Mechanisms of cognitive impairment in epilepsy

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Cognitive impairment and dementia are increasingly reported as people with epilepsy grow older, with major impact on quality of life. The underlying mechanisms of cognitive dysfunction, however, and the magnitude of associated dementia risk in epilepsy remains unclear. This thesis will explore how cardiovascular risk factors and hippocampal dysfunction are two important mechanistic links between epilepsy and dementia.

Using data from a large population-based cohort, the studies in this thesis demonstrate that cardiovascular risk factors are closely related to impairment of executive function. One finding highlighted a continuous dose-response relation of cognition with blood pressure, even in non-hypertensive individuals. The relationship between cardiovascular risk and cognition was mediated through changes in both frontoparietal white and grey matter structural networks. In the same cohort, people with epilepsy and a high cardiovascular risk were over 13 times more likely to develop dementia compared to healthy controls with low cardiovascular risk. People with epilepsy had a greater risk of developing dementia even compared with individuals with a history of stroke, with associated changes to hippocampal volume.

To examine specific hippocampal-related cognitive mechanisms that may underlie memory difficulties in epilepsy, I examined two processes believed to be central to encoding and retrieval in the hippocampus: pattern separation and pattern completion. I devised a novel computer-based behavioural paradigm called the Memory Pinhole Task to distinguish them. Impairment of these two cognitive operations have been identified in ageing and other

conditions such as Alzheimer's disease. Compared to healthy controls, pattern separation deficits were observed in people with epilepsy while reduced pattern completion was seen in healthy older individuals. I then mapped these findings from the Memory Pinhole task onto potential brain mechanisms through computational modelling using a neural network.

The work in this thesis describes how modifiable cardiovascular risk factors significantly contribute to cognitive ageing and dementia risk in healthy individuals and people with epilepsy. This has important implications for personal health practices and clinical guidelines, especially in people with epilepsy as there is no current guidance to mitigate dementia risk. Further, I describe a framework for testing encoding and retrieval of information into memory which may allow us to better understand difficulties seen in both health and disease.

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Published:

Veldsman M*, Tai XY*, Nichols T, Smith S, Peixoto J, Manohar S, et al. *Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing*. **Nat Communications.** 2020 Dec 1;11(1).
- Manuscript described in Chapter 2, Joint primary author

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Tai XY, Husain M, Manohar S. *Separating pattern separation from pattern completion: a critical review*

Tai XY, Subtirelu R, Husain M, Manohar S. *Pattern separation and pattern completion in health and epilepsy*
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Chapter 1. General Introduction

1.1 Epilepsy, cognition and dementia – overview

The incidence of epilepsy is highest incidence in the older population, especially in developed countries, while individuals who develop epilepsy at a younger age are living longer (1,2). Studies suggest that people with epilepsy are at higher risk of cognitive impairment and dementia as they grow older (3). The underlying mechanisms of cognitive dysfunction, however, and the magnitude of associated dementia risk in epilepsy remains unclear.

There are three potential mechanistic links between epilepsy and dementia (Figure 1-1). Firstly, abnormal electrical activity can affect brain function in the absence of overt clinical seizures. This activity can be in the form of sub-clinical epileptic 'spiking' phenomena or long-term changes to baseline connectivity (4–7). Certain brain regions are more sensitive to this epileptic activity including the medial temporal lobe and the hippocampus. These structures are widely considered to be important to memory and are involved early in dementias such as Alzheimer's disease (8). Sub-clinical epileptic discharges within the hippocampus are associated instantaneous disruption of memory (9,10) and have also been observed in Alzheimer's disease patients (11). Therefore, examining dysfunction within these regions may offer insight into cognitive mechanisms underlying memory difficulties in people with epilepsy.

Secondly, cardiovascular risk factors which can cause vascular cognitive impairment and dementia (12) are also causally implicated in focal epilepsy, especially in older individuals who develop epilepsy following stroke (13,14). Understanding the contribution of shared cardiovascular risk factors in healthy ageing and epilepsy is important as these are potentially modifiable and offer a treatment strategy to mitigate risk of developing dementia, including in epilepsy.

Finally, at a cellular level, the same pathological protein tau which is characteristic of dementias such as Alzheimer's disease, is also observed in people with temporal lobe epilepsy and is associated with poorer cognitive outcomes in these individuals (15,16). In the next sections, I consider the current literature linking epilepsy to impaired cognition and dementia.

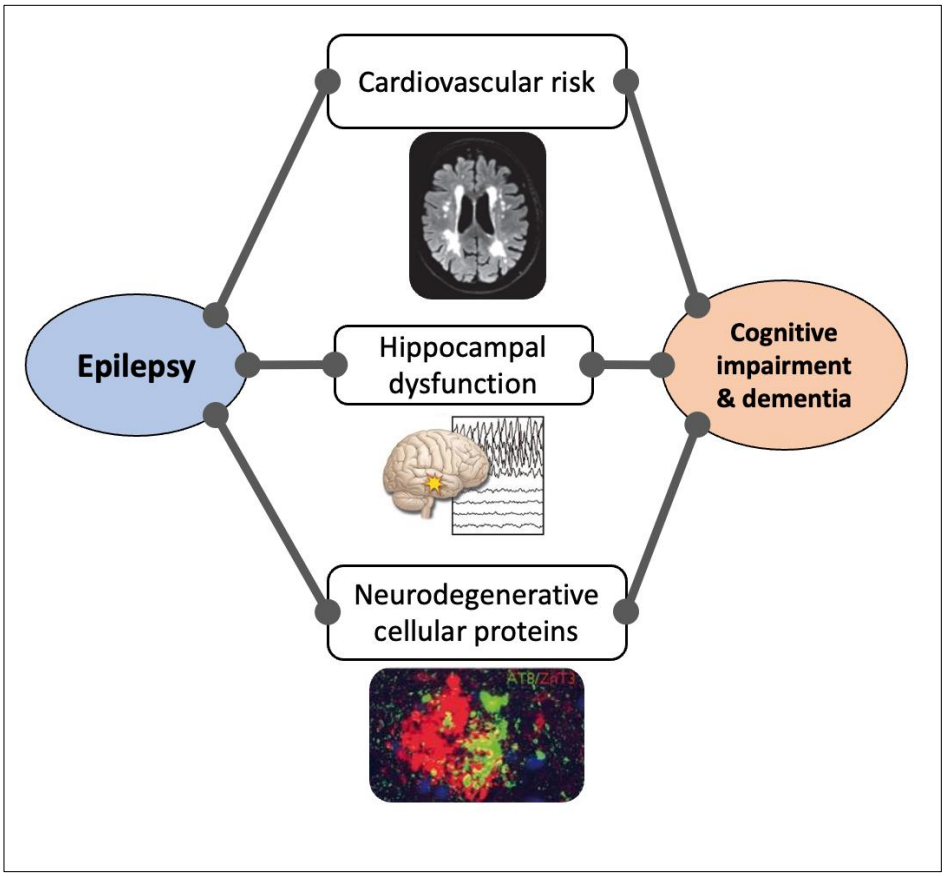


Figure 1-1. Three potential mechanistic links between epilepsy and dementia

Dysfunction of the hippocampus and neighbouring temporal lobe regions (middle) are implicated in memory difficulties in epilepsy owing to, for example, clinical and sub-clinical seizure activity. These areas are also affected early in the pathogenesis of Alzheimer's disease and related dementias. Cardiovascular risk factors (top) leading to cerebrovascular disease can result in seizures and are also a driving factor for developing vascular dementia. At a cellular level (bottom), the same pathological proteins observed in Alzheimer's disease are also seen in epilepsy. All three paths represent potential mechanistic links between epilepsy and dementia.

1.1.1 Epidemiology and aetiology of epilepsy in the ageing population

Epilepsy was declared a public health imperative by the World Health Organization in 2019 and has increasing global prevalence with around 50 million people with epilepsy worldwide (17). Epilepsy has a prevalence of almost 1% in the United Kingdom (UK) (18) and is one of the most common neurological conditions. The incidence of epilepsy peaks in the ageing population with a quarter of new cases being diagnosed in those above the age of 65 years. Additionally, people who developed epilepsy during childhood or early adulthood are now living to an older age due to improvements in healthcare.

The term 'epilepsy' represents a heterogenous group of aetiologies including inherited complex genetic disorders and neurodevelopmental syndromes to acquired causes such as rare infections of the brain (19). Most adult-onset epilepsy cases are acquired, and fall under the category of 'focal epilepsy' whereby focal seizures begin in a specific part of the brain and may propagate to other regions or generalize to affect the whole brain. This reflects the concept of epilepsy being a network disorder and provides a rationale as to why seizures which start from different brain regions may lead to similar presentations. For example, this may explain why a person with temporal lobe epilepsy may report similar cognitive difficulties to those with other focal seizure sub-types. In older individuals, the aetiology of epilepsy is more homogenous with cerebrovascular disease considered as the most common cause accounting for up to 70% of new cases (13) with a 20-fold increase risk of developing epilepsy reported in the year following a stroke (14), but epilepsy also increases with small vessel cerebrovascular disease (20). These findings point to the potential importance of considering cardiovascular health in epilepsy not only from the perspective of developing seizures but also in regards to co-morbidities such as epilepsy-related dementia.

1.1.2 Cognitive difficulties in epilepsy across multiple domains

There is increasing concern over cognitive impairment and dementia in people with epilepsy as they grow older. Once thought to be a disorder of discrete seizure attacks with a return to cognitive baseline in between seizures, evidence now suggests that epilepsy is associated with ongoing cognitive impairment (3). The exact nature and magnitude of cognitive impairment in epilepsy, however, remains a subject of intense debate. Furthermore, although temporal lobe epilepsy is often considered the archetypal focal epilepsy causing cognitive difficulties (21), it is becoming evident that different epilepsy sub-types have a range of different cognitive profiles with considerable overlap (22).

While subjective memory complaints are frequently reported by people with epilepsy (23), few studies have systematically or mechanistically addressed cognition in older individuals while even less is known about cognitive trajectory and dementia risk in people with epilepsy. There are several reasons for this uncertainty including the heterogenous nature of epilepsy and confounding factors such as anti-seizure medications side-effects (24,25). Equally important, cognition is not a static entity and most major domains will decline across age with a few exceptions, such as semantic memory (26). The overall cognitive impact of epilepsy, therefore, can only be appreciated if studied in the context of age and other confounding factors.

Several studies, mainly cross-sectional, have identified objective cognitive deficits across a range of different domains in older people with epilepsy compared with age-matched controls (3). Table 1-1 summarises the cognitive domains shown to be impaired across investigations in both younger adults (early- to mid-life) and older adults (late life) with focal epilepsy. Having focal epilepsy with seizure onset in both temporal and extra-temporal regions has been specifically associated with worse executive function, including working memory, task switching, attentional processing speed as well as short- and long-term visual

memory and verbal memory (27–30). Other reports concluded that people with epilepsy performed worse in across all domains tested (31).

An important consideration is the potential confounding effect of taking anti-seizure medications which commonly have cognitive side-effects. There have been two useful reports in this regard, Witt et al. identified executive and subjective deficits in an older group of 257 individuals, mean age 67.7 years, with new-onset focal epilepsy prior to starting anti-seizure medications (27) and another study in 155 young adults with new-onset focal epilepsy, mean age 35.0 years, found similar results with executive function and verbal memory testing prior to starting medication (32). These findings suggest that cognitive impairment is intrinsic to the disease and not a side-effect of medication. Other investigations have also shown that anti-seizure medication polytherapy correlated with worse cognitive outcomes (28,31,33). This raises the question whether the number of anti-seizure medications could be a proxy for worse disease or that taking more anti-seizure medications will worsen an individual's cognitive profile or, more likely, both may be true.

Cognitive trajectories in people with epilepsy have been hard to investigate. A cross-sectional study of over a thousand people with temporal lobe epilepsy aged between six and 80 years of age identified poorer development of verbal memory skills during childhood and a lower plateau reached in early adulthood when compared to age-matched controls at a population level (34). After development, however, the declining trajectory over later life was similar between groups. People with epilepsy reached a threshold considered as 'cognitively impaired' at an earlier age due to a lower starting baseline rather than an accelerated decline. Another cross-sectional investigation which examined 382 patients between 18 and 65 years of age with drug-resistant temporal lobe epilepsy reported similar findings of a deficit in memory and language skills but relatively stable trajectory across the age groups (35).

By contrast, several longitudinal studies have indicated that epilepsy is associated with progressive cognitive decline that is worse than age-matched controls. Such reports have focussed mostly on younger people with epilepsy and are small in sample size with relatively short follow-up durations. Piazzini et al. (2006) examined 50 temporal lobe epilepsy patients and 50 controls, mean age 37.2 years, at baseline and followed up once between 1-5 years. People with epilepsy showed significant decline in attention and psychomotor speed but not other domains (36). Duration of epilepsy, age of onset, history of tonic-clonic seizures and low educational level were identified as important associated factors in this study.

Other domains identified as showing progressive decline include verbal memory (37), mental manipulation (38) and, in one study, there was deterioration across all cognitive domains (39). Griffith et al. (2007) examined 17 older people with epilepsy, mean age 64.5 years, and an equal number of age-matched controls. Worsening executive function was the only domain to decline faster over three years of follow-up compared with healthy controls despite worse delayed recall at baseline in the individuals with epilepsy (40).

These disparate observations have led to different hypotheses to describe cognitive deficits in epilepsy. Firstly, seizures may have a negative developmental effect on cognitive abilities. This will result in a worse *baseline* level of cognition in early adulthood that then declines as expected with age (41). Another possibility is that seizures can cause a cognitive 'hit' which would deplete an individual's cognitive reserve leading to worse cognitive performance. Such an insult can occur once or may be repeated across the life of an individual depending on disease specific factors – although no single factor has consistently been identified in the literature. As described in Table 1-1, one study reported that cognitive deficits correlated with earlier age at seizure onset, longer duration and higher lifetime seizure count. However, most reports did not identify a clear factor other than the number of anti-seizure medications, potentially a proxy for epilepsy severity. A final hypothesis contends that epilepsy may lead to

ongoing, progressive cognitive dysfunction and ultimately dementia through accumulation of neurodegenerative pathologies (e.g. deposition of tau protein). This will be discussed in the next section. Overall, although the evidence considered here shows that cognitive dysfunction is associated with epilepsy, the exact underlying mechanisms remain poorly defined.

Table 1-1. Results of studies examining cognitive impairment in young and older adults

Study	Sample size (Epilepsy)	Mean age (SD)	Comparator	Epilepsy localisation	Cognitive domains worse in epilepsy	Factors associated with cognitive deficits
Young adults						
Black et al., 2010 (42)	N epilepsy = 207	38.3 years (10.9)	Non-epileptic seizure disorder	Temporal lobe epilepsy	Intelligence Executive Functions	Earlier age at seizure onset, Longer disease duration, Higher lifetime seizure count
Gul et al., 2015 (43)	N Epilepsy = 30	23.5 years (0.86)	Healthy controls	Frontal lobe epilepsy	Task switching Social cognitive scores (Executive functions)	-
Ozer et al., 2015 (44)	N Epilepsy = 11	28.8 years (13.1)	Non-epileptic seizure disorder & Healthy controls	Focal epilepsy (frontal or temporal lobe)	Verbal learning and memory scores Long-term memory total recognition test scores	-
Taylor et al., 2010 (32)	N epilepsy = 155	35.0 years (14.4)	Healthy controls	Focal epilepsy (any localisation)	Psychomotor speed Verbal memory Verbal fluency Mental flexibility/ executive testing Mood	*Findings prior to starting ASMs
Wang et al., 2020 (45)	N Epilepsy = 257	23.9 years (8.26)	nil comparator *Normative values used	Focal epilepsy (any localisation)	Verbal fluency Working memory Attention Vocabulary	Greater seizure frequency
Older adults						
Martin et al., 2005 (28)	N epilepsy = 25	64.6 years (3.9)	Healthy controls	Focal epilepsy (any localisation)	Global cognitive functioning Immediate and long-term memory Verbal fluency	ASM polytherapy
Griffith et al., 2006 (29)	N epilepsy = 26	64.7 years (3.8)	Mild cognitive impairment	Focal epilepsy (any localisation)	Global cognitive functioning Immediate and long-term	-

					memory Verbal fluency	
Griffith et al., 2007 (40)	N epilepsy = 17	67.7 years (4.2)	Healthy controls	Focal epilepsy (any localisation)	Global cognitive functioning Immediate and long-term memory Executive control	-
Piazzini et al., 2006 (31)	N epilepsy = 40	67.0 years (5.9)	Healthy controls	Focal epilepsy (any localisation)	Intelligence Attention Abstraction Short and long term visual memory Learning Language *All domains tested	ASM polytherapy
Witt et al., 2014 (27)	N epilepsy = 257	71.5 years (7.2)	Healthy controls	Focal epilepsy (any localisation)	Executive Function Subjective cognitive ratings	*Findings prior to starting ASMs
Miller et al., 2016 (33)	N epilepsy = 38	65.2 years (7.9)	Healthy controls	Focal epilepsy (any localisation)	Global Cognition Verbal memory Visual memory Attention Executive Function Language Visuospatial	ASM polytherapy, Anxiety

Abbreviations - ASM, anti-seizure medication

1.1.3 Epilepsy and dementia: a bidirectional link?

The incidence of seizures is substantially higher in individuals with dementia compared with healthy individuals of the same age (46). Higher seizure risk is observed across different dementia sub-types. One study identified 10-fold increased risk seizures in people with Alzheimer's disease (47) while another identified an odds ratio of 5.7 for developing seizures associated with vascular dementia compared with healthy controls (48). It is unsurprising, perhaps, that neurodegenerative processes, whatever their nature, might leave the brain vulnerable to aberrant connectivity and seizure generation.

Conversely, there is some evidence to support the view that people with epilepsy may be at increased risk of developing dementia (49–52). A recent observational study of US veterans described older individuals, above the age of 50 years, who developed seizures in late adulthood were approximately twice as likely to be diagnosed with dementia compared to controls during study follow-up period (53). Similarly, data from three national Dutch morbidity registers identified a relative risk of 1.5 for individuals with epilepsy being diagnosed with dementia over an eight-year period (54).

A meta-analysis of eight case-control studies has identified increased risk for developing Alzheimer's disease in people with epilepsy (55). Intriguingly, when stratified by the duration of having epilepsy, individuals who were recently diagnosed with epilepsy within the last 10 years had a higher Alzheimer's disease risk (relative risk of 2.5) compared with those who were diagnosed with epilepsy more than 10 years ago (relative risk of 1.4). This may indicate that duration of epilepsy may not be important to dementia risk or there may be an element of reverse causation whereby the seizures occurred in the context of an undiagnosed dementia process. Other investigations, however, have reported no association between having epilepsy or duration of epilepsy and developing dementia (56–58).

Population data therefore supports the idea that dementia is a risk factor for seizures and having epilepsy might increase the risk of developing dementia. However, several questions remain. Is there a bidirectional link between epilepsy and dementia or do they both simply share common risk factors? Does epilepsy increase dementia risk more so than other non-degenerative neurological conditions, such as stroke? Also, could developing seizures later in life reflect the early stages of an undiagnosed dementia that will progress rapidly?

These are important questions because there is currently no clinical guidance to mitigate the risk of dementia in people with epilepsy. One way to gain a better understanding of these questions is to consider potential underlying mechanisms linking epilepsy and dementia. The following sections will examine the role of cardiovascular health in developing dementia in healthy individuals and then in epilepsy. Next, the pathological link between epilepsy and dementia at a cellular level will be discussed and, finally, I will consider how hippocampal-specific processes may help to understand cognitive mechanisms underlying memory difficulties in epilepsy.

1.2 Mechanistic links between epilepsy and dementia

1.2.1 Cardiovascular health, cognition and dementia in the general population

Healthy cognitive ageing is an important public health priority and a key societal issue as the world's ageing population grows exponentially each year (59). Coupled with a general decline across most cognitive domains as humans age (26), identifying factors that could modify age-related decline and promote healthy cognitive ageing is critical.

Cardiovascular risk factors represent a group of modifiable factors with potentially significant impact on cognition as humans grow older. There is a growing body of literature examining how targeting cardiovascular health may help protect brain health. For example, not only is type two diabetes associated with worse cognitive performance across several domains (60,61) but results from a

pooled meta-analysis based on 2.3 million individuals with the condition also showed approximately a 60% increased risk of developing dementia (62). Similarly, hypertension is associated with a higher dementia risk with some reports identifying mid-life blood pressure control as crucial (63), although others suggest this may not be the case (64). Risk factors such as body mass index (BMI), smoking and alcohol have also been implicated in increasing risk of developing dementia (65,66).

While our knowledge in this area has increased substantially in recent years, there have been several limitations within this field of research. Most investigations have used relatively small sample sizes with variable results and outcomes of having dementia or mild-cognitive impairment often based on relatively insensitive measures or clinical rating scores such as the mini-mental state examination (MMSE) or Clinical Dementia Rating (CDR). These are important issues because changes in cognitive abilities due to cardiovascular risk factors may be subtle, so require sensitive tests to measure them, but nevertheless still have important implications on daily function.

Key questions remain around how cardiovascular risk factors affect cognition and underlying brain structure. For example, while hypertension is detrimental to brain health, at what level does blood pressure become 'high' and is this the same for cardiovascular outcomes such as myocardial infarction? White matter lesions on MRI neuroimaging are considered classic markers of cerebrovascular disease (67) yet some studies suggest there is no correlation between white matter lesion burden and cognitive outcomes (68). Could more sensitive measures of white matter integrity or considering larger brain networks be more explanatory? Individual cardiovascular and metabolic conditions such as myocardial infarction and diabetes lead to poor cognitive outcomes, but what is the impact of having several cardiovascular conditions on brain health? To date, studies have generally been poorly powered to answer whether the effect of *cardiometabolic multimorbidity* may plateau if individual conditions are on the same causal pathway or they may have an additive, or even multiplicative, effect on dementia risk.

Therefore, although cardiovascular risk is a promising target to modify cognitive ageing, better understanding of the exact relationship with cognition and dementia in healthy individuals is warranted before considering the impact of cardiovascular disease in neurological conditions such as epilepsy.

1.2.2 Cardiovascular risk factors and epilepsy-related dementia

Aside from healthy cognitive ageing, the impact of cardiovascular risk factors in epilepsy on cognitive outcomes has been poorly explored. Specifically, could there be a synergy between the 'normal' cardiovascular impact and the 'epileptic impact' on cognition? This is especially relevant when considering the high incidence of new epilepsy diagnoses in older individuals and the ageing epilepsy population (18). Furthermore, age-accelerated atherosclerosis measured as increased carotid artery intima media thickness has been documented in people with epilepsy (69) which may suggest an inherent risk, but what is the quality of evidence regarding these questions?

First, as discussed above, established stroke is a major risk factor for developing epilepsy in older adults (70) while post-stroke epilepsy is considered predictive of poor cognitive outcomes and worse quality of life (71). However, an unanswered question is the impact of modifiable, cardiovascular risk factors in people with epilepsy who do not have an established stroke.

Second, some evidence highlights cardiovascular risk factors as important for developing epilepsy including a prospective cohort study of over 15 000 individuals that identified several vascular and lifestyle risk factors were associated with late-onset epilepsy (72). Other results have been conflicting, however, as a recent study found that raised body mass index (BMI), being hypertensive or diabetic did not increase the risk of incident epilepsy in the absence of stroke (13).

Third, even less is known about the relationship between cardiovascular risk factors and cognitive outcomes in epilepsy. Most studies and systematic reviews (73) focus on whether epilepsy-specific factors such as seizure control and duration of having seizures are linked with poor cognitive performance (74–76) or risk of developing dementia (77). However, such investigations do not

consider the impact of modifiable cardiovascular risk factors. Poor sample size and lack of longitudinal data are common limitations in such studies.

Currently, there is no specific guidance on reducing the risk of dementia in people with epilepsy. Identifying modifiable risk factors could be an important intervention to reduce dementia risk in people with epilepsy with wide implications on clinical practice and personal health practices for this population. Further, examining the role of cardiovascular health specifically may lead to low-cost risk reduction strategies that may be implemented in resource poor, as well as resource privileged, settings.

1.2.3 Shared pathology between epilepsy and dementia

Cerebrovascular pathology observed in vascular and mixed dementia ranges from atherosclerotic vessel disease, blood-brain barrier changes, white matter axonal myelin loss, perivascular space dilatation and cerebral amyloid angiopathy (78). A few pathology studies have examined the overlap with epilepsy and vascular pathology with a focus on blood-brain barrier dysfunction (79,80). Drug-resistant epilepsy has been associated with increased parenchymal IgG staining of entorhinal cortex tissue and reduced expression of tight junctions thought to reflect a 'leaky' blood-brain barrier compared with age-matched controls (81). Findings in human and rat brain tissue suggest that barrier dysfunction may occur during epileptogenesis and lead to seizures (82) while other reports indicate that seizures lead to increased vascularisation and formation of immature, leaky vessels with high level of angiogenic vascular endothelial growth factor (VEGF) (83). It is unclear whether blood-brain barrier dysfunction is a cause or an effect of seizures or, perhaps, there may be a cyclical process of worsening vascular pathology in epilepsy.

Chronic epilepsy has also been associated with increased atherosclerotic disease and carotid artery intima thickness, however these observations have generally been in the context of long-term anti-seizure medication treatment and may not be a direct consequence of the disease (69,84–86).

Recently, a prominent theory linking dementia and epilepsy describes a pathological mechanism where seizures may trigger cellular cascades and accumulation of pathological proteins in the brain. Hyperphosphorylated tau and amyloid-beta are pathological hallmarks of Alzheimer's disease which accumulate in the medial temporal lobe, and specifically hippocampus, during early stages of this disease (8). Two recent pathology studies that examined temporal lobectomy tissue from temporal lobe epilepsy patients identified neurofibrillary tangles containing hyperphosphorylated tau around several hippocampal regions, more than expected for age (15,87). In one of these investigations, the amount of tau pathology followed the Braak staging, the pathological scale used in Alzheimer's disease, and correlated with post-operative cognitive outcomes one year later. Similarly, a large post-mortem study identified an age-accelerated pattern of tau pathology in middle-aged patients, between 40-60 years of age, with chronic drug-resistant epilepsy (88). In older individuals, tau aggregation has also been described in regions of focal cortical dysplasia, a specific seizure-generating brain pathology, whereas adjacent tissue was clear of tau pathology (89).

While there appears to be a greater focus on tau pathology, one study identified higher levels of immunoreactive amyloid-beta precursor protein (90) while another reported a higher burden of amyloid-beta containing senile plaques (91) in temporal lobectomy tissue resected from people with epilepsy compared to age-matched controls (see Romoli et al. for a review on the theoretical and experimental relationship between beta-amyloid, cognition and seizures (92)). Amyloid pathology has not been consistently identified, however, as one investigation reported no amyloid staining in 28 out of 33 cases (15) while another study found some amyloid pathology which did not correlate with cognitive measures (88). Also, few cases with hyperphosphorylated tau or amyloid plaques were reported in surgical specimens of fifty-six young patients who had a median age of 34 years at the time of operation (93). While the authors concluded that these findings suggested against an Alzheimer's like process occurring in epilepsy, this may also point towards an important interaction whereby seizures within the ageing brain may trigger pathological processes.

Taken together, there appears to be a pathological link at a cellular level between epilepsy and dementia in that chronic seizures may result in a tau-specific, or both tau and amyloid, neurodegenerative process (16) which correlate with cognitive outcomes, at least in some reports. This is a potentially important mechanistic link between epilepsy and dementia although not explored specifically in this thesis.

1.2.4 Hippocampal dysfunction in epilepsy and dementia

A range of cognitive domains are impaired in epilepsy, as discussed above, including both short- and longer-term memory. Examining hippocampal function may therefore provide better understanding into cognitive mechanisms that are affected in epilepsy and dementia. Alzheimer's disease preferentially affects the hippocampus and entorhinal cortex early in the disease process (94) and, conversely, the temporal lobe is sensitive to seizure activity and a common site of seizure onset or propagation (95–97). Hippocampal sclerosis is the primary pathology in temporal lobe epilepsy, which is the most common focal-onset epilepsy in adults (98,99). Of note, development of epilepsy associated with cerebrovascular small vessel disease, in the absence of established stroke, primarily leads to temporal lobe seizures even if the vascular white matter burden in the brain is located away from the temporal lobe (100). This reflects the epileptogenic nature of the temporal lobe and hippocampus which are structures that seizure activity frequently propagates to due to being highly connected to other parts of the brain(101,102).

Are there specific hippocampal cognitive processes that may link both epilepsy and dementia apart from general "memory difficulties" identified from neuropsychological assessments and questionnaires such as the MMSE? Accelerated long-term forgetting (ALF) or rapid loss of newly learnt information is a cognitive phenomenon described in transient epileptic amnesia (103), a syndrome commonly associated with temporal lobe seizures and typically characterised by episodes of recurrent, brief anterograde and retrograde amnesia that often occur on awakening. ALF has also been observed in Alzheimer's disease (104) and investigated in vascular dementia (105).

People with transient epileptic amnesia and ALF appear to encode information normally but only retain such memories for short periods of time with poor recall after days to weeks. Studies of ALF have used a variety of standardised and novel tests of different design (106). For example, Muhlert et al. (2010) recorded videos of events experienced by participants and tested their memory after a day, a week and three weeks later while another investigation took participants to a cafeteria and later asked them to describe the event after short and long delays (107). Recall of events and specific details were generally preserved if probed within an hour of the event. With a longer interval of 6 weeks, however, recall was poorer than matched controls. Taken together, deficits in ALF can be explained by disruption of information maintenance in memory or, potentially, at retrieval. While recollection at shorter time scales is reportedly preserved in ALF, detection of earlier deficits may have been identified if more sensitive measures were used.

Pattern separation and pattern completion, two cognitive processes thought to be mediated by the hippocampus (108,109), may provide a link between epilepsy and dementia that may also bridge the gap between short-term and longer-term memory complaints. Pattern separation and pattern completion are two complementary operations that are hypothesized to facilitate storage and retrieval of information in memory (110). The theory underpinning these two paradigms is grounded in computational and neuroanatomical models which will be discussed in following sections. Functionally, pattern separation refers to the process whereby similar stimuli are stored as *separate* neural representations, potentially to discriminate better between them. Pattern completion, on the other hand, is the process of *restoring* entire and accurate neural representations of such stimuli when presented with a partial or degraded cue. Both processes are practically important to daily life. A descriptive everyday example, depicted in Figure 1-2, is the situation in which a person can 'separately' encode and later remember similar locations of where they parked their car in the same car park amongst other cars of similar colour and model on different days (111).

1.2.5 Pattern separation and pattern completion in epilepsy and dementia

Several lines of evidence suggest these two processes may be important in both epilepsy and dementia. Firstly, pattern separation deficits have been described in older individuals (112–114), with mild cognitive impairment (115) and Alzheimer's disease (116) while Madar et al. (2021) recently reported poor pattern separation ability in a group of temporal lobe epilepsy individuals and an animal model of temporal lobe epilepsy (117). Second, one study intriguingly reported an improvement of pattern separation performance in individuals with mild cognitive impairment without epilepsy following two weeks of treatment with levetiracetam, a commonly prescribed anti-seizure medication (118). This effect correlated with suppression of abnormal fMRI hippocampal signal which was described as pathological hippocampal 'over-activity' – an increasingly recognized phenomenon in early Alzheimer's disease and mild cognitive impairment (119). The concept of abnormal brain over-activity is widely reported in epilepsy including increased fMRI signal related to inter-ictal epileptic 'spike' discharges (4,5) or abnormal connectivity within the default mode network (6,7).

Pattern separation and pattern completion may therefore offer a framework to better understand memory in health and disease, specifically epilepsy and dementia. This may lead to clinical opportunities as there are ongoing efforts to target inter-ictal epileptic activity using anti-seizure medications to improve cognitive deficits (120,121). Results, however, have been mixed as studies tend to find that some individuals show cognitive improvement when treating inter-ictal activity while others do not (122,123). One prominent double-blind crossover clinical trial using lamotrigine to target inter-ictal epileptic activity showed improvements in behaviour for a small sub-set of 61 participants who had well-controlled epilepsy at baseline (124) but another investigation in children reported deterioration in cognitive function associated with reduced centro-temporal spikes following treatment with the sulthiame (125). Nonetheless, using anti-seizure medications to try to benefit cognition may prove a promising avenue of investigation which has recently been applied to people with Alzheimer's disease. Double-blind placebo controlled cross-over studies using

levetiracetam have been initiated (126,127). One of these studies has not formally been reported (127) whilst the other demonstrated improvement in cognition in a sub-set of study participants who had baseline EEG abnormalities but not across the whole cohort (126). In view of these mixed findings, understanding the cognitive mechanisms that underlie the effects of inter-ictal activity may allow better study design or participant selection.

The next section will explore in more detail how pattern separation and pattern completion is typically assessed behaviorally in humans, what is meant by these cognitive operations from a basic cognitive neuroscience perspective and consider some controversies around accurate assessment of these two distinct but related hippocampal-related processes.

1.3. Pattern separation and pattern completion: a framework for memory encoding and retrieval

1.3.1 Current pattern separation tasks in the literature

How is pattern separation and the effect of similarity typically assessed in humans? Behavioural tasks of pattern separation generally focus on mnemonic discrimination using a delayed recognition task. One popular paradigm, termed the 'Mnemonic Similarity Task', involves presentation of a set of visual objects (example in Figure 1-2). After a delay, participants are presented a series of probes and asked to identify whether it is the same object (*repeat*), completely different (*foil/new*) or similar to the original object (*lure*) (128). There are different levels of similarity between objects and their lures.

Pattern separation is inferred based on retrieval error. A measurement called the 'lure discrimination index' is calculated from the correct rejection accuracy when identifying *lures* (similar objects but not the same as shown during encoding). Some studies control for a bias in responding 'similar' by subtracting the rate that new objects are identified as similar (129). Other pattern

separation paradigms employ verbal stimuli, using English words (130), or more abstract visual stimuli (131,132).

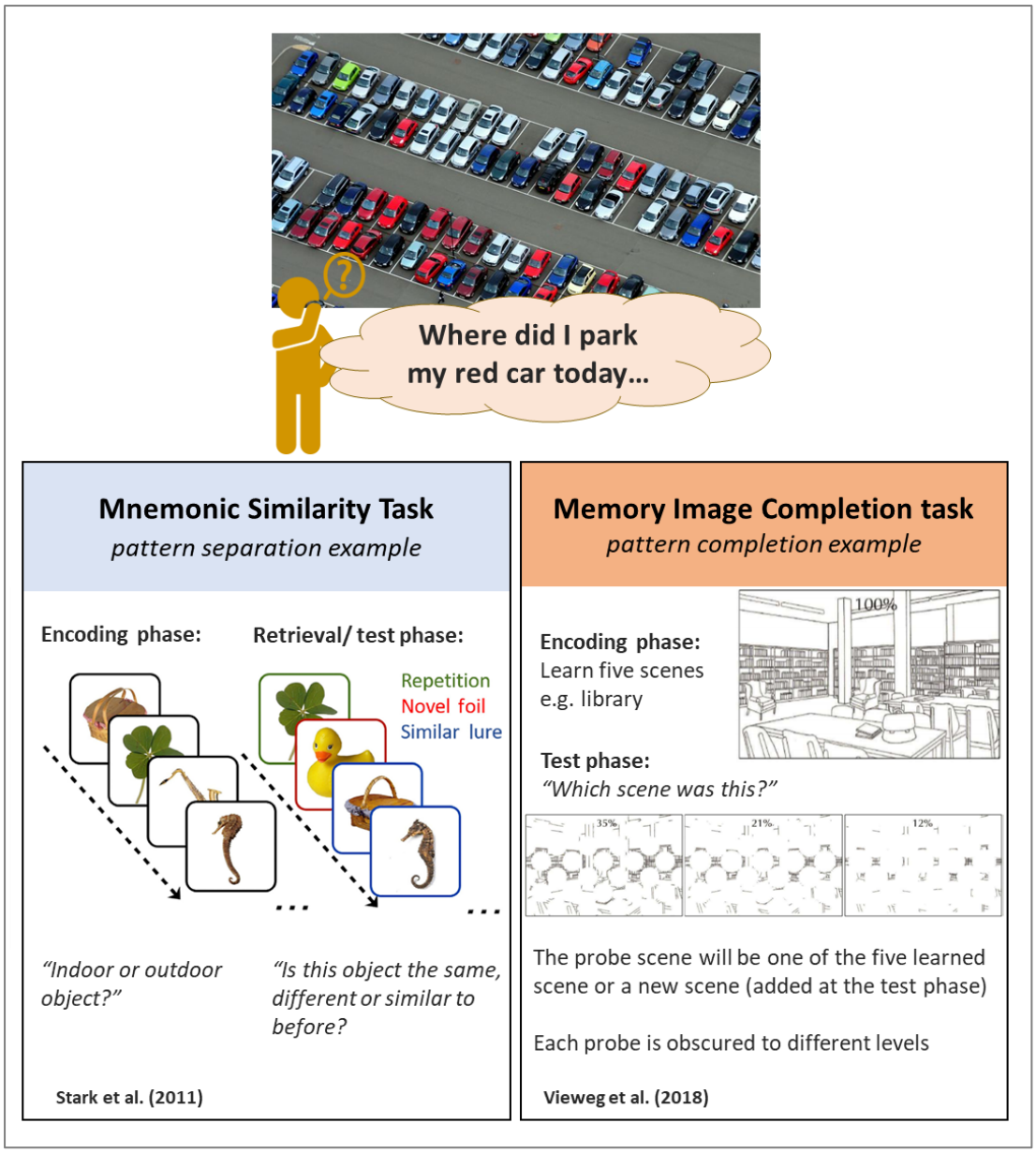


Figure 1-2. Pattern separation and pattern completion – examples current tasks

A practical example (top) where a person will need to separately encode the location of their parked car amongst other cars of similar appearance and similar locations of previous days. Later, they will need to retrieve this information upon re-entering the car park. The Mnemonic Similarity Task is a popular pattern separation task (bottom left) where participants are shown a series of objects during the encoding phase. Following a delay, they are shown another set of objects which are either the same (repeat), new (foil) or similar (lure). The memory image completion task is an example of a pattern completion task (bottom right). Participants learn five scenes during an encoding phase. During a test phase they have to identify which of the learned scenes is depicted by a partially obscured probe, or if it is a new scene.

In general, tasks of pattern separation predict a linear relationship between index of discrimination and level of similarity between corresponding encoding stimulus and probe (129). This can be problematic because similarity is indexed in different ways and often using subjective measures. For example, the Mnemonic Similarity Task uses everyday objects and similar 'lures' which have a similarity score from 1-5 based on a subjective rating (114). Other tasks employ an objectively measurable stimulus alteration design, such increasing rotation of everyday object pictures (133). Whether the task uses a parametric or non-parametric measure of similarity is important for interpretation of the results.

1.3.2 Current pattern completion tasks in the literature

Tasks designed to probe pattern completion tend to use partial or noisy cues. The 'Memory Image Completion' task uses a visual delayed recognition paradigm where participants learn a set of scenes during the training phase and are then asked to identify the learned scenes, masked to different degrees, with new scenes mixed in (134). As expected, accuracy for correctly identifying learned scenes decreased when scenes were more masked/covered. A pattern completion metric termed as a 'bias' towards pattern completion was derived by subtracting the accuracy of identifying a new scene (not present during the training phase and participants would choose 'none of these') from the accuracy of identifying previously learned scenes. However, this pattern completion 'bias' could either arise from incorrectly *separating* a degraded new scene from an old scene (discrimination error), or incorrectly completing scenes which they have learned previously, an error in *completion*. Inclusion of a new scene during the probe phase might introduce a confusing element of pattern separation during the probe phase in some trials which would be difficult to disentangle from pattern completion.

Another example of a pattern completion paradigm examines learned direct or indirect associations between multi-element 'events' comprised of three words (135,136). For example a participant is shown the three words "cup-Obama-house" during encoding and later will be tested with "cup-?-

house". This tasks assesses whether elements are stored as coherent representations by the hippocampus and retrieved holistically when one element is presented (considered a partial cue). Another example of a pattern completion paradigm examines how well participants learn spatial locations based on different numbers of available location cues (137).

1.3.3 Neurocomputational models of pattern separation and pattern completion

While the two previous sub-sections describe current behavioural tasks in the literature, pattern separation and pattern completion have specific historical reference to computational cognitive operations based on neuronal models which incorporate anatomy of the hippocampus. David Marr (1970) described his theory of the archicortex (hippocampus) to act as a 'temporary content-addressable memory unit' whereby events, represented by a pattern of activity in a selected population of neurons, are stored and subsequently reactivated in full upon re-presentation of a small part of this pattern (138). This process was thought as 'technically necessary' to store raw sensory information directly and temporarily, prior to further processing in the neocortex. Marr contended that the function of the neocortex was to reorganise and classify information and discard according to usefulness. It would therefore be inefficient to store transient information in the neocortex and another structure would be needed (139). Furthermore, computational modelling of such a structure would substantiate the logic behind his ideas using formal mathematical reductions of descriptive and mechanistic theories (140).

The hippocampus is well suited to combine different information modalities from various cortical areas to form a contextual memory *snapshot* (141). Marr's early model described a tri-synaptic network where information passes from the entorhinal cortex to the dentate gyrus and then to CA3 of the hippocampus. This represented a coherent structure to allow model predictions, refine our understanding of pattern separation and completion and offer a mechanistic basis for long term memory (142–144).

1.3.4 Pattern separation at the dentate gyrus

Theoretical models describe the divergence of synaptic projections from the entorhinal cortex onto the granule cell layer of the dentate gyrus as a key contributor to pattern separation (in the rat, there are ~200 000 neurons in the entorhinal cortex) (145). Neuronal projections then re-converge, via mossy fibre projections, to the pyramidal CA3 neurons (~160 000 neurons in the rat).

