*(3), 223–230. https://doi.org/10.1016/j.pscychresns.2009.04.016

Zaehle, T., Jordan, K., Wustenberg, T., Baudewig, J., Dechent, P., & Mast, F. W. (2007). The neural basis of the egocentric and allocentric spatial frame of reference. *Brain Res*, *1137*(1), 92–103. https://doi.org/10.1016/j.brainres.2006.12.044

Zaehle, T., Jordan, K., Wüstenberg, T., Baudewig, J., Dechent, P., & Mast, F. W. (2007). The neural basis of the egocentric and allocentric spatial frame of reference. *Brain Research*, *1137*(1), 92–103. https://doi.org/10.1016/j.brainres.2006.12.044

Zhang, Y., Schuff, N., Camacho, M., Chao, L. L., Fletcher, T. P., Yaffe, K., Woolley, S. C., Madison, C., Rosen, H. J., Miller, B. L., & Weiner, M. W. (2013). MRI Markers for Mild Cognitive Impairment: Comparisons between White Matter Integrity and Gray Matter Volume Measurements. *PLoS ONE*, *8*(6), 29–32. https://doi.org/10.1371/journal.pone.0066367

Appendices

Appendix A. Data refereeing to Chapter three. Total scores, standard deviations (SD), Z-case control (Zcc) scores, confidence intervals from a modified paired samples t-test for patient and control group on the Spatial Battery at Time 1.

Measure	*Condition*	*Patient Score*	*Control sample mean (n=14)*	*SD*	*t-value*	*p value*	*size effects(Z_cc)*	*95% CI*
Virtual Supermarket Test	**Egocentric**	**4***	**12.9**	**0.9**	**-9.529**	<0.001	**-9.889**	**-13.83 to -5.95**
	Allocentric	1.5	8.1	3.2	-0.201	NS	-0.206	-3.03 to -1.07
The Clock Test	**Heading**	**6***	**12.5**	**2.1**	**-2.983**	**<0.01**	**-3.095**	**-4.42 to -1.75**
	Cardinal	**1***	**3.9**	**0.9**	**-3.105**	<0.01	**-3.222**	**-4.59 to -1.83**
	Right Angel	**1***	**3.6**	**0.6**	**-4.176**	<0.001	**-4.333**	**-6.12 to -2.53**
	Mixed	1	3.9	1.7	-1.644	NS	**-1.706**	-2.56 to -0.83
	Total	**3***	**11**	**2.6**	**-2.965**	**0.01**	**-3.077**	**-4.4 to -1.74**
Statue Test	Wall easy	4	4	0	0	NS	**-3.077**	-0.54 to 0.54
	Wall medium	**1***	**2.6**	**0.5**	**-3.085**	**0.01**	**-3.16**	**-4.51 to 1.79**
	Wall hard	0	0.3	0.6	0	NS	0	-1.08 to 0.09
	Stool easy	0	3.7	0.4	-0.723	NS	-0.75	0.12 to 1.36
	Stool medium	**4***	**2.2**	**0.8**	**-0.482**	**0.02**	**-2.687**	**-3.87 to -1.48**
	Stool hard	2	0.2	0.6	-0.482	NS	0.5	-1.07 to 0.09

+The statue test was used at time 1 but not at time 2.

Appendix B. Chapter four ANCOVA output for the Clock Orientation Test (COT).

	CVR+	HC	F	P	η_p^2
Total score	10.16(1.24)	10.45(1.43)	0.21	0.67	0.004
RT	48.58 (41.24)	39.4(24.5)	0.21	0.71	0.004

Appendix C. Chapter four ANCOVA output for the Virtual Supermarket Test (VST).

	CVR+	HC	F	P	η_p^2
Egocentric	8.29(3.43)	8.25(2.61)	3.1	0.09	0.07
Allocentric	203.79(75.78)	191.87(64.08)	1.58	.22	0.04
Heading	10(2.73)	11.1(2.1)	2.23	0.14	0.05

Appendix D. Chapter four ANCOVA output for all Sea Hero Quest Levels (SHQ).

Level		CVR+	HC	F	P	η_p^2
L14	Accuracy	2.67 (.48)	3	5.22	0.03	0.21
	Duration	37.35(14.3)	28.06(5.41)	6.24	0.018	0.2
L19	Accuracy	2.79(.5)	3	0.54	0.46	0.01
	Duration	38.5 (17.62)	35 (6.03)	2.45	0.12	0.07
L24	Accuracy	2.08 (.88)	1.88(.92)	2.84	0.1	0.07
	Duration	38.07(5.24)	36.9(5.74)	0.01	0.92	0
L34	Accuracy	2.25(.89)	1.94(.76)	1.25	0.27	0.03
	Duration	44.78(17.7)	44.23(16.58)	0.94	0.38	0.03
L6	Distance	304.86(14.96)	308.47(18.32)	0.05	0.82	0.002
	Duration	26.16(3.96)	28.46(7.3)	0.62	0.43	0.02
L8	Distance	1410(907)	957(587)	0.04	0.83	0.001
	Duration	169.83(123.98)	113.63(101.01)	0.01	0.92	0
L11	Distance	1281(954.1)	1031(700.2)	1.27	0.26	0.04
	Duration	129.57(110.55)	102.23(99.1)	1	0.32	0.03

L, level