Pattern separation is theoretically implemented as neural activity from the entorhinal cortex is transmitted to the dentate gyrus leading to a sparse representation within an expanded neuronal space (also known as expansion coding). Due to the dentate gyrus having comparatively many more neurons, two neural activity patterns from the entorhinal cortex will have a low probability of activating the same neuronal subpopulation and overlapping entorhinal cortex patterns would become 'separated' at the dentate gyrus (see Figure 1-3 A for a schematic representation of pattern separation). Such minimization of overlap is a property of a competitive network model aimed to *reduce interference between patterns* before reaching CA3 (143,146).

1.3.5 CA3 as an auto-associative network

A unique characteristic of CA3 neurons, unlike cortical regions, is the predominant connection with other CA3 neurons (145). This extensive 'recurrent' network has been modelled as an auto-associative network that facilitates pattern completion through rapid retrieval of stored information in response to a partial or degraded cue (Figure 1-3 B). The CA3 network can represent memories as stable, persistent activity patterns known as *stable point attractors or basins* (143). Furthermore, the hippocampal CA3 system is ideally situated to combine information from different cortical areas and form a memory *snapshot* which may incorporate visual stimuli and other sensory input with contextual information (141). The CA3 neurons project to CA1 neurons via the Schaffer collaterals which then connect to neocortical areas. Based upon these neuroanatomical models, pattern separation and pattern completion are distinct processes within this two-layer model.

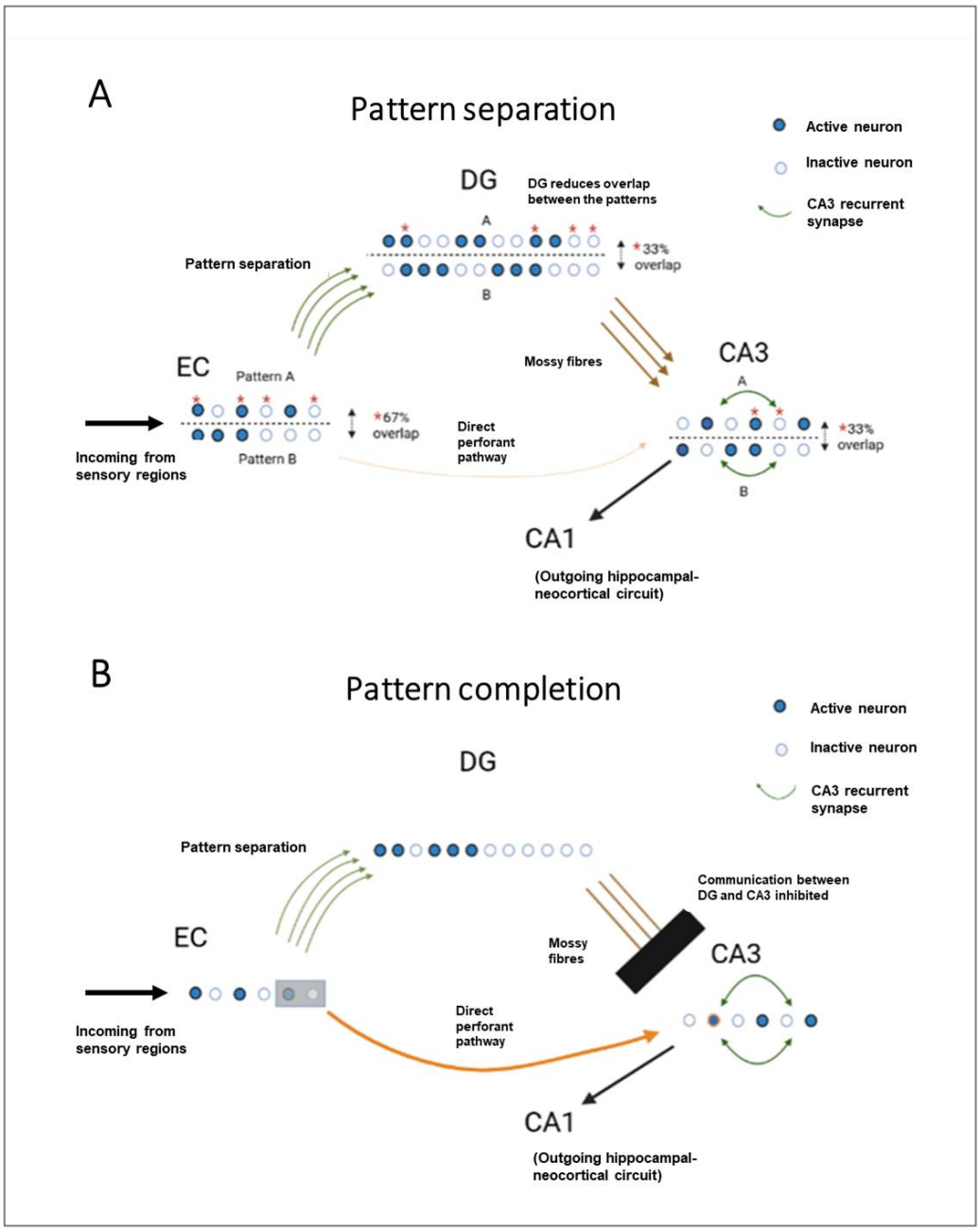


Figure 1-3. Schematic representation of pattern separation and pattern completion when a pattern of activity arrives from the entorhinal cortex and travels to hippocampal subfields.

A, Pattern separation performed as two similar patterns of neural activation come from sensory brain regions into the EC and are transmitted to the dentate gyrus which has comparatively more neurons. Sparse representations are created with less overlap between the patterns within the dentate gyrus. These are then transmitted, via mossy fibre projections, to CA3 for encoding. The CA3 neurons project to CA1 neurons via the Schaffer collaterals, which has neocortical connections **B,** A schematic for pattern completion whereby a partial cue arrives to the EC and is transmitted directly to CA3 where it activates the recurrent network leading to restoration of the original pattern. Note that the partial cue neural pattern may also be transmitted to the dentate gyrus occur but this will out-competed by the neuronal activity of the restored pattern in CA3. EC-entorhinal cortex, DG-dentate gyrus, MF- mossy fibres

1.3.6 Unresolved question in the literature

Pattern separation and pattern completion offer an intriguing framework to consider encoding and retrieval of information in memory. These cognitive processes may also help us understand information retrieval in the context of short- and longer-term memory as pattern separation should be a key component of restoring a previously stored representation after seconds as well as over hours to days. However, several fundamental questions remain. First, how do these two theoretically distinct processes – pattern separation and completion – map onto human behaviour? Second, can distinct measures of pattern separation and pattern completion be obtained from a single cognitive task? Although this should be possible based on theoretical models, no current task achieves this.

1.4 Measuring pattern separation and pattern completion in a single behavioural task

Designing a behavioural task to examine both pattern separation and completion is difficult because, despite being theoretically distinct, *both* processes are related and involved with encoding and retrieving information from memory (see Hunsaker et al. (2013) for a review of animal and human literature and Liu et al. (2016) for a systematic review of human tasks).

A potential misconception within the literature is that pattern separation and completion are two ends of a unitary spectrum rather than being distinct processes (147,148). This misconception occurs partly because tasks often have one behavioural outcome, i.e. the participant is correct or incorrect, and many studies interpret that if a pattern has not been *discriminated* from a previous pattern, then pattern separation did not occur and erroneous pattern completion to a previously stored item in memory must be responsible for the outcome (114,115,149). Alternatively, newer behavioural tasks often only focus on either pattern separation or pattern completion without considering the

confounding effect of the other process (150–152). This section will critically review features of behavioural tasks in respect to concurrent measurement of pattern separation and pattern completion tasks, explore why they do not successful index both pattern separation and completion and then consider whether it is possible to measure both in a single behavioural task.

1.4.1 Two ends of a unitary spectrum?

One measure of concurrent pattern completion from the same paradigm is derived from the Mnemonic Similarity Task using everyday objects whereby the false alarm rate (when similar items are labelled as 'old') is used as metric for *erroneous* pattern completion activity, or 'over-activity'(114,149,153,154). This could in fact be a misinterpretation of the false alarm behavioural response. Alternative explanations for the false alarm response include that the original stimuli was poorly encoded during initial presentation leading to incorrect discrimination during the probe phase. This was suggested by a study that found that false alarm rates were related to differential saccade focus during encoding rather than retrieval (155). The original stimuli may also be forgotten following encoding and vulnerable to subsequent memory interference. This may explain worse performance associated with a longer delay between stimulus and probe, regardless of similarity, in a continuous version of the Mnemonic Similarity Task (156). Therefore, I argue that pattern completion should *not* be considered as the inverse of pattern separation in a single task.

1.4.2 Are pattern separation and pattern completion behaviourally dissociated?

Being distinct operations, it should be possible to test pattern separation and pattern completion independently. One strategy has been to sequentially apply a task focussed on pattern separation followed by a pattern completion-specific task and correlate the findings. A case study of a patient with bilateral dentate gyrus damage reported poorer mnemonic discrimination of similar items in the mnemonic similarity task, suggesting a reduced pattern separation ability, along with performance on the memory image completion task which showed similar accuracy for identifying previously learned images at all levels of completeness however significantly worse accuracy on

identifying the new scenes (157). This was reported as both poor pattern separation ability and a bias towards pattern completion, however, these findings may simply be due to difficulty discriminating new objects and new scenes explained by pattern separation deficits which would be consistent with dentate gyrus damage. Another study applied this sequential pattern separation then pattern completion task approach in healthy individuals and show no significant correlation between the respective metrics (158).

1.4.3 A gap in the pattern separation and pattern completion field

Therefore, there is a pressing need to show that pattern separation and pattern completion can be measured independently within the same task to support underlying theoretical models. It might indeed be that both operations are inversely coupled so that poor ability to orthogonalise neural representations goes together with increased ability to also restore full representations from a partial cue. However, it would be incorrect to assume this. Furthermore, there ought to be conditions, including situations of selective damage, that would lead to deficits in both processes. Having a way to assess this would help investigate and explain memory difficulties.

A potential solution to this problem is to employ two experimental manipulations to test pattern separation and completion, respectively, within the same task. This may not be easy to achieve, however, as a single manipulation is likely to affect both the pattern separation and pattern completion process. Careful design consideration is required including stimuli similarity, probe completeness and type of probe question. Furthermore, any manipulation to assess pattern separation should be performed on different dimensions to those used to test pattern completion. Measuring the two cognitive processes in such a way will provide an opportunity to obtain distinct measures in a single task. This will be explored empirically in this thesis.

1.4.4 Computational modelling of pattern separation and pattern completion

Several computational models of pattern separation or pattern completion have been developed to complement and explore the underlying neuroanatomical theory described above. Such models bring several advantages to the field of cognitive neuroscience by creating controlled environments to study complex concepts such as encoding and retrieval of information in memory. Predictions can be tested in an expanded parameter space that is not easily achieved in human or animal studies. Importantly, computational models can simulate disease and "the patient" which is a valuable and scarce resource.

A popular model of pattern completion is the Hopfield autoassociative network, a variation of a recurrent artificial neural network (159), that has origins in information data storage and retrieval (160). Hopfield networks have also been used in the field of memory research and, in particular, as a model for the CA3 autoassociative network found in the hippocampus (108). Units interact via a Hebbian learning rule which reflects a biological strengthening of synaptic weights when learning occurs. Figure 1-4 provides a visual explanation of memory encoding and retrieval performed by a Hopfield network.

While several other models of pattern completion (161) and pattern separation exist (162–164), Hopfield autoassociative models offer a good opportunity to better understand pattern separation and pattern completion in health and disease. To this extent, combining behavioural testing with computational modelling to test and refine predictions that pattern separation and pattern completion could be measured distinctly and would be a valuable addition to the field.

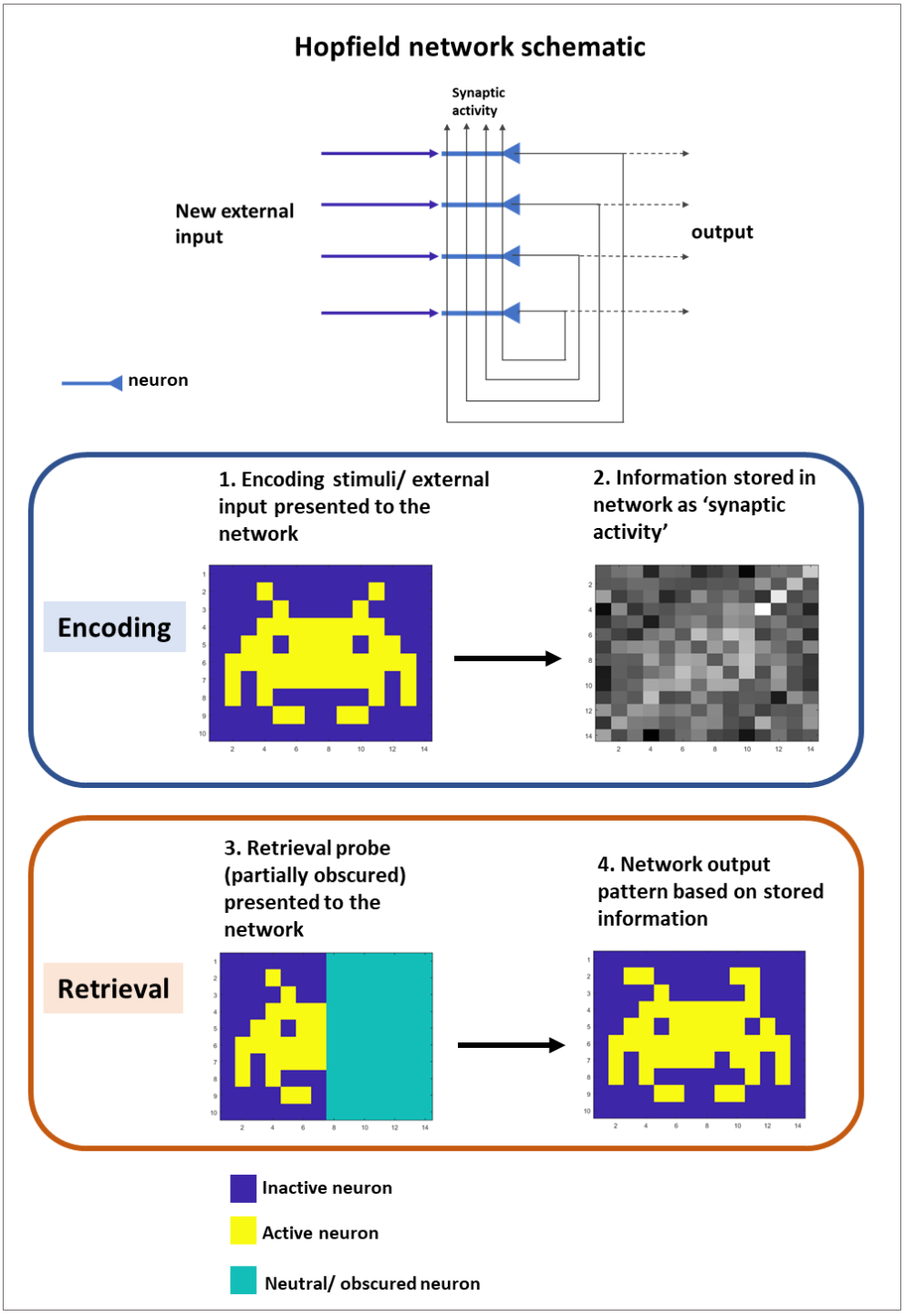


Figure 1-4. Autoassociative neural network to model information encoding and retrieval

Schematic representation (above) of an autoassociative network, adapted from Rolls (2013) (165) Information presented to the network is stored as synaptic activity between neurons. Each neuron is connected to all other neurons in the network. A visual example (below) using a 'picture' derived from active or inactive neurons which are ***encoded*** in the network. In this example, each row of the stimuli is encoded as an item into the network to be encoded. The network can later be presented an image or partial image and will ***retrieve*** the full image based on stored representations.

1.5 Mechanisms of cognitive impairment in epilepsy

In the above sections, I have presented evidence that epilepsy is consistently associated with cognitive difficulties and, potentially, an increased risk of developing dementia compared to the general population. This is important in view of the aging epilepsy population and the high incidence of epilepsy in older individuals (166). However, the extent and exact nature of this cognitive impairment is poorly understood as studies often report a broad and inconsistent range of cognitive domains being affected. I propose that exploring underlying mechanisms between epilepsy, cognitive impairment and dementia is important to understanding the scale and nature of this question.

There are three main mechanistic pathways which link epilepsy with cognitive impairment and dementia. Cardiovascular risk is increasingly considered an important risk factor for brain health and dementia risk in recent years. Broadly, improving overall cardiovascular health may reduce the population prevalence of dementia by up to 15% and represents a major public health priority (166). However, even in healthy individuals, the relationship between individual cardiovascular risk factors and cognitive function has been difficult to elucidate and impact on brain structure is poorly understood. Furthermore, there have been few studies that has established the impact of having multiple cardiovascular conditions on dementia risk due studies having small sample sizes or inadequate follow-up duration. It is important to gain such understanding in healthy individuals before considering changes in neurological disease. In this thesis, I ask the following questions:

1) What is the relationship between a composite score of cardiovascular risk and executive function? How are changes in specific risk factors, such as blood pressure, associated with worse cognitive outcomes? Can consideration of grey and white matter structural networks better explain the impact of cardiovascular risk factors over traditional brain imaging markers of vascular health such as white matter lesions?

I investigate these questions using data from the UK Biobank, a large prospective cohort of over half a million healthy individuals, who had demographic, cognitive and health measurements obtained at study baseline. Chapter 1 examines data on 22,059 individuals who attended for neuroimaging which included structural volumetric, white matter diffusion tractography and white matter hyperintensity sequences. A composite cardiovascular health score was derived including smoking pack years, waist-to-hip ratio, history of hypertension, high cholesterol and diabetes. An executive function summary statistic was derived from performance on different working memory and reaction time testing. A structural equation model was created to better understand the complex relationship between these variables and other physiological parameters such as age.

2) What is the impact of having multiple cardiovascular or metabolic conditions on risk of developing dementia? How does this compare with genetic risk of developing dementia?

Using the UK Biobank, in chapter 2, I investigate the association between cardiometabolic multimorbidity and the risk of developing all-cause dementia over the study follow-up period (up to 15 years). Cardiometabolic multimorbidity was defined as having a history of diabetes, myocardial infarction and stroke at baseline assessment in the study based on prior literature. From a mortality perspective, having all three of these conditions increases the risk of dying in a multiplicative manner compared with having individual or pairs of these conditions (167). It is not immediately obvious if the same relationship exists between multimorbidity and dementia outcomes. There may be an additive or sub-additive effect of multimorbidity as work from animal models suggest that these conditions affect common pathological pathways (168). To put the impact of cardiometabolic multimorbidity in context, I also examine the effect of genetic factors on developing dementia as quantified by a comprehensive polygenic risk score developed from a meta-analysis of genome-wide association studies (GWAS) of risk loci associated with Alzheimer's disease (169). Understanding dementia risk in the context of cardiometabolic multimorbidity and genetic risk is important from a public health and personal individual perspective.

3) Does epilepsy increase the risk of developing dementia and how does this compare with other common neurological conditions such as stroke and migraine? How does cardiovascular health impact the risk of dementia associated with having epilepsy?

Building on the previous lines of investigation in healthy individuals, in chapter 3, I examine the risk of developing all-cause dementia associated with having epilepsy compared to other neurological conditions of stroke or migraine based on UK Biobank data. I hypothesized that having either stroke or epilepsy will significantly increase dementia risk with stroke likely to be associated with the highest risk, considering the close relationship between cerebrovascular disease and vascular dementia (170). Whether migraine is a risk factor for dementia is an interesting question as there are mixed results described in the literature (171). Furthermore, I considered the impact of cardiovascular risk factors on the relationship between epilepsy and dementia by incorporating the composite cardiovascular risk score described in chapter 1.

4) Can pattern separation and pattern completion be distinctly measured in a single task? Do these hippocampal-related functions offer a mechanism underlying cognitive difficulties seen in people with epilepsy?

Following a broader investigation of cardiovascular health on cognition and dementia in healthy individuals and people with epilepsy, in chapter 4, I take a close look at hippocampal-related cognitive function that may be impaired in people with epilepsy. I designed a novel behavioural task called the 'Memory Pinhole Task' to provide distinct measures of pattern separation and pattern completion. This was achieved by manipulating similarity and pattern completeness through different dimensions of the same memory stimuli and helps to resolve an existing tension in the literature. I then applied this task to healthy young, healthy older individuals and people with epilepsy to examine how memory is affected.

5) Can the same neural network simulate both pattern separation and pattern completion? How does modelling the results of the Memory Pinhole task inform us about underlying processes which affected in epilepsy and aging?

The Memory Pinhole Task identified specific deficits in pattern separation and pattern completion across healthy aging and people with epilepsy. In chapter 5, I used a neural network of memory encoding and retrieval to model the results of the Memory Pinhole task. This model should simulate better accuracy when memory probes are more similar to encoding stimuli (pattern separation) and when the memory probe is more complete (pattern completion). To gain a better mechanistic understanding, I examined whether differences in behavioural performance can be explained by changing parameters in the network such as bias and available neuronal populations.

Chapter 2. Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing

2.1 Chapter summary

Healthy cognitive ageing has become an important societal and public health priority as the global population grows older. Cerebrovascular risk factors increase the likelihood of dementia in older people but their impact on cognitive ageing in younger, healthy brains is less clear. The UK Biobank provides cognition and brain imaging measures in the largest population cohort studied to date. I show that cognitive abilities of healthy individuals (N=22 059) in this sample are detrimentally affected by cerebrovascular risk factors. Structural equation modelling revealed that cerebrovascular risk is associated with reduced cerebral grey matter and white matter integrity within a fronto-parietal brain network underlying executive function. Notably, higher systolic blood pressure was associated with worse executive cognitive function in mid-life (44-69 years), but not in late-life (>70 years). Importantly during mid-life, for people taking anti-hypertensives, this association did not occur in the systolic range of 110 – 140 mmHg suggesting that there is an effective treatment window which can be targeted for cognitive benefit. Here I report evidence that cerebrovascular risk factors impact directly on brain structure and cognitive function in healthy people. Targeted management of such risk factors may, therefore, have the potential to optimise trajectories of healthy cognitive ageing.

2.2 Introduction

As the world's ageing population becomes one of the most significant societal transformations of the twenty-first century (172), understanding healthy cognitive ageing has become a critical public health priority. Two key questions have emerged. First, are there modifiable factors that can protect or improve cognition as people age? Second, what changes within brain networks underpin cognitive decline as humans grow older (173)? Several lines of evidence suggest that cerebrovascular risk factors might potentially have a significant impact on cognitive trajectories (174) and are associated with neuroimaging markers that are considered to have disruptive effects on brain networks critical for cognitive function (175). However, the strength of inferences that can be made on the basis of current findings is quite limited, either because of relatively small sample sizes or highly variable results. Moreover, many studies have used dementia or pre-dementia (mild cognitive impairment, MCI) as primary outcomes (176), and are based on relatively insensitive clinical measures such as the mini-mental state examination (MMSE). Such indices would not be capable of detecting some of the mild cognitive changes that occur during ageing which can be subtle but nevertheless significantly impact daily quality of life (177).

Notwithstanding these limitations, the results from several different cohorts suggest that cerebrovascular risk factors might be an important target to protect brain health and thereby reduce the risk of developing dementia. For example, a community-based study followed 6330 non-demented individuals, aged 45-99 years, and showed that midlife diabetes and impaired glucose tolerance conferred an increased risk of dementia (178,179). More recently, a community-based investigation in the US reported that mid-life hypertension is a significant risk factor for later-life dementia (*N*=4761) (180). However, a study of 465 UK individuals, aged 69-71 years born on the same week, found no evidence that blood pressure (BP) during early adulthood into midlife affected pre-clinical Alzheimer cognitive scores (64) or cerebral amyloid-β pathology, measured by positron emission tomography (PET), despite showing an association with reduced brain volumes. Therefore,

the results from several investigations of hypertension and risk of developing dementia have been inconsistent (181). Other risk factors variably implicated in increasing dementia risk in the literature include body-mass index, hypertriglyceridemia and smoking (182,183).

In addition to these disparate findings relating to long-term dementia risk, the relationship between cerebrovascular risk factors and current cognitive function in people without dementia or MCI also remains unclear. Several studies have suggested an association between cerebrovascular burden and cognition in healthy cohorts (reviewed, for example here (184)). However, most investigations have assessed the presence of vascular risk factors or risk factor modification and related these to global cognition, using either MMSE or composite cognitive scores (185–189). One recent study has reported a benefit of statin and blood pressure-lowering medication using a more sensitive digit-symbol substitution score in healthy people without any known cardiovascular disease (190). Overall, however, to the best of my knowledge there has been no clear demonstration of a parametric effect of risk factors (e.g., BP level, rather than simply presence or absence of hypertension or BP lowering treatment) associated with systematic differences in cognitive performance. This represents an important gap in current knowledge.

In addition, the strength of any conclusion regarding the impact of cerebrovascular risk factors – or their modification – on cognition would be most convincing if they were shown to be accompanied by changes in brain structure, ideally in a large sample in which cognitive function was concurrently measured with tests that are more sensitive than the MMSE or other global measures of cognition. However, to date, we lack data from a large-scale investigation that combines sensitive measure of cognition with modern brain imaging markers to provide more definitive conclusions.

It is well established that cerebrovascular risk factors are associated closely with the macroscale marker white matter hyperintensities (WMH) (191) on magnetic resonance imaging (MRI). WMH have generated significant interest as a key marker of cerebrovascular burden in the ageing brain (192,193). However, reports of their effect on cognitive function has been variable. While some

studies have concluded that there is a deleterious association between WMH and speed of processing or working memory (194,195), others showed no such relationship(196). Advances in neuroimaging now allow more precise estimation of microscale degeneration of grey and white matter in complex brain networks. The frontoparietal network is especially vulnerable to grey matter atrophy (197) and white matter degeneration (198) in aging (199,200), associated with significant cognitive consequences (201,202). White matter degeneration has specific cognitive effects, with the integrity of tracts connecting frontal and parietal regions impacting upon executive cognitive function, while integrity of tracts connecting posterior and visual regions is related to visual memory (202). Integration of advanced MRI measures of microstructural network integrity therefore has the potential to provide early and sensitive markers of the impact of cerebrovascular burden, and may improve mechanistic models of its neurocognitive consequences. However, few studies have leveraged the combination of clinical assessment, task-based cognitive tests and multi-modal neuroimaging in large populations.

To summarise, the existing literature leaves several important unanswered questions. What are the effects of cerebrovascular risk factors on cognitive function in healthy people across the lifespan? And is it possible to show a relationship, in a parametric manner, between a risk factor such as blood pressure level and cognition? Does treatment of a modifiable risk factor, such as hypertension, affect cognitive function? If so, is there a range of blood pressure over which this treatment has an impact? Finally, does the integrity of a distributed brain network underlying a specific cognitive function explain decline in that function across the lifespan as a result of cerebrovascular burden?

Here, in the most extensive cross-sectional study to date, I investigated data from the UK Biobank, a large population cohort of over 500 000 middle-to-older age individuals who underwent medical, sociodemographic and cognitive assessment between 2006 and 2010(203). I examined data from 22,059 individuals from the UK Biobank who also attended for multi-modal neuroimaging. Previous studies have examined the relationship between either cardiovascular risk and brain health, or

between brain health and cognition, or between cognition and individual cardiovascular risk factors. Given the large sample, I was able to include all these variables into one large, complex model that allowed us simultaneously to examine multiple relationships and establish how cerebrovascular risk and grey *and* white matter integrity in a frontoparietal network relates to cognitive decline, specifically with respect executive function, in healthy ageing.

My study objectives were three-fold. First, I aimed to better understand the relationship between cerebrovascular risk factors and cognition, by characterising the effect of each risk factor on a continuous measure of executive function. Second, I investigated the potential effects of risk factor modification, focussing on how hypertension treatment affects the relationship between systolic blood pressure and executive function. Third, I tested the role of the frontoparietal network in the relationship between age, cerebrovascular risk factors, WMH and executive function using structural equation modelling (SEM). Semi-partial correlation and mediation analysis were used to quantify directional relationships between MRI markers of brain health and their impact on cognition to develop a mechanistic model of neurocognitive aging.

2.3 Methods

Participants

The UK Biobank recruited 500 000 people aged 40-69 between 2006 and 2010, of which 100 000 will have brain imaging alongside the detailed health, demographic and cognitive assessments. Magnetic resonance imaging (MRI) data from 22 059 people were available when the study was conducted under the UK Biobank application numbers 32011 and 8107. All participants provided written, informed consent and the study was approved by the Research Ethics Committee (REC number 11/NW/0382).

I excluded individuals with a history or current diagnoses of neurological disease, brain injury, stroke, transient ischaemic attack, subdural or subarachnoid haematoma; infection of the nervous system; brain abscess, haemorrhage or skull fracture; encephalitis, meningitis, chronic neurological problem, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's or Alzheimer's disease, epilepsy, head injury, alcohol, opioid and other dependency according to the non-cancer illnesses codes (http://biobank.ndph.ox.ac.uk/showcase/coding.cgi?id=6).

Cognitive Testing

Cognitive tests were administered via touchscreen on the same day as the MRI scan. Data from a pairs matching and simple reaction time task were analysed, indexing executive function and speed of processing respectively(204). In the pairs matching task, participants memorised the position of six pairs of matching cards presented simultaneously. The cards were then turned over and participants were required to touch the locations of the matching pairs with as few attempts as possible. The number of errors made was recorded. The simple reaction time task was a variation of the card game, Snap. Participants were required to press a button when two simultaneously presented cards matched. Mean reaction time over 12 rounds was recorded. Trials in which responses were below 50ms were excluded as they reflected anticipation and trials over 2000ms were excluded as the cards were no longer visible at this point.

Cerebrovascular risk score

I calculated a cerebrovascular risk (CVR) score as the sum of known risk factors for cerebrovascular and brain health including hypertension, hypercholesteremia, smoking, diabetes, high waist-to-hip ratio (WHR) and apolipoprotein-E (*APOE*-ε) polymorphism status (Supplementary Figure S2-1c). I chose not to use cardiovascular risk scores (such as the Framingham risk score(205)) as these require specific measures, such as high density lipoprotein (HDL) levels which were not available from the UK Biobank at the time of analysis. These scores are used to calculate risk of future cardiovascular events whereas I am interested in cerebrovascular burden on neurocognitive health.

Blood pressure was measured automatically on an Omron digital blood pressure monitor, or a manual sphygmomanometer when the automated monitor was not available. The average across two readings, taken moments apart, for diastolic and systolic blood pressure (BP) was used. The threshold for hypertension was set at 140/90 mmHg according to the NICE guidelines for hypertension management(206). Both the diastolic and systolic BP reading above the threshold was required to be classified as hypertensive and increase the CVR score. Taking cholesterol or blood pressure lowering medication increased the CVR score. Waist-to-hip ratio was calculated as the ratio between waist circumference and hip circumference measured manually in centimetres. The threshold for WHR as a cerebrovascular risk was set according to WHO guidelines for each sex(207).

Diagnosed diabetes increased the CVR score by one. Smoking status included those who currently smoke or were past smokers based on pack year history, calculated as the daily number of cigarettes divided by 20 (pack size) and multiplied by the number of years smoking. The number of years smoking was estimated by the age an individual stopped smoking (or age at scan if current smoker) minus the age smoking was started. The number of pack years was adjusted for those who gave up smoking for more than six months. Important to my pack year calculation, the UK Biobank only collected information on number of cigarettes smoked in ex-smokers if they indicated that they smoked on “most or all days”. An equivalent of 10-50 pack years increased the CVR score by one and greater than 50 pack years increased the score by two. Carrying *APOE* ε3/3 alleles did not increase the CVR score, but ε4 carriage increased the score by one point for heterozygous carriers and two points for homozygous carries, based on the known risk to cardiovascular disease(208) and the development of sporadic dementia(209). Genotyping was conducted by Affymetrix for UK Biobank using bespoke Axiom arrays(210).

MRI data acquisition and analysis

Imaging data were acquired on a Siemens Skyra 3T scanner with a 32-channel head coil. The full imaging protocol including acquisition details is openly available

(https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Of relevance to this study, a T1 weighted, 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence with 1mm isotropic resolution, a T2 weighted fluid attenuated inversion recovery (FLAIR) sequence (1.05x1x1mm resolution) and a diffusion weighted, 2mm isotropic voxel spin echo multiband echo-planar sequence, with 50 *b*=1000 s mm and 50 *b*=2000 s mm diffusion weighted volumes (100 encoding directions) were acquired. Imaging data were processed and quality checked using an automated pipeline that is openly available (211). The pipeline produces imaging derived phenotypes (IDPs), summary information for each imaging modality. A subset of the IDPs provided by UK Biobank were used for the work in this thesis. An overview of the analysis that had been used to generate the IDPs is given below.

White matter hyperintensity load estimation

The FLAIR image was gradient distortion and bias field corrected and linearly registered to the T1 image and to Montreal Neurological Institute (MNI152) atlas space. White matter hyperintensity segmentation was carried out using the Brain Intensity Abnormality Classification Algorithm (BIANCA) (212). BIANCA is a fully automated method for classifying voxels based on relative intensity and spatial features (such as distance to ventricles). The output is a probability map that is thresholded at 0.8 to produce a binary map of lesion location and total WMH burden in mm^3.

Grey matter volume estimation

The key stages of the T1 processing pipeline included correction for gradient distortion, registration to MNI 152 space, segmentation into grey matter, white matter and cerebrospinal fluid (CSF) using FAST (fMRIB's automated segmentation tool) and bias field correction(213). The volume of different tissue types and whole brain volume (grey and white matter) were estimated using SIENAX(214). Regional cortical grey matter volumes were normalised for head size. I examined grey matter volume in frontoparietal cortex (Figure 2-1.c) using the canonical frontoparietal functional network derived by Yeo et al.,(215). The Yeo et al., (2011) network parcellation is based on clustering

performed on resting state fMRI data in 1000 subjects. I took the peak coordinates from each of the nodes in the frontoparietal control network (see Supplementary Table S2-3 for MNI coordinates and field IDs of IDPs) and found the IDPs that best spatially overlapped with this peak coordinate. For each region, grey matter volume was summed across hemispheres.

Neurite Orientation Dispersion and Density Imaging

Traditional measures of white matter microstructure such as fractional anisotropy and mean diffusivity are based on a crude diffusion tensor model that cannot distinguish contributions to white matter structure from intracellular and extracellular water. These indices also lack sensitivity to complex crossing fibre architecture present in over 90% of white matter connections(216). Multicompartment models such as neurite orientation dispersion and density imaging (NODDI) aim to be more biologically plausible than simple ellipsoid based tensor models and estimate neurite density (intracellular volume fraction) and measures of tract coherence and complexity (orientation dispersion)(217).

Diffusion weighted images were corrected for eddy currents and head motion using FSL's eddy tool and then gradient distortion corrected. NODDI modelling was implemented using the AMICO (Accelerated microstructure imaging via convex optimization) toolbox to generate IDPs representing intra-cellular volume fraction (ICVF) and orientation dispersion (OD). NODDI maps were aligned to a standard space white matter skeleton using optimised registration methods(213). IDPs for 48 tracts derived from the John Hopkins University tractography atlas were generated by averaging NODDI indices within each mask. The IDPs representing NODDI indices for the superior longitudinal fasciculus were extracted for use here (Figure 2-1.d). The superior longitudinal fasciculus is a major associative tract known to support the frontoparietal network in monkeys and humans(200,218). Intracellular volume fraction (ICVF) is the fraction of restricted versus unrestricted diffusion and a measure of neurite density. Orientation dispersion is a measure of angular variation indexing the configuration of axons in which smaller values are associated with tighter bundles (Figure 2-1.b).

Head size and scan-date-derived confounds were regressed out of all imaging IDPs before further analyses as they are known confounds(219).

Statistical analysis

Calculations were performed in Matlab R2018a or in R, using the Lavaan package(220) for structural equation modelling. For preprocessing, all variables were median absolute deviation normalised. Total WMH load was cube root transformed to correct for a heavily skewed distribution. Three latent variables were estimated using confirmatory factor analysis (CFA). A major advantage of the use of latent variables is control of measurement error, which can artificially reduce the relationship between measured variables in standard univariate analyses but this effect is strongly attenuated in SEM(221). Latent variables also allow a continuous representation of multiple measures which may not be easily combined otherwise. A latent variable representing speed of processing and executive function was estimated (performance in the simple reaction time and pairs matching task). Speed of processing and executive function are the cognitive domains that show the steepest declines in aging (26) and are most frequently associated with cerebrovascular burden(222). Given their frequent covariance I reasoned that they may be indexing a latent variable, which for simplicity I termed, Executive Function. Latent variables for white matter integrity of the superior longitudinal fasciculus (orientation dispersion and intra-cellular volume fraction), and grey matter integrity (IDPs representing grey matter volume in the frontoparietal network) were estimated in the same model (Supplementary Figure S2-1). There are reliable and robust decreases in fractional anisotropy with increasing age, but the measure is not specific to the underlying cause of integrity changes. The NODDI measures of ICVF and OD index neurite density and tract complexity, respectively. A recent, in depth analysis of the microstructural measures showed that 75.71% of the relationship between age and FA was mediated by ICVF and OD(223). My latent variable for white matter integrity therefore included ICVF and OD as sensitive measures of white matter integrity within the superior longitudinal fasciculus. Finally, my latent variable representing grey matter volume of the

frontoparietal network, was based on the principle of network level structural covariance which assumes covariance amongst regions within the same network.

Multiple regression was used to examine the relationship between individual cerebrovascular risk factors and the Executive Function latent variable, adjusted for age and socio-economic status, as estimated by the Townsend Deprivation Index. The Townsend Deprivation Index is a measure of deprivation based on unemployment, home and car ownership and household overcrowding calculated according to participant postcode. The regression model was tested for multicollinearity using variance inflation factor. I set the threshold for statistical significance at $p<0.001$.

The relationship between systolic blood pressure and Executive Function was tested between individuals on antihypertensive medications and those not on antihypertensive medications. I used being on hypertension medication as a proxy for established hypertension. While similar numbers of individuals provided a self-report of hypertension, use of antihypertensive medication provided a hard index of hypertension that was less likely to be affected by recall bias and would be supported by criteria recommended by current UK NICE guidance using either ambulatory BP monitoring, home automated BP monitoring or, previously, repeated measures over several assessments following a single high reading before treatment initiation(224).

I used a model-free sliding window approach to study the relationships between the Executive Function latent variable and systolic blood pressure, and with age. This method does not assume a linear relationship. A systolic-window of observations (each containing 10% of the participants) of fixed systolic-quantile width was moved along the systolic blood pressure distribution (code: conditionalPlot.m available here: https://osf.io/vmabg/) (225),(226). I applied a smoothing gaussian kernel of 10 using the moving average method. Results from using ten fixed systolic bins, with 16 mmHg widths (rather than fixed number of observations), is shown as Supplementary Figure S2-2. Pearson correlations were calculated between Executive Function and systolic blood pressure, and Bonferroni-correction was applied. Comparison of correlation co-efficients between participants on

antihypertensives and those not on antihypertensives were done following Fisher's r to Z transformation. Deconfounding age was performed using age-residuals within the quantile bins described above.

Path modelling was used to estimate the directional dependencies between the latent variables and observed variables. Observed variables were WMH load (total lesion volume), age (at MRI scan) and total cerebrovascular risk score. Correlated residual paths identified from modification indices were included in the model. I included correlated error between volumes in the grey matter volume latent variable on the basis that some of these regions may have participation in other structural covariance networks beyond the frontoparietal network. Missing data were assumed to be missing at random and were estimated using full information maximum likelihood which gives unbiased parameter estimates and standard errors. I compared my hypothesised structural and path model to a model excluding grey matter volume and a model excluding white matter integrity (by fixing all paths that included these variables to zero). An identical structural equation model replacing the frontoparietal network regions and SLF with regions and tracts associated with the language network was used to test the specificity of my findings to the frontoparietal network (Supplementary Figure S2-3, Table S2-5).

Semi-partial correlations and mediation analyses were conducted to estimate the directional influence of brain imaging variables to executive function for the purposes of clarifying the mechanisms underlying executive dysfunction in healthy ageing. Mediation analysis was run in Lavaan, with nonparametric bootstrapping with 10000 iterations to estimate direct and indirect effects between variables.

2.4 Results

2.4.1 Population characteristics of 22 059 healthy ageing adults

Clinical, demographic, cognitive and brain imaging data were analysed in 22 059 people from the UK Biobank aged 44-73 (mean age 62, SD 7) at the time of their MRI scan (Figure 2-1., Supplementary Table S2-1). The APOE allele frequency, an established genetic risk factor for Alzheimer's disease, within this cohort was 76% with ε3/3 allele, 19% with one ε4 allele and 1% having ε4/4 genotype, similar to expected numbers of a representative Caucasian population (227). Five percent of the cohort were diabetic, 21% were on cholesterol lowering medication and 22% were on antihypertensive medication. Smoking rates were relatively low, reflecting UK Biobank characteristics, with 78% classified as non-smokers (228).

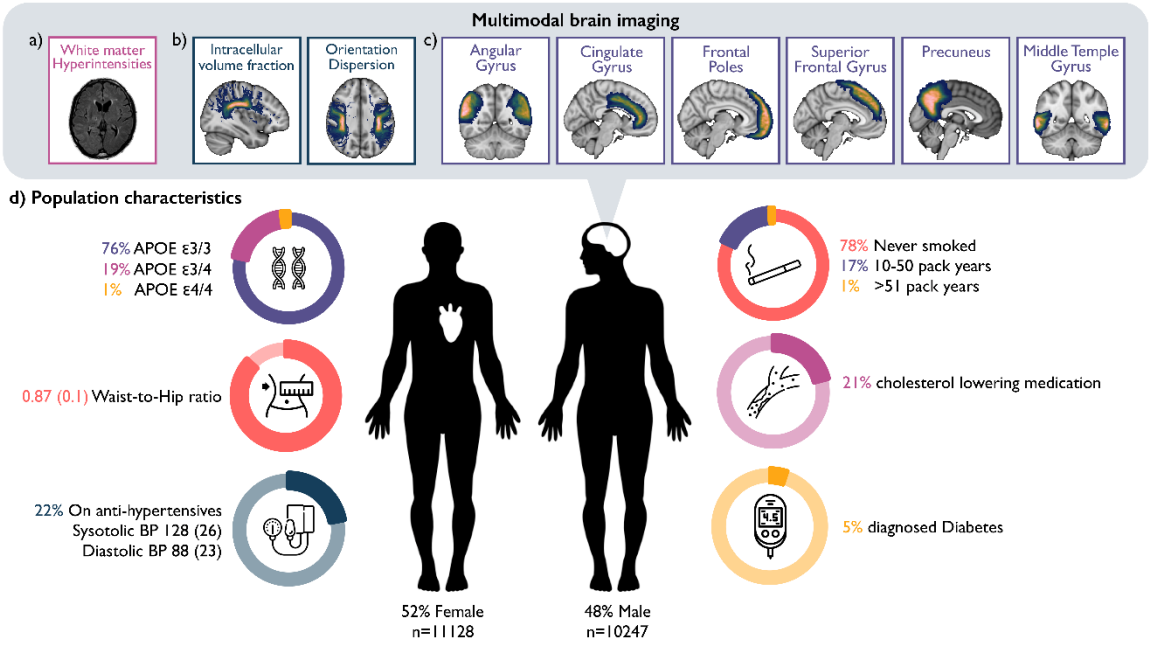


Figure 2-1. Population characteristics and multimodal imaging of 22 059 healthy ageing adults.

Multimodal imaging - **a)** estimation of white matter hyperintensity load, **b)** measures of white matter integrity and **c)** grey matter volume in the frontoparietal network. **d) Population characteristics** – including mean systolic and diastolic blood pressure in mmHg (standard deviation). These characteristics are used to derive a total cerebrovascular burden risk score. APOE: apolipoprotein E; BP: blood pressure.

2.4.2 Cerebrovascular risk predictors of Executive Function

I used confirmatory factor analysis to estimate a continuous latent variable representing Executive Function. This latent variable predicted performance in the simple reaction time task and pairs matching task (standardised beta estimates 0.49 and 0.25 respectively, $p<0.001$, see Supplementary Table S2-4). Multiple regression with the Executive Function latent variable as the dependent variable and with age, socioeconomic status and individual cerebrovascular risk factors as covariates was significant, $F(8,15330)=1010$, $p<0.0001$, explaining 35% of the variance in Executive Function. Age was the strongest predictor (Table 2-1.) followed by antihypertensive medication use, having diabetes and APOE status. I used these cerebrovascular risk factors to derive a risk score to represent total cerebrovascular burden within individuals and related it to measures derived from the multimodal neuroimaging in the structural equation model.

Table 2-1. Cerebrovascular risk predictors of Executive Function

Variable	Unstandardized beta estimate	Standard Error	Standardized beta estimate	t	p
Intercept	2.86	0.06		45.66	0.0001
Waist to hip ratio	0.03	0.06	0.003	0.50	0.616
Smoking Status	-0.03	0.01	-0.02	-2.92	0.004
Medicated cholesterol	-0.03	0.01	-0.02	-2.42	0.016
Medicated hypertension	-0.07	0.01	-0.04	-5.66	0.0001
Diabetic	-0.09	0.02	-0.03	-4.05	0.0001
APOE ε status	-0.04	0.01	-0.02	-3.60	0.0003
Age at assessment	-0.06	0.001	-0.57	-81.99	0.0001
Socio-economic status	-0.01	0.002	-0.03	-3.86	0.0001

Abbreviations: APOE, apolipoprotein E

2.4.3 Relationship between blood pressure and Executive Function

Further analysis focused on whether systolic blood pressure (SBP), a continuous variable, predicted Executive Function. In addition, I examined the effect of using antihypertensive medication, which can be considered to be a robust index of established hypertension. Sliding window analysis revealed a graded reduction in Executive Function performance with increasing SBP in individuals not taking antihypertensive medication (Figure 2-2a). Participants on antihypertensives (with established hypertension) had lower corresponding Executive Function than those not on medication, significantly different when comparing correlation coefficients following Fisher's r to z transformation ($z= -3.87$, $p < 0.001$). For these individuals on antihypertensives, Executive Function was stable for the SBP range less than 140 mmHg, while SBP measurements >140 mmHg was associated with a decline in Executive Function.

I regressed out the confounding effects of age using quantile-based, age-residual analysis. Figure 2-2b shows the relationship between age and SBP while Figure 2-2c displays the relationship between age and Executive Function. From this, I calculated and plotted the age-residuals for SBP against Executive Function showing a significant relationship for those not taking antihypertensives (Pearson correlation $r= -0.155$, $p <0.001$, Figure 2-2d) and those who are on antihypertensives (Pearson correlation $r= -0.093$, $p<0.001$, Figure 2-2e), demonstrating significant relationships after controlling for age. For those on antihypertensives, however, the relationship was significantly weaker ($z= -3.84$, $p<0.001$).

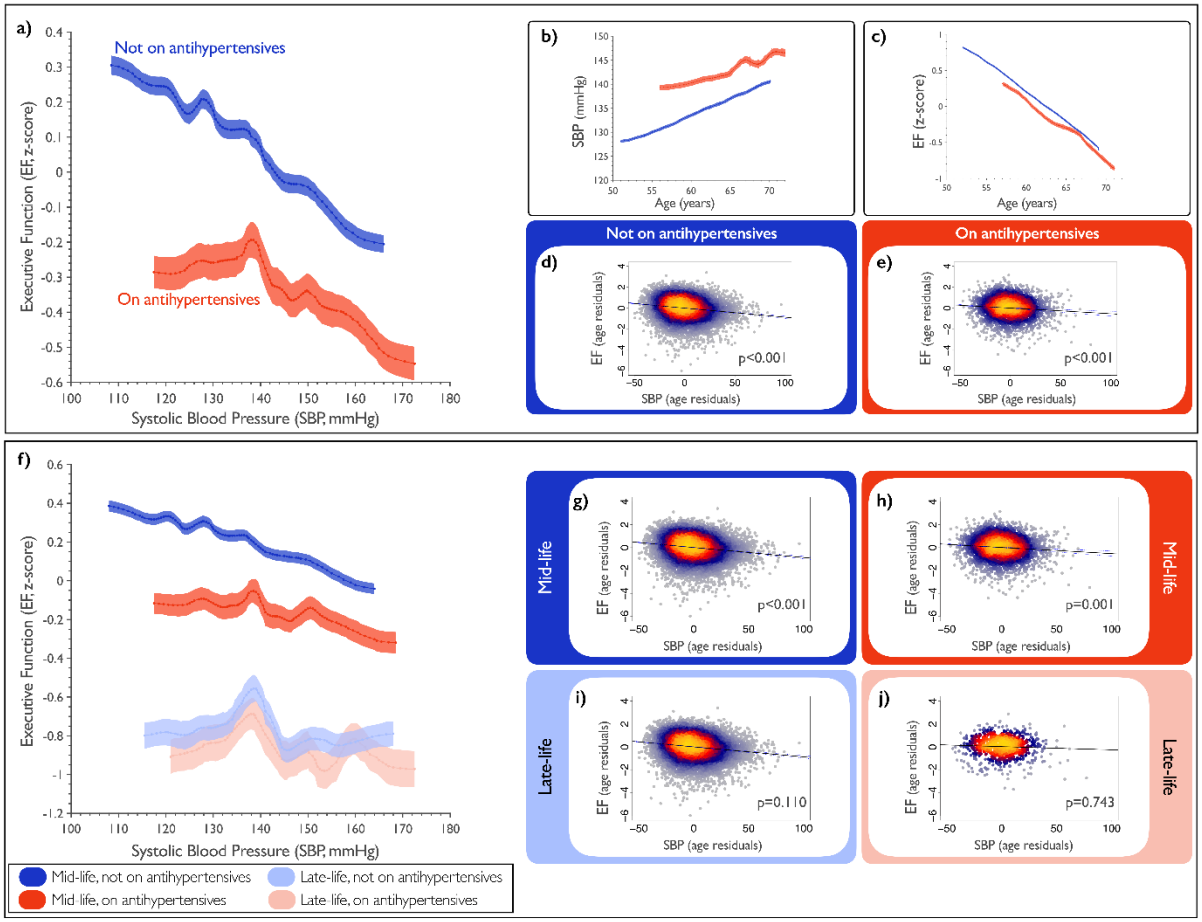


Figure 2-2. Relationship between blood pressure and Executive Function.

a) Higher systolic blood pressure, SBP, was associated with lower Executive Function, EF, for both participants who were on antihypertensives and those who were not. For those on antihypertensives, there was a non-linear relationship as EF was not associated with a decline for SBP measurements <140 mmHg (EF standardised into z-score, a-c, f: shaded area represents standard error around the mean.. b) and c) SBP increased with age, while EF declines with age, respectively for participants who take antihypertensives and those who do not. d) and e) Association between EF and SBP using age-residuals (adjusting for age) for participants who were not on antihypertensive medication (Pearson correlation, r = –0.155, 95% CI [-0.172, -0.139], p<0.001, n= 16410) and participants who are (r = -0.093, 95% CI [-0.126, -0.060], p<0.001, n= 4699) with the difference between correlation coefficients being significant following Fisher r to Z transformation, z=-3.84, p<0.001). f) When considering age groups, higher SBP was associated with lower EF in mid-life (44-69 years) participants but not in the late-life (70-73 years) group (shaded area represents standard error). g) and h) Age-adjusted analysis between SBP and EF for participants not on an antihypertensives (r = -0.134, 95% CI [-0.152, -0.115], p <0.001, n= 13242) and those who were on antihypertensives (r = -0.062, 95% CI [-0.100, -0.024], p=0.001, n= 3071) , within the mid-life group (difference between group correlation coefficients, z = -3.62, p<0.001). i) and j) Same relationship in the late-life group showing no significant correlation between SBP and Executive Function regardless of whether they were on antihypertensive medication (r = -0.056, 95% CI [-0.1247, 0.0129] , p=0.110, n= 1869 and r = 0.008, 95% CI [-0.0416, 0.0582], p=0.743, n=949. SBP- systolic blood pressure, EF- executive function, CI- confidence interval

2.4.4 Blood pressure and Executive Function in mid- and late-life

Next, I examined the relationship between SBP and Executive Function, in the context of antihypertensive medication, in two age groups: midlife (44-69 years) and late-life (>70 years) (Figure 2-2f). The patterns observed above in the entire population (Figure 2-2a) were present in the mid-life group, but crucially not in the late-life group. When controlling for age, the relationship between SBP and Executive Function was significant for the mid-life group for both individuals on antihypertensives ($r= -0.06$, $p=0.001$) and those who were not on such medication ($r= -0.13$, $p<0.001$) (Figure 2-2g and Figure 2-2h), with a significant difference between the correlation co-efficients ($z= -3.63$, $p<0.001$). For the late-life group, once age was controlled, there was no significant relationship between SBP and Executive Function, either for those on ($p=0.743$) or not on antihypertensives ($p=0.110$; difference between correlation co-efficients was also not significant, $p=0.106$) (Figure 2-2i and Figure 2-2j).

2.4.5 Frontoparietal network integrity predicts Executive Function

Structural equation modelling was used to quantify the multivariate, directional relationships between age, cerebrovascular risk burden, WMH load, frontoparietal grey matter volume, white matter integrity and Executive Function with path model relationships based on current literature. The frontoparietal network was selected due to close association with executive and cognitive control mechanisms(218). The same analysis was performed on a control, language network (Supplementary Figure S2-3).

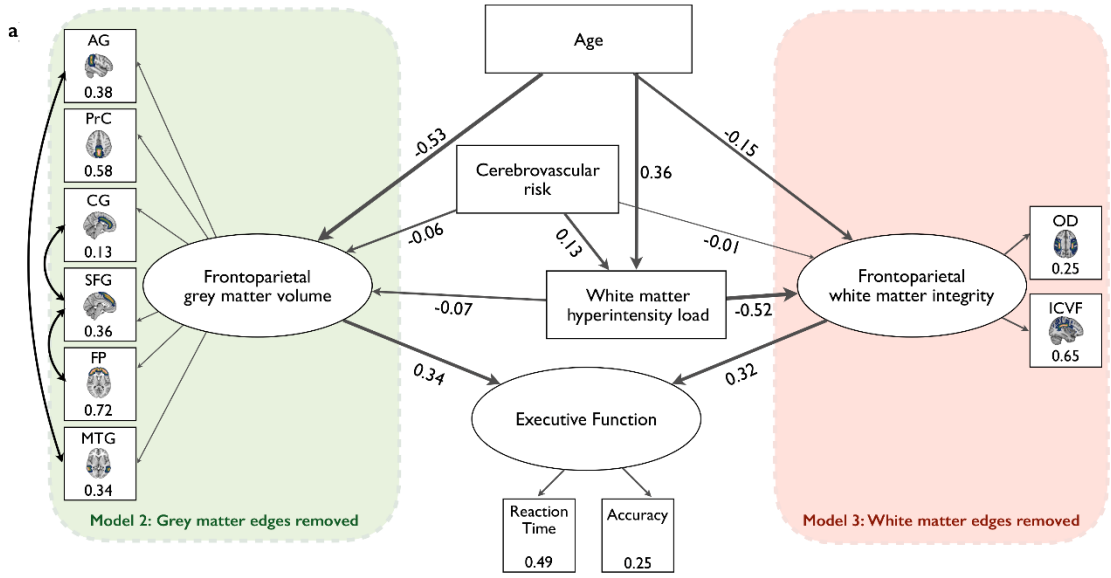
In my full path model (Figure 2-3), all relationships were in the expected direction. All paths were significant, $p<0.001$, except for the path between cerebrovascular risk and frontoparietal white matter integrity. Increasing age resulted in reduced frontoparietal grey matter volume and frontoparietal white matter integrity, and increased WMH load, reflecting age-related brain changes. Cerebrovascular risk was a better predictor of WMH load ($\beta=0.13$, $p<0.001$) than grey matter volume ($\beta=-0.07$, $p<0.001$) or white matter integrity ($\beta=-0.01$, $p=0.26$, Supplementary Table S2-4). The path

between cerebrovascular risk and frontoparietal white matter integrity would be significant if there were no path from WMH load to frontoparietal white matter integrity. In line with my hypotheses, frontoparietal grey and white matter integrity were strong predictors of Executive Function. The strength of the relationship between frontoparietal white matter integrity and Executive Function (β=0.34, p<0.001) and frontoparietal grey matter volume and Executive Function (β=0.32, p<0.001) were similar, suggesting important roles for both aspects of the frontoparietal network in maintaining executive function. Alongside robust model fit statistics, penalising overly complex models (Figure 2-3b), the significant paths in the expected direction provide evidence that this model is a good fit for the data.

Model comparison indices provide evidence that the model, which includes both grey and white matter structural integrity of the frontoparietal network (Figure 2-3b), better explains the relationship between cognition and WMH load than a model that excludes frontoparietal grey matter volume (Figure 2-3 green panel, CFI=0.73, RMSEA=0.08) or excludes frontoparietal white matter integrity (Figure 2-3 red panel, CFI=0.83, RMSEA=0.06). Formal comparison confirmed the full model was a better fit than either the nested model constraining white matter integrity (χ^2 (4)=2745, p<0.001) or constraining grey matter volume (χ^2 (4)=4537, p<0.001). A model including a language network as a control was a poor fit (CFI=0.82, TLI=0.79, RMSEA=0.06, Supplementary Table S2-5) for the data (Supplementary Figure S2-3), confirming effects were specific to the frontoparietal network.

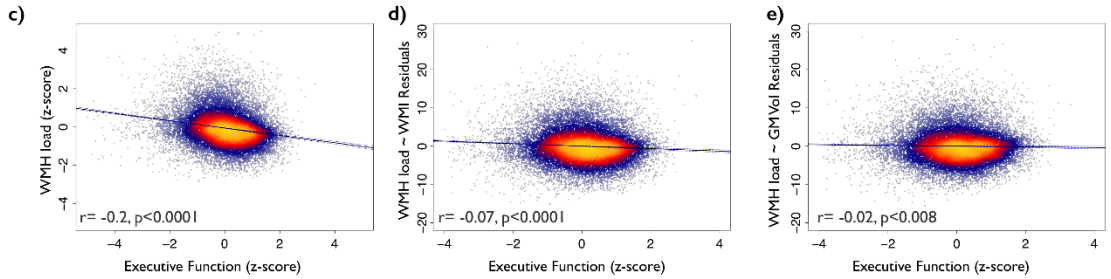
Semi-partial correlation and mediation were used to further interrogate the relationship between Executive Function and brain imaging variables. There was a significant negative correlation between WMH load and Executive Function (r=-0.20, p<0.001; Figure 2-3c). However, semi-partial correlation showed the magnitude of this relationship was significantly reduced when controlling for white matter integrity (r=-0.07, p<0.001, Figure 2-3d) and for grey matter volume (r=-0.02, p<0.01, Figure 2-3e). Therefore, much of the relationship between Executive Function and WMH load is explained

by frontoparietal network integrity. This finding may help to resolve a longstanding debate as to the impact of WMH on executive function(222), suggesting at least part of this relationship is explained by microstructural changes and grey matter atrophy of a major network responsible for executive processing. To further clarify the relationship between frontoparietal grey matter volume and white matter integrity on executive function, mediation analysis was performed (Figure 2-3f). I hypothesised that the relationship between grey matter volume and Executive Function was mediated by frontoparietal white matter integrity. In support of this proposal, partial mediation was found, with the relationship between Executive Function and frontoparietal grey volume reduced from a beta estimate 0.47 to 0.19 when controlling for white matter integrity (Figure 2-3f).



b)

	Model Fit Index	Model 1	Model 2	Model 3
CFI	Comparative fit index	0.92	0.74	0.81
TFI	Tucker-Lewis Index	0.89	0.65	0.75
RMSE	Root mean square error of approximation	0.04	0.08	0.06



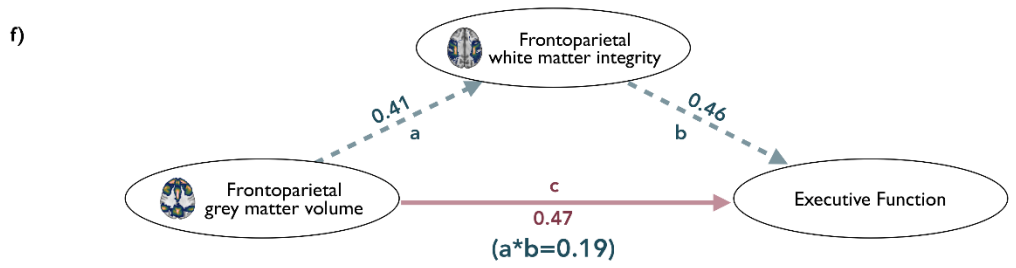


Figure 2-3. Structural equation model, semi-partial correlation and mediation analysis

a) Full structural model. All figures represent standardised beta coefficients. All paths significant to p<0.001 except the path between cerebrovascular risk and frontoparietal white matter integrity. Black arrows represent covariances. **Green box:** Indicates the frontoparietal grey matter edges that have been fixed to zero in Model 2 **Red box:** The frontoparietal white matter integrity edges that have been fixed to zero in Model 3. **b)** Model fit indices comparing nested models (green and red boxes). Semipartial correlation plots showing relationship between **c)** WMH load (z-score) and Executive Function (z-score) **d**) controlling for white matter integrity and **e**) controlling for grey matter volume. **f)** Mediation analysis. Values are standardised beta estimates. Path a: Relationship between frontoparietal white matter integrity and frontoparietal grey matter volume. Path b: relationship between Executive Function and frontoparietal white matter. Path c: Direct relationship

between frontoparietal grey matter volume and Executive Function. Figures in brackets show beta estimates for the indirect path in which the relationship between frontoparietal grey matter volume and executive function is mediated by frontoparietal white matter integrity. AG: Angular Gyrus; PrC: precuneus; CG: Cingulate Gyrus; SFG: superior frontal gyrus; FP: Frontal Pole; MTG: middle temporal gyrus; OD: orientation dispersion; ICVF: intracellular volume fraction;WMH: white matter hyperintensity; GM Vol: grey matter volume; WMI: white matter integrity.

2.5 Discussion

The results of this chapter show that combining cerebrovascular risk factors with measurements of cognitive function and neuroimaging markers of brain health leads to important and actionable insights into optimising cognitive health across normal ageing. Multivariate modelling allowed me to leverage extensive lifestyle, physiological, neuroimaging and genomic data to investigate the complex relationship between fronto-parietal network integrity, white matter hyperintensity (WMH) burden and executive function to facilitate a mechanistic understanding of how cerebrovascular risk factors affect cognitive health. Antihypertensive medication, diabetes and *APOE* status were all significant predictors of executive function. Effect sizes were significant despite being expectedly small.

In addition to identifying important associations between cerebrovascular risk and executive function, the potential mechanistic paths underpinning this process were examined statistically. Structural equation modelling supported a pathway in which cerebrovascular risk factors mediate their impact on cognition through disruption of the distributed fronto-parietal brain network underlying executive function (Figure 2-3). This importantly shifts substantial focus from macroscale markers of cerebrovascular risk, namely WMHs, to more insidious degeneration of normal-appearing grey and white matter which are already burdened through normal ageing (229). A substantial literature has debated the association between executive function and white matter hyperintensity burden (222). The data presented here statistically show that this relationship is at least in part explained by the microstructural integrity and volume of the frontoparietal network. The mediation analysis showed the relationship between frontoparietal grey matter volume and executive function

was substantially mediated through frontoparietal white matter integrity. This result supports the hypothesised process of network-wide grey matter atrophy, likely reflecting secondary degeneration from disconnection due to white matter degeneration (230).

Risk factor modification of systolic blood pressure (SBP) had a significant effect on executive function. Overall, executive function declined with increasing SBP (Figure 2-3). Individuals who were on antihypertensives, i.e., with an established diagnosis of hypertension, showed an effective systolic range below ~140 mmHg corresponding to stable executive function while, above this threshold, increasing SBP was associated with a decline in executive function. Demonstrating this threshold and effect of SBP, in a parametric manner, on a continuous score of executive function was made possible by two unique factors of this study: the large sample size of the UK Biobank and the use of a latent variable based on neuropsychological testing which is likely more sensitive than traditionally used total cognitive test scores. Intriguingly, this BP threshold actually reflects current American and European guidelines which are based primarily on end-points of cardiovascular events and associated morbidity (231,232).

The findings of the current study have the potential to provide meaningful evidence on BP targets for cognitive health in normal ageing. They are in accord with recent findings which emphasise the importance not simply to treat, but to treat effectively and monitor for response. The prospective SPRINT-MIND study (233) released results on the impact of intensive vs standard BP control (defined as <120 mmHg vs. 120-140 mmHg respectively) on cognitive impairment risk (*N*= 9361). This trial was terminated early and was considered underpowered. However, available results suggested no significant reduction in incidence of MCI (233) from aggressive BP control. The results presented in this investigation would be consistent. They show, in a parametric manner, that controlling SBP below 140 mmHg had no added benefit on executive function. Unlike previous studies which use BP levels to categorize groups, the findings presented here, using BP as a continuous variable, offer insights on a precise blood pressure target for optimal cognitive health, albeit with the caveats

associated with a cross-sectional study. These results have potentially important implications for rational treatment guidance. SBP levels above 140 mmHg are associated with a measurable detrimental impact on current executive function. Conversely, systolic levels below 140 mmHg confer no additional benefit. Therefore, very aggressive treatment of BP risks hypotension and other side-effects, without necessarily providing a positive impact on cognition.

Further age-group analysis examining mid- and late-life groups showed striking differences. SBP predicted executive function within the mid-life group, but not in late-life individuals (aged >70 years). While previous studies have suggested that higher systolic levels in mid-life may lead to worse cognitive performance in late-life (187,234), my results show the parametric benefit of hypertension treatment on current cognitive health in mid-life, but no significant effect of antihypertensives in late-life. This finding, in combination with the results of a recent study that examined dementia incidence associated with mid- to late-life BP patterns(63), emphasizes the potential importance of treating mid-life hypertension for current cognitive function as well as for later dementia risk. The data presented here suggest a therapeutic age window to modify hypertension in relation to healthy cognitive ageing and provides a strong argument for robust blood-pressure assessments and clinical decision making for BP treatment in middle-age, otherwise healthy, individuals.

In the context of large prospective cohort analysis, the findings presented here should be assessed in relation to methodological and population considerations. My observations were derived from cross-sectional data from the UK Biobank imaging cohort with fewer co-morbid diseases and from less deprived areas than the general population(228). This selection bias may affect generalisability but also reflects a healthy ageing population with effects of cerebrovascular risk being potentially larger in more population-representative cohorts. The age range of UK Biobank participants may also lead to different environmental exposures during their lifespan. UK Biobank reliance on self-reported data may introduce information bias. However, I used surrogate markers, such as

medication prescription to indicate established disease, to mitigate this when possible. Future release of prospective UK Biobank data will add a valuable temporal dimension to my interpretation, including longitudinal effect of antihypertensives on executive function and additional dementia outcomes.

In the rapidly growing context of our ageing society, the findings presented here demonstrate the relationship between key cerebrovascular risk factors and healthy cognitive ageing, within the UK Biobank cohort, with implications on lifestyle practices for middle- and late-age populations. Moreover, the results are suggestive of targeted and time-sensitive blood pressure control being beneficial to cognitive and brain health.

2.6 Supplementary Material for Chapter 2

Supplementary Table S2-1. Population demographics

Total N	22059
Sex	
Number Female (%)	11128 (52)
Number Male (%)	10247 (48)
Mean age (SD)	61.7 (7.0)
Number Midlife (44-69) (%)	17399 (90)
Number Late life (70+) (%)	1956 (10)
Median Townsend Index (IQR)	-2.7 (3.2)
Median years education (IQR)	18 (6)
Systolic blood pressure mean (SD) mmHg	128 (25.5)
Diastolic blood pressure mean (SD) mmHg	88 (23)
Blood pressure lowering medication	
ON (%)	4699 (22)
OFF (%)	16410 (78)
Blood pressure lowering medication (by age group)	
Mid-life ON (%)	2656 (19)
Mid-life OFF (%)	11316 (81)
Late-life ON (%)	807 (34)
Late-life ON (%)	1543 (66)
Cholesterol lowering medication	
ON (%)	4509 (21)
OFF (%)	16600 (79)
Smoking status	
Number never smoked (%)	13966 (78)
Number 10-50 pack years (%)	2938 (17)
Number >50 pack years (%)	293 (1)
Diagnosed diabetes	
YES (%)	1098 (5)
NO (%)	20066 (95)
APOE ε Status	
Number ε3/3 (%)	16854 (76)
Number ε3/4 (%)	4239 (19)
Number ε4/4 (%)	402 (2)
Mean waist to hip ratio (SD)	0.87 (0.1)
Male	0.93(0.06)
Female	0.81(0.07)
Mean white matter hyperintensity load (SD) mm^3	4467 (5621)

SD: standard deviation; IQR: interquartile range; APOE: apolipoprotein E.

Supplementary Table S2-2. Biobank showcase variables used in all analyses

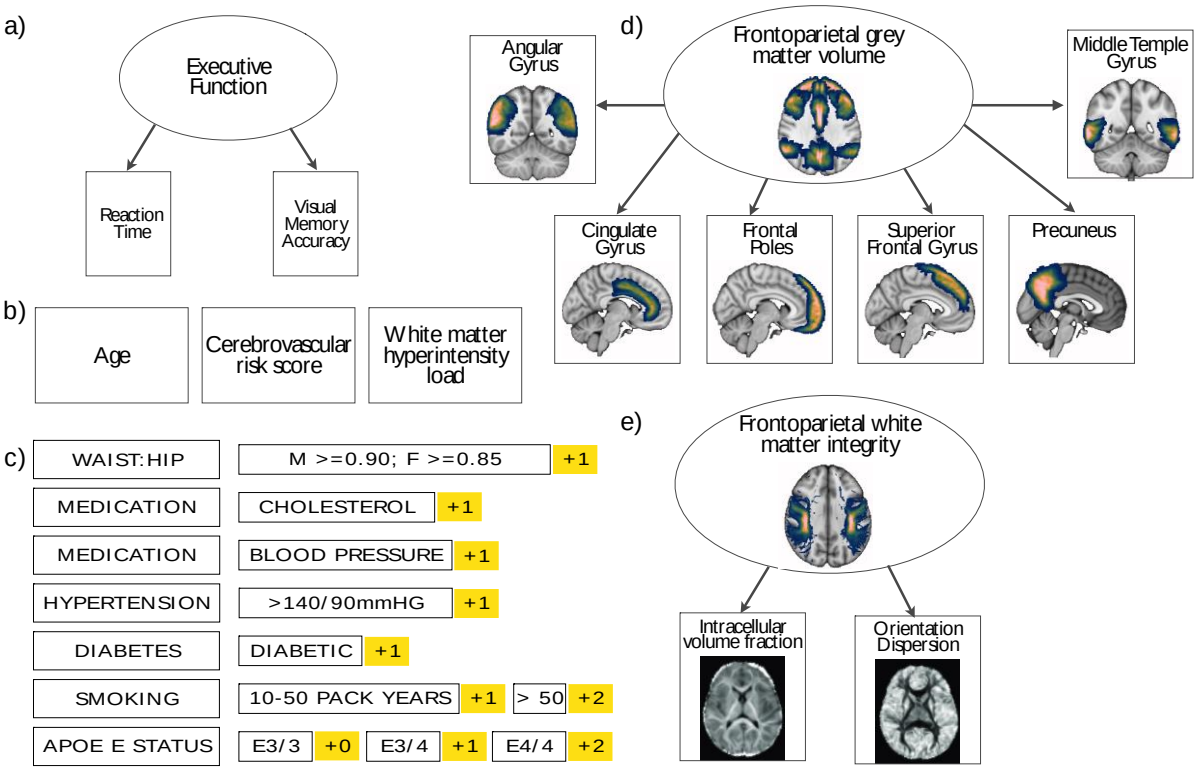
VARIABLE	FIELD ID	BIOBANK SHOWCASE LINK	INSTANCE
REACTION TIME	20023	http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=20023	2
PAIRS MATCHING ACCURACY	399	http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=399	2
PACK YEARS CALCULATION	20161	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20161	2
EVER SMOKED	20160	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20160	2
SMOKING STATUS	20116	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20116	2
NUMBER OF CIGARETTES SMOKED DAILY (CURRENT SMOKERS)	2887	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2887	2
NUMBER OF CIGARETTES SMOKED DAILY (PREVIOUS SMOKERS)	6183	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6183	2
AGE STARTED SMOKING (CURRENT SMOKERS)	3436	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=3436	2
AGE STARTED SMOKING (FORMER SMOKERS)	2867	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2867	2
EVER TRIED TO STOP SMOKING	3486	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=3486	2
STOPPED SMOKING (>6 MONTHS)	2907	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2907	2
AGE STOPPED SMOKING	2897	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=2897	2
CHOLESTEROL LOWERING MEDICATION	6177	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=6177	2
BLOOD PRESSURE MEDICATION	6177	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=6177	2
DIABETES-DIAGNOSED BY A DOCTOR	2443	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=2443	2
SYSTOLIC BLOOD PRESSURE – AUTOMATIC READING	4080	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=4080	2
SYSTOLIC BLOOD PRESSURE – MANUAL READING	93	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=93	2
DIASTOLIC BLOOD PRESSURE – AUTOMATIC READING	4079	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=4079	2
DIASTOLIC BLOOD PRESSURE – MANUAL READING	94	http://biobank.ctsu.ox.ac.uk/showcase/field.cgi?id=94	2
WAIST CIRCUMFERENCE	48	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=48	2

HIP CIRCUMFERENCE	49	http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=49	2
WHITE MATTER HYPERINTENSITY VOLUME	25781	http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=25781	NA

Supplementary Table S2-3. Coordinates for nodes in frontoparietal control network derived by Yeo et al.

Yeo et al., (2011) coordinates			Overlapping imaging derived phenotype	Field ID in Biobank Showcase
X	Y	Z		
-40	50	7	Frontal Pole	Right: 25783 Left: 25782
-43	-50	46	Angular Gyrus	Right: 25823 Left: 25822
-57	-54	-9	Middle temporal gyrus (temporo-occipital)	Right: 25807 Left: 25806
-5	22	47	Superior Frontal Gyrus	Right: 25787 Left: 25786
-6	4	29	Cingulate Gyrus	Right: 25839 Left: 25838
-4	-76	45	Precuneus cortex	Right: 25843 Left: 25842

Coordinates given in Montreal Neurological Institute (MNI) template space.



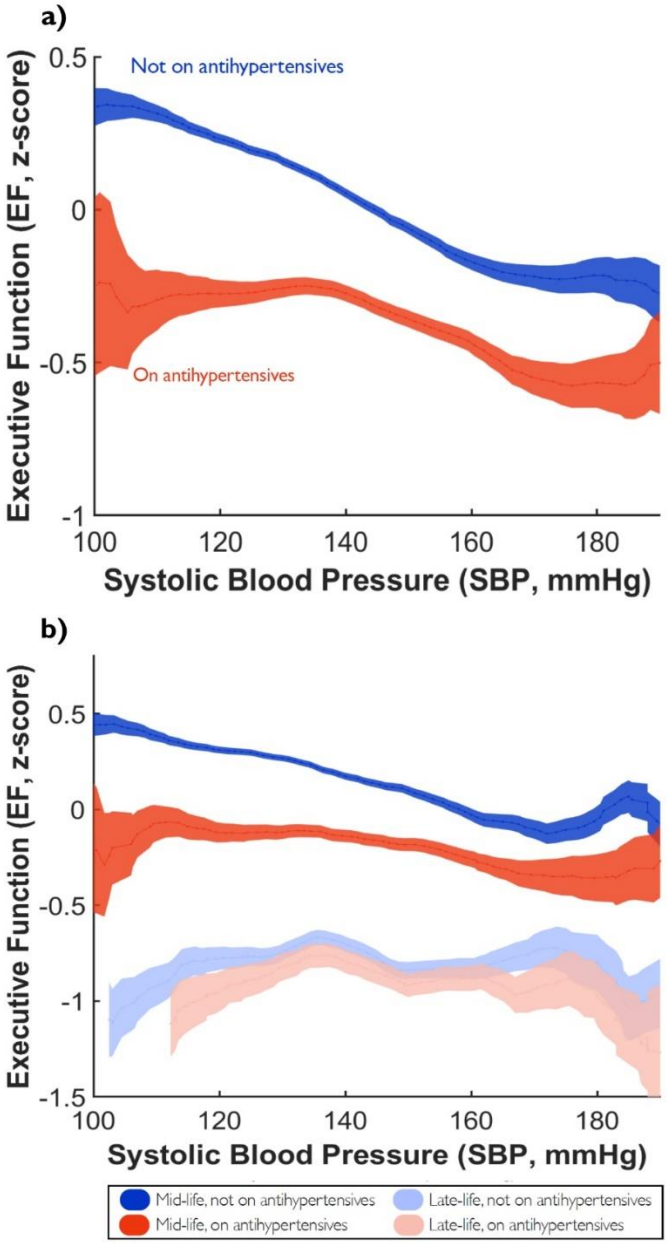
Supplementary Figure 2-1. Cognitive, neuroimaging and cerebrovascular risk factor variables

a) Executive Function latent variable b) Observed variables in the structural equation model include age, white matter hyperintensity (WMH) load and cerebrovascular risk score which is a sum of the listed risk factors with the weightings shown in the yellow boxes (c). d) Regions of frontoparietal network included in the frontoparietal grey matter volume latent variable. e) Microstructural indices of the superior longitudinal fasciculus as indicators in the frontoparietal white matter integrity latent variable.

M: male; F: female; mmHg: millimetres of mercury; APOE: apolipoprotein E.

Supplementary Table S2-4. Results of confirmatory factor analysis and path analysis. SLF- superior longitudinal fasciculus, CVR – cerebrovascular risk factor

Latent variable	Indicator	Standardised beta estimate	R^2	P-Value
Executive Function	Reaction time	0.49	0.24	0.0001
	Accuracy	0.25	0.06	0.0001
Frontoparietal white matter integrity	SLF Orientation Dispersion	0.25	0.06	0.0001
	SLF Intracellular Volume Fraction	0.65	0.42	0.0001
Frontoparietal grey matter volume	Frontal Pole	0.72	0.51	0.0001
	Angular Gyrus	0.38	0.15	0.0001
	Middle temporal gyrus (temporo-occipital)	0.34	0.12	0.0001
	Superior Frontal Gyrus	0.36	0.13	0.0001
	Cingulate Gyrus	0.13	0.02	0.0001
	Precuneus cortex	0.58	0.34	0.0001
Latent variable	**Regressor**	**Standardised beta estimate**		**P-Value**
Executive Function	Frontoparietal white matter integrity	0.32		0.0001
	Frontoparietal grey matter volume	0.34		0.0001
Frontoparietal white matter integrity	Age	-0.15		0.0001
	CVR score	-0.01		0.261
	White matter hyperintensity load	-0.52		0.0001
Frontoparietal grey matter volume	Age	-0.53		0.0001
	CVR score	-0.06		0.0001
	White matter hyperintensity load	-0.07		0.0001
White matter hyperintensity load	Age	0.36		0.0001
	CVR score	0.13		0.0001

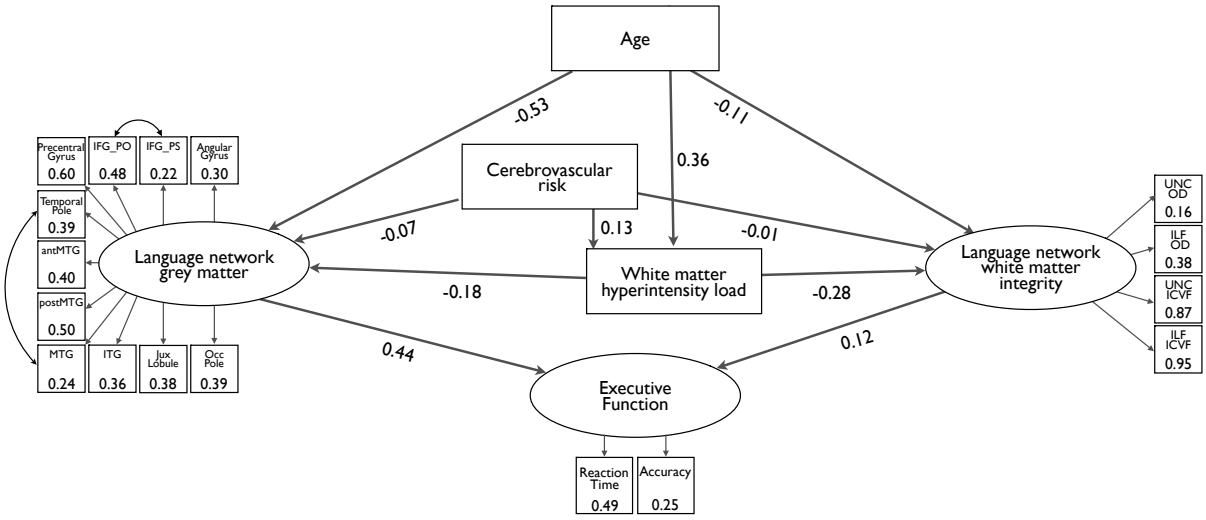


Supplementary Figure S2-2. Sliding window curves with fixed systolic-bins against Executive Function latent variable.

a) Compares participants on antihypertensives with those who are not. b) Examines participants on or not on antihypertensive in mid-life and late life groups

Control network derivation and analysis

To test whether the structural model was specific to the frontoparietal control network I tested the same model but replaced the regional grey matter volumes and white matter tracts with those relevant to the language network. I used Neurosynth (235) to do a meta-analysis of 1101 studies using the term 'language' to identify regions of the brain consistently activated in language studies. From this meta-analysis a statistical map of the most consistently activated regions, thresholded at p<0.01 (false discovery rate) was created. This was visually inspected and I manually selected the grey matter volume imaging derived phenotypes (IDPs) with the greatest overlap with the regions in the language meta-analysis mask. Tthe uncinate fasciculus and the inferior longitudinal fasciculus was chosen based on their established roles in the language network (236–238). Akaike Information Criterion (AIC) and Bayesian Information Criterion (Table 3) model fit indices, useful when two different non-nested models are compared, showed that indices for the control model (AIC= -642 894, BIC= -642589) were three times the magnitude of the full model (AIC=-214 446, BIC=-214 092).



Supplementary Figure S2-3. Control language network model. All values represent standardised beta estimates.

Abbreviations: ILF: inferior longitudinal fasciculus; UNC: uncinate fasciculus; IFG_PO: inferior frontal gyrus pars opercularis; IFG-PS: inferior frontal gyrus pars triangularis; antMTG: anterior middle temporal gyrus; postMTG: posterior middle temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus; Jux: Juxtapositional; Occ: occipital

Supplementary Table S2-5. Model fit indices comparing nested and control networks

	Model Fit Index	Interpretation	Model 1	Model 2	Model 3	Control Network
CFI	Comparative fit index	Higher is better; >0.9	0.92	0.74	0.81	0.82
TFI	Tucker-Lewis Index	Higher is better; >0.9	0.89	0.65	0.75	0.79
RMSE	Root mean square error of approximation	Lower is better; <0.06	0.04	0.08	0.06	0.06
AIC	Akaike Information Criterion	Lower is better	-214446	-209917	-211708	-642894
BIC	Bayesian Information Criterion	Lower is better	-214092	-209594	-211386	-642589

Model 1 is the full model. Model 2 is the nested model with constrained grey matter integrity. Model 3 is the nested model with white matter integrity constrained. The control network model replicated the full model using regions and tracts from a language network.

Chapter 3. Cardiometabolic multimorbidity, genetic risk and dementia: a prospective cohort study

3.1 Chapter summary

Individual cardiometabolic disorders and genetic factors are associated with increased dementia risk, however, the relationship with cardiometabolic multimorbidity is unclear. I investigated whether cardiometabolic multimorbidity increases the risk of dementia, regardless of genetic risk, and examined for associated brain structural changes.

I examined health and genetic data from 203 038 UK Biobank participants of European ancestry, aged 60 years or older without dementia at baseline assessment (2006-2010) and followed until 2021, as well as brain structural data in a nested imaging sub-sample of 12 236 participants. A cardiometabolic multimorbidity index consisting of stroke, diabetes and myocardial infarction (one point for each), and a polygenic risk score for dementia (with low, intermediate and high risk groups) were calculated for each participant. The main outcome measures were incident all-cause dementia and brain structural metrics.

Dementia risk associated with high cardiometabolic multimorbidity was three times greater than that associated with high genetic risk, hazard ratio of 5.55 (95% confidence interval 3.39 – 9.08) and hazard ratio of 1.68 (95% confidence interval 1.53 – 1.84), respectively. Participants with both a high genetic risk and a cardiometabolic multimorbidity index of two or greater had an increased risk of developing dementia, hazard ratio of 5.74 (95% confidence interval 4.26 - 7.74), compared to those with a low genetic risk and no cardiometabolic conditions. Crucially, there was no interaction between cardiometabolic multimorbidity and polygenic risk (P = 0.18). Cardiometabolic multimorbidity was independently associated with more extensive, widespread brain structural

changes including lower hippocampal volume ($F (2, 12110) = 10.70$, $p < 0.001$) and total grey matter volume ($F (2, 12236) = 55.65$, $p < 0.001$).

Cardiometabolic multimorbidity was independently associated with risk of dementia and extensive brain imaging differences to a greater extent than genetic risk. Targeting cardiometabolic multimorbidity may help to reduce risk of dementia, regardless of genetic risk.

3.2 Introduction

Stroke, diabetes and myocardial infarction are strong independent cardiometabolic risk factors for dementia (170,239–244). Cardiometabolic multimorbidity, defined as two or more cardiometabolic conditions, is rapidly rising in prevalence(245,246) and is strongly predictive of mortality (167). However, the extent to which cardiometabolic multimorbidity predicts risk of dementia and associated brain structural change is largely unknown. In addition, it is unclear how the strength of this association compares or interacts with genetic risk of dementia.

The majority of adult dementia cases are sporadic, wherein no single gene mutation is considered causative, and multiple genes influence risk (247). A meta-analysis of genome-wide association studies of people of European ancestry identified risk loci associated with late-onset Alzheimer's disease (169), in addition to the widely known ε4 allele of the apolipoprotein E gene (248). Polygenic risk scores provide a useful quantification of genetic risk by combining multiple risk alleles of generally small but cumulative effect and have shown to be predictive for all-cause dementia (249). While some studies examining polygenic risk and upstream risk factors of healthy lifestyle and cardiovascular risk suggest no interaction between genes and environment (250,251), one study has found the opposite (252). To my knowledge, no previous study has examined the relationship between cardiometabolic multimorbidity, polygenic risk and dementia incidence.

I analysed data from the UK Biobank prospective cohort to test the hypothesis that both cardiometabolic multimorbidity and genetic risk were independently associated with the risk of incident dementia and brain structural measures. I determined the extent to which low cardiometabolic multimorbidity is associated with reduced risk of dementia among participants with different genetic risk as this may have important implications for a targeted approach for dementia risk reduction, taking into account an individual's genetic risk.

3.3 Methods

This study is based on data from the UK Biobank(203) that received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Multicentre Research Ethics Committee. All participants provided informed consent through electronic signature.

Study population

The UK Biobank is a population-based cohort of more than 500 000 participants, aged 40 to 73 years, who underwent assessment in one of 22 centres across the United Kingdom between 2006 and 2010 (203). Participants provided biological samples, completed touch-screen questionnaires and physical examination. A sub-group of participants re-attended for brain imaging between 2014 and 2020 (253). For this study, analyses were restricted to individuals aged at least 60 years at baseline who had genetic information available (N= 203 038, and an imaging sub-sample N=12 236 participants). I restricted the analysis to participants aged 60 or older since most sporadic dementia occurs in older individuals and to reduce the likelihood of identifying cases with monogenic risk of early-onset dementia. Participants with prevalent dementia at baseline, history of central nervous system infection, encephalitis, meningitis, amyotrophic lateral sclerosis, multiple sclerosis, previous subdural or subarachnoid haemorrhage were excluded. All baseline diagnoses in this study were based on a combination of self-report and hospital inpatient records (information on UK Biobank codes are found in Supplementary Table S3-1). Certain variables, such as stroke diagnosis, were previously derived by the UK Biobank by combining these different sources of information and have been validated elsewhere (254).

Cardiometabolic multimorbidity

A primary objective was to investigate the relationship between stroke, diabetes and myocardial infarction with dementia risk as several studies show that the combination of these conditions

contribute significantly to mortality(167), and separately to dementia risk (239,240). First, to explore the impact of each condition, I derived an 8-level categorical variable by separating participants into mutually exclusive groups according to baseline prevalent diseases of: (1) stroke, (2) myocardial infarction, (3) diabetes, (4) stroke and myocardial infarction, (5) stroke and diabetes, (6) myocardial infarction and diabetes, (7) diabetes, stroke, and myocardial infarction, (8) none of these (the reference group). Next, a cardiometabolic multimorbidity index was calculated for each participant whereby the three cardiometabolic conditions were considered as separate binary variables and a point was assigned based on the presence or absence of the condition, and ranged from 0 (none of the conditions) to 3 (all conditions). This approach would allow better comparison with polygenic risk.

Dementia diagnosis

All-cause dementia was established using hospital inpatient records or from death register linkage data as an underlying/ contributory cause. Diagnoses were documented using the International Classification of Diseases (ICD) coding system using ICD-9 and ICD-10 codes for Alzheimer disease and other dementia classifications (Supplementary Table S3-1).

Polygenic risk score

A polygenic risk score, reflecting each participant's Alzheimer's disease-related genetic risk was constructed as has been described in detail previously (see eMethods from Lourida *et al.*) (250). The polygenic risk score was based on the results of a genome-wide association study of individuals of European Ancestry and includes the Apolipoprotein E (APOE) region (169). The present study, therefore, was restricted to individuals whose self-reported racial/ethnic background was white (British, Irish, or other white background). Single nucleotide polymorphisms (SNPs) associated with Alzheimer's disease that were common and available in the UK Biobank were selected using "clumped results", referring to the most significant variant per linkage disequilibrium block (N = 249 273, with an inclusion threshold P<0.5). The number of associated alleles were weighted

according to their association strength with Alzheimer's disease (169), summed, and then z-standardized to derive a polygenic risk score. Polygenic risk was grouped according to quintiles as low (quintile 1), intermediate (quintiles 2, 3 and 4) and high risk (quintile 5) categories.

Covariates

All models were adjusted for age; sex; education, categorized as higher (college/university degree or other professional qualification), upper secondary (second/final stage of secondary education), lower secondary (first stage of secondary education), vocational (work-related qualifications), or other; socioeconomic status (categories derived from Townsend deprivation index(255) quintiles 1, 2 to 4, and 5, combining information on social class, employment, car availability, and housing); third-degree relatedness of individuals in the sample; the first 20 principal components of ancestry; and assessment centre. Models including the polygenic risk score were adjusted for the number of alleles included in the score to account for SNP-level variation (250).

Brain imaging measures

Magnetic resonance imaging (MRI) data were acquired on a Siemens Skyra 3T scanner including high-resolution, T1-weighted, 3D magnetization-prepared gradient echo structural images and a T2 weighted fluid-attenuated inversion recovery images. The full imaging protocol and processing pipeline have been previously described(256). I used imaging summary statistics (imaging derived phenotypes) of total hippocampal, grey matter and white matter hyperintensity. Median absolute deviation was used to exclude outliers (257), and volumes were adjusted for potentially confounding baseline measures of age, age squared, head size and imaging site (256).

Statistical analysis

Hazard ratios (HRs) were calculated using Cox proportional hazards regression models with time to incident all-cause dementia as the dependent variable. I calculated HRs for each of the seven mutually exclusive cardiometabolic multimorbidity groups compared with the baseline group having

no cardiometabolic conditions. For my main model, I tested the association of cardiometabolic multimorbidity index and genetic risk groups with time to incident all-cause dementia (nine categories with low genetic risk and cardiometabolic multimorbidity index zero as reference). Cardiometabolic multimorbidity indices of two and three were combined due to small sample sizes. The proportionality of hazards assumption was assessed using the Schoenfeld residuals technique(258) and satisfied (P = 0.29 for testing departures from proportionality). Complete case analysis was applied to missing or "not known" data for all exposure and covariates with less than 3% missing values. A total of 6673 (2.9%) participants were excluded due to having missing data. For categorical variables (education and the Townsend Deprivation Index), I included 'missing' as a separate category. Participants were considered at risk for dementia from baseline and until the date of first diagnosis, death, loss to follow-up, or the last surveyed hospital admission date (March 31, 2021, for England and Scotland and February 28, 2018, for Wales), whichever came first. These were censoring dates recommended by UK Biobank and to which the data is estimated to be over 90% complete in England, Scotland and Wales. Information was accurate up to these dates and did not rely on multiple research reassessments.

Total hippocampal and grey matter volume was normally distributed while total white matter hyperintensity volume was log-transformed to correct for a positively skewed distribution. Two-way ANOVA was performed to examine the association of cardiometabolic multimorbidity index (0, 1 or 2+) and polygenic risk (low, moderate or high) as predictors with each brain measure as the outcome. Post-hoc analysis investigated pairwise differences between individual levels of cardiometabolic multimorbidity and polygenic risk using Tukey and Holm–Bonferroni correction for pairwise and multiple comparisons. A linear regression model was used to control for all remaining baseline covariates. P-values were 2-sided with statistical significance set at $P<0.05$. Analyses were performed in Matlab R2018a or in R, using the *survival* package.

Secondary and sensitivity analyses

Secondary data analyses examined how additional cardiovascular conditions of atrial fibrillation, heart failure and peripheral vascular disease would change the association of the three main cardiometabolic conditions and dementia risk. I also considered myocardial infarction, atrial fibrillation and heart failure as a single composite 'heart disease' variable in a separate sensitivity analysis. One model included additional covariates of systolic blood pressure, total cholesterol level, body mass index and glycosylated haemoglobin (HbA1c) to examine the extent to which these upstream cardiometabolic risk markers may explain the associations between cardiometabolic multimorbidity and dementia risk. Further sensitivity analyses for risk of incident dementia used genetic risk quintiles, to check for differences with grouping genetic risk into three groups, and genetic risk adjusting for APOE Ɛ4 allele status. Analysis stratified by different follow-up durations of up to 10 years and 10 to 14 years was performed to consider earlier risk of developing dementia and potential reverse causation, respectively.

3.4 Results

3.4.1 Population characteristics of 203 038 individuals without dementia at baseline

The UK Biobank baseline sample comprised 502 536 participants. After excluding participants younger than 60 years, those of non-European descent and those with prevalent dementia, 203 038 participants were included. Mean (SD) age was 64.9 (3.0) years and 52.8% were female (baseline characteristics are found in Table 3-1, study flowchart found Supplementary Figure S3-1). Over 2 354 857 follow-up person-years (median 12.0, interquartile range 11.2-12.7), 4766 cases of all-cause incident dementia were observed. The polygenic risk score was normally distributed across participants and was not associated with any cardiometabolic condition (Supplementary Figure S3-2).

Table 3-1. Baseline characteristics of study participants

Characteristic	No. (%)	
	No incident dementia (n = 198 272)	Incident dementia (n = 4766)
Age, mean (SD), years	64.9 (3.0)	66.6 (2.8)
Sex		
Female	105017 (52.9)	2226 (46.7)
Male	93255 (47.1)	2540 (53.3)
Education[a]		
Higher	64750 (32.6)	1198 (25.1)
Upper Secondary	14361 (7.2)	352 (7.4)
Lower Secondary	17880 (9.0)	397 (8.3)
Vocational	46240 (23.3)	929 (19.5)
Other	55041 (27.6)	1890 (39.6)
Socioeconomic status quintile[b]		
1 (least deprived)	39731 (20.0)	833 (17.5)
2-4	119043 (60.0)	2689 (56.4)
5 (most deprived)	39335 (20.0)	1239 (26.0)
Cardiometabolic conditions		
Stroke only	3006 (1.5)	157 (3.3)
Diabetes only	11068 (5.6)	524 (11.0)
MI only	5646 (2.9)	235 (4.9)
Stroke & MI	508 (0.3)	50 (1.1)
Stroke & diabetes	598 (0.3)	66 (1.4)
MI & diabetes	1372 (0.7)	107 (2.3)
Stroke & MI & diabetes	122 (0.06)	16 (0.3)
No cardiometabolic conditions	176318 (88.9)	3659 (76.8)
Number of cardiometabolic conditions[c] **(cardiometabolic multimorbidity index)**	176318 (88.9)	3659 (76.8)
0	19720 (10.0)	916 (19.2)
1	2112 (1.1)	175 (3.7)
2	122 (0.06)	16 (0.3)
3		
Genetic risk category[d]		
Low	39879 (20.1)	729 (15.3)
Moderate	119019 (60.0)	2803 (58.8)
High	39374 (19.9)	1234 (25.9)

Percentages may not sum to 100 because of rounding.

[a] Higher education defined as college/university degree or other professional qualification; upper secondary, second/final stage of secondary education; lower secondary, first stage of secondary education; vocational, work-related practical qualifications.

[b] Socioeconomic status assessed with the Townsend deprivation index,27 which combines information on social class, employment, car availability, and housing.

[c] Cardiometabolic multimorbidity index groups are mutually exclusive.

[d] Genetic risk categories defined according to a polygenic risk score as low (lowest quintile), intermediate (quintiles 2 to 4), and high (highest quintile)

Abbreviation: SD, standard deviation; IQR, interquartile range; MI, myocardial infarction.

Of 203 038 participants, 3163 (1.7%) had a history of stroke only at baseline assessment, 11 592 (5.7%) had a history of diabetes only, 5881 (2.9%) had a history of MI only, 420 (0.3%) had both stroke and MI, 526 (0.2%) had both stroke and diabetes, 1341 (0.7%) had both MI and diabetes while 138 (0.07%) had diabetes, stroke and MI.

3.4.2 Cardiometabolic multimorbidity associated with a monotonic increase in dementia risk

Compared to the reference group with no cardiometabolic conditions, the adjusted HRs for dementia incidence were 2.13 (95% CI 1.82- 2.50) for participants with a history of stroke only, 2.03 (95% CI 1.85 - 2.23) in those with diabetes only, 1.63 (95% 1.43 - 1.86) in those with MI only. For participants with multimorbidity, the adjusted HRs for dementia incidence were 3.50 (95% CI 2.50 - 4.91) in those with stroke and MI, 4.33 (95% CI 3.28 - 5.73) in those with stroke and diabetes, 3.08 (95% CI 2.50 - 3.80) in those with both MI and diabetes, and 5.39 (95% CI 3.30 - 8.82) in those with stroke, diabetes and MI (Figure 3-1).

A cardiometabolic multimorbidity index was assigned based on the presence of each cardiometabolic condition. There were 20 636 (10.3%) participants with a cardiometabolic multimorbidity index of one, 2287 (1.1%) had a cardiometabolic multimorbidity index of two while 138 (0.07%) had a cardiometabolic multimorbidity index of three. Risk of developing dementia increased monotonically with increasing cardiometabolic multimorbidity index. Compared to baseline, participants with a cardiometabolic multimorbidity index of one had an adjusted HR for dementia incidence of 1.94 (95% CI 1.80 - 2.08), participants with a cardiometabolic multimorbidity index of two had a HR of 3.46 (95% CI 2.97 - 4.04) and participants with a cardiometabolic multimorbidity index of three had a HR of 5.55 (95% CI 3.39 - 9.08). In terms of genetic risk, the adjusted HR for dementia incidence was 1.27 (95% CI 1.17 - 1.38) for participants with moderate polygenic risk and 1.68 (95% CI 1.53 - 1.84) for participants with high polygenic risk, compared to low genetic risk (Supplementary Table S3-2).

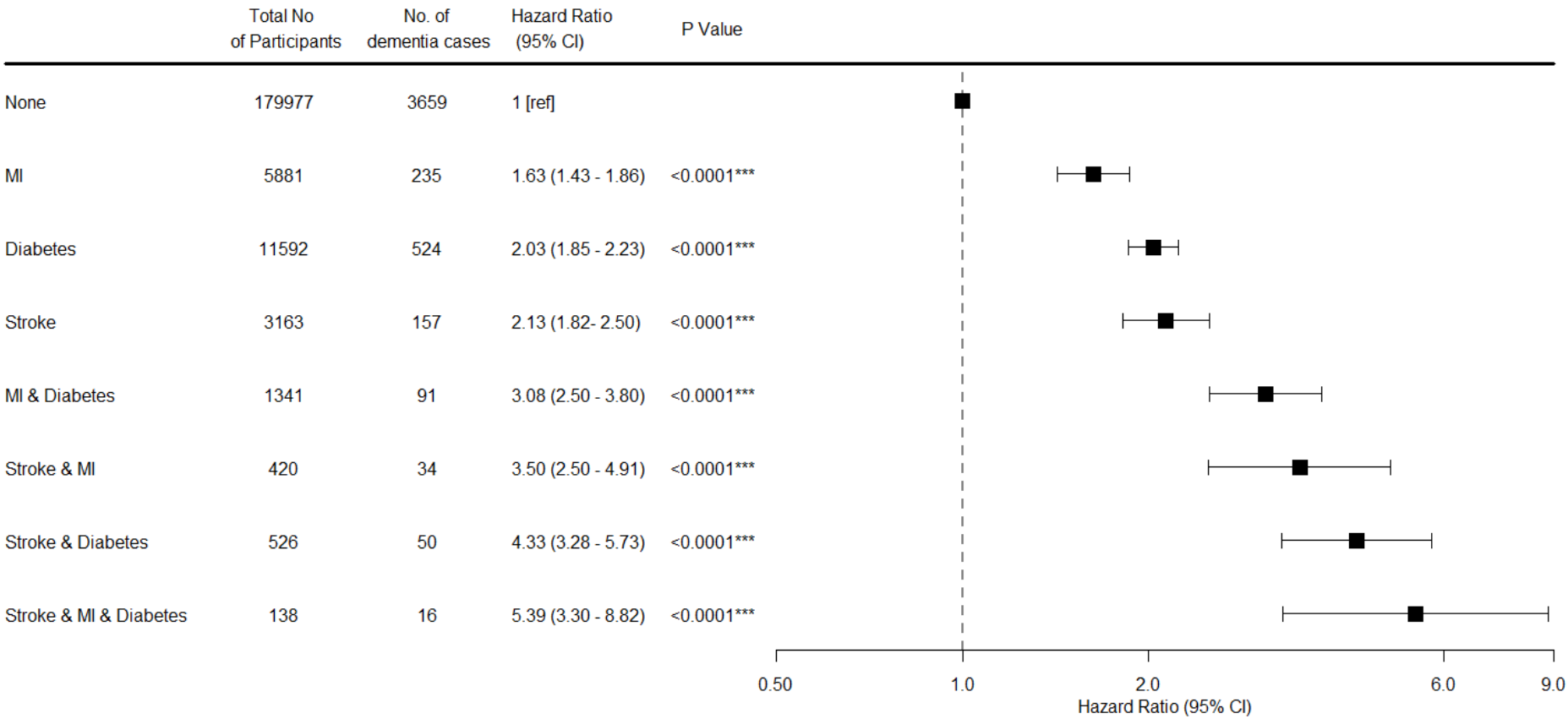


Figure 3-1. Risk of incident dementia by cardiometabolic disease status at baseline

Shown are hazard ratios for incident dementia, associated with mutually exclusive groupings of cardiometabolic conditions. The model has been adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Unadjusted model results displayed in Supplementary Figure S3-7. *Abbreviations: MI, myocardial infarction*

3.4.3 Genetic risk and cardiometabolic multimorbidity were independently associated with dementia

Within each genetic risk group, increasing cardiometabolic multimorbidity led to an increased risk of dementia (Figure 3-2.). Of participants with high genetic risk and cardiometabolic multimorbidity index of two or more, 9.3% developed dementia compared to 1.5% of participants with low genetic risk and cardiometabolic multimorbidity index zero (HR 5.74 [95% CI 4.26 - 7.74]). There was no significant interaction between cardiometabolic multimorbidity and polygenic risk (P=0.18) indicating that the association between cardiometabolic multimorbidity with dementia incidence was not substantially modified by genetic risk.

Similar patterns of association were observed in sensitivity analyses including when considering additional cardiovascular conditions of atrial fibrillation, heart failure and peripheral vascular disease individually (Supplementary Figure S3-4) or combining MI, atrial fibrillation and heart failure together as a composite “heart disease” variable (Supplementary Figure S3-5). Considering polygenic risk quintiles in the model (Supplementary Table S3-3) and additionally adjusting for APOE Ɛ4 allele status (Supplementary Table S3-4) yielded similar associations with dementia risk. Stratified analyses based on follow-up duration demonstrated a similar pattern in participants developing all-cause dementia within 10 years of follow-up and those developing dementia 10-14 years after baseline assessments (Supplementary Table S3-5). The main difference was a non-significant relationship between individuals with stroke, MI and diabetes and risk of dementia between 10-14 years of follow-up, likely due to the presence of only one incident dementia case in this sub-group. Hazard ratios were attenuated slightly after adjustment for markers of upstream cardiometabolic risk including systolic blood pressure, total cholesterol level, body mass index and glycosylated haemoglobin levels (HbA1c) (Supplementary Figure S3-6), but the overall pattern of association was unchanged.

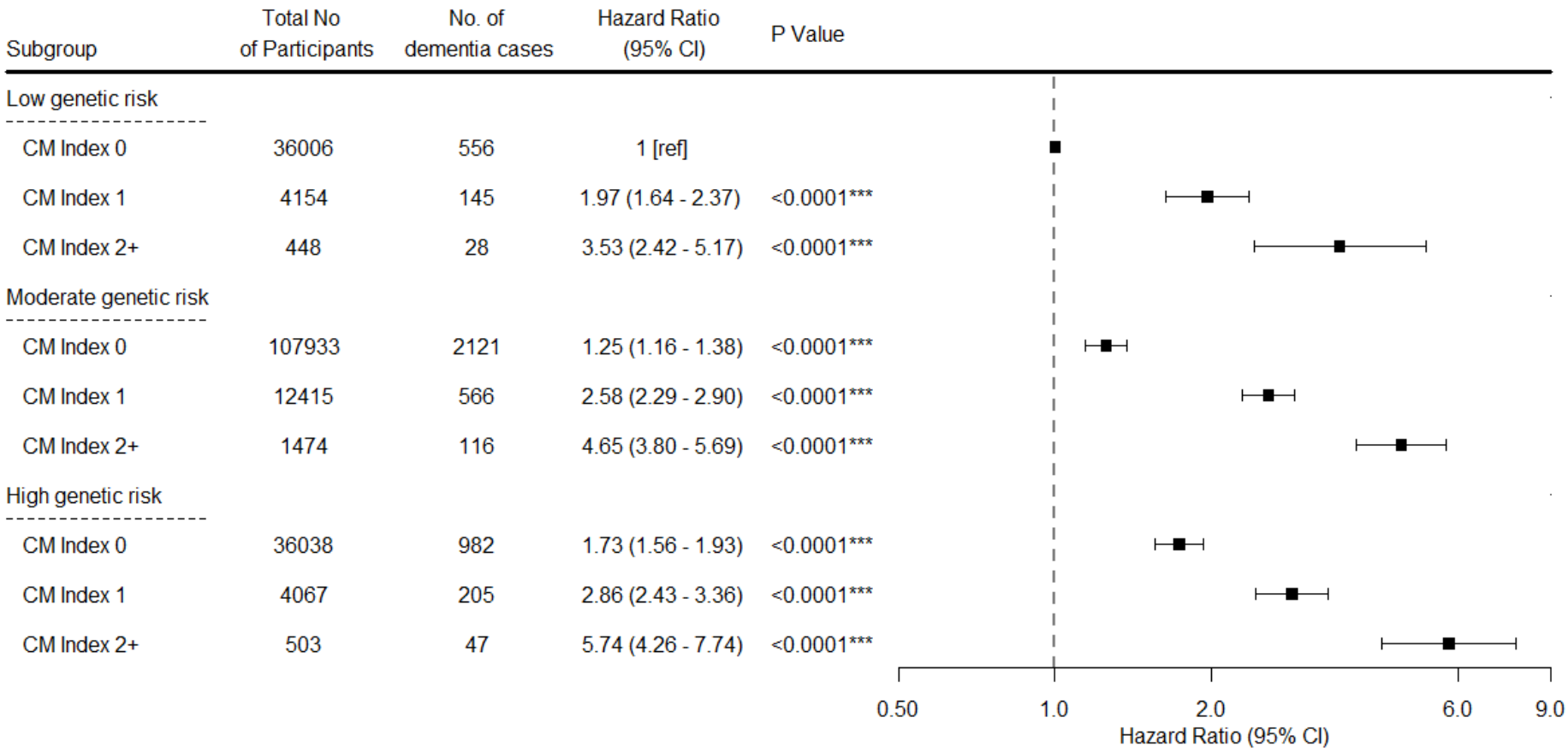


Figure 3-2. Risk of incident dementia by according to cardiometabolic multimorbidity index and genetic risk

Shown are the hazard ratios for incident dementia, according to cardiometabolic multimorbidity index and genetic risk. The reference group were participants with low genetic risk and a CM Index of zero. Horizontal bars indicate 95% confidence intervals. The model has been adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Unadjusted model results displayed in Supplementary Figure S3-8. *Abbreviations: CM, cardiometabolic multimorbidity*

3.4.4 Cardiometabolic multimorbidity were associated with widespread brain structural changes

I examined the relationship of cardiometabolic multimorbidity and polygenic risk on total hippocampal volume, total grey matter volume and white matter hyperintensity volume which represent regions-of-interest related specifically to Alzheimer's disease, whole brain structural integrity, and cerebrovascular burden, respectively (Figure 3-3.). Cardiometabolic multimorbidity was significantly associated with lower hippocampal volume ($F(2, 12110) = 10.70$, $p < 0.001$), total brain grey matter volume ($F(2, 12236) = 55.65$, $p < 0.001$) and higher white matter hyperintensity volume ($F(2, 10827) = 4.48$, $p = 0.011$). By contrast, higher genetic risk was significantly associated with a lower hippocampal volume only ($F(2, 12110) = 3.45$, $p = 0.032$) but not total grey matter ($F(2, 12236) = 1.67$, $p=0.1889$) or white matter hyperintensity volume ($F(2, 10827) = 0.98$, $p =0.376$). No interaction was identified between cardiometabolic multimorbidity and polygenic risk for any of the brain measures (Supplementary Table S3-6) and post-hoc analysis showed differences between individual indices of cardiometabolic multimorbidity and polygenic risk groups. A fully adjusted linear regression model accounting for all baseline characteristics demonstrated the same pattern of associations (Supplementary Table S3-7).

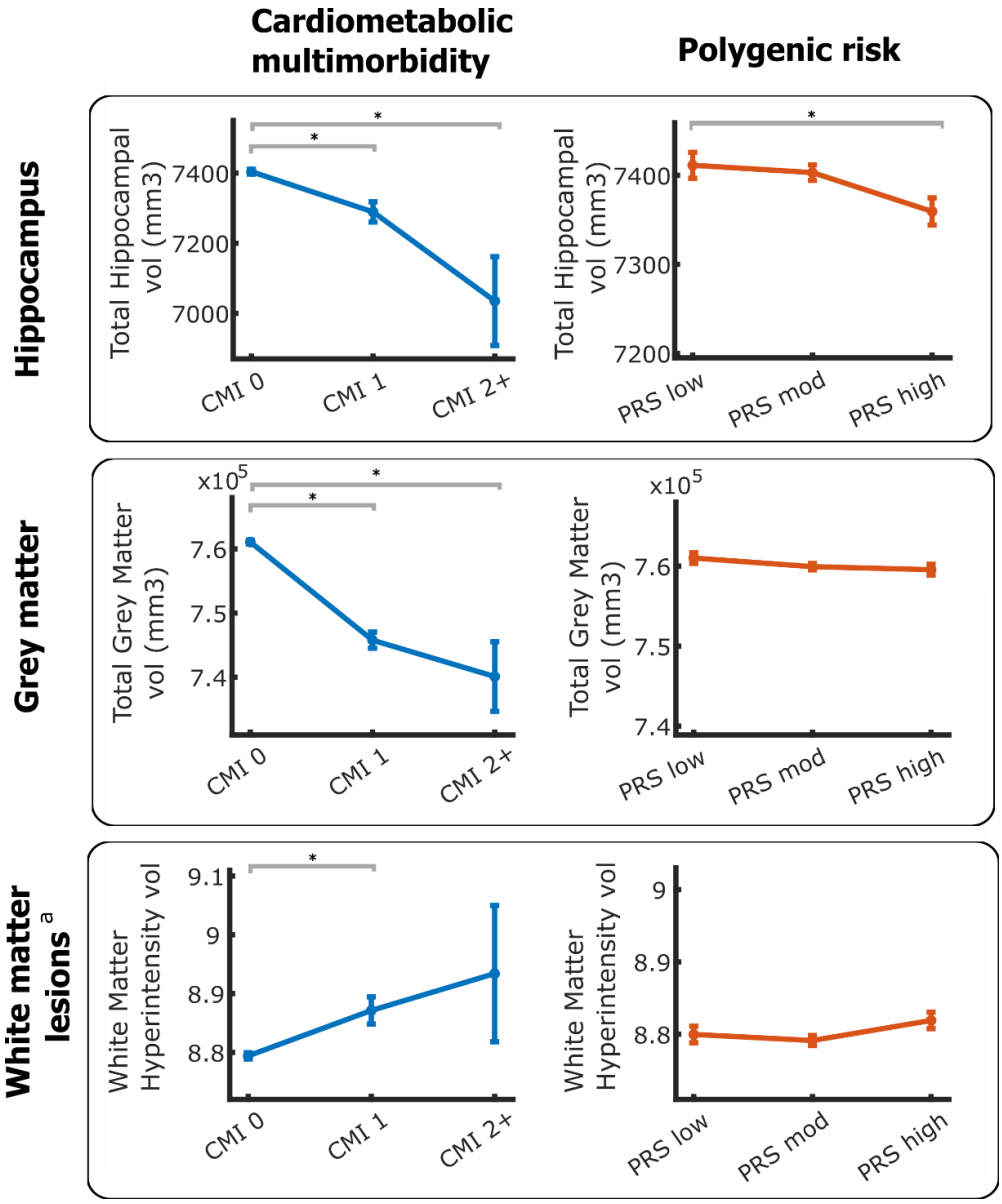


Figure 3-3. Total hippocampal volume, total grey matter volume and white matter hyperintensity volume associated with cardiometabolic multimorbidity index and polygenic risk.

Data are brain volumes of the hippocampi, total grey matter and white matter hyperintensities stratified according to cardiometabolic multimorbidity index (left column) and genetic risk (right column). Cardiometabolic multimorbidity was significantly associated with lower hippocampal volume [F (2, 12106) = 10.70, *p < 0.001], whole brain grey matter volume [F (2, 12236) = 55.65 , *p < 0.001] and higher white matter hyperintensity volume [F (2, 10827) = 4.48 , *p = 0.011]. By contrast, higher genetic risk was significantly associated with a lower hippocampal volume only [F (2, 12110) = 3.45, *p = 0.032]. There was no interaction between CMI and genetic risk. The I bars represent standard error.

[a]White matter hyperintensity volume has been log-transformed due to skew distribution.
Abbreviations: CMI, cardiometabolic multimorbidity index; PRS, polygenic risk score

3.5 Discussion

This large population-based study adds to the existing knowledge by examining how cardiometabolic multimorbidity and genetic risk are associated with dementia incidence. Cardiometabolic multimorbidity and genetic risk were independently associated with all-cause dementia. Therefore, within any genetic risk category, increasing cardiometabolic morbidity was associated with an additive risk of developing dementia. Cardiometabolic multimorbidity was also associated with lower total hippocampal and grey matter volumes, and higher white matter hyperintensity volume, while polygenic risk was associated with lower hippocampal volume only.

As reported in the recent 2020 Lancet Commission on dementia prevention and care, there is a high prevalence of cardiovascular multimorbidity in dementia patients (259). However, few studies have examined the relationship of having multiple cardiometabolic conditions and dementia risk with these being limited by small sample size. Grande *et al*. identified a HR of 1.61 (95% CI 1.17-2.29) for developing dementia with multiple cardiovascular conditions(260) while another study reported a HR of 50.30 (95% CI 14.57-173.57) with stroke and congestive cardiac failure(261) in cohorts of 2478 and 1701 individuals, respectively. By contrast, most studies have focused on upstream lifestyle or cardiometabolic risk factors (262–264), such as high blood pressure and blood glucose, and show that poor control of individual risk factors may be associated with up to two times increased risk of developing dementia. A meta-analysis identified similar associations with dementia risk including a pooled relative risk of 2.21 (95% CI 1.78 to 2.73) for three or more cardiovascular risk factors compared to none (265). In terms of lifestyle factors, in the same UK Biobank cohort as the present study, participants with an unhealthy lifestyle profile demonstrated an increase HR of 1.35 (95% CI 1.15-1.58) compared to participants with a favourable risk profile reflecting a significant but modest effect on dementia risk (250).

Examining established cardiometabolic conditions provides a more complete understanding on the impact of upstream risk factors. In the present study, participants with only one cardiometabolic

condition demonstrated a HR for dementia risk of around two, which is comparable to previous reports examining diabetes (239), myocardial infarction(240) and stroke(266) individually. Importantly, I observed that participants with all three conditions had more than a fivefold increase in all-cause dementia risk and suggests a monotonic, additive relationship between increasing cardiometabolic multimorbidity and dementia risk which was largely unchanged when considering upstream cardiometabolic risk factors. Therefore, the association of cardiometabolic multimorbidity and dementia risk is greater than that of combined lifestyle and cardiovascular risk factors and emphasizes the importance of both clinical guidance and public health initiatives to aggressively prevent cardiometabolic disease, particularly in individuals with a pre-existing cardiometabolic condition.

To my knowledge, no previous study has examined the relationship between cardiometabolic multimorbidity, polygenic risk and dementia incidence. Several studies have examined *APOE* Ɛ4 status and individual cardiovascular conditions(261) or risk factors (267), while one recent study investigated cardiovascular risk factors and a polygenic risk score based on 23 single nucleotide polymorphisms (251). Rasmussen et al. examined a comprehensive list of cardiovascular risk factors and genetic risk in relation to dementia and showed the highest 10-year absolute risk of all-cause dementia in smoking individuals with diabetes, low education, APOE Ɛ4 and 22–31 GWAS risk alleles.[25] Results have been inconsistent due to limited statistical power as some studies indicated no interaction between genetic risk and cardiovascular risk factors(251,268) while other findings suggest factors such as midlife smoking increases dementia risk in *APOE* Ɛ4 carriers but not non-carriers(269) and a favourable risk profile corresponded to reduced dementia risk in *APOE* Ɛ4 non-carriers only (252). Compared to previous work, the present study is an order of magnitude larger in sample size and incorporates a more comprehensive indicator of genetic risk. The finding that the association of cardiometabolic multimorbidity with dementia incidence was both greater than, and independent of, genetic risk highlights the key message that risk factor modification appears critical for every individual, regardless of pre-determined genetic factors.

Previous studies have shown that individual cardiometabolic conditions including stroke(270) and diabetes(271) are associated with smaller overall brain volume while high polygenic risk has been associated with smaller hippocampal volume in some cross-sectional studies(272,273) but not in others (274). My findings show that cardiometabolic multimorbidity was associated with larger and more widespread negative effects on brain measures and independent of differences associated with genetic risk. These findings, in combination with recent reports examining the contribution of vascular and neurodegenerative pathology on cognitive trajectories(275,276), suggest that different mechanisms may underpin dementia risk. Cardiometabolic multimorbidity may result in combined global cerebrovascular and neurodegenerative processes(277) whereas genetic risk is more closely related to pathways involving pathological protein tau and beta-amyloid aggregation which have hippocampal specificity, especially during early stages of Alzheimer's dementia (278). More targeted studies are needed to fully elucidate this relationship but, nonetheless, the association of widespread, independent brain changes provides further reason to address cardiometabolic multimorbidity.

This study should be considered in the context of several limitations. Due to the observational nature of this study, the association between cardiometabolic multimorbidity and dementia risk cannot be taken as causal. The UK Biobank cohort is more likely to be from less deprived areas and with fewer health conditions, such as cardiovascular disease, than the general population (228). The effects of cardiovascular risk and incident cardiovascular disease may potentially be larger in more representative cohorts due to this selection bias. However, there may also be a survivor bias, in that, if the incident cardiovascular disease is very severe, individuals may pass away before developing dementia. Although analyses were adjusted for a range of known potential confounders and participants were followed up for a median of 12.0 years, there remains a possibility of unmeasured confounding and reverse causation. Medical condition information was obtained from self-report or from medical records, where there was risk of incorrect reporting or

missed diagnoses (279). The future release of comprehensive primary care data may help corroborate medical condition information. I examined polygenic risk derived for Alzheimer's disease and this has previously been shown to be predictive for all-cause dementia (249). The relevance of this polygenic risk score with brain regions related to Alzheimer's disease is less certain however recent work has shown corroborative hippocampal findings(272) and suggests this is an appropriate comparison. Examining the relationship between cardiometabolic multimorbidity and dementia subtypes would be interesting, however, subtypes are currently poorly captured by medical records and dementia cases are likely to be Alzheimer's disease, vascular or a mixed picture (254) While this is one of the largest samples to investigate this question with a considerable follow-up period, certain study groups have low numbers which may lead to a potential bias and studies with larger sub-groups would be useful to corroborate my results. My study was restricted to participants of European ancestry, aged between 60 and 73 years at baseline, and further research is needed to investigate whether these findings generalize to other populations. Neuroimaging analyses were cross-sectional and further research is necessary to establish the prospective association between cardiometabolic multimorbidity and dementia-related imaging features.

In conclusion, both cardiometabolic multimorbidity and genetic risk were significantly and independently associated with a higher risk of dementia and associated neuroimaging features. Future interventions targeting cardiometabolic risk factors may in turn prove effective in preventing dementia regardless of genetic predisposition.

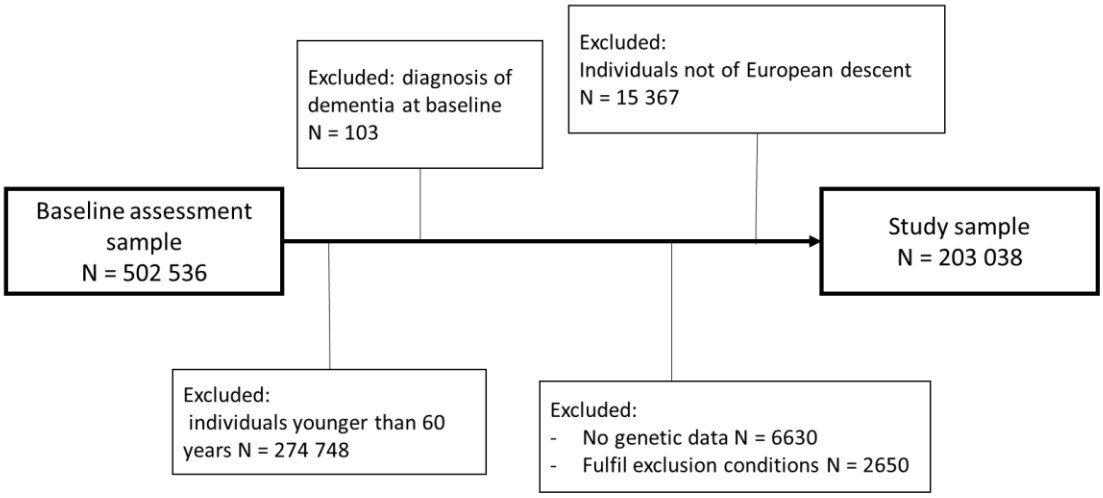
3.6 Supplementary material for Chapter 3

Supplementary Table S3-7. Associations between total hippocampal, total grey matter, total white matter hyperintensity volume with cardiometabolic multimorbidity index, polygenic risk and other baseline characteristics.

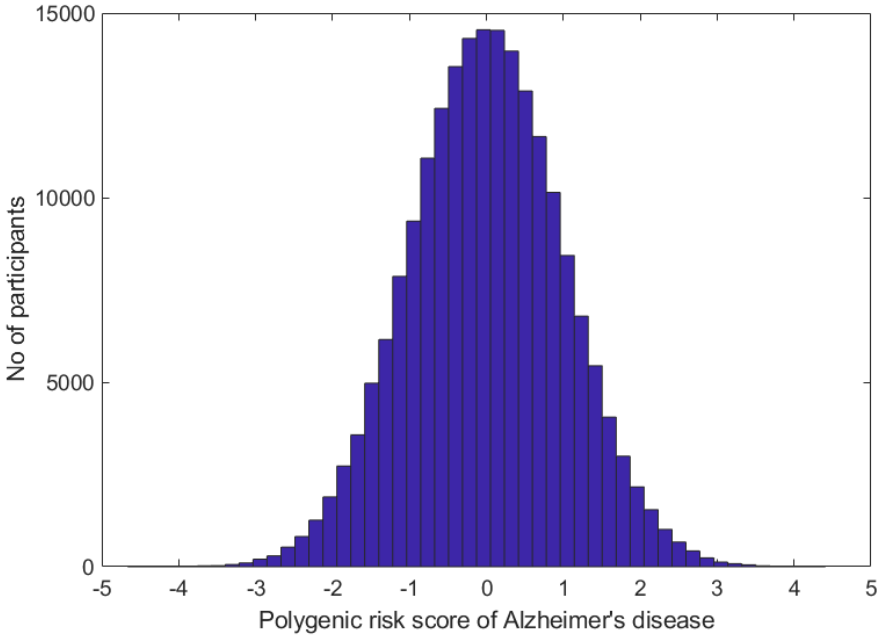
Supplementary Table S3-1. Codes used in the UK Biobank study to identify dementia and cardiometabolic condition cases and exclusion diagnoses

	Algorithmically-derived	Self-report (includes non-cancer and treatment self report)	Illness code: ICD-10	Illness code: ICD-9
Dementia	-	1263	AD: F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, G30.9 VaD: F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3 FTD: F02.0, G31.0, Other codes for all-cause dementia: A81.0, F02, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G31.1, G31.8	AD: 331.0 VaD: 290.4 FTD: 331.1 Other codes for all-cause dementia: 290.2, 290.3, 291.2, 294.1, 331.2, 331.5
Myocardial Infarction	All-cause myocardial infarction: 42000	-	-	-
Stroke	All-cause stroke: 42006	-	-	-
Diabetes	-	2443, 6153, 6177,	E10, E100, E101, E102, E103, E104, E105, E106, E107, E108, E109 E11, E110, E111, E112, E113, E114, E115, E116, E117, E118, E119, E12, E120, E121, E122, E123, E124, E125, E126, E127, E128, E129, E13, E130, E131, E132, E133, E134, E135, E136, E137, E138, E139, E14, E140, E141, E142, E143, E144, E145, E146, E147, E148, E149,E15, E150, E151, E152, E153, E154, E155, E156, E157, E158, E159	'25000', '25001', '25009', '25010', '25011', '25019', '25029', '2503', '2504', '2505', '25099'
Atrial Fibrillation	-	1471, 1483	I48	4273
Heart Failure	-	-	I110 , I130, I132, I255, I420, I425, I428, I429, I500, I501, I509	4254, 4280, 4281, 4289
Peripheral vascular disease		1067, 1087		
Infection of the central nervous system	-	1244	-	-
Encephalitis	-	1246	-	-
Meningitis	-	1247	-	-
Amyotrophic lateral sclerosis	-	1259	-	-
Multiple Sclerosis	-	1261	-	-

Head Injury	-	1266	-	-
Subdural Haematoma	-	1083	-	-
Subarachnoid Haemorrhage	-	1086	-	-



Supplementary Figure S3-1. Study flow chart

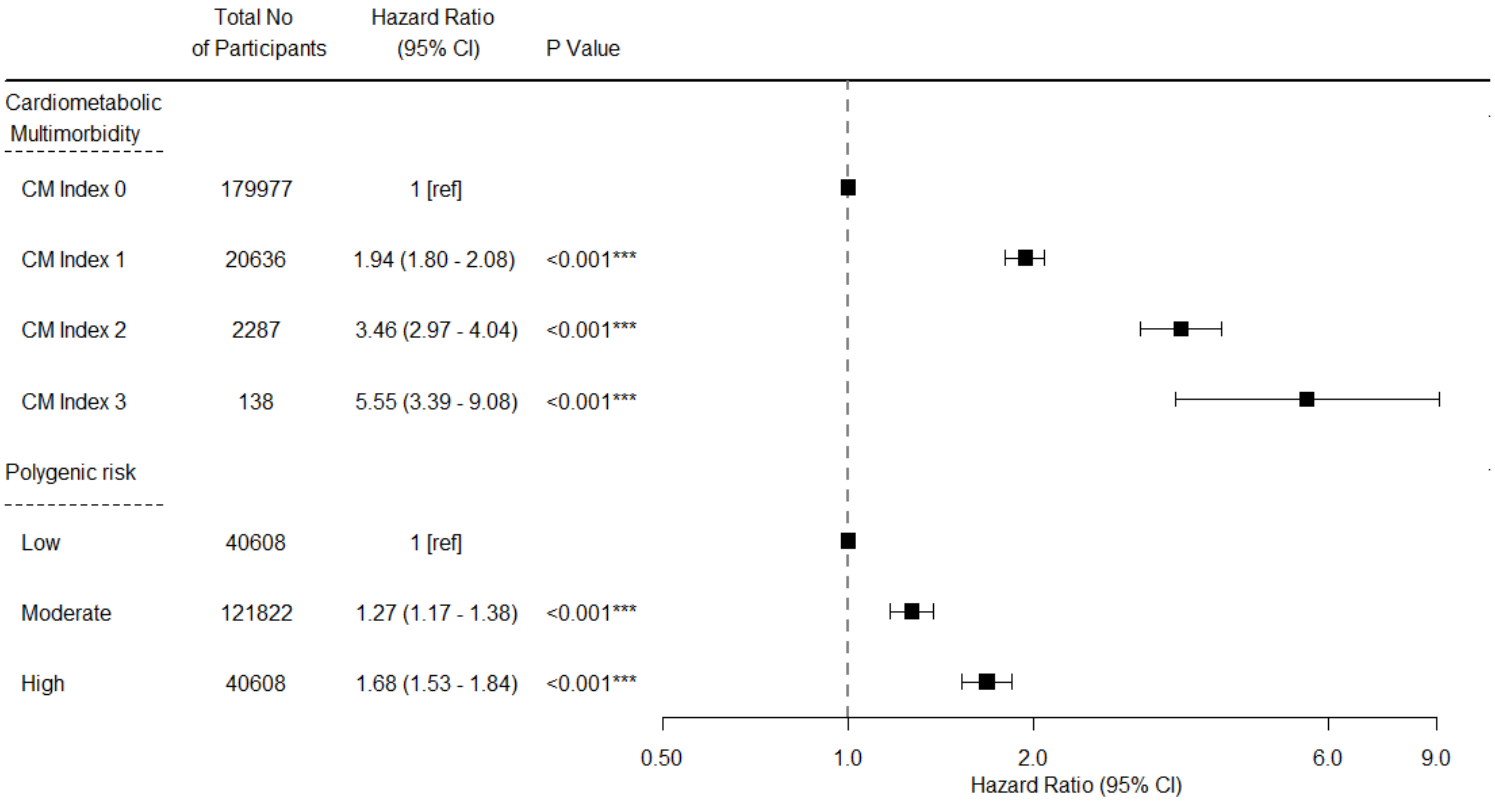


Supplementary Figure S3-2. Distribution of polygenic risk score for Alzheimer's Disease.

Supplementary Table S3-2. Association between cardiometabolic multimorbidity index and polygenic risk score

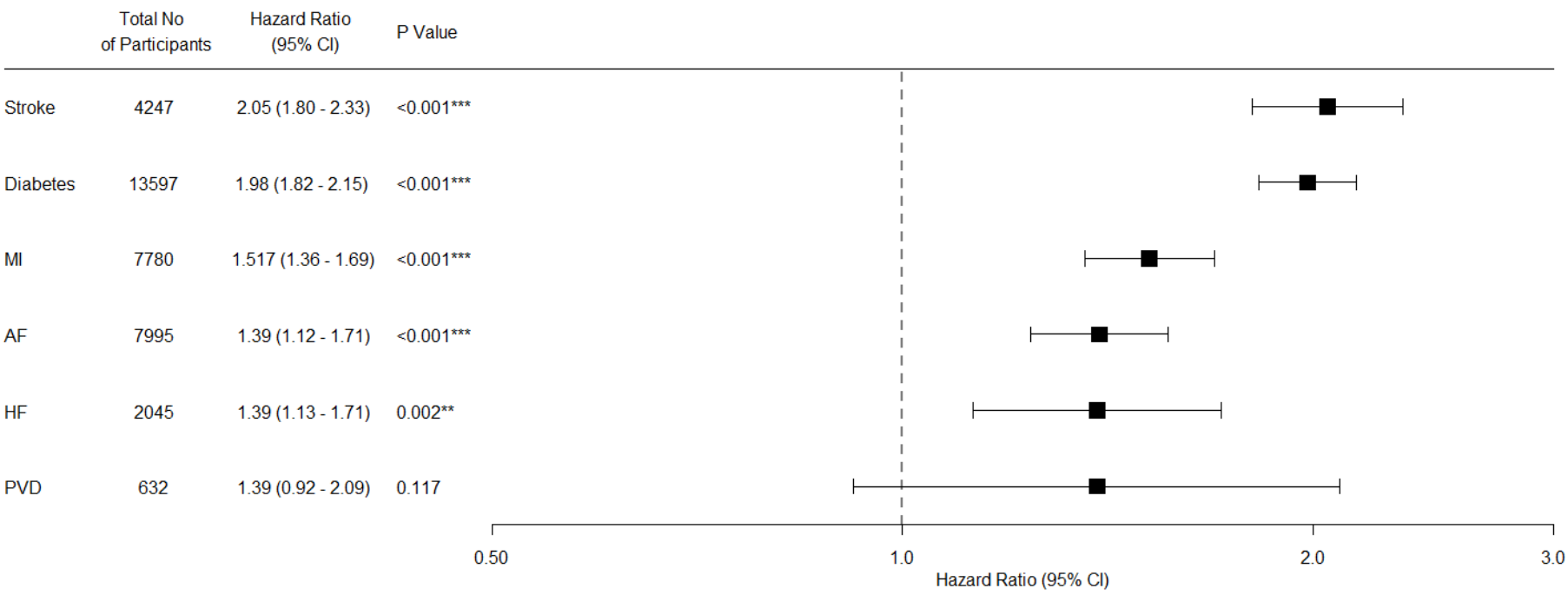
	Polygenic risk score	
	β	**p**
CM index 1	-5.1481e-07	0.103
CM index 2	7.0729e-07	0.459
CM index 3	-6.9069e-06	0.103

Note: β =unstandardised betas. Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre.



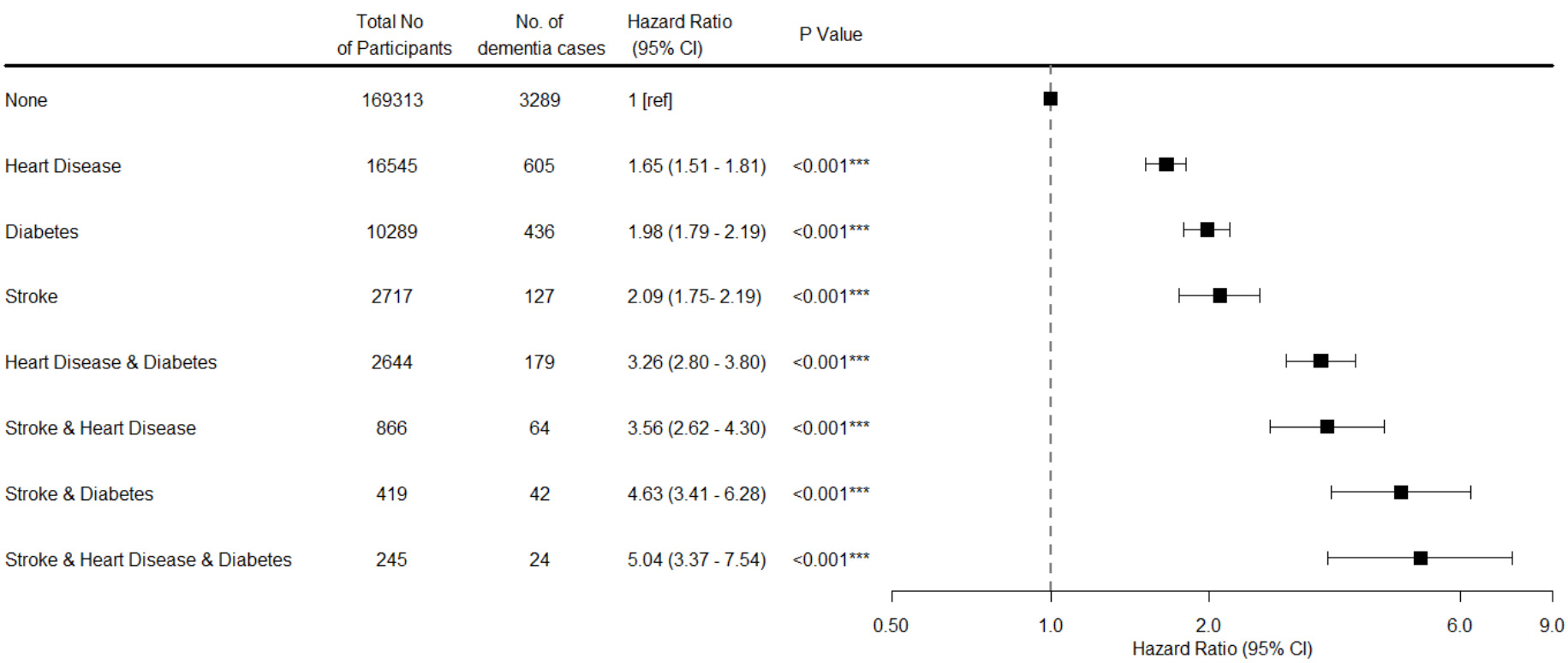
Supplementary Figure S3-3. Risk of incident dementia based on cardiometabolic multimorbidity index and polygenic risk group.

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Abbreviation: CM, cardiometabolic multimorbidity



Supplementary Figure S3-4. Risk of incident dementia stratified by individual cardiovascular and metabolic conditions

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Abbreviation: MI, myocardial infarction; AF, atrial fibrillation; HF, heart failure; PVD, peripheral vascular disease.



Supplementary Figure S3-5. Risk of incident dementia by cardiometabolic condition groups with myocardial infarction, atrial fibrillation and heart failure represented by a single 'heart disease' variable

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre.

Supplementary Table S3-3. Dementia risk by cardiometabolic index and polygenic risk quintiles

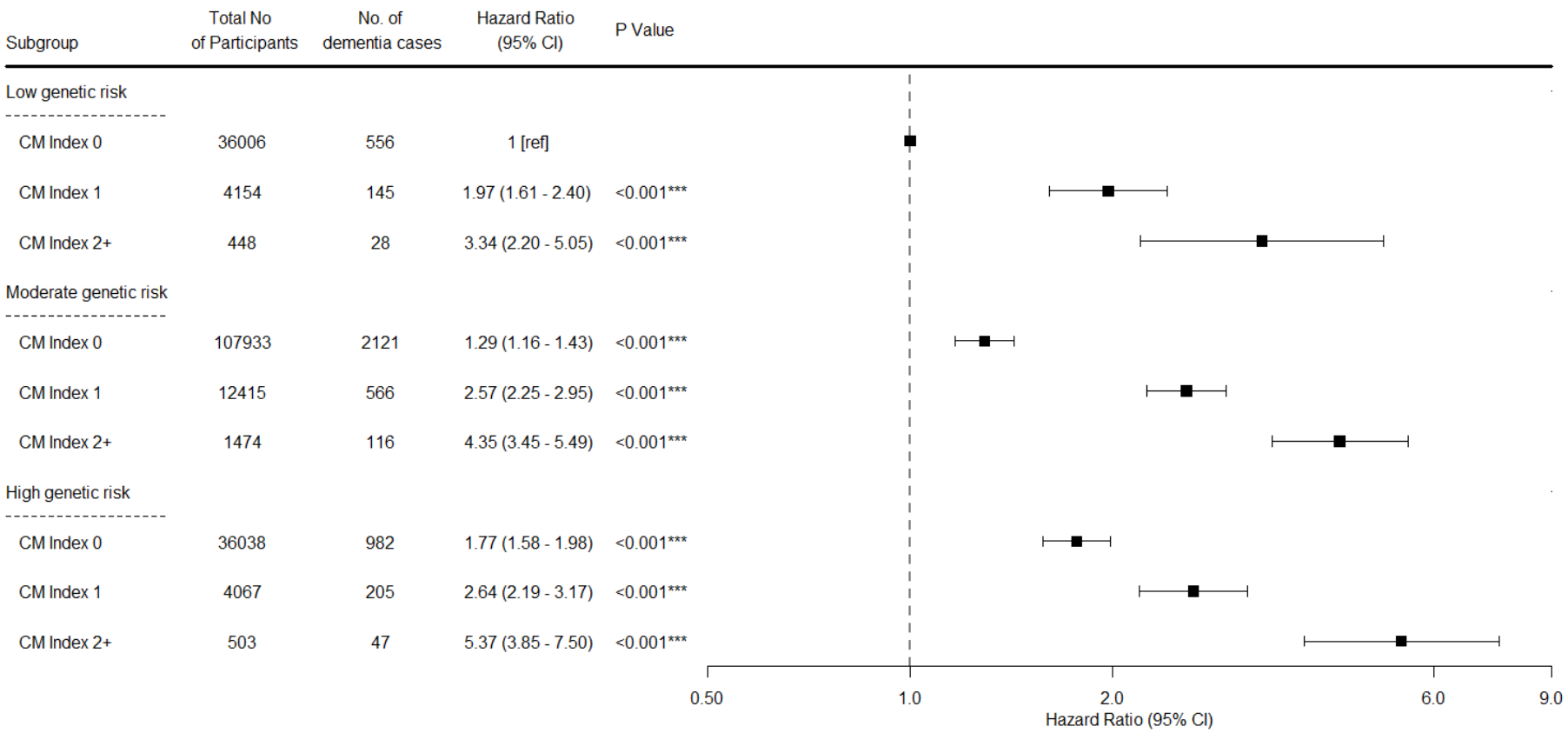
	Dementia risk	
	Hazard Ratio (95% CI)	***P*-value**
CM Index 0	*1.00*	*[Ref]*
CM Index 1	1.94 (1.80 - 2.08)	***<0.001
CM Index 2	3.45 (2.96 - 4.03)	***<0.001
CM Index 3	1.94 (1.73 - 2.18)	***<0.001
PRS quint 1	*1.00*	*[Ref]*
PRS quint 2	1.20 (1.09 - 1.33)	***<0.001
PRS quint 3	1.22 (1.10 - 1.34)	***<0.001
PRS quint 4	1.38 (1.25 - 1.52)	***<0.001
PRS quint 5	1.68 (1.53 - 1.84)	***<0.001

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Abbreviations: CM, cardiometabolic multimorbidity; PRS, polygenic risk score; CI, confidence interval

Supplementary Table S3-4. Risk of incident dementia according to cardiometabolic multimorbidity and genetic risk, controlling for APOE Ɛ4 status

	Dementia risk	
	Hazard Ratio (95% CI)	***P*-value**
Low genetic risk		
CM Index 0	1.00	[Ref]
CM Index 1	1.98 (1.65 - 2.38)	***<0.001
CM Index 2+	3.55 (2.43 - 5.20)	*0.004
Moderate genetic risk		
CM Index 0	1.15 (1.04 - 1.26)	***<0.001
CM Index 1	2.33 (2.07 - 2.62)	***<0.001
CM Index 2+	4.16 (3.40 - 5.10)	***<0.001
Moderate genetic risk		
CM Index 0	1.42 (1.28 - 1.57)	***<0.001
CM Index 1	2.35 (2.00 - 2.76)	***<0.001
CM Index 2+	4.90 (3.63 - 6.61)	***<0.001

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Abbreviations: CM, cardiometabolic multimorbidity; PRS, polygenic risk score; CI, confidence interval



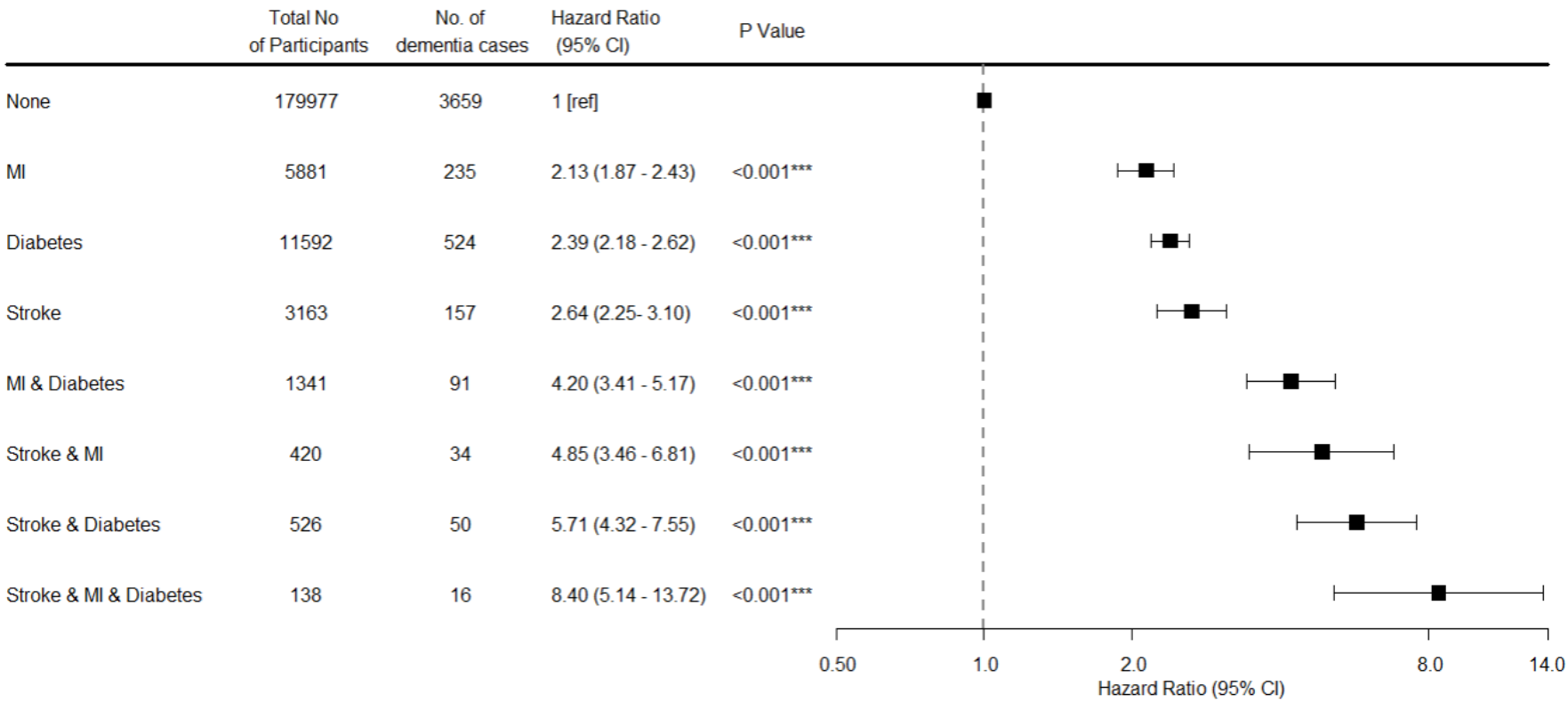
Supplementary Figure S3-6. Risk of incident dementia by according to cardiometabolic multimorbidity index and genetic risk (additionally controlled for upstream risk factors)

Shown are the hazard ratios for incident dementia, according to cardiometabolic multimorbidity index and genetic risk with further adjustment for markers of upstream cardiovascular and metabolic risk factors (systolic blood pressure, total cholesterol, body mass index and glycosylated haemoglobin levels) in addition to for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. *Abbreviations: CM, cardiometabolic multimorbidity*

Supplementary Table S3-5. Dementia risk by cardiometabolic condition status with different follow-up periods

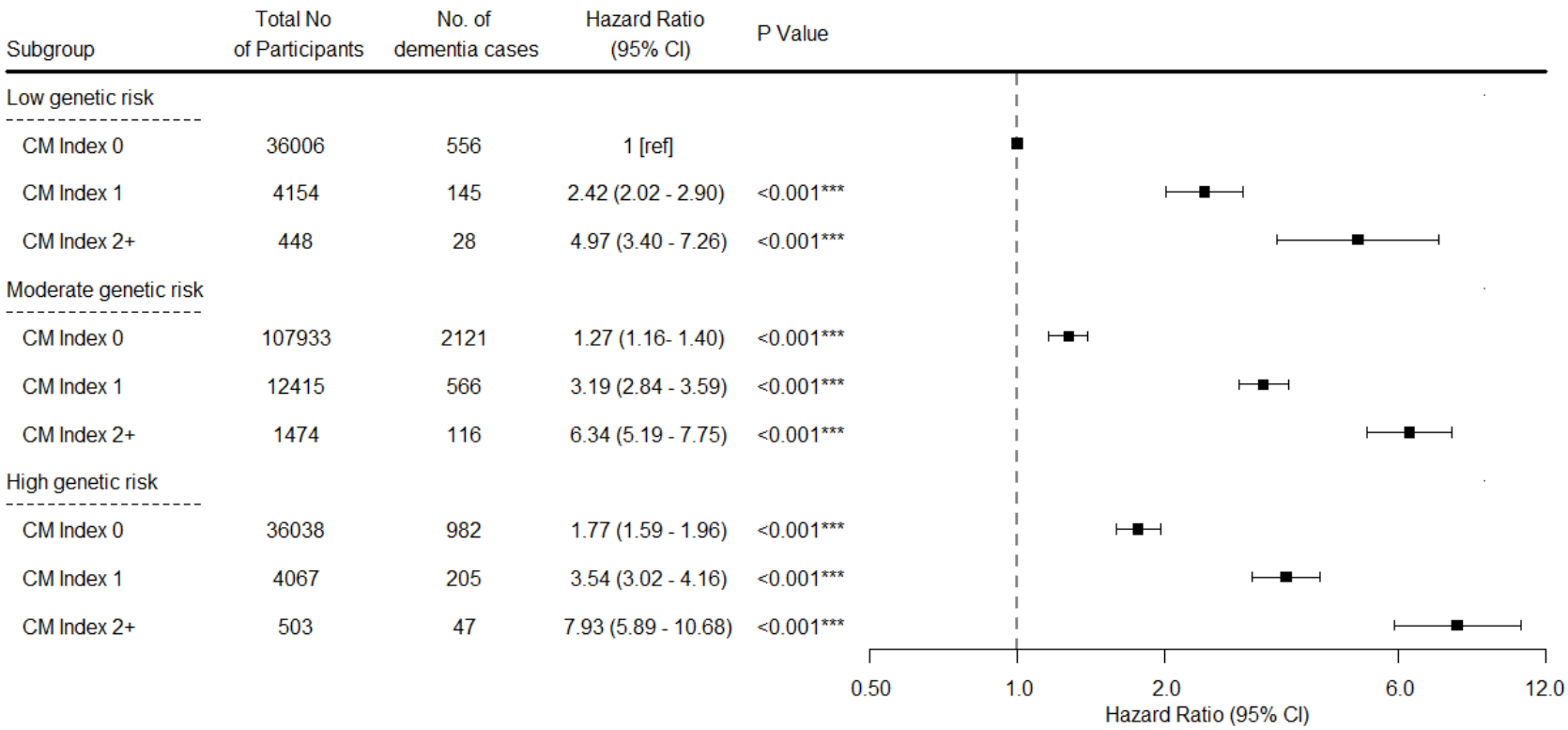
Subgroup	Dementia risk at 10 years			Dementia risk between 10 - 14 years		
	No. of dementia cases	**Hazard Ratio (95% CI)**	***P*-value**	**No. of dementia cases**	**Hazard Ratio (95% CI)**	***P*-value**
No cardiometabolic conditions (baseline)	*2308*	*1.00*	*[Ref]*	*1352*	*1.00*	*[Ref]*
Stroke	112	2.45 (2.05 - 2.94)	***<0.001	45	1.87 (1.41 - 2.48)	***<0.001
MI	164	1.79 (1.53 - 2.09)	***<0.001	71	1.56 (1.23 - 1.97)	***<0.001
Diabetes	329	1.94 (1.73 - 2.18)	***<0.001	195	2.29 (1.97 - 2.65)	***<0.001
Stroke & MI	36	3.41 (2.28 - 5.10)	***<0.001	14	4.37 (2.53 - 7.55)	***<0.001
Stoke & Diabetes	51	4.70 (3.39 - 6.50)	***<0.001	15	4.09 (2.46 - 6.81)	***<0.001
MI & Diabetes	74	3.02 (2.34 - 3.90)	***<0.001	33	3.69 (2.60 - 5.24)	***<0.001
Stroke & MI & Diabetes	15	7.34 (4.41 - 12.21)	***<0.001	1	1.28 (0.18 - 9.12)	0.80

Note: Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, first 20 principal components of ancestry and assessment centre. Abbreviations: MI, myocardial infarction; CI, confidence interval



Supplementary Figure S3-7. Risk of incident dementia by cardiometabolic disease status at baseline (unadjusted model)

Shown are hazard ratios for incident dementia, associated with mutually exclusive groupings of cardiometabolic conditions. The model was unadjusted.
Abbreviations: MI, myocardial infarction



Supplementary Figure S3-8. Risk of incident dementia by according to cardiometabolic multimorbidity index and genetic risk (unadjusted model)

Shown are the hazard ratios for incident dementia, according to cardiometabolic multimorbidity index and genetic risk. The reference group were participants with low genetic risk and a CM Index of zero. Horizontal bars indicate 95% confidence intervals. This model was unadjusted. *Abbreviations: CM, cardiometabolic multimorbidity*

Supplementary Table S3-6. Post-hoc comparisons examining the differences between individual indices of cardiometabolic multimorbidity and polygenic risk groups

	Total Hippocampal Volume			Total Grey Matter Volume			Total White Matter Hyperintensity Volume		
	F	p		F	p		F	p	
CM Index	10.70	*< .001		55.65	*< .001		4.48	*0.011	
Polygenic Risk	3.45	*0.032		1.67	0.189		0.98	0.376	
CM index * Polygenic Risk	1.59	0.174		0.87	0.334		0.42	0.795	
Post-hoc analysis	**t**	**p_{holm}**	**p_{tukey}**	**t**	**p_{holm}**	**p_{tukey}**	**t**	**p_{holm}**	**p_{tukey}**
CM Index									
CM0 – CM1	3.73	*< .001	*< .001	10.54	*< .001	*< .001	-2.76	*0.017	*0.016
CM0 – CM2+	2.79	*0.016	*0.015	3.093	*0.006	*0.006	-1.20	0.691	0.453
CM1 – CM2+	1.826	0.204	0.161	0.517	0.990	0.821	-0.56	0.990	0.841
Polygenic risk									
Low – mod	2.00	0.138	0.113	1.656	0.217	0.171	-0.84	0.990	0.678
Low – high	2.48	*0.039	*0.035	0.919	0.705	0.461	-1.39	0.493	0.346
Mod – high	1.030	0.909	0.558	-0.408	0.990	0.971	-0.82	0.990	0.688

Post-hoc analysis of relationship between individual indices of CM index and polygenic risk groups assessed with Holm–Bonferroni correction applied to account for multiple comparisons and with Tukey pairwise analysis.
Abbreviations: CM, cardiometabolic multimorbidity**;** mod, moderate

Supplementary Table S3-7. Associations between total hippocampal, total grey matter, total white matter hyperintensity volume with cardiometabolic multimorbidity index, polygenic risk and other baseline characteristics.

	Total Hippocampal Volume		Total Grey Matter Volume		Total White Matter Hyperintensity Volume	
	β	p	β	p	β	p
CM Index	-102.977	*< .001	-12511.345	*< .001	0.100	*< .001
Polygenic Risk	-23.069	*0.041	-785.262	0.131	0.004	0.629
Sex	-20.202	0.171	-2356.547	< .001	-0.125	< .001
Education						
Upper Secondary	-19.031	0.450	-308.849	0.787	-0.018	0.385
Vocational	-3.723	0.901	-79.918	0.953	0.018	0.451
Higher ed	16.744	0.341	1175.365	0.142	-0.047	< .001
Socio						
Quintile 2-4	1.011	0.953	-1071.334	0.171	0.003	0.817
Quintile 5	-35.958	0.149	-3317.742	0.003	0.044	0.031
Relatedness	6.549	0.676	1327.823	0.062	0.005	0.677
Allele number	0.003	0.850	0.808	0.208	0.000	0.383
pc1	-3.304	0.396	438.139	0.013	0.001	0.871
pc2	-3.580	0.342	155.665	0.363	0.002	0.430
pc3	-0.446	0.914	-32.310	0.864	-0.001	0.843
pc4	-0.365	0.877	228.648	0.032	0.002	0.379
pc5	-1.294	0.289	-68.036	0.220	0.002	0.117
pc6	1.306	0.755	101.619	0.593	-0.003	0.407
pc7	0.726	0.813	87.500	0.531	0.003	0.260
pc8	1.607	0.633	-132.038	0.387	0.004	0.139
pc9	-1.498	0.431	-17.008	0.844	0.002	0.316
pc10	0.782	0.837	114.314	0.507	0.001	0.656
pc11	0.280	0.922	15.310	0.906	0.004	0.076
pc12	1.237	0.746	38.719	0.823	0.003	0.327
pc13	2.990	0.505	-211.409	0.299	-0.005	0.130
pc14	7.602	0.002	241.725	0.026	0.000	0.890
pc15	5.194	0.210	489.477	0.009	-0.003	0.299
pc16	-5.251	0.035	-207.580	0.067	0.000	0.819
pc17	-4.732	0.196	82.284	0.620	-0.001	0.658
pc18	4.776	0.048	150.318	0.170	-0.004	0.033
pc19	-5.994	0.016	-331.785	0.003	-0.002	0.390
pc20	0.957	0.706	-13.321	0.908	0.000	0.812

Note: β = unstandardised betas coefficients. All volume measures have been deconfounded for age and age^2 at imaging visit, a scaling factor for head size and imaging site. White matter hyperintensity volume was log-transformed due to a skew distribution.
Abbreviations: CM, cardiometabolic multimorbidity; pc, principal component

Chapter 4. Dementia risk in epilepsy: impact of modifiable cardiovascular risk factors

4.1 Chapter summary

Epilepsy has been associated with cognitive impairment, and potentially dementia, in older individuals. However, the extent to which epilepsy may increase dementia risk, how this compares to other neurological conditions, and how modifiable cardiovascular risk factors may impact this risk remains unclear.

I analysed data from the prospective UK Biobank cohort and compare the risk of subsequent dementia for focal epilepsy compared to stroke and migraine as well as healthy controls, stratified by cardiovascular risk. A sample of 495149 participants were eligible for this study, aged between 38 and 72 years, without dementia at baseline and an imaging sub-sample of 42353 participants. I identified mutually exclusive groups of participants with epilepsy, stroke and migraine at baseline assessment and controls (none of these conditions). Individuals were divided into low, moderate or high cardiovascular risk groups based on factors including waist-to-hip ratio, history of hypertension, hypercholesterolemia, diabetes and smoking pack-years. The outcomes examined were incident all-cause dementia, measures of executive function and brain total hippocampal, grey matter and white matter hyperintensity volumes.

Of the 495149 participants (225481 [45.5%] men, mean [SD] age, 57.5 [8.1] years), 3864 had a diagnosis of focal epilepsy only, 6397 had a history of stroke only while 14518 had migraine only. Executive function was comparable between participants with epilepsy and stroke, and worse than the control and migraine group. Focal epilepsy was associated with a higher risk of developing dementia (hazard ratio [HR] 4.02, 95%CI 3.45 – 4.68, p<0.001), compared with stroke (HR 2.56, 95%CI 2.28 – 2.87, p<0.001), or migraine (HR 1.02, 95%CI 0.85-1.21, p=0.940). Participants with focal

epilepsy and high cardiovascular risk were over 13 times more likely to develop dementia (HR 13.66, 95%CI 10.61 – 17.60, p<0.001) compared to controls with low cardiovascular risk. Lower hippocampal volume (t = -2.175, p=0.030) and total grey matter volume (t = -4.293, p<0.001) was observed in epilepsy participants compared to controls but no significant difference in white matter hyperintensity volume (p=0.256).

Focal epilepsy was associated with a significant risk of developing dementia, to a greater extent than stroke, which was magnified substantially in individuals with high cardiovascular risk. Further findings suggest that targeting modifiable cardiovascular risk factors may be an impactful intervention to reduce dementia risk in individuals with epilepsy.

4.2 Introduction

Epilepsy is a common neurological condition characterised by unprovoked seizures. The incidence of epilepsy is highest in older life and progressively increases after 55 years of age (77,280,281). As individuals with epilepsy age, studies suggest an increased risk of cognitive impairment and, potentially, dementia (54,73). However, the extent to which epilepsy affects dementia risk and potential underlying mechanisms remains unclear. In addition, there are no specific clinical guidelines around mitigating the risk of dementia in epilepsy.

While recent evidence has highlighted a shared pathology link of tau accumulation in epilepsy and dementia(16,88,282), another intriguing line of inquiry is the role of modifiable cardiovascular risk factors which contribute to dementia risk in the general ageing population (166,283). Established stroke is a risk factor for developing epilepsy in older adults (70), however, the impact of upstream cardiovascular risk factors is less clear with conflicting findings (13,72). Similarly, while post-stroke epilepsy is considered predictive of cognitive outcomes (71), how dementia risk in epilepsy may change according to an individual's burden of modifiable cardiovascular risk factors in the absence of stroke remains unknown.

A recent systematic review (73) identified disease duration, seizure frequency and anti-seizure medication as potential predictors of cognitive impairment in epilepsy although studies were limited by small samples of patients and controls, and the lack of consideration for lifestyle and cardiovascular risk factors (74–76). Correspondingly, a meta-analysis examining dementia risk in epilepsy identified similar limitations and was unable to calculate period prevalence owing to insufficient pooled sample size (77). To guide clinical management, it is important to understand the epilepsy-related dementia risk compared other neurological conditions to provide comparator context for clinical decisions.

In this study, I analysed the risk associated with developing dementia across a range of neurological conditions in the UK Biobank prospective cohort. Specifically, my aim was to determine the extent to

which focal-onset epilepsy is associated with risk of developing dementia compared with individuals with stroke or migraine, two other non-degenerative neurological conditions, as well as healthy controls. I hypothesized that epilepsy would be associated with higher dementia incidence than migraine and controls but less than stroke which is strongly linked to vascular cognitive impairment and dementia. Further, I determined the extent to which having low cardiovascular risk is associated with reduced risk of dementia in epilepsy as this may help develop dementia risk reduction strategies for people with epilepsy.

4.3 Methods

This cross-sectional study is based on data from the UK Biobank, a population-based cohort of over 500 000 participants aged 38-72 years who underwent physiological measurements, cognitive testing and provided biological samples at one of 22 centres across the UK between 2006 and 2010 (203). A subset re-attended for brain imaging between 2014 and 2020 (253). All participants provided written informed consent. UK Biobank received approved from the North West Multi-centre Research Ethics Committee (REC number 21/NW/0157). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The primary study objective was to investigate the risk of incident dementia associated with having focal epilepsy compared to stroke or migraine and healthy controls at baseline study assessment. Participants with prevalent dementia at baseline assessment (<1%) were excluded along with other neurological conditions including a history of CNS infection, encephalitis, meningitis, amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, or previous subdural or subarachnoid haemorrhage. Baseline diagnoses were identified using self-report and hospital inpatient records (UK Biobank codes are found in Supplementary Table S4-1).

Dementia and focal epilepsy diagnoses

All-cause dementia cases were identified during longitudinal follow-up from hospital inpatient records, coded using the International Classification of Diseases (ICD) coding system ICD-9 and ICD-10 codes for Alzheimer's disease and other dementia classifications, or from death register linkage data as an underlying or contributory cause.

The epilepsy sub-group was restricted to focal-onset, non-genetic epilepsy at baseline based on ICD codes. I excluded individuals coded for a genetically-associated epilepsy including 'Generalized idiopathic epilepsy and epileptic syndromes' (G40.3), such as syndromes of juvenile myoclonic epilepsy and childhood absence epilepsies, and 'Other generalized epilepsy and epileptic syndromes' (G40.4) which includes epileptic encephalopathies such as Lennox-Gaustaut and West syndrome, as these can be associated with clear cognitive deficits related to an underlying genetic mechanism or developmental delay (284). To investigate the potential confounding effects of anti-seizure medication, I compared the relationship between cognitive scores and number of anti-seizure medication (list in Supplementary Table S4-2) in individuals with a diagnosis of focal epilepsy and those without a diagnosis but taking the medication for another reason. Information on seizure onset zone in the brain was not available, however, the majority of focal-onset, acquired epilepsy may be of temporal lobe origin (98).

Cardiovascular risk score

Cardiovascular risk was assessed based a previously published score (285) with a point given for a diagnosis or being treated for hypertension, high cholesterol or diabetes (one point for each condition), waist-to-hip ratio (one point if greater than sex-specific threshold set by WHO guidelines)(207), smoking pack years (one point if more than 20 pack years) and APOE e4 allele status (two points for two e4 alleles, one point for a single e4 allele and zero points for any other allele combination or when allele status was unclear). Participants were placed in low (score 0), moderate (score 1 & 2) or high risk (score 3+) groups based on quintile boundaries 1, 2 to 4 and 5 respectively.

Cognitive testing

UK Biobank cognitive testing was computer-based and performed at the initial baseline visit, repeated at the imaging visit and via online questionnaire. Not all cognitive tasks were performed at each instance while some were repeated. I analysed data from five tasks of working memory or speed of processing and used the first available timepoint data. This included a pairs-matching and snap reaction time, trail-making, tower-rearranging, and symbol-digit substitution tasks and has been described in detail elsewhere (286). Reliability and re-test effect over time for these cognitive tasks have been previously assessed (287).

Main covariates

All full models were adjusted for age (continuous), sex (female vs male), education (categorised as higher [college or university degree or other professional qualification], upper secondary [second or final stage of secondary education], lower secondary [first stage of secondary education], vocational [work-related qualifications], or other), socioeconomic status (categories derived from Townsend deprivation index (255) quintiles 1, 2 to 4, and 5) and cardiovascular risk group.

Brain imaging variables

Magnetic resonance imaging (MRI) data were acquired on a Skyra 3T scanner (Siemens; Munich, Germany) including high-resolution, T1-weighted, three-dimensional magnetisation-prepared gradient echo structural images and T2-weighted fluid-attenuated inversion recovery images. Full imaging protocols and processing pipeline have been previously described (256). I used imaging summary statistics of total hippocampal, grey matter and white matter hyperintensity volumes. These regions were chosen as previous epilepsy studies have found hippocampal atrophy (288–290) and hippocampal tau deposition (282). Total grey matter volume is a useful measure of widespread, global change while white matter hyperintensity is a useful marker of vascular burden. Median

absolute deviation was used to exclude outliers, and volumes were adjusted for potentially confounding baseline measures of age, age squared, head size, and imaging site (256).

Statistical analysis

Confirmatory factor analysis (CFA) was performed on cognitive variables to produce a continuous, summary latent measure of working memory and reaction time which I termed "Executive Function" for simplicity (this method has been previously described) (257,286) In brief, cognitive variables were pre-processed to correct for heavily skewed distribution prior to CFA. Standard fit indices were measured with higher comparative fit index (CFI) and Tucker-Lewis Index (TLI) considered better (>0.9 are commonly used as acceptable fit cut-offs) while lower root mean square error of approximation (RMSEA) and standardised root mean square error residual (SRMR) is considered better (<0.06 and <0.08, respectively, are commonly used cut-offs for acceptable fit). Estimating a latent variable has the methodological advantage of controlling measurement error that can artificially reduce the relationship between measured variables in standard univariate analyses (291). Missing cognitive data were estimated using full information maximum likelihood, which gives unbiased parameter estimates and standard errors.

I examined mutually exclusive groups of focal epilepsy, stroke and migraine. Combinations of conditions, such as having epilepsy and stroke, were not reported due to small sample sizes. The relationship between Executive Function across age was examined for each group. I then controlled for age in two different ways for robustness- using a model-free, sliding window approach with fixed age-quantile widths moved along the age distribution (described previously (225,226,286), code: conditionalPlot.m available: https://osf.io/vmabg/) or by including age as a covariate in a general linear model along with other baseline characteristics. I compared the difference in Executive Function between condition groups using ANOVA with post-hoc Tukey analysis to account for pairwise or multiple comparisons, p-values were two-sided with statistical significance set at $p<0{\cdot}05$ for all analyses. Brain measures were analysed in the epilepsy sub-group using the same methods.

Hazard ratios (HRs) were calculated using Cox proportional hazards regression models with time to incident all-cause dementia as the dependent variable. I calculated HRs for mutually exclusive groups of focal epilepsy, stroke, migraine compared with none of these conditions as the baseline. For my main model, I tested the dementia risk associated with having focal epilepsy, stroke or neither condition, stratified by cardiovascular risk groups (nine categories with low cardiovascular risk and neither epilepsy or stroke as the baseline). Migraine had similar HRs to controls from initial testing and was not included in this model. For the main exposures and covariates, there were less than 3% missing or not known data and complete case analysis was applied. Participants were considered at risk for dementia from baseline until the date of first diagnosis, death, loss to follow-up, or the last surveyed hospital admission date (March 31, 2021, for England and Scotland and Feb 28, 2018, for Wales), whichever came first. These censoring dates were recommended by UK Biobank as the data was estimated to be over 90% complete in England, Scotland, and Wales.

Secondary data analyses examined dementia risk with different follow-up durations of 10 years and 5-15 years to consider earlier risk of developing dementia and potential reverse causality, respectively. Further sensitivity analysis considered dementia risk associated with stroke and epilepsy stratified by a cardiovascular risk score that did not include APOE e4 genetic information to consider only modifiable lifestyle risk. The association between dementia risk and epilepsy controlling for number of anti-seizure medication was investigated within the epilepsy sub-group only. Analyses were done in Matlab R2018a or in R version 4.0.3 using the Lavaan (220) or survival package.

4.4 Results

4.4.1 Study demographics

The UK Biobank cohort comprised 502 536 participants at baseline. After excluding those who did not meet the inclusion criteria (N = 7216) and those with prevalent dementia at baseline (N = 120), my study included 495 149 individuals (flowchart in Supplementary Figure S4-1). Participants had a mean (SD) age of 57.5 (8.1) years and 54.5% were female (baseline demographics in Table 4-1.). Over 5 803 006 total follow-up years (median 12.0, interquartile range 11.2-12.7), 6115 cases of all-cause incident dementia were observed.

At baseline assessment, 3864 (0.78%) participants had a diagnosis of focal epilepsy only, 6397 (1.3%) had a history of stroke only while 14518 (2.93%) had migraine only. There were 134 249 (27.1%) participants with low cardiovascular risk while 274 098 (55.4%) and 86 802 (17.5%) had a moderate and high cardiovascular risk, respectively (breakdown in Supplementary Table S4-3).

Table 4-1. Baseline characteristics of study participants

Characteristic	Controls No. (%)		Epilepsy No. (%)		Stroke No. (%)		Migraine No. (%)	
	No incident dementia (n = 464 138)	**Incident dementia (n = 5471)**	**No incident dementia (n = 4121)**	**Incident dementia (n = 198)**	**No incident dementia (n = 6679)**	**Incident dementia (n = 337)**	**No incident dementia (n = 15 835)**	**Incident dementia (n = 174)**
Age, mean (SD), years	57.4 (8.1)	65.3 (4.8)	57.1 (8.1)	63.5 (6.1)	61.5 (6.9)	65.4 (4.7)	56.1 (7.8)	63.7 (6.2)
Sex								
Female	250 752 (54.0)	2619 (47.9)	2071 (50.3)	77 (38.9)	2766 (41.4)	119 (35.3)	12 363 (78.1)	117 (67.2)
Education[a]								
Higher	217 148 (46.8)	1813 (33.1)	1623 (39.4)	55 (27.8)	2257 (33.8)	86 (25.5)	7810 (49.3)	53 (30.4)
Upper Secondary	58464 (12.6)	550 (10.1)	547 (13.3)	23 (11.6)	807 (12.1)	33 (9.8)	1939 (12.2)	17 (9.8)
Lower Secondary	25227 (5.4)	253 (4.6)	202 (4.9)	10 (5.1)	302 (4.5)	19 (5.6)	919 (5.8)	11 (6.3)
Vocational	77047 (16.6)	746 (13.6)	708 (17.1)	23 (11.6)	1045 (15.6)	42 (12.5)	2793 (17.6)	22 (12.6)
Other	86252 (18.6)	2109 (38.5)	1047 (25.4)	85 (42.9)	2268 (34.0)	157 (46.6)	2374 (15.0)	71 (40.8)
Socioeconomic status quintile[b]								
1 (least deprived)	93326 (20.1)	990 (18.1)	641 (15.5)	28 (14.1)	959 (14.4)	39 (11.6)	3161 (20.0)	31 (17.8)
2-4	278742 (60.1)	3151 (57.6)	2317 (56.2)	96 (48.5)	3629 (54.3)	176 (52.2)	9588 (60.5)	91 (52.3)
5 (most deprived)	91495 (19.7)	1323 (24.2)	1166 (28.2)	74 (37.4)	2084 (31.2)	122 (36.2)	3061 (19.3)	52 (29.9)
n/a	575 (0.1)	7 (0.1)	2 (0.05)	0 (0.0)	7 (0.1)	0 (0.0)	25 (0.2)	0 (0.0)
Cardiovascular risk group (score) [c]								
Low (0)	127055 (27.3)	495 (9.0)	997 (24.2)	21 (10.6)	531 (8.0)	13 (3.9)	5490 (34.7)	31 (17.8)
Moderate (1-2)	258527 (55.7)	2695 (49.3)	2309 (56.0)	91 (46.0)	2700 (40.4)	97 (28.8)	8585 (54.2)	87 (50.0)
High (3+)	78556 (16.9)	2281 (41.7)	815 (19.8)	86 (43.4)	3448 (51.6)	227 (67.4)	1760 (11.1)	56 (32.2)

Percentages may not sum to 100 because of rounding.

[a] *Higher education defined as college/university degree or other professional qualification; upper secondary, second/final stage of secondary education; lower secondary, first stage of secondary education; vocational, work-related practical qualifications.*

[b] *Socioeconomic status assessed on the Townsend deprivation index, which combines information on social class, employment, car availability, and housing.*

[c] *Cardiovascular risk group calculated from cardiovascular risk score based on history of hypertension, high cholesterol, diabetes, waist-hip-ratio, smoking history and genetic APOE genotype*

4.4.2 Epilepsy and stroke were associated with worse cognitive performance than migraine and in controls

A continuous cognitive function latent variable of Executive Function was estimated from five cognitive tasks of working memory or speed of processing (model and fit indices shown in Supplementary Figure S4-2). Executive Function declined uniformly with age (Figure 4-1) among all groups, consistent with previous findings (257,286). I controlled for age using a model-free, residual method and showed that focal epilepsy was associated with a lower Executive Function than controls and migraine (mean difference = -0.085 [95% CI -0.070 – -0.099], t = 14.70, p_{Tukey} <0.001 and mean difference = -0.082 [95% CI -0.099 – -0.101], t = -12.82, p_{Tukey} <0.001, respectively, using post-hoc Tukey analysis). There was no significant difference between Executive Function in focal epilepsy or stroke (mean difference = 0.005 [95% CI -0.014 – 0.023], t = 14.70, p_{Tukey} = 0.909, further details in Supplementary Table S4-4). The associations between Executive Function and neurological conditions remained consistent with a fully adjusted linear model accounting for other baseline characteristics (Supplementary Table S4-5).

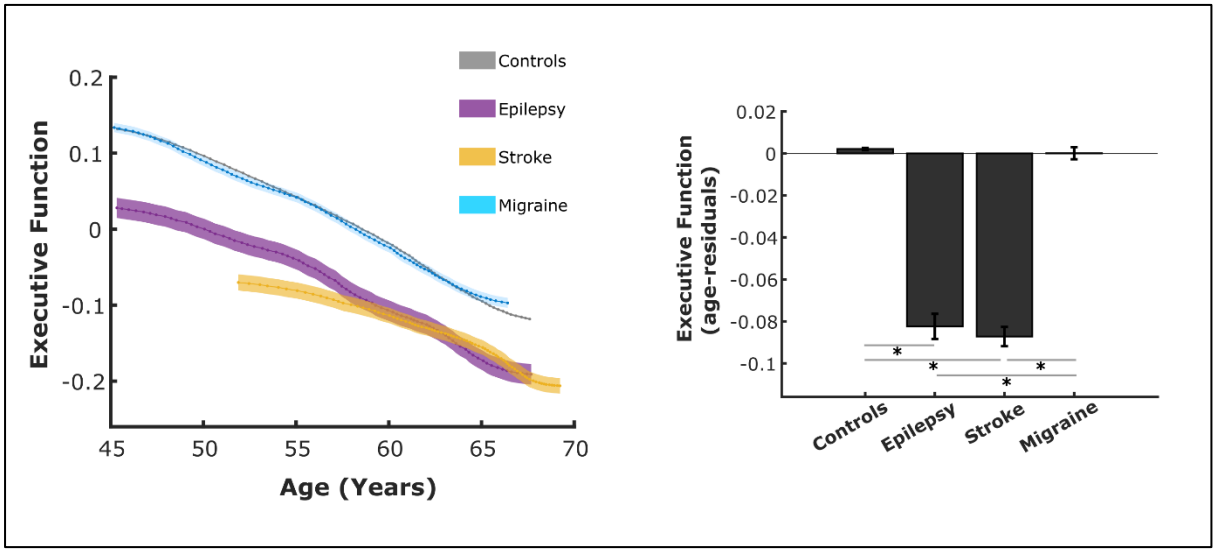


Figure 4-1. Relationship between Executive Function and age in participants with epilepsy, stroke, migraine and controls.

Participants with epilepsy and stroke have lower Executive Function (z-scored values) across all ages compared to controls with no history of epilepsy, stroke or migraine (left). Shaded area represents standard error. When adjusting for age (right), using an age-residual approach, there is a group

difference F(3,489069)=201.97, p<0.001. Post-hoc pairwise comparison shows that having epilepsy or stroke was associated with significantly lower Executive Function compared to controls (t = 14.70, p_{Tukey} <0.001, and t = 19.90, p_{Tukey} <0.001, respectively) and participants with migraine (t = -12.82, p_{Tukey} <0.001, and t = -16.35, p_{Tukey} <0.001, respectively). There was no significant difference in Executive Function between participants with migraine and controls (p_{Tukey} = 0.906) or between participants with epilepsy or stroke (p_{Tukey} = 0.909). All groupings are mutually exclusive, i.e. the epilepsy group has no history of stroke or migraine.

4.4.3 Epilepsy was associated with a higher dementia risk than stroke

During the study follow-up, the adjusted HR for incident dementia was 4.02 (95% CI 3.45 – 4.68) for participants with focal epilepsy (Figure 4-2), which was higher than stroke (HR 2.56, 95% CI 2.28 – 2.87) and migraine (HR 1.02, 95% CI 0.85 – 1.21). Within moderate and high cardiovascular risk groups, a having focal epilepsy was associated with a higher risk of developing dementia compared with stroke (). Of participants with high cardiovascular risk and focal epilepsy, 9.1% developed dementia compared while 0.4% control participants with low cardiovascular risk (HR 13.66, 95% CI 10.61 – 17.60). When considering only individuals with high cardiovascular risk, those with focal epilepsy had a HR of 3.73 (95% CI 2.94 - 4.76) for developing dementia compared to controls while participants with stroke had a HR of 1.90 (95% CI 1.65 - 2.20) compared to controls. Risk of dementia within moderate and low cardiovascular risk groups are detailed in Supplementary Table S4-6).

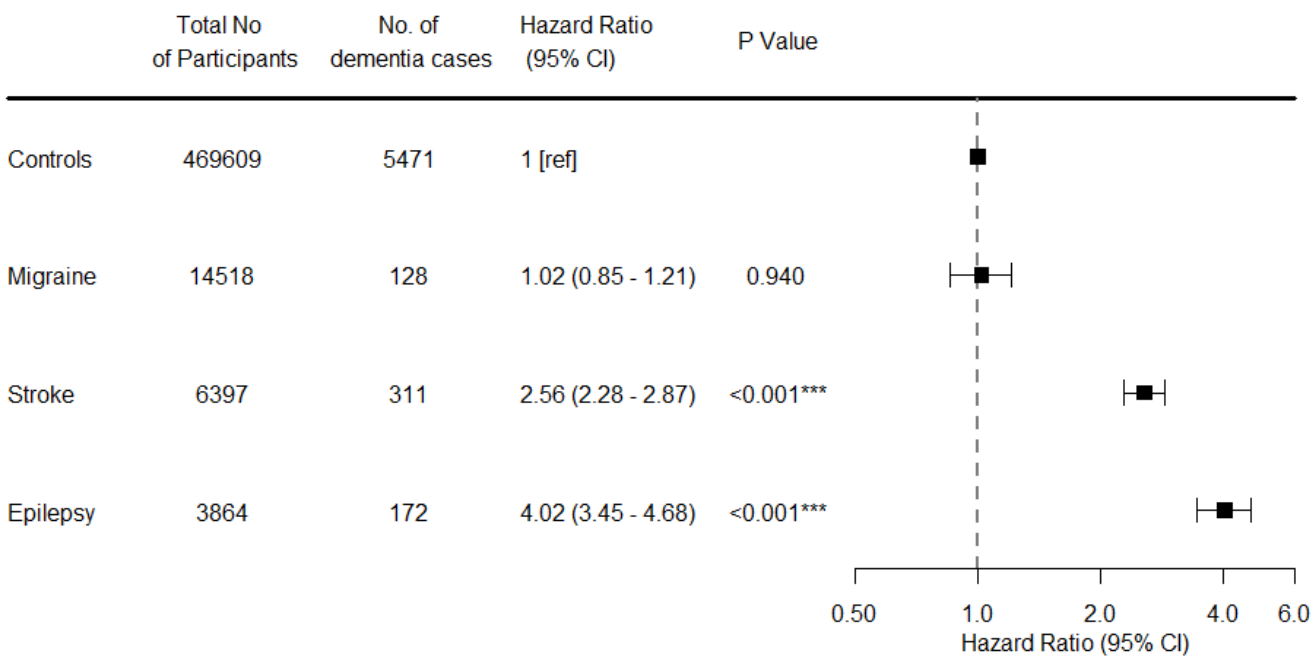


Figure 4-2. Risk of incident dementia by neurological disease status at baseline

Data are HRs for incident dementia, associated mutually exclusive conditions of migraine, stroke and epilepsy compared with a control group (no migraine, stroke or epilepsy). The model has been adjusted for age, sex, education, socioeconomic status and assessment centre. Horizontal bars indicate 95% confidence intervals. *HR=hazard ratio.*

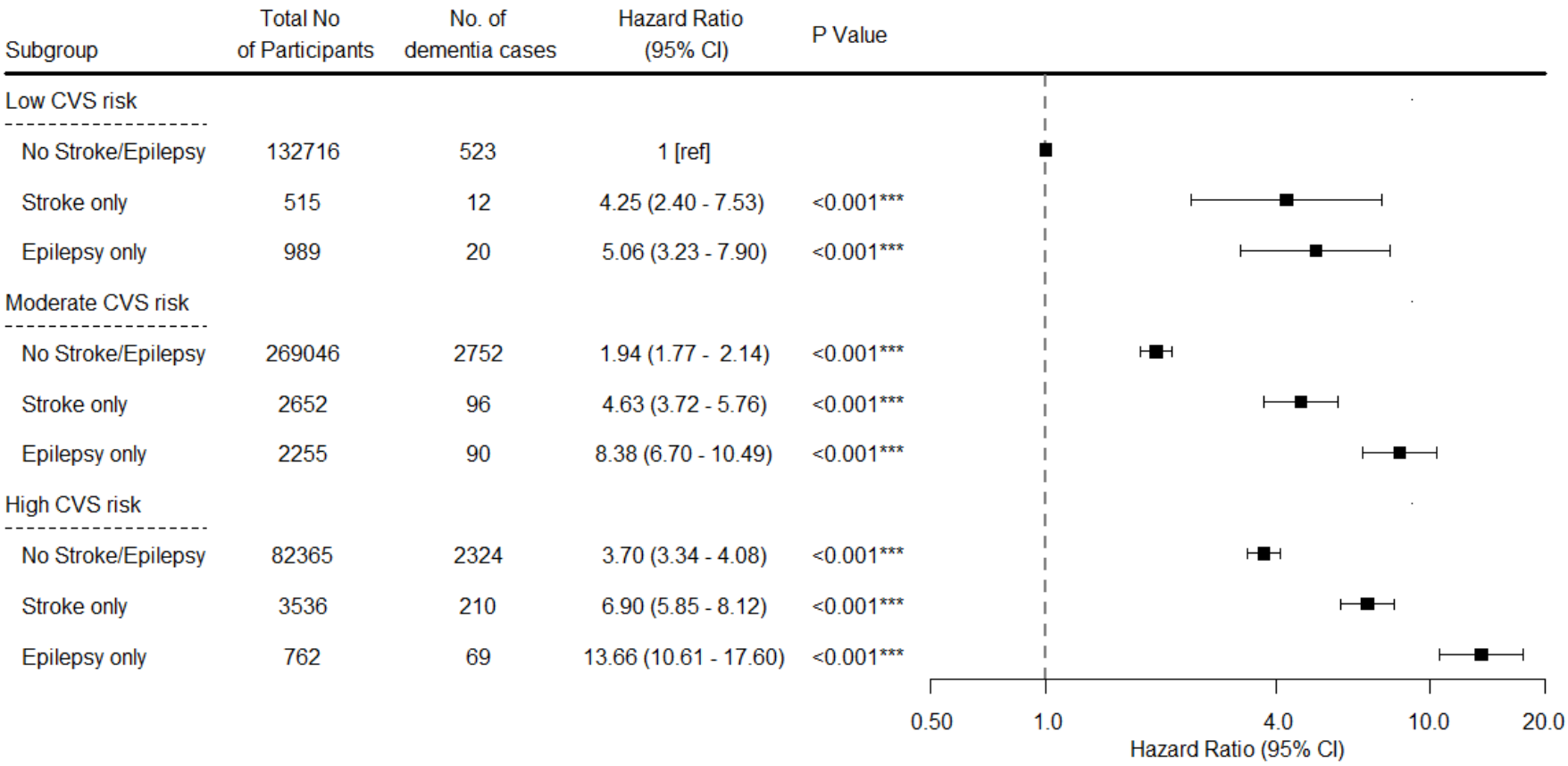


Figure 4-3. Risk of incident dementia associated with epilepsy and stroke according to cardiovascular risk

Data are HRs for incident dementia, associated with groupings of no stroke/epilepsy, stroke only or epilepsy only stratified by CVS risk groups. The model has been adjusted for age, sex, education, socioeconomic status and assessment centre. Horizontal bars indicate 95% confidence intervals. *HR=hazard ratio, CVS = cardiovascular*

Sensitivity analysis

Similar patterns of association were observed with epilepsy and stroke when considering risk of incident dementia at 10 years following baseline assessment and a follow-up period between 5-14 years which was performed to mitigate potential for reverse causation or undetected dementia at baseline assessment (Supplementary Table S4-7). There were 3804 cases of dementia identified for the 10 year follow-up period after baseline assessment and 5110 cases identified for the 5-14 year follow-up period. To examine modifiable risk factors more closely, I considered a cardiovascular risk score which did not include genetic APOE e4 genotype but instead controlled for the APOE e4 genetic risk status in the model. The magnitude of association between each condition and dementia risk was attenuated, but with similar overall pattern, as participants with high cardiovascular risk and epilepsy had a HR of 7.53 (95% CI 5.62 – 10.10) compared to the baseline group of low cardiovascular risk and no epilepsy (Supplementary Figure S4-3).

4.4.4 Epilepsy sub-analyses

Considered an index of epilepsy disease severity, taking more anti-seizure medications was associated with lower Executive Function in those with focal epilepsy (Supplementary Figure S4-4). To control for the possibility that the medication themselves might be affecting cognition, I also examined individuals taking anti-seizure medication who did *not* have a diagnosis of epilepsy. In this group, the relationship was not present (evidenced by a significant interaction between having a diagnosis of focal epilepsy and number of anti-seizure medications, t=2.187, p=0.028). The median age of focal epilepsy onset was 25.5 years which indicated that seizure onset in this epilepsy cohort generally started during adulthood. Despite the use of more anti-seizure medications being associated with a lower Executive Function (Supplementary Table S4-8), using more anti-seizure medication was not associated with a higher risk of developing dementia (Supplementary Table S4-9). The risk of developing dementia associated with late-onset focal epilepsy (>50 years) was

comparable (HR 2.82 [95% CI 1.97 - 4.04]) to the risk associated with early-onset focal epilepsy (<50 years of age, HR 2.46 [95% CI 1.93 - 3.13], with further details in Supplementary Table S4-10).

4.4.5 Epilepsy was associated with reduced hippocampal and total brain volume

Focal epilepsy was associated with lower hippocampal volume (mean difference = -0.167 [95% CI -0.017 – -0.317], t = -2.175, p = 0.030) and lower total grey matter volume (mean difference = -0.327 [95% CI -0.178 – -0.477], t = -4.293, p <0.0001) compared to controls (Figure 4-1), however, there was no significant difference in white matter hyperintensity volume (mean difference = 0.096 [95% CI -0.070 – 0.262], t= 1.1362, p = 0.256). Across age, the difference in hippocampal volume was more apparent in older individuals with focal epilepsy. A fully adjusted linear regression model accounting for other baseline characteristics and cardiovascular risk demonstrated the same pattern of associations (Supplementary Table S4-11).

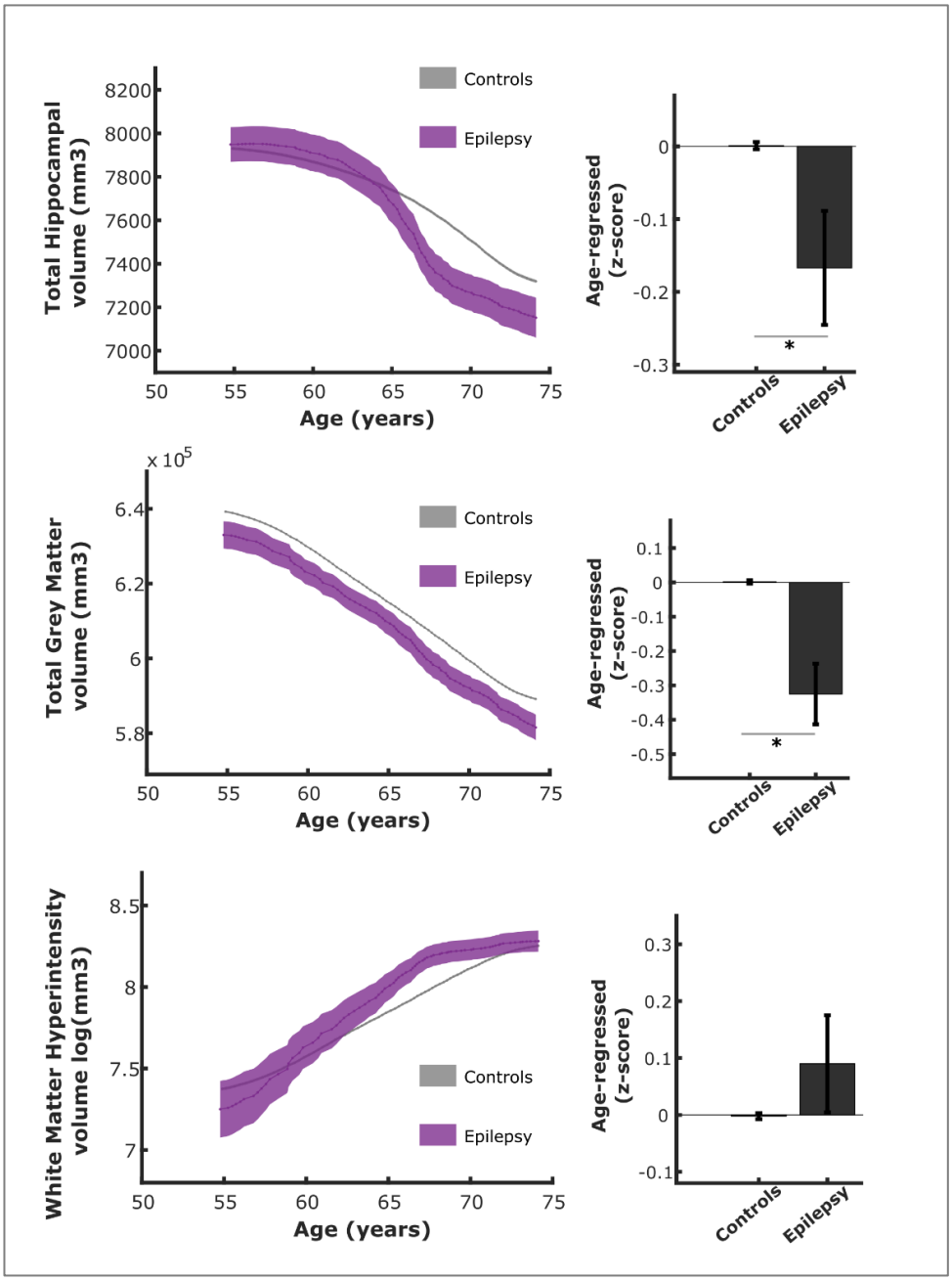


Figure 4-4. Total hippocampal volume, total grey matter volume and white matter hyperintensity volume in participants with focal epilepsy and controls

Data are brain volumes of the hippocampi, total grey matter and white matter hyperintensities comparing participants with focal epilepsy compared to controls across age (left column) and with age-regressed and z-score transformed values (right column). Total hippocampal volume was lower in older individuals with focal epilepsy while total grey matter volume was in individuals with focal epilepsy of all ages. When regressing out the effect of age, having epilepsy was significantly associated with lower total hippocampal (mean difference = -0.167 [95% CI -0.017 – -0.317], t = -2.175, p = 0.030) and grey matter volume (mean difference = -0.327 [95% CI -0.178 – -0.477], t = -4.293, p <0.0001). No significant difference in white matter hyperintensity was found between individuals with epilepsy and controls (mean difference = 0.096 [95% CI -0.070 – 0.262], t= 1.1362, p = 0.256).

4.5 Discussion

The results of this study show that having focal epilepsy is associated with worse cognitive function in mid-to-late life individuals compared with controls. Furthermore, by leveraging a large epilepsy cohort with longitudinal data on dementia outcomes, I show a higher dementia risk in individuals with focal epilepsy compared to those with stroke, which was substantially worse in those with greater cardiovascular risk burden. Focal epilepsy was associated with widespread structural brain change reflected by lower total hippocampal and total grey matter volume.

Several studies have demonstrated worse cognition in epilepsy as individuals grow older(28,29,31,76,292), although these are mostly cross-sectional and have generally been small in sample size with less than a hundred individuals. One study(27) showed objective executive function impairment in a larger epilepsy group (n=257) prior to starting anti-seizure medication. With a sample size an order of magnitude larger than previous studies, this current investigation identified worse cognitive function throughout mid-to-late life individuals with focal epilepsy compared with healthy controls, which was comparable to individuals with a history of stroke. Taking more anti-seizure agents was associated with worse cognition in those with focal epilepsy which may reflect severity of disease in addition to potential for medication side-effects. My findings offer an important contribution to understanding the cognitive impact of epilepsy at a group level.

Few studies have suggested epilepsy as a risk factor for dementia (49–51,53,293,294) while other investigations did not find an association (56–58). Stefanidou et al. identified an increased dementia risk among 43 people with epilepsy in the Framingham Heart study (HR 1.9 [95% CI (1.11-3.57)] compared with controls (52) which was slightly lower than my findings. In such studies, cardiovascular risk factors may be controlled for in analyses models or not considered at all. To investigate the potential impact of cardiovascular burden, I stratified individuals based on a previously published cardiovascular risk score (257) and found more than a 13-fold increase risk of dementia in individuals who have high cardiovascular risk and epilepsy compared to those with no

epilepsy and low cardiovascular risk. This increased dementia risk was greater than that of stroke. The lack of association with number of anti-seizure medication prescribed excludes an important potential confounder as some older anti-seizure medications are also associated with increased vascular risk markers (295). Dementia risk associated with early-onset and late-onset epilepsy was comparable in my study which is consistent with other investigations showing that measures of epilepsy disease-duration did not correspond with worse cognitive impairment (296) or tau pathology burden (282). The relationship between epilepsy and dementia may represent shared risk factors between epilepsy and a vascular dementia-like process (297) or an interplay between mixed underlying pathology which is increasingly reported in dementia (275,277) In either event, my findings highlight a key clinical message that cardiovascular risk factor modification may be critical for managing cognitive outcomes in focal epilepsy.

Epilepsy neuroimaging studies have observed widespread structural changes in addition to hippocampal atrophy (288–290). The present study confirms this finding whilst incorporating important covariates such as education, socioeconomic status and cardiovascular risk factors which are often not considered. Structural changes at the whole brain level may reflect widespread network effects of epilepsy regardless of the focal-onset of seizures (298,299). I did not find a statistically significant difference in white matter hyperintensity burden between individuals with epilepsy and controls, although this trend was present. The finding of widespread structural changes in this cohort is important to understand the effects of epilepsy on the brain.

My study has several limitations. Due to the observational nature of this cohort, the association of greater incident dementia in epilepsy cannot be taken as causal. Medical information was based on hospital records, death certificate data or self-report which may be incorrect (279). I identified individuals with non-genetic or ‘focal-onset’ epilepsy through medical coding, however, this may be inaccurate and I do not have information on seizure origin, laterality, frequency or presence of hippocampal sclerosis which may have an impact on cognitive performance. Such epilepsy

characteristics were not captured by the UK Biobank which was designed to recruit healthy individuals with no single disease in focus. Results of specific clinical investigations, such as EEG, were not available but would be a beneficial addition to future data releases of the study. Data from all participants in the UK Biobank, aged 38 to 72 years, were used to include as many diagnoses of epilepsy, stroke and migraine as possible. I recognise that the younger participants may have a higher chance of developing dementia in later years past the follow-up period of this study. Despite adjustment for potential confounders, the relatively long follow-up period and additional analysis of dementia incidence from five to 15 years, there may be unmeasured confounders and potential for reverse causality. While I considered all-cause dementia risk in this study, examining the relationship with dementia sub-types would be interesting; however, subtypes are currently poorly captured in the UK Biobank and with dementia cases are likely to be Alzheimer's disease, vascular, or a mixed picture (254). The UK Biobank cohort is generally considered healthy and likely to be from less deprived areas (228), therefore the effects of cardiovascular risk may be greater in a more representative cohort. Similarly, individuals with focal epilepsy from this cohort are less likely to have drug-resistant, uncontrolled epilepsy that may result in worse cognitive outcomes.

In conclusion, focal epilepsy was significantly associated with worse cognitive performance, higher incident dementia risk and widespread brain differences. Cardiovascular risk substantially increased the risk of dementia in people with focal epilepsy and therefore interventions targeting modifiable risk factors may offer an effective management strategy in preventing dementia in epilepsy.

4.6 Supplementary Material for Chapter 4

Supplementary Table S4-1. Codes used in the UK Biobank study to identify dementia and cardiometabolic condition cases and exclusion diagnoses

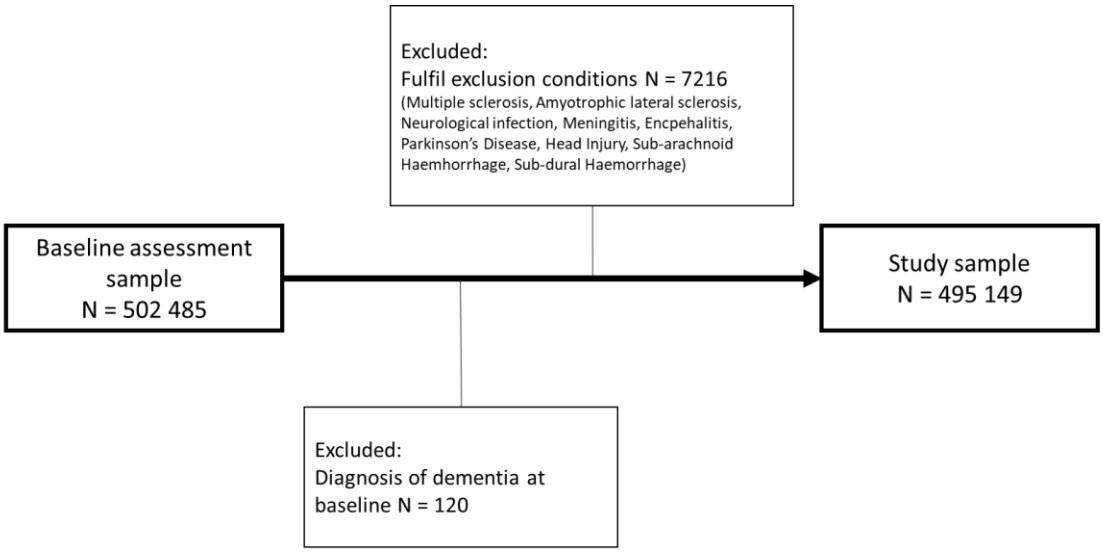
	Algorithmically-derived	Self-report (includes non-cancer and treatment self report)	Illness code: ICD-10	Illness code: ICD-9
Dementia	-	1263	AD: F00, F00.0, F00.1, F00.2, F00.9, G30, G30.0, G30.1, G30.8, G30.9 VaD: F01, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3 FTD: F02.0, G31.0, Other codes for all-cause dementia: A81.0, F02, F02.1, F02.2, F02.3, F02.4, F02.8, F03, F05.1, F10.6, G31.1, G31.8	AD: 331.0 VaD: 290.4 FTD: 331.1 Other codes for all-cause dementia: 290.2, 290.3, 291.2, 294.1, 331.2, 331.5
Stroke	All-cause stroke: 42006	1081	I630, I631, I632, I633, I634, I635, I636, I638, I639,	43491
Epilepsy	-	1264	G40, G400, G401, G402, G405, G406, G407, G408, G409, G41, G410, G411, G412, G418,G419	34540, 34540, 34541, 34550, 34551
Migraine		1265	G43, G430, G431, G432, G433, G438, G439	34690
Diabetes	-	2443, 6153, 6177,	E10, E100, E101, E102, E103, E104, E105, E106, E107, E108, E109 E11, E110, E111, E112, E113, E114, E115, E116, E117, E118, E119, E12, E120, E121, E122, E123, E124, E125, E126, E127, E128, E129, E13, E130, E131, E132, E133, E134, E135, E136, E137, E138, E139, E14, E140, E141, E142, E143, E144, E145, E146, E147, E148, E149,E15, E150, E151, E152, E153, E154, E155,	'25000', '25001', '25009', '25010', '25011', '25019', '25029', '2503', '2504', '2505', '25099'

			E156, E157, E158, E159	
Infection of the central nervous system	-	1244	-	-
Encephalitis	-	1246	-	-
Meningitis	-	1247	-	-
	-	1262		
Amyotrophic lateral sclerosis	-	1259	-	-
Multiple Sclerosis	-	1261	-	-
Head Injury	-	1266	-	-
Subdural Haematoma	-	1083	-	-
Subarachnoid Haemorrhage	-	1086	-	-

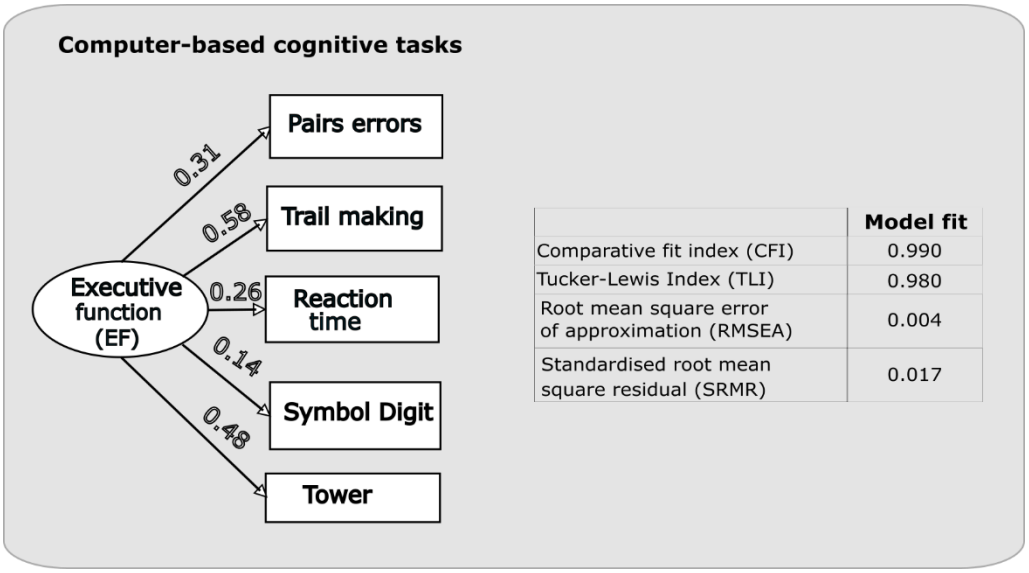
Supplementary Table S4-2. Codes for anti-epileptic medication recorded in the UK Biobank and simplified medication name

Coding	Medication reference	Medication (simplified)
1140856568	acetazolamide [ep] 250mg tablets	acetazolamide
1140875868	acetazolamide	acetazolamide
1140875870	diamox 250mg tablet	acetazolamide
2038459704	carbamazepine	carbamazepine
1140872064	carbamazepine product	carbamazepine
1140872072	tegretol 100mg tablet	carbamazepine
1140863268	clobazam	clobazam
1140863272	frisium 10mg capsule	clobazam
1140872150	clonazepam	clonazepam
1140872152	rivotril 500mcg tablet	clonazepam
1140863152	diazepam	diazepam
1140863170	diazemuls 10mg/2ml injection	diazepam
1140856506	stesolid 5mg/2.5ml rectal solution	diazepam
1140863172	dialar 2mg/5ml syrup	diazepam
1140872160	ethosuximide	ethosuximide
1140872162	emeside 250mg capsule	ethosuximide
1140872164	zarontin 250mg capsule	ethosuximide
1140879744	fenfluramine	fenfluramine
1140867982	ponderax 60mg m/r capsule	fenfluramine
1140872228	gabapentin	gabapentin
1140872236	neurontin 100mg capsule	gabapentin
1140872290	lamotrigine	lamotrigine
1140872302	lamictal 25mg tablet	lamotrigine
1141171932	levetiracetam	levetiracetam
1141171940	keppra 250mg tablet	levetiracetam
1140863302	lorazepam	lorazepam
1140863364	ativan 1mg tablet	lorazepam
1141175204	oxcarbazepine	oxcarbazepine
1141175212	trileptal 150 tablet	oxcarbazepine
2038460068	phenobarbitone	phenobarbital
1140872172	methylphenobarbitone	phenobarbital
1140872174	prominal 30mg tablet	phenobarbital
1140872180	methylphenobarbitone 30mg tablet	phenobarbital
1140872186	phenobarbitone product	phenobarbital
1140850874	cantil+phenobarbitone tablet	phenobarbital
1140909812	methylphenobarbital	phenobarbital
1140910706	phenobarbital	phenobarbital
1141181616	phenobarbital product	phenobarbital
2038460076	phenytoin	phenytoin
1140872098	phenytoin product	phenytoin

1140872112	epanutin 25mg capsule	phenytoin
1140872304	piracetam	piracetam
1140872306	nootropil 800mg tablet	piracetam
1141200004	pregabalin	pregabalin
1141200072	lyrica 25mg capsule	pregabalin
1140872132	primidone	primidone
1140872134	mysoline 250mg tablet	primidone
1140872198	sodium valproate	sodium valproate
1140872200	epilim 100mg crushable tablet	sodium valproate
1140872214	valproic acid	sodium valproate
1140872216	convulex 150mg e/c capsule	sodium valproate
1140872268	orlept 200mg e/c tablet	sodium valproate
1141172838	depakote 250mg e/c tablet	sodium valproate
1141182592	epival cr 300mg m/r tablet	sodium valproate
1141168436	tiagabine	tiagabine
1141168444	gabitril 5mg tablet	tiagabine
1140923484	topiramate	topiramate
1140927692	topamax 25mg tablet	topiramate
2018602634	vigabatrin	vigabatrin
1140872280	vigabatrin product	vigabatrin
1140872284	sabril 500mg tablet	vigabatrin



Supplementary Figure S4-1. Study flowchart



	Model fit
Comparative fit index (CFI)	0.990
Tucker-Lewis Index (TLI)	0.980
Root mean square error of approximation (RMSEA)	0.004
Standardised root mean square residual (SRMR)	0.017

Supplementary Figure S4-2. Confirmatory factor analysis of computer-based cognitive tasks

Path diagram (left) used to create a single latent variable of Executive Function (EF) using confirmatory factor analysis. Fit indices shown on the right.

Supplementary Table S4-3. Cardiovascular risk score breakdown

	N (%)
Cardiovascular risk score	
0	134249 (27.1)
1	169266 (34.2)
2	104832 (21.2)
3	53932 (10.9)
4	24409 (4.9)
5	7292 (1.5)
6	1109 (0.2)
7	60 (0.01)
Score components	
Hypertension	135882 (27.4)
High Cholesterol	81240 (16.1)
Diabetes	26945 (5.4)
WHR (above threshold)	241931 (48.8)
APOE one E4 allele	123636 (24.9)
APOE two E4 alleles	11256 (2.3)

Supplementary Table S4-4. Post-hoc comparisons examining the differences between individual neurological conditions (mutually exclusive groups) and controls

	Executive Function		
	F	p	
Neurological conditions & control groups	201.965	*< .001	
Post-hoc analysis	Mean diff (95% CI)	t-stat	P_{Tukey}
Individual groups			
Controls – Epilepsy	0.085 (0.070 - 0.099)	14.70	*< .001
Controls – Stroke	0.089 (0.078 - 0.101)	19.89	*< .001
Controls – Migraine	0.002 (-0.006 - 0.010)	0.68	0.906
Epilepsy – Stroke	0.005 (-0.014 - 0.023)	0.67	0.909
Epilepsy – Migraine	-0.082 (-0.099 - -0.066)	-12.82	*< .001
Stroke – Migraine	-0.087 (-0.101 - -0.074)	-16.35	*< .001

Post-hoc analysis of relationship between individual groups of neurological conditions and controls with a Tukey correction applied to account for multiple comparisons. CI- confidence interval.

Supplementary Table S4-5. Association between Executive Function with neurological conditions using a general linear model controlling for other baseline characteristics

	Executive Function					
	Full Model[a]			Partial Model[b]		
	β	t-stat	p	β	t-stat	P
Epilepsy	-0.072	-10.88	*< .001	-0.081	-14.16	*< .001
Stroke	-0.077	-13.98	*< .001	-0.063	-19.377	*< .001
Migraine	0.003	1.08	0.270	-0.002	-0.52	0.605
Age	-0.012	-168.08	*< .001	-0.012	-195.37	*< .001
CVS risk group						
Low		Baseline				
Moderate	-0.017	-12.72	*< .001	-	-	-
High	-0.034	-18.23	*< .001	-	-	-

[a]Full model: General linear model adjusted for baseline characteristics including age, CVS risk group, sex, education, socioeconomic status and assessment centre. β = unstandardised betas
[b]Partial model: Only age included as a covariate together with neurological conditions
Note: β = unstandardised betas. CVS – cardiovascular

Supplementary Table S4-6. Dementia risk for focal epilepsy and stroke within each cardiovascular risk group

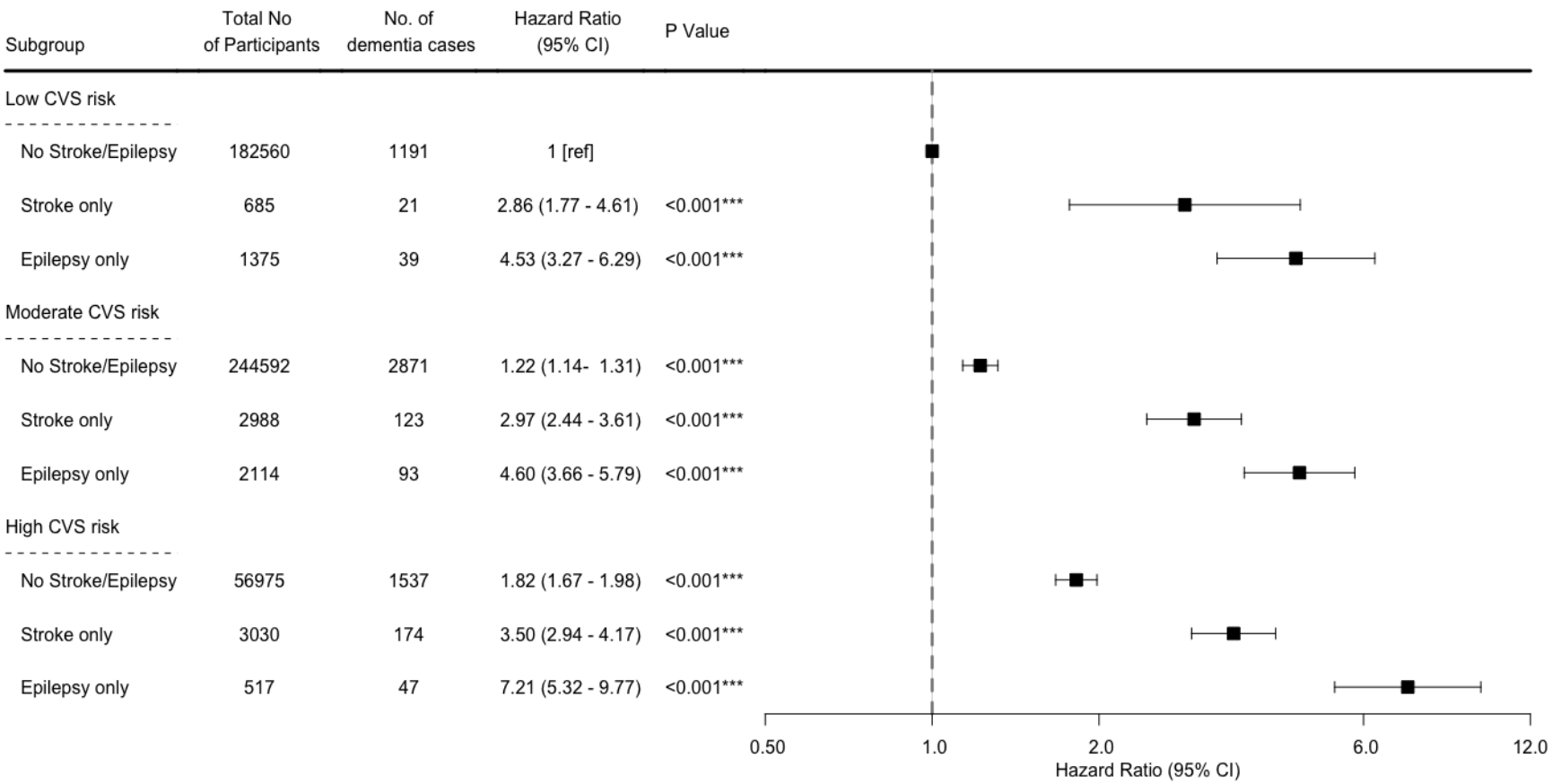
	Dementia risk								
	Low cardiovascular risk			Moderate cardiovascular risk			High cardiovascular risk		
Subgroup	**No. of dementia cases**	**HR (95% CI)**	***P*-value**	**No. of dementia cases**	**HR (95% CI)**	***P*-value**	**No. of dementia cases**	**HR (95% CI)**	***P-value***
Controls	495	1 [reference]	-	2695	1 [reference]	-	2281	1 [reference]	-
Stroke	12	4.36 (2.45 – 7.74)	***<0.001	93	2.41 (1.97 - 2.98)	***<0.001	206	1.90 (1.65 - 2.20)	***<0.001
Epilepsy	19	4.81 (3.04 - 7.61)	***<0.001	85	4.23 (3.41 – 5.25)	***<0.001	68	3.73 (2.94 - 4.76)	***<0.001

HRs for participants with stroke only and focal epilepsy only are compared to a baseline reference group of participants with no history of migraine, stroke or epilepsy. The model has been adjusted for age, sex, education, socioeconomic status and assessment centre.

Supplementary Table S4-7. Dementia risk for each neurological condition (mutually exclusive groups) with different follow-up periods

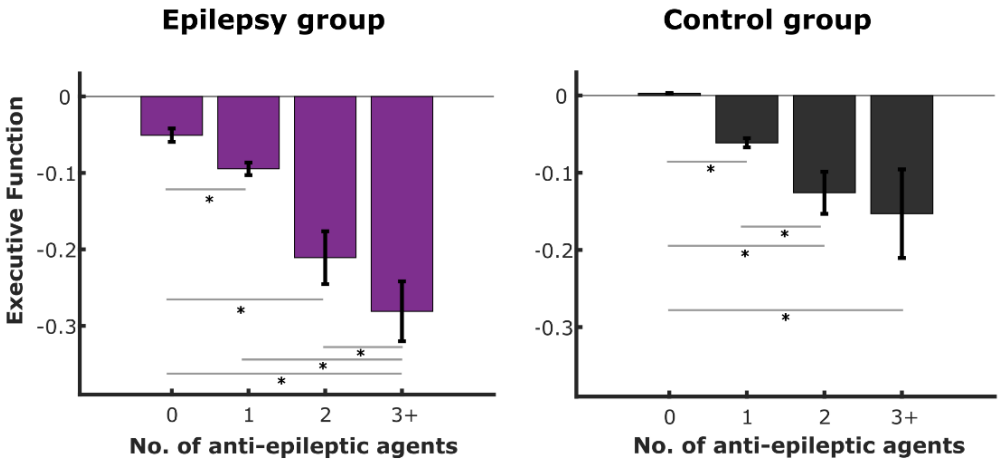
Subgroup	Dementia risk at 10 years			Dementia risk between 5 - 14 years		
	No. of dementia cases	Hazard Ratio (95% CI)	*P*-value	No. of dementia cases	Hazard Ratio (95% CI)	*P*-value
Migraine	74	0.96 (0.76 - 1.21)	0.732	106	0.99 (0.82- 1.20)	0.930
Stroke	215	2.81 (2.44 – 3.23)	***<0.001	255	2.51 (2.21 - 2.85)	***<0.001
Epilepsy	134	4.93 (4.15 - 5.86)	***<0.001	126	3.52 (2.95 – 4.12)	***<0.001

HRs are compared to a baseline reference group of participants with no history of migraine, stroke or focal epilepsy. The model has been adjusted for age, sex, education, socioeconomic status and assessment centre.



Supplementary Figure S4-3. Risk of incident dementia associated with focal epilepsy and stroke according to cardiovascular risk groups (calculated without considering APOE e4 status)

Data are HRs for incident dementia, associated with groupings of no stroke/epilepsy, stroke only or focal epilepsy only stratified by CVS risk groups (calculated without APOE e4 status). The model has been adjusted for age, APOE e4 genotype, sex, education, socioeconomic status and assessment centre. HR=hazard ratio, CVS = cardiovascular



Supplementary Figure S4-4. Relationship between Executive Function and number of anti-epileptic agents in participants with focal epilepsy and controls

Executive Function (z-scored values) is lower in participants with focal epilepsy (left) with increasing number of anti-epileptic drugs. There is a group difference F(3,4225) = 13.61 with post-hoc pairwise comparisons showing a significant difference between taking 0 and 1, 2 or 3 antiepileptic agents (t = 3.43, p_{Tukey} = 0.003, t = 4.29, p_{Tukey} <0.001, t = 5.35, p_{Tukey} <0.001, respectively). There was also a difference between 1 and 3 anti-epileptic agents (3.94, p_{Tukey} < 0.001) and between 2 and 3 anti-epileptic agents (2.72, p_{Tukey} = 0.033). Participants in the control group (right), taking anti-epileptic agents for other reasons, have lower executive function than those who do not take anti-epileptic drugs but to a lesser extent than the focal epilepsy group. There is a group difference F(3,464644) = 65.5 with post-hoc pairwise comparisons showing a significant difference between taking 0 and 1, 2 or 3 antiepileptic agents (t = 11.99, p_{Tukey} < 0.001, t = 6.51, p_{Tukey} <0.001, t = 3.37, p_{Tukey} =0.004 respectively). There was also a significant difference between taking 1 and 2 anti-epileptic agents in this group (t = 3.16, p_{Tukey} = 0.009).

Supplementary Table S4-8. Association between Executive Function and number of anti-epileptic medication within focal epilepsy sub-group using a general linear model controlling for other baseline characteristics

	Executive Function					
	Full Model[a]			Partial Model[b]		
	β	t-stat	p	β	t-stat	P
Number of anti-epileptic drugs	-0.026	-2.20	*0.028	-0.034	-3.10	0.002
Age	-0.011	-9.95	*< .001	-0.011	-11.52	*< .001

[a]Full model: General linear model adjusted for baseline characteristics including age, CVS risk group, sex, education, socioeconomic status and assessment centre. β = unstandardised betas
bPartial model: Only age included as a covariate together epilepsy characteristics of disease duration and number of anti-epileptic drugs
Note: β = unstandardised betas. CVS – cardiovascular

Supplementary Table S4-9. Dementia risk associated with epilepsy-related factors within the sub-group of participants with focal epilepsy

	Risk of incident dementia	
Epilepsy subgroup	**Hazard Ratio (95% CI)**	***P*-value**
Number of anti-epileptic drugs	1.17 (0.59 – 1.23)	0.391

This model examines the sub-group of participants with focal epilepsy. The model has been adjusted for age, sex, education, socioeconomic status, cardiovascular risk group and assessment centre.

Supplementary Table S4-10. Dementia risk for individuals with early- vs late-onset diagnosis of epilepsy

	Dementia Risk	
Epilepsy subgroup	**Hazard Ratio (95% CI)**	***P*-value**
Early-onset (<50 yrs)	2.46 (1.93 – 3.13)	***<0.001
Later-onset (>=50 yrs)	2.82 (1.97- 4.04)	***<0.001

HRs for epilepsy only participants are compared to a baseline reference group of participants with no history of migraine, stroke or epilepsy. The model has been adjusted for age, sex, education, socioeconomic status and assessment centre.

Supplementary Table S4-11. Associations between total hippocampal, total grey matter, total white matter hyperintensity volume with neurological conditions of epilepsy, stroke and migraine considering other baseline characteristics.

	Total Hippocampal Volume			Total Grey Matter Volume			Total White Matter Hyperintensity Volume		
	β	t-stat	p	β	t-stat	p	β	t-stat	p
Epilepsy	-112.2	-1.98	*0.047	-9045.8	-4.46	*< .001	0.05	0.77	0.444
CVS risk group									
Low		Base			Base			Base	
Moderate	-42.6	-5.2	*<0.001	-2498.4	-8.50	*< .001	0.06	6.11	*< .001
High	-117.5	-9.1	*<0.001	-9033.4	-19.31	*< .001	0.10	6.14	*< .001

Note: All volume measures have been deconfounded for age and age^2 at imaging visit, sex, a scaling factor for head size and imaging site. General linear model adjusted for other baseline characteristics including CVS risk group, education and socioeconomic status.
β = unstandardised betas. CVS – cardiovascular.

Chapter 5. Pattern separation and pattern completion in health, ageing and epilepsy

5.1 Chapter summary

People with epilepsy show worse general cognitive performance in both short- and long-term measures compared with age-matched healthy controls. However, the underlying cognitive mechanism remains unclear. The hippocampus, a key brain region implicated in short- and long-term memory, is a potential site of disruption being a common source of focal seizure onset and frequently involved in epileptogenic networks.

In this chapter, I examine pattern separation and pattern completion – two cognitive processes which are thought to be mediated by the hippocampus and may be vulnerable in ageing and disease. I first attempt to resolve an existing tension in the literature on whether pattern separation can be measured distinctly from pattern completion by designing a novel paradigm which tests both these processes. This was first tested on healthy younger individuals to show that different dimensions of the same stimulus can be manipulated to measure the effects of similarity and probe completeness distinctly. I then apply this paradigm in three cohorts of healthy young, healthy older individuals and people with epilepsy, to examine whether differences in performance can be explained by differences in these cognitive mechanisms. The results suggest that individuals with epilepsy show a specific deficit of pattern completion, while healthy older individuals show less pattern separation. This paradigm offers a new framework to assess memory encoding and retrieval to better understand ageing and disease.

5.2 Introduction

Pattern separation and pattern completion are two specific and complementary neurocomputational operations that facilitate storage and retrieval of information in our memory (110). Functionally, pattern separation is the process whereby similar stimuli are stored as separate neural representations. Pattern completion is the process of restoring entire and accurate neural representations of such stimuli when presented with a partial or degraded cue. Both processes are practically important to daily life.

Theoretical and computational models describe distinct hippocampal circuitry being well suited for each of these operations to be performed orthogonally (110,139,142,300) and experimental animal models have provided some corroborative evidence. However, a fundamental question that remains is how these two theoretically distinct processes map onto human behaviour. Current behavioural tasks tend to focus on one process or the other which makes it difficult to disambiguate between the two. Uncertainty partly arises because most paradigms have one behavioural outcome, wherein the participant gives an answer which is correct or incorrect, but try to extract two distinct measures from this performance.

A popular pattern separation paradigm, named the 'Mnemonic Similarity Task' (MST), is a change detection task whereby participants are shown a series of visual stimuli during the encoding phase followed by series of probe stimuli. Participants must identify whether the probe is the same (*repeat*), similar (*lure)* or different (*foil/new*) to the encoding set. There may be different levels of similarity between original objects and their lures and pattern separation is inferred based on retrieval error. A 'lure discrimination index' is calculated from the rate accuracy in correctly identifying *lures* (similar objects but not the same as during encoding) and some studies correct for a bias in responding 'similar' by subtracting the rate that new objects are identified as similar (129). Many authors consider the false alarm rate (when similar items are reported as 'old') as a metric for erroneous pattern completion activity, or 'over-activity' (114,149,153,154) However there may be

other reasons for this response such as poor encoding of the original stimulus or forgetting due to intervening memory interference. Hit-rate accuracy is directly related to false alarm rate and, therefore, this measure of pattern completion is likely to be an over-interpretation of the behavioural response.

An example of a pattern completion task is called the 'Memory Image Completion' (MIC) task which uses a visual delayed recognition paradigm where participants learn a set of scenes during the training phase and are then asked to identify the learned scenes, with new scenes mixed in, which are masked to different degrees (134). Accuracy for correctly identifying learned scenes decreased when scenes were more masked/ covered. A pattern completion metric termed as a 'bias' towards pattern completion was derived by subtracting the accuracy of identifying a new scene (not present during the training phase and participants would choose 'none of these') from the accuracy of identifying previously learned scenes. While this pattern completion measure could arise from incorrectly completing a previously stored scene, it may also be confounded by incorrectly discriminating a degraded new scene and reflect both processes of pattern separation and completion. Therefore, current tasks in the literature are lacking in their ability to cleanly assess both cognitive processes.

Another interesting point is that pattern separation and pattern completion are two cognitive processes involved in encoding and retrieval across different timeframes. While behavioural tasks of pattern separation and pattern completion are usually probed as 'episodic' memory measures, other studies have shown these memory effects at shorter working memory timescales as well (137,152). Therefore, deficits in these two cognitive processes may potentially bridge short- and long-term memory complaints that are reported across different conditions.

Pattern separation and pattern completion therefore offers an intriguing framework to consider encoding and retrieval of information in memory in heath as well as disease. Studies in older individuals and people with Alzheimer's disease report reduced pattern separation activity reflected

by worse performance on the Mnemonic Similarity Task which has been explained by 'over-pattern completion' (114,115,301). As explained above, I would argue that this conclusion should not be drawn directly from the performance on this single behavioural paradigm. A few studies in people with epilepsy show reduced pattern separation behaviorally (302,303), while other studies examining individuals with specific hippocampal damage with two separate tasks of pattern separation and pattern completion performed sequentially suggests there may be a deficit in both processes compared to controls (157). While this may be true, each task is limited by the degree to which pattern completion or pattern separation is adequately controlled for. Furthermore, the metrics to assess pattern separation and completion are dependent on overall task accuracy, which is likely to be lower generally in patients with neurological conditions such as epilepsy and dementia.

An interesting line of thought is to consider what would the mechanism of disruption be in these studies? Ageing and dementia are often associated with a loss of neurons which could explain why there may be less pattern separation or completion. In epilepsy, however, epileptogenic networks are often considered hyperdynamic and this may lead to over-activity of the hippocampal CA3 auto-associative network which results in erroneous bias to complete patterns to previously stored representations.

In this chapter, I present a series of experiments which develop a paradigm that offers distinct measurement of both pattern separation and pattern completion. I then apply this to a cohort of healthy young, healthy older and individuals with epilepsy to identify whether overall memory performance can be explained by specific deficits in these two cognitive processes.

5.3 Aims and hypothesis

Aim: Create a short-term or working memory task with two distinct measures of pattern separation and pattern completion and examine the difference in performance in healthy young, healthy older individuals and people with epilepsy

Hypothesis: Stimuli which are more similar will be more difficult to discriminate (pattern separate) whereas partial probes with more features covered/ occluded will be harder to identify (pattern complete).

Based on existing literature, older individuals would show a deficit in pattern separation while people with epilepsy would show a deficit in both pattern completion and pattern separation.

5.4 Experiment one: encoding two stimuli and asking whether a probe matches any of the encoding stimuli

5.4.1 Methods

Participants & ethics

Twenty-four healthy volunteers (fifteen female, mean age 24 years, range 19-34) were recruited via a local database. Participants were paid £10-15 for their participation, based on their performance. This study was approved by the local ethics committee and written consent was obtained from all subjects.

Working memory task – two encoding stimuli and one retrieval probe (binary response)

I designed a computer-based change detection task where participants were shown two similar multi-dimensional stimuli during an encoding phase and then probed with a partially covered stimuli after a delay (Figure 5-1). Participants were seated in front of a desktop computer running PsychToolBox, implemented in MATLAB (Mathworks, USA), and registered their responses using the keyboard. The experiment had 192 trials over 12 blocks with all stimuli created during the experiment following counterbalanced to have equal conditions of similarity probe cover.

To obtain a distinct measure of pattern separation and pattern completion from the same task, I reasoned that two separate manipulations were needed:

1) Having different levels of similarity between the two encoding stimuli i.e. more similar stimuli would be more difficult to distinguish as this requires more pattern separation
2) Having a probe stimulus which was covered to different degrees i.e. probes which were covered up more would be harder to identify correctly as this requires more pattern completion

This version was designed using simple stimuli with four different arms (or dimensions) which were either long (140 pixels) or short (60 pixels). A two-by-two design was employed as similarity was manipulated by having one or two arms different in length between encoding stimuli while the partial nature of the probe was manipulated by covering up either one or two arms. On each trial, participants were asked if the probe stimuli was present during the encoding screen based on the available visual information. Importantly, the dimensions in which similarity was altered were *always different* to the dimensions which were covered up in the probe. This was designed to achieve distinct pattern separation and pattern completion effects in the task. The specific parameters of altering either one or two dimensions for both similarity and partial probe meant that stimuli were either different or covered by one or all four arms. Feedback was given after each trial on whether the answer was correct.

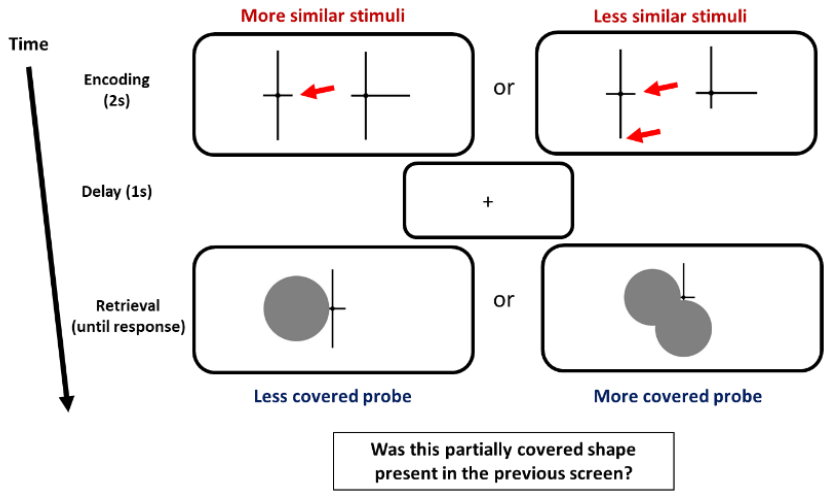


Figure 5-1. Working memory paradigm: binary response

Participants were shown two stimuli at encoding, each with four arms which were either *long* or *short*. Stimuli at encoding were either **more similar** to each other (one arm different) or **less similar**

(two arms are different) as denoted by the red arrows. Following a delay, participants were probed with a covered up shape which was either **less covered** (one arm covered) or **more covered** (two arms covered). The arms used to manipulate similarity were always different from the arms which were covered up.

Other design considerations during the initial planning phase included using stimuli with different numbers of arms. Pilot versions of the task were run with four or five participants using stimuli with eight and six arms but participants scored close to chance or gave feedback that the task was too difficult. A version was also trialled where participants had to choose if the probe was either on the 'left' or the 'right' of the screen during the encoding phase but I decided to keep the simpler 'yes' or 'no' response to facilitate higher performance since I aimed to test patients at a later stage. Moreover, this may test something different, such as pattern separation of encoded stimuli at the probe stage. When creating the partial probes, an early version simply omitted the arm rather than obscuring it with a grey circle. However, this was more likely to be interpreted as a new shape (based on the principles of amodal perceptual completion) and less likely to engage pattern completion.

Statistical analysis

The primary analysis was conducted using a rm-ANOVA with the accuracy being the dependent variable.

5.4.2 Results

The main findings from this early task showed a main effect of higher accuracy with less occluded retrieval probes [F(1 ,46) = 6.69, p=0.014] which matched my hypothesis that probes will be easier to discriminate when more information was available. However, participants showed higher accuracy with more similar encoding stimuli, although this main effect was not statistically significant [F(1,46 = 3.38, p=0.068] (Figure 5-2). There was no interaction between these two conditions.

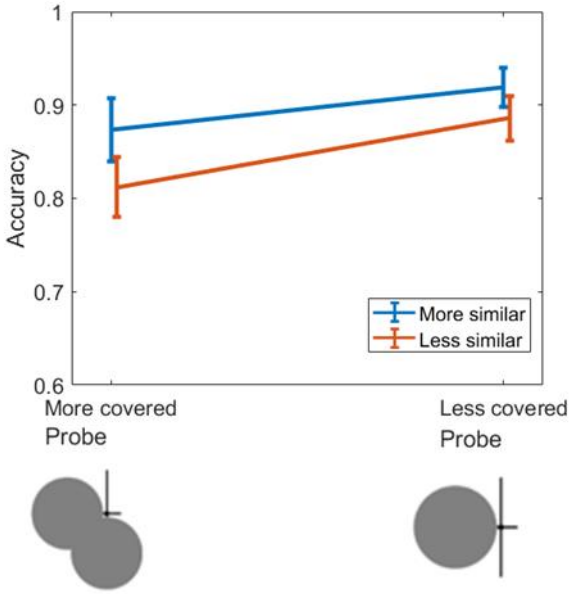


Figure 5-2. Accuracy according to similarity and probe cover

Accuracy was higher with stimuli pairs which were more similar at encoding and with retrieval probes which were less covered. Error bars denote standard error of the group mean.

5.4.3 Summary of Experiment 1

Accuracy was higher when probes were less covered compared to more covered. This fit my hypothesis and corresponded with a pattern completion effect. One explanation is that, with less available information, the participants needed to place more cognitive resource to complete the pattern prior to making a judgement whether this was the same shape as seen in the encoding phase. The use of circles to cover different dimensions was chosen to engage a completion process. Instead of covering probe dimensions, an earlier task version tested a probe stimulus in which the arm was simply not drawn. Early feedback suggested this was confusing and may be considered as a new stimulus (with less arms), rather than encouraging a participant to complete the pattern. Interestingly, completing the pattern with this design was not strictly required to successfully answer

each trial as there were always enough information from the uncovered dimensions to answer correctly. Based on informal feedback following the task, however, most participants tended not to realise this was the case. I therefore considered this a 'passive completion' effect.

Greater similarity between stimuli pairs led to higher accuracy in the task. Despite not being statistically significant, this effect was *opposite* to my expectation and contrasts with the pattern separation literature which shows poorer discrimination in change detection tasks when lure stimuli are more similar to the original stimulus. I considered why this was the case and debated whether this result was due to the binary nature of the task response which may not be sensitive enough to detect the similarity effect or whether the passive completion nature of the probe was a confounding factor. In the next experiment, I considered paradigm which required participants to provide a continuous response while actively completing a probe dimension.

5.5 Experiment two – two encoding stimuli and one retrieval probe asking the participant to draw a missing arm

5.5.1 Methods

Participants

Twenty healthy volunteers (thirteen female, mean age 23 years, range 19-29) were recruited via a local database. Participants were paid £10-15 for their participation, based on their performance.

Working memory task – two encoding stimuli and one retrieval probe (continuous response)

The change detection task from experiment one was redesigned where participants were still shown two stimuli with four arms during an encoding phase and then probed with a partially covered stimuli at retrieval. In this case, participants had to recreate a covered arm from the probe using the mouse (Figure 5-3). Participants were seated in front of a desktop computer and the experiment remained the same in length (192 trials over 12 blocks).

The manipulation of similarity (either one or two arms different) and probe cover (either one or two probe arms covered) remained in place. Instead of fixed lengths, arms varied around a baseline of long or short lengths *plus or minus 30 pixels* which was generated randomly at each trial. Participants used the mouse to re-draw the length of the covered arm. One arm was probed for each trial, indicated by an arrow. Performance was assessed by the difference in the distance drawn by the participant when completing the probe and the actual distance of the arm probed.

Statistical analysis

The primary analysis conducted was a rm-ANOVA with the absolute error being the dependent variable.

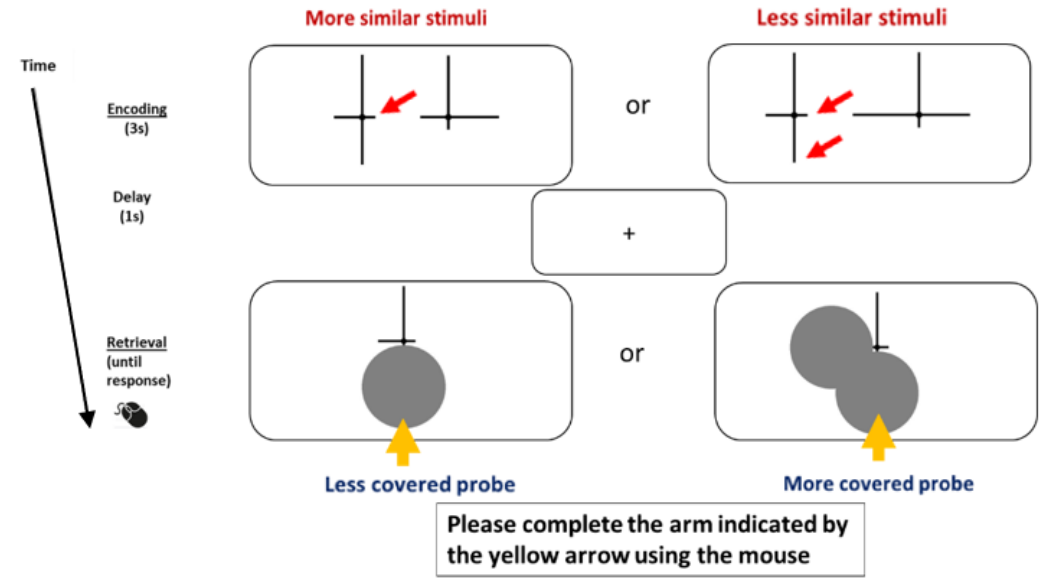


Figure 5-3. Working memory paradigm: continuous response

Participants were shown two stimuli at encoding, each arm was different lengths with four arms which were either *long* or *short*. Stimuli at encoding were either **more similar** to each other (one arm different) or **less similar** (two arms are different). Following a delay, participants were probed with a covered up shape which was either **less covered** (one arm covered) or **more covered** (two arms covered) and asked to re-draw the length of a covered up arm.

5.5.2 Results

The main findings from this task showed higher absolute error (by pixel length) with less similar stimuli when probes were more covered however participants showed slightly lower absolute error for less similar stimuli when probes were less covered (Figure 5-4). While this suggested a possible interaction between similarity and probe cover, the interaction term ($p>0.05$) and main effect of both similarity [$F(1, 38) = 1.86$, $p>0.05$] and probe cover [$F(1, 38) = 2.11$, $p>0.05$] was not significant. The same analysis was performed based on z-score values of absolute error within either long or short arm probes and showed the same pattern of results. Instances where participants drew a long arm and the original stimulus had a short arm, or vice versa, may indicate that the original arm was forgotten or misbound and would lead to a potentially large absolute error. Excluding such trials, however, made no overall difference the results.

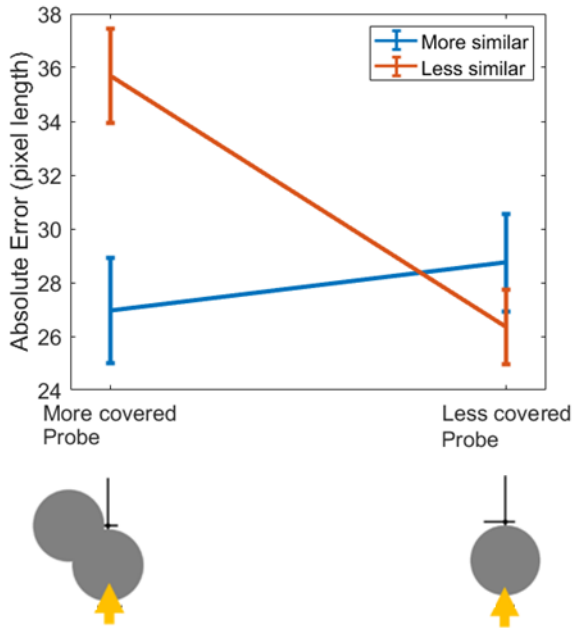


Figure 5-4. Absolute error according to similarity and probe cover

Absolute error was higher with less similar stimuli pairs when probes were more covered. When probes were less covered, absolute error was slightly higher with more similar stimuli. Error bars denote standard error of the group mean.

5.5.3 Summary of Experiment 2

In contrast to the first experiment, this task design required active completion as participants would need to remember and actively recreate the representation of the original stimuli to answer each trial. Furthermore, a continuous response measure was employed to obtain a more sensitive measure of accuracy and better detect the effects of the two task conditions. Instead, however, participants reported focussing on whether the arms were simply long or short from memory rather than the exact length which was not the desired effect. Mean overall accuracy remained higher for more similar stimuli (specifically with more covered probes) and suggested that this paradoxical beneficial similarity effect, also seen in the first experiment, was not related to either passive/active completion or sensitivity of the response.

Several questions came to mind when attempting to understand the opposite effect of similarity that was observed- was this due to the working memory design whereas most pattern separation tasks probe 'episodic' memory? Is pattern separation only active during longer-term or episodic memory and not at this short time-frame? Did the stimuli need to have more representation richness as pattern separation probes are often complex daily objects or scenes? Reviewing the literature offered some useful insight. In experiments one and two, the similarity manipulation was done at encoding. Pattern separation tasks commonly alter similarity between a shape at encoding and the probe. A previous working memory task which used three coloured squares at encoding showed that performance for detecting change in the colour was increased when these colours were more similar to each other (304). This may reflect the need for a smaller representational space in memory when stimuli are more similar at encoding due to 'chunking' or some ensemble representation. This would allow better detection of change during retrieval. To the best of my knowledge, no task has examined the effects manipulating similarity at encoding and retrieval within the same task. I explore this further in a separate experiment using the same task framework. While these results are not described in detail in this thesis, briefly, I found that higher similarity at encoding improves performance whereas distinctly manipulating probes to have a higher similarity

at retrieval leads to worse performance. This may reflect a 'chunking' or information compression effect at encoding while, at retrieval, there may be increased cognitive burden to separate the two similar representations in memory.

In the next experiment, I examined the effect of manipulating similarity at retrieval with a task that has both passive and active separation and also increased stimuli complexity.

5.6 Experiment three (final version) – Memory Pinhole task

5.6.1 Methods

Participants

There were three participant cohorts tested in this experiment. A healthy young group of individuals with forty-eight healthy volunteers (34 female, mean age 27 years, range 19-34) were recruited via a local database or the online platform Prolific. Participants were paid £10-15 for their participation, the task was performed in front of a desktop computer under my supervision or at home via the online platform. A healthy older group of 28 volunteers (18 female, mean age 65 years, range 45-77) were recruited via a local database and the task was done at home via the online platform Pavlovia. Three older volunteers did not understand the task properly and were excluded from the study.

A group of 38 people with epilepsy (20 female, mean age 34 years, range 19-59) were recruited from the John Radcliffe hospital epilepsy video telemetry unit. These participants were admitted to hospital for at least one week to have continuous monitoring of seizure activity. Most of this group had their anti-epileptic medications reduced during their hospital stay with the majority being tested off medication. Further demographics can be found in Table 5-1. The task was performed in hospital seated in front of a laptop with concurrent EEG monitoring. EEG activity was also recorded during the task, including event-related potentials, but this will not be discussed here. Four people with epilepsy were excluded as they did not complete the task due to fatigue or a seizure occurring

during the task. Addenbrooke Cognitive Examination (ACE-III) was performed in the epilepsy group but not the other cohorts due partly to logistical reasons as face-to-face testing was not carried out for a substantial proportion of the study. All participants were asked a subjective question of: "do you feel as if your memory is not as good as it should be". Other disease-specific data was collected such as seizure duration, main seizure semiology, depressive or anxiety symptoms and cardiovascular co-morbidity in the epilepsy cohort.

Table 5-1. Demographic data on cohort groups

	Healthy younger	Healthy older	Epilepsy patients
N	48	28	34
Age, mean (range)	28 (18-45)	65.6 (53-77)	34.9 (18-59)
Sex, female (%)	34 (70%)	18 (64%)	22 (65%)
Subjective memory complaints	0 (0%)	2 (7%)	21 (62%)
Primary Pathology	-	-	• Temporal lobe epilepsy (82%) • Frontal lobe epilepsy (14%) • Other (2%)
ACE-III, mean (range)	-	-	87.3 (70-99)
Seizure duration in years, median (range)	-	-	13 (2 – 39)
Seizure onset age, mean (range)	-	-	20 (2-55)
Mood/anxiety issues, yes (%)	-	-	29 (85%)
Cardiovascular comorbidity, yes (%)	-	-	12 (35%)

Working memory task- Memory Pinhole task

This version of the task, named the 'Memory Pinhole task', employed the same principles of manipulating similarity and probe cover as experiments one and two. The stimuli followed the same

base shape with four arms, either long or short (fixed lengths of 140 or 60 pixels), with a random angle of 15 degrees to either side of the base arm (Figure 5-5a). Altering arm lengths remained the crucial manipulation of similarity within a trial and were considered 'trial-relevant'. To create more complex and visually rich stimuli, additional features were added including a coloured background shape as well as end-arm, central and middle shapes. These features were considered 'trial-irrelevant' as they were held constant throughout the working memory part of the task.

The Memory Pinhole task had three different probe stages:

1) **Working memory change detection (main probe)**
   During each trial, participants would see one stimulus at encoding and, after a delay, would be presented with a single probe which was either the same as the stimulus at encoding, similar with one arm different (more similar) or two arms different (less similar). The probe was either more covered (two arms obscured) or less covered (one arm obscured). Participants were asked whether the probe was either the *same* or *different*. This probe stage was designed to assess pattern separation (two different similarity levels) and passive pattern completion (two different levels of probe cover).

2) **Working memory arm completion**
   Following their first response, participants were asked to indicate whether a covered-up arm was either *long* or *short* to assess active completion – as per the previous experiment in 5.5. Only one arm was probed per trial.

3) **Longer-term memory**
   Finally, every four trials, a longer-term memory probe was shown and participants were asked if this stimulus was the *same* or *different* to a few trials ago. The full probe was shown (no arms were covered) and the arm lengths were either the all the same or all different.

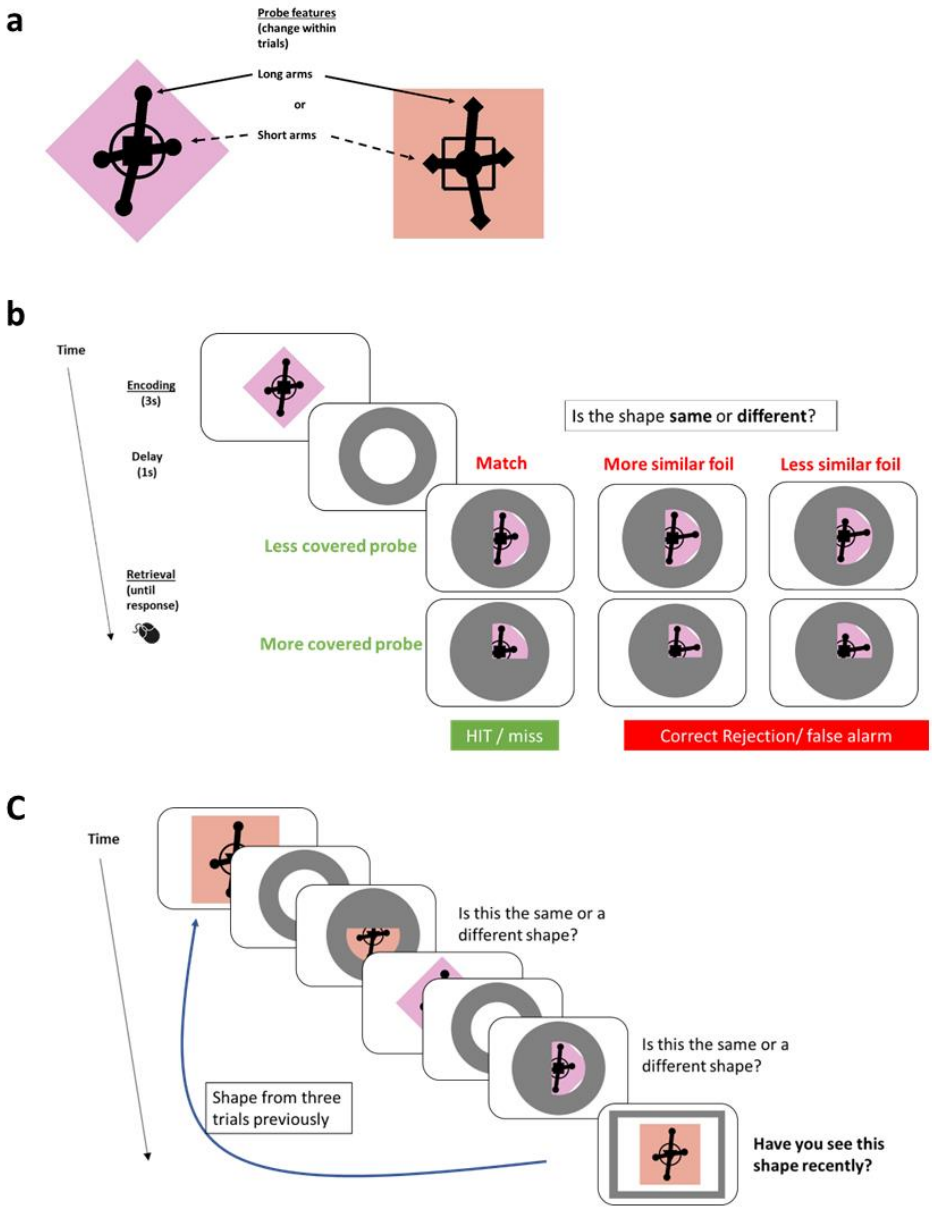


Figure 5-5. Memory Pinhole task design

a Example of two stimuli used in the Memory Pinhole task. Each stimuli had four arms which were either long or short which were used to manipulate similarity between encoding stimuli and probe. Other features included a coloured background shape as well as a middle, intermediate and end-arm shape which were not changed within a trial. **b** Task design showing a single encoding shape followed by a single probe. The probe would either be a match, more similar foil (different by one arm) or less similar foil (different by two arms). Probes were either more or less covered. **c** After every three trials, participants would be shown a whole longer-term memory probe which was either a match or non-match (all arms were different).

Statistical analysis

Within each cohort group, results were analysed using a rm-ANOVA with the accuracy being the dependent variable or an unpaired Student's T-test to compare means between two groups. Signal detection theory was also applied to check for discriminability and bias. When appropriate, Bayes factor was calculated to examine for evidence towards the null hypothesis using an unbiased prior distribution, such as theta = beta(1,1) or a stretched version. A 'pattern separation index' (PS index) was derived by taking the difference between mean accuracy of trials with less similar probes minus trials with less similar probes:

$$\boldsymbol{PS\ index = \ Accuracy\ of\ less\ similar\ probes - accuracy\ of\ more\ similar\ probes}$$

A 'pattern completion index' (PC index) was derived by taking the difference in mean accuracy between trials with less covered probes minus trials with more covered probes on trials where the probe was the *same* as the encoding stimuli:

$$\boldsymbol{PC\ index = \ Accuracy\ of\ less\ covered\ probes - accuracy\ of\ more\ covered\ probes}$$

The rationale behind taking the difference in performance based on similarity and probe cover was because these would be purer measures of pattern separation and completion, respectively, regardless of overall memory performance of an individual. For the longer-term memory trials, probes were either the same or different on four dimensions to facilitate better discrimination in memory as there was a concern this task would be quite difficult.

To complement the ANOVA approach, all the participants were tested together using a generalised logistic mixed-effect model specifically to check for higher-level interactions within the experiment. The model was specified based on prior hypothesis and preliminary results to that point. This was done using the *fitglme* function within MATLAB, Mathworks, with the outcome of each trial as the dependent variable. Match (vs non-match trials), similarity level, cover level, patient group (epilepsy vs. healthy), age and sex were fixed effects while a subject ID was entered as a random effect. An

interaction term was included between patient variable and match, similarity and probe cover level. Dummy variable coding was implemented for categorical variables which were more than two levels and mean centred around zero. The similarity variable was only relevant for non-match trails (match trials had a value of zero).

Reaction time was investigated separately as a factor that may explain overall performance and also whether non-match trials were slower which may reflect a two-step recall-then-reject process.

5.6.2 Results (Part 1) for the Memory Pinhole task

In this section, I will first describe the results in the healthy younger individuals to establish baseline performance of the Memory Pinhole task before comparing the main findings across the three different cohorts.

When examining the working memory probe, healthy younger individuals demonstrated a high overall discriminability (d' = 3.58) and low criterion (c=0.05, not significantly different to zero) across all trials. For match trials, accuracy was higher for probes which were less covered [$F(1, 94) = 5.43$, $p=0.021$] and reflected a pattern completion effect (Figure 5-6a). For non-match trials, accuracy for less similar probes was greater than more similar probes [$F(1, 94) = 11.30$, $p=0.002$] which reflected a pattern separation effect. Comparing the pattern separation index against the pattern completion index for each individual showed a weak negative relationship (Figure 5-6b) which was significant ($r^2= 0.08$, $p = 0.02$).

For the active arm completion probe, accuracy was higher for stimuli which were less covered ($t = 2.17$, $p = 0.026$). This effect was consistent with the passive completion result described above (Figure 5-6c). Active arm completion accuracy was higher for match conditions compared to non-match (0.96 vs 0.91). Overall accuracy for longer-term probes was 0.62 (SE = 0.12) with four individuals scoring below chance level (0.5).

Accuracy for longer-term memory probes was comparable between match and non-match trials (0.63 vs 0.59, $t = 1.12$ $p= 0.83$, when testing the difference in means, Figure 5-6d). Across the cohort,

97% of correct longer term memory trials followed being correct on the relevant main working memory probe three trials back while = 95.0% of correct longer term memory trials followed an accurate response in the corresponding active completion trial. There was no relationship between accuracy on episodic memory trials and PC index at a group level (r^2= <0.001, p = 0.99). There appeared to be a negative relationship between episodic memory accuracy and PS index but this was not significant (r^2= 0.02, p = 0.41).

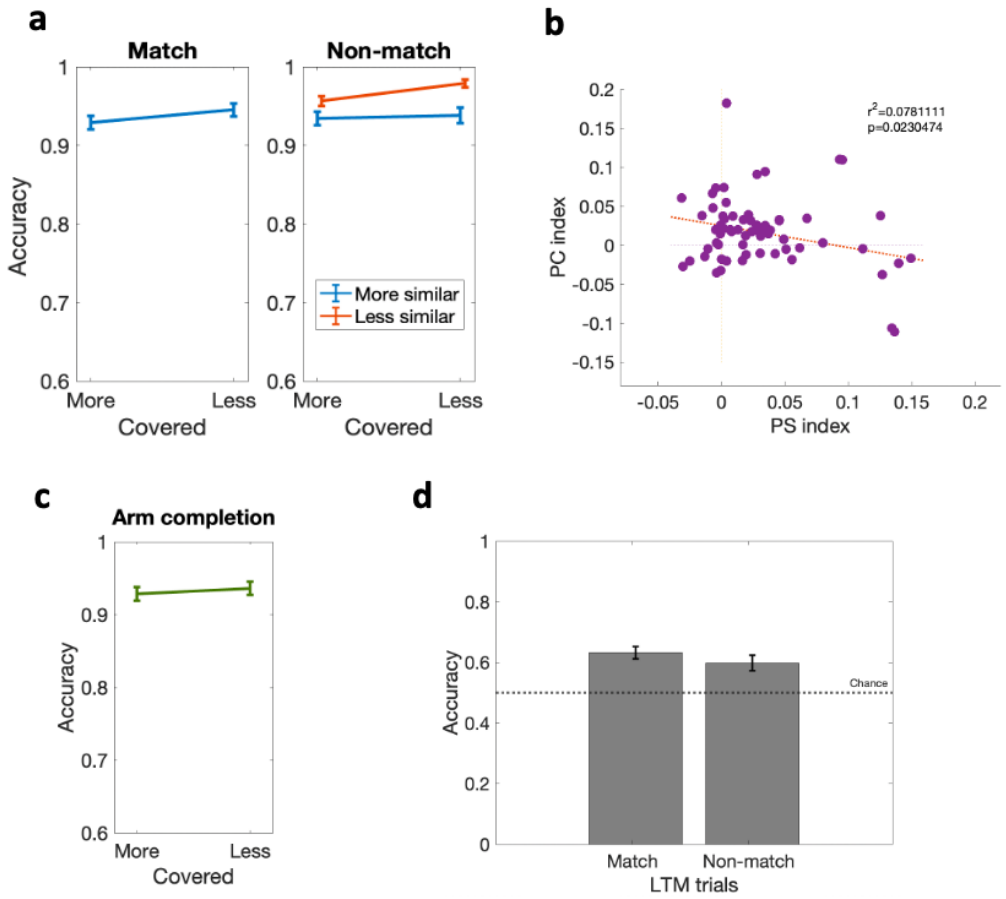


Figure 5-6. Memory Pinhole task results in healthy young participants

a For match trials, accuracy was higher for less covered probes compared to more covered probes. For non-match trials, accuracy was higher for less similar probes compared to more similar probes. b Across the cohort, a higher pattern separation index corresponded to a lower pattern completion index. c Accuracy for active arm completion probes was higher with less covered probes. d For longer-term memory probes, accuracy was slightly higher for match probes compared with non-match probes. Error bars denote standard error of the group mean. PC – pattern completion, PS – pattern separation, LTM – longer-term memory.

5.6.3 Interim summary for Experiment 3 | Part 1

Results of the Memory Pinhole test showed accuracy was higher when probes were less similar and when probes were less covered which reflected a measure of pattern separation and completion from a single probe. These two measures were poorly correlated with each other suggesting that the underlying processes may be related but not directly dependent as suggested in the literature. This relationship would fit better with theoretical and computation models of pattern separation and pattern completion. Overall, the mean accuracy for the main conditions was above 0.9 which was below ceiling and thought to be at a suitable level because this task will also be used for testing patient cohorts who were expected to perform at a lower baseline level.

While the first working memory probe offered a passive measure of pattern completion, the active arm completion probe showed consistent results to indicate that either active or passive measures would be valid. The passive measure has the advantage of being probed concurrently with pattern separation which should facilitate identifying distinct measures of each process.

Some information about each stimuli was stored in longer-term memory rather than simply being held in working memory in order to answer each trial. This was suggested by the higher-than-chance performance for longer-term memory probes and the fact that almost all the correct longer-term memory answers followed a correct response in the main working memory trial and the active completion trial. This indicated that participants were likely recreating the original stored representation rather than simply guessing. Furthermore, these results suggest that the abstract, mathematically-derived stimuli may work in more traditional episodic-like tasks. The longer-term probe in this experiment, however, was not well suited to identify a pattern separation or pattern completion effect as there was no manipulation of similarity or probe completeness. This is being further examined in a separate paradigm with only longer-term trials.

5.6.3 Results (Part 2): Comparing healthy younger, older and people with epilepsy

Working memory change detection (main probe)

Across all working memory change detection trials, both healthy younger and older individuals showed d' >4 and crit <0.1 (not significantly different from zero). People with epilepsy had a d'=2.44 and crit = -0.13 (significantly different from zero, t=-3.12, p = 0.028). The epilepsy cohort had a significatly greater mean accuracy on match trials compared with non-match trials (accuracy of 0.87 vs 0.80 respectively, t=2.87, p = 0.007 when testing the difference in means) which may suggest a bias towards picking 'same'.

Performance on match trials (Figure 5-7a) showed higher accuracy for less covered probes compared to more covered probes and was statistically significant in healthy young [$F(1, 54) = 11.30$, $p=0.001$] and healthy older individuals [$F(1, 54) = 6.25$, $p=0.012$] but not in people with epilepsy [$F(1, 64) = 2.58$, $p=0.078$].

For non-match trials (Figure 5-7b), accuracy was higher in probes which were less similar compared to more similar in healthy younger [$F(1, 94) = 5.43$, $p=0.02$] and people with epilepsy [$F(1, 64) = 4.83$, $p=0.042$] but not in healthy older individuals [$F(1, 54) = 0.45$, $p=0.50$].

PS Index was weakly correlated with PC index for healthy young individuals but not for healthy older individuals or people with epilepsy (Figure 5-7c). The Bayes Factor suggested weak evidence towards the null hypothesis for each of the latter two cohorts ($BF_{01} = 5.36$ and $BF_{01} = 4.87$, respectively).

To account for possible ceiling effects, an arcsine transform was applied to the data but this did not change the associations between PS index and PC index in any of the cohort groups.

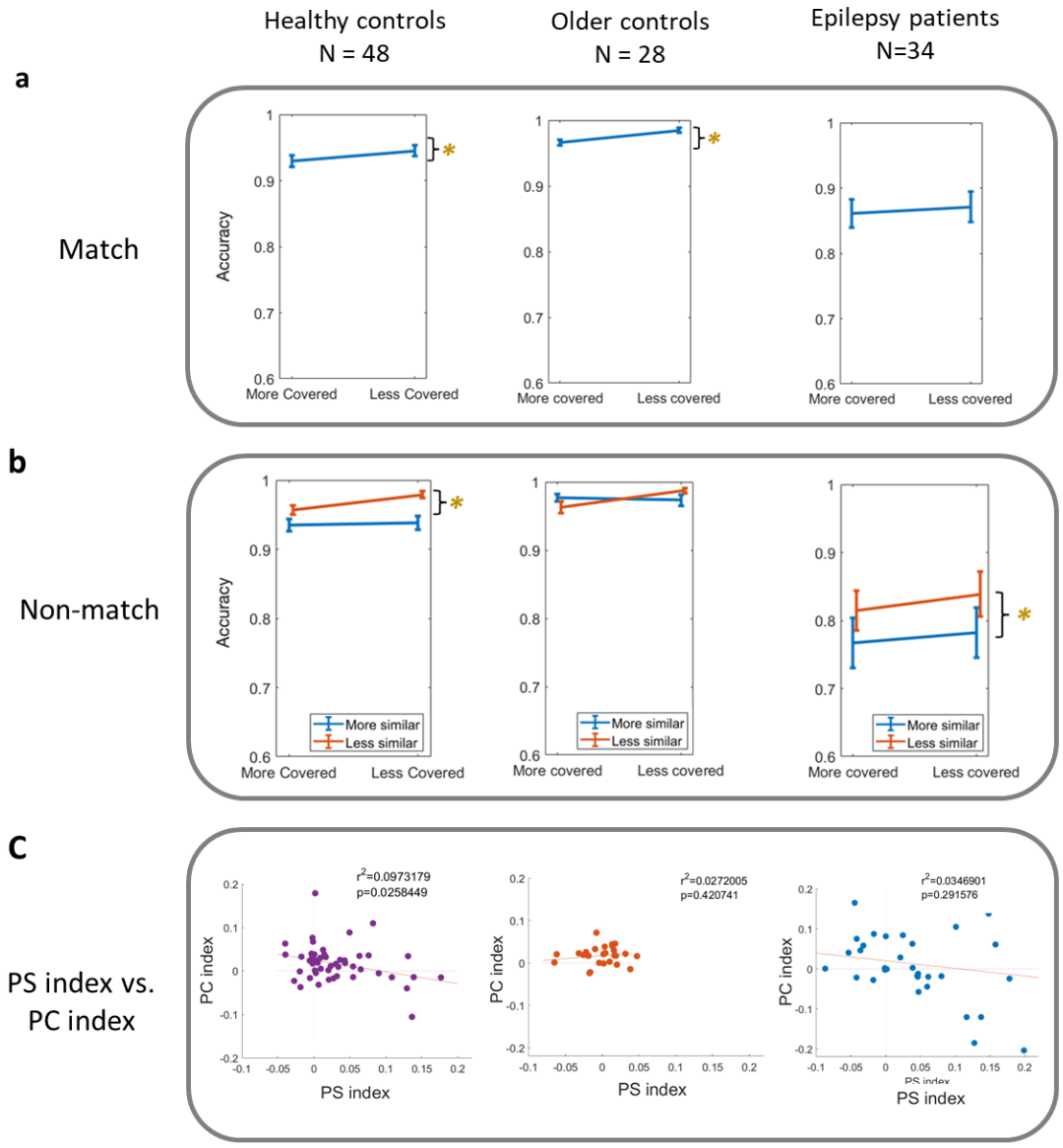


Figure 5-7. Memory Pinhole task results across healthy young, older and people with epilepsy.

a Accuracy was significantly higher in match trials for probes which were less covered in the healthy young and healthy older cohorts but not people with epilepsy. **b** For non-match trials, healthy young and people with epilepsy had higher accuracy for probes which were less similar. **c** Correlation between PS index and PC index across the three cohorts showing a weak correlation for healthy young individuals only.

Generalised Logistic Mixed Effect model

Analysis using a trial-level generalised logistic mixed effect model produced corroborative results (Figure 5-8). There was a significant interaction between match trials and being a person with epilepsy (t= -6.83, p<0.001), consistent with the bias to choose 'same' noted above, and a significant interaction between probe cover level and being a person with epilepsy (t= 2.20, p=0.023) which reflects the significant effect of probe cover in healthy young and older individuals but not in the epilepsy cohort. There was no significant interaction between probe similarity level and being a person with epilepsy (t= -0.88, p=0.375). There were significant main effects of match trials (t=3.13, p=0.002), more covered probes (t= -4.68, p<0.001), less similar probes (t= 5.82, p<0.001), being a person with epilepsy (t= -6.08, p<0.001) and older age (t= 2.31, p=0.02).

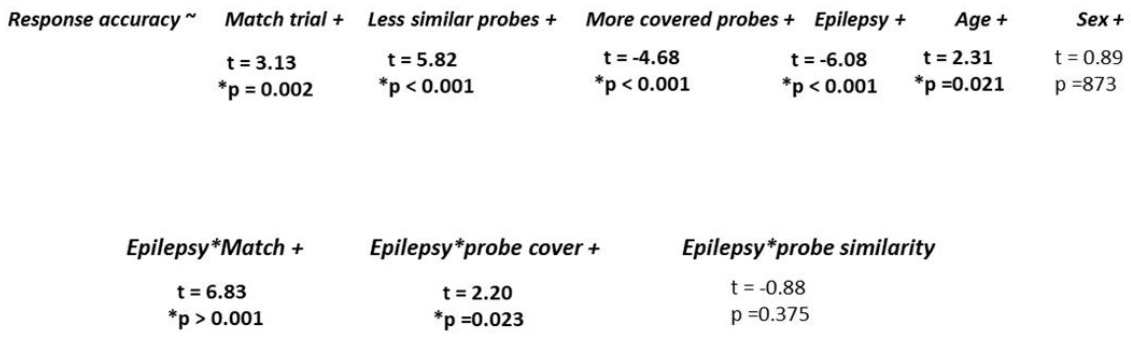


Figure 5-8. Generalised Logistic Mixed Effects model

Significant interactions between having epilepsy and match, probe cover and probe similarity. Main effects of match, probe similarity, probe cover, having epilepsy and age.

Reaction times

Average time taken to give a response for match and non-match trials were similar within each cohort group (no significant difference) as younger individuals had the fastest average reaction time while people with epilepsy took the longest to respond (Figure 5-9a). When plotting reaction time

against accuracy at a trial level for each cohort, a speed-accuracy trade-off was observed with the healthy older cohort demonstrating a longer reaction time corresponding to higher accuracy (Figure 5-9

b).

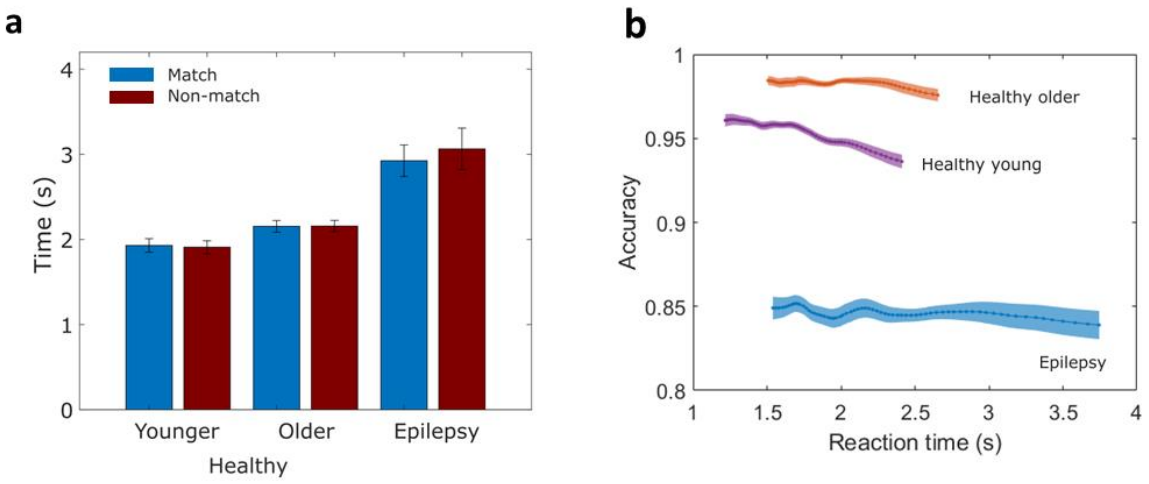


Figure 5-9. Reaction time analysis

a Within cohorts, there was no difference between match and non-match trial reaction times. Healthy young individuals had the fastest reaction times, followed by healthy older individuals and people with epilepsy. **b** Speed-accuracy trade-off visualised by plotting reaction time against accuracy.

5.6.4 Summary Experiment 3 | Part 2

In summary, this experiment has demonstrated measures of pattern separation and pattern completion with dissociable effects observed between the three cohorts of healthy young, healthy older and people with epilepsy. This will be considered further in the discussion.

5.7 Discussion

The Memory Pinhole task provides potentially distinct measures of pattern separation and pattern completion from a single memory paradigm. The results demonstrate evidence that the effects of

similarity and probe completeness could be evaluated by manipulating different dimensions of the same stimuli in a single task.

Healthy younger individuals demonstrated the hypothesised effect that higher similarity and less stimuli completeness would be associated with worse performance. The indices of pattern separation and pattern completion had a weak negative association which suggests that they are complementary cognitive processes which is consistent with theoretical models, but the low correlation coefficient also rebuts the idea that they lie on opposite ends of a unitary spectrum.

Comparing the performance with older individuals and people with epilepsy provided insight on the effects of age and a specific disease. While previous studies suggest that older individuals perform worse in change detection tasks due to 'under-separation' and 'over-completion' (114,149,153,154), results from the present experiment indicates a similar level of pattern completion to that seen in healthy younger individuals but less pattern separation occurring. The healthy older cohort performed better on average than the younger cohort and this is likely explained by a speed-accuracy trade-off. There is a possibility that a ceiling effect may be present in the performance of the older group however applying an arcsine transform to account for this did not change the results.

An advantage of the Memory Pinhole task is having measures of pattern separation and pattern completion that do not solely relate with overall memory accuracy as several other cognitive processes may contribute to performance. Rather, taking the difference between condition performance should provide a relatively clean measure of each process. This is important as patients with neurological conditions may often perform worse than healthy controls which, in current tasks described in the literature, would usually be observed as deficits in pattern separation or pattern completion. For this reason, simply using separate pattern separation and pattern completion tasks is not the solution.

People with epilepsy performed worse overall compared with healthy individuals but still showed better discrimination of probes which were less similar which reflects a pattern separation process akin to the results seen in healthy younger individuals. By contrast, level of probe cover did not have a significant effect on performance which may reflect a deficit in pattern completion. Using a GLM approach to account for individual random effects, this was reflected by a significant interaction between level of probe cover and having epilepsy but no interaction between level of similarity and having epilepsy. This is the first report of a dissociable deficit of these two processes.

For both healthy older individuals and people with epilepsy, a significant association between the PS index and PC index was not seen. This may reflect a differential decoupling in the relationship between pattern separation and pattern completion that is seen in healthy younger individuals or it may be that a larger sample size is required to detect this relationship.

One interesting consideration is the bias to choose 'same' in people with epilepsy which may reflect a tendency to 'over-complete'. While a biological mechanism cannot be inferred from this study, one may speculate that aberrant, hyperdynamic connectivity associated in epilepsy may be driving auto-association within the CA3 sub-field of the hippocampus which, in turn, explained the bias to judge a stimulus to be a match.

It is important to consider limitations to the current behavioural paradigm. While the stimuli were grounded in a mathematical framework that was designed to precisely manipulate similarity and probe completeness, some may argue that their abstract nature will make it difficult to employ in a more episodic paradigm with longer delay and more interference between encoding and retrieval. Adding more context and complexity to the probes will help with this. However, it is also true that pattern separation and pattern completion likely occurs at shorter timescales than was probed with this working memory paradigm. The similarity manipulation is currently restricted to changing one or two arms of the probe while the remaining two arms were used to manipulate probe completeness. It may be useful to test further levels of similarity which would require more

dimensions which will increase the difficulty of the task. Another approach to test different similarity levels is to simulate additional dimensions using a computational model which I will explore in the next chapter.

Lastly, pattern separation and pattern completion was inferred by the performance difference between similarity and probe completeness conditions which, as discussed, allows these measures to not reply solely on overall memory accuracy. However, some individuals showed no difference in performance between respective conditions or even a difference in the opposite direction. These participants were likely to be utilising a different cognitive process or strategy, but this was difficult to interpret clearly. Collecting baseline cognitive measures in healthy participants would have been preferred but this was not possible due to disruption to in-person testing during the study.

In conclusion, this chapter demonstrates a novel paradigm to assess both pattern separation and pattern completion within a single task. Results suggest that these two cognitive processes do not lie on a unitary spectrum but rather are two related but distinct operations. This is consistent with theoretical models and helps to resolve an existing debate in the literature. Pattern separation and pattern completion may be a useful framework of memory encoding and retrieval to understand changes in health and disease with dissociable effects of age and epilepsy demonstrated here. In the next chapter, I consider a novel computational model of pattern separation and pattern completion that would support existing findings in the literature, replicate findings from the Memory Pinhole task and predict performance across a larger parameter space than was tested in these sets of experiments.

Chapter 6. A neural network model of pattern separation, pattern completion and disease

6.1 Chapter Summary

Pattern separation and pattern completion are two cognitive operations proposed to have a strong computational basis. Different regions of the hippocampus are described to be important for each process to occur. The previous chapter describes a behavioural paradigm designed to provide a distinct metric for pattern separation and pattern completion. This chapter demonstrates how computational modelling can be used to better our understanding of memory processes and make predictions of behaviour in health and disease. I use a modified Hopfield network to model pattern separation and pattern completion and demonstrate basic memory characteristics, such as the set size effect, and simulate the results from the Memory Pinhole task. Using a novel method to determine the model decision in a change detection task, performance of the healthy young, healthy older and people with epilepsy were simulated by lesioning different populations of neurons within the network. Other pattern separation and pattern completion findings from the literature can also be simulated through similar manipulations of the network or by adjusting the model bias. These findings help build our understanding of underlying cognitive and potentially neurobiological mechanisms of memory.

6.2 Introduction

Pattern separation and pattern completion may represent a useful framework for memory encoding and retrieval. As demonstrated in the previous chapter, these two cognitive processes can be distinctly detected within a single delayed recognition, working-memory task. To better understand these processes, I have developed a computational model of memory encoding and retrieval that would simulate behavioural results of the Memory Pinhole task as well as other pattern separation and pattern completion paradigms in the literature.

Why model memory?

Computational models of memory provide controlled environments for studying the complex and interactive nature of information encoding and retrieval in the brain. In addition to descriptive theories of memory, the value of a model is to encourage researchers to be explicit about their hypotheses and clearly delineate components that underpin their theories.

Implementing models allows us to test predictions in a parameter space beyond what is feasible or easily achieved with human or animal subjects. This will, in turn, allow us to derive new predictions and test these through further simulation. Importantly, computational models can move outside of physiology to simulate disease and “the patient” which is a considerably scarcer resource. This can be done by removing or altering components of the model to examine the effect on the output and will be discussed below.

Modelling any complex concept, however, has several drawbacks and may lead to misinterpretation of the data (305). While it is often easy to find a specific feature of a complex system that is not accounted for by a model, this also represents an opportunity to question the underlying construct and learn why this has not worked. The ideal approach, therefore, is to combine robust behavioural testing with computational modelling to test and refine predictions of a specific cognitive operation and further examine generalizability of the model to other behavioural datasets.

What are Hopfield networks?

A Hopfield network is a variation of a recurrent artificial neural network that was popularized by John Hopfield in the 1980s (159). Primarily an associative, content-addressable memory system used in the application of information data storage and retrieval, Hopfield networks have also been used to model human memory (160).

The main architecture of a classic Hopfield network comprises of binary threshold units, i.e. having one of two possible values, while more modern iterations of the network allow for continuous unit values (306). Each unit of a Hopfield network is connected to every other unit in the network which gives rise to the term 'auto-associative' network. Units interact via a Hebbian learning rule which reflects a biological strengthening of synaptic weights when learning occurs. A brief mathematical description behind Hopfield Networks are found below in the methods.

Why model pattern separation and completion with a Hopfield network?

In terms of hippocampal circuitry, the CA3 sub-region is often described as a network of neurons with dense recurrent collaterals whereby cells synapse together with other cells of the sub-region to a much greater extent than cells outside the region. The architecture of a Hopfield network resembles that of the CA3 region and has been used to simulate neural activity of pattern completion output in the literature (108). Other computational models of pattern completion include feed-forward support vector machine networks and sparse distributed memory (SDM) (161).

The dentate gyrus has many more neurons than the entorhinal cortex which it receives input from (145). Pattern separation is theoretically implemented as neural activity from the entorhinal cortex is transmitted to the dentate gyrus leading to a sparse representation within an expanded neuronal space (also known as expansion re-coding). Mossy fibres travel from the dentate gyrus into CA3 and input appears to be very sparse (307). One hypothesis describes how sparse signals between patterns reduces the chance of overlapping representations (308). Several models of pattern

separation exist using expansion recoding, Winner Takes All competition and sparse synaptic connectivity (162–164). There remains a question, however, whether an autoassociative network can show properties of both pattern completion and pattern separation. Furthermore, can such a network model behavioural results of both pattern separation and pattern completion from a single task?

In this chapter, I present a series of experiments that demonstrate how a modified Hopfield network can offer insight on both pattern separation and pattern completion. I then model the Memory Pinhole task to better understand the results and predict performance over a wider parameter space. Through lesioning different parts of the network, I attempt to understand potential mechanisms underlying the performance differences in healthy young, healthy older and people with epilepsy.

6.3 Aims and Hypotheses

Aim: Create a neural network model of memory encoding and retrieval that could simulate pattern separation and pattern completion. This will model the behavioural results described in chapter 5 including the Memory Pinhole task.

Hypothesis: Pattern separation and pattern completion can be modelled as distinct processes using the principles of a Hopfield network.

6.4 Methods

Most memory models have three common components:

1) Formal representation of the information to be encoded
2) An equation or set of equations to allow storage of the information
3) An equation or set of equations to retrieve the information

Using the principles of a Hopfield network, I created an auto-associative neural network to model recurrent collateral connections between neuronal cells. This could represent the hippocampal CA3 region. Stimuli were represented by patterns of neural activity and stored as memories in the synaptic connections between neurons.

Mathematically, an external input e_i is applied to each neuron i of the network through unmodifiable synapses to produce output firing y_i. The output from each neuron is connected via recurrent collateral connections to the other neurons in the network and stored in a modifiable weights matrix w_{ij}. This organization allows the initial activity of these neurons to be associated and 'learned' with itself to model information encoding.

A modified Hebbian local learning rule is applied to the recurrent synapses in the network:

$$\delta w_{ij} = \alpha(y_i - y)(y_j - y) \qquad \text{eq (1)}$$

Where α is a constant and y approximates the average value of yi and yj.

Subtracting the value y will prevent increasingly positive or negative, i.e. exploding, weight values. Once this stimuli information is stored, a subsequent recall probe can be presented to the network as a full or partial cue as an external input to produce neural output firing in the pattern of the original 'learned' input. This process can be repeated to improve the recall of a retrieved pattern.

During recall, an external input e_i activates neurons , and this activity propagates through the recurrent collateral system to produce an activation output of each neuron. The activation vector h_i is the sum of activations produced in proportion to the firing rate of each axon y_i operating through each modified synapse w_{ij}.

$$h_i = \sum_j y_i w_{ij} \qquad \text{eq (2)}$$

Where the sum is over the C input axons to each neuron, indexed by j. The output firing y_i is a function of the activation produced by the recurrent collateral activity (internal recall) and the external input (e_i), where f is a non-linear (e.g. arc tan) activation function.

$$y_i = f(h_i + e_i) \qquad \text{eq (3)}$$

Model characteristics:

External inputs to the model

Following the classic Hopfield network literature, external input values fed into the network were generally constrained to either '1' or '0'. This is often depicted as an 'active' or 'inactive' neuron but could also be interpreted as a 'long' or 'short' arm of a visual stimuli to be stored into the network. Input values do not need to be binary and, depending on the specific question or experiment of interest, this input value could be manipulated to reflect an experimental parameter. For example, an external input of '0.5' could represent a hidden or uncertain arm length in the context of other inputs being either '1' or '0'.

Model sparseness

Sparseness level of model inputs is an important characteristic of an autoassociative network. At a population level, sparseness S refers to the number of neurons which are firing at a given time. Therefore, S will range from 1/N to the S = 1 when all the neurons are firing, or 'active', and S = 0.5 if half the neurons are 'active' for a given neuronal pattern. Input pattern sparseness has important

implications on the network storage capacity (309). The sparseness level was a modifiable parameter, however for simplicity, it was fixed at S = 0.5 for my experiments.

Task and context neurons

This model had two main neuronal populations. Task neurons were the neurons which were directly involved with encoding a stimulus pattern into the network and retrieving the stored representation. For example, the activity of one neuron may correspond to one component or feature dimension of the stimulus. By contrast, context neurons were a second set of neurons whose activities were chosen randomly for each stimulus, presented together with the pattern to be remembered (also with sparse level S=0.5). Despite not being directly involved in encoding or retrieval of a specific pattern, context neurons helped to provide a stable representation of each pattern within the network. Conceptually, they can be considered as providing some related information such as an environmental association or potential spatial or temporal context specific to that pattern. Binding of remembered information into a unique environmental context, such as time, place and person, are often considered an essential attribute of hippocampal memories. As a baseline model architecture, simulations use 100 task neurons (N=100) with an equal number of context neurons unless otherwise specified, for example, when the model was specifically 'lesioned' to simulate pathology.

Modelling similarity

Pattern similarity can be manipulated in different ways. Following Euclidean geometry, the magnitude of the dot product between two vectors is a measurement of similarity whereby a higher value indicates greater similarity (this can also be represented by the cosine similarity) (310). To manipulate similarity between two patterns, I start with one pattern and took the inverse of the neuronal state of one component (dimension) of the pattern, which I will refer to as 'flipping' the

component. For example, two similar patterns can be created by taking pattern A and flipping one component neuron state from ‘active’ to ‘inactive’ to create pattern B and leaving all other components the same. Figure 6-1a shows how pattern A is changed to pattern B (more similar) by flipping one active and one inactive neuron or to pattern B’ (less similar) by flipping all neuron states. As more components are flipped to create a new pattern B, the dot product between the patterns A and B decreases as they become less similar to each other. Generally for the experiments outlined in this chapter, a pair of inactive and active neurons were flipped at the same time to maintain the same model sparseness (S=0.5).

Similarity within a pattern can also be changed by repeating each component of the pattern so that it is represented twice within a set of neurons. For example, in Figure 6-1b, pattern A is comprised of 12 components with the first six components being the same as the second six components reflecting a high within-pattern similarity. Pattern A’ has a lower within-pattern similarity as the second six components are randomly different from the first six components.

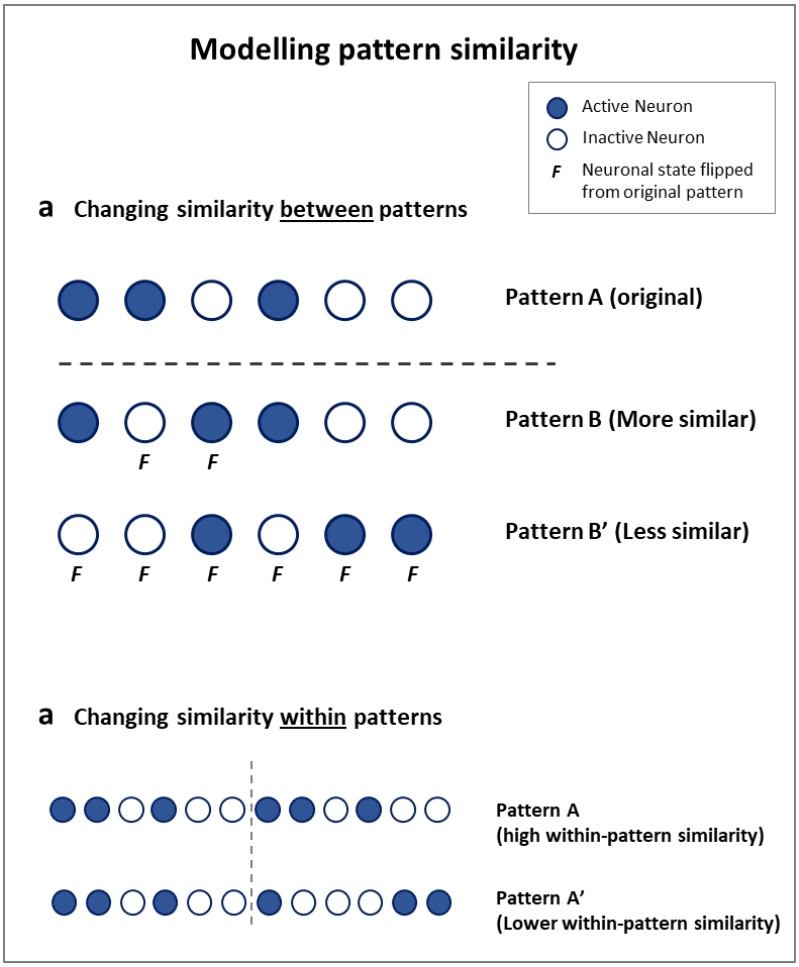


Figure 6-1. Modelling similarity between and within patterns

a Pattern A can be changed by flipping the state of one active and one inactive neuron to create a more similar pattern B (*between-pattern similarity*). Flipping the states of all the neurons will create a less similar pattern B'. **b** Modelling *within-pattern similarity* can be adjusted by having segments of repeat neuron activation patterns. Pattern A has high within-pattern similarity as the first six neuronal states are repeated whereas pattern A' has lower within-pattern similarity with a random activation of the second six neurons.

Model output: accuracy

The output of the recall phase is a set of neural patterns which most closely matches the external input, based on the original learned patterns. These output patterns are generated from the firing rate of each neuron once the external input probe has passed through the recurrent collateral system. The representational space for the neuronal firing rate is continuous and will generally follow a gaussian distribution.

To convert the firing rates into binary patterns, the neuronal activity can be interpreted as an 'active' or 'inactive' neuronal state by applying a threshold activation value. This threshold is often based on the sparseness value of the original stimuli. For example, if the original pattern had a sparseness S = 0.5, then the threshold for being considered active was the median activation value of all neurons. Once each output pattern was interpreted as a 0 or 1, then this output pattern can be directly compared with the original learned patterns to calculate a *model accuracy* for a given set of probes i.e. how closely does the model output neural patterns match the learned input patterns for a given set of probes.

Model output: "Same" or "different" decision

To model a delayed recognition task, such as the Memory Pinhole task, a decision on whether the recalled memory or model output pattern is the "same" or "different" to the original learned stimuli is required. One straightforward way to do this was to set a minimum accuracy level for the model to consider the pattern as being "same". If the model output does not resemble the learned pattern, then the accuracy for that pattern would be low and would be considered as "different". This, however, is not biological plausible as it requires the model to know the ground truth, i.e. correct answer, to compare with the model output pattern before making a decision.

As an alternative, I used the raw firing output of each neuron as a *certainty* measurement for whether that component of the pattern was 'active' or 'inactive'. Based on the Hebbian learning principle applied to binary model inputs, the stored synaptic values for active pattern components will be positive while the firing rate values for stored inactive pattern components will be negative. Therefore, the model will be more likely to recall a more positive firing rate neuron as 'active' and a more negative firing rate as 'inactive' whereas values in the middle may be considered either active or inactive by the model. This likelihood represents a *certainty* measure for the model. Since more positive and more negative values reflects certainty, I took the absolute value of each neuronal firing rate and applied a threshold to indicate whether the model is certain that the external input pattern

matched a stored representation. This threshold was set at the median firing rate to indicate an *unbiased prior* for choosing "same" or "different" and generally reflects having counterbalanced conditions within a psychological task. This threshold can be set differently according to task conditions. Furthermore, changing this threshold can reflect a bias which may arise with age or disease and this is explored later.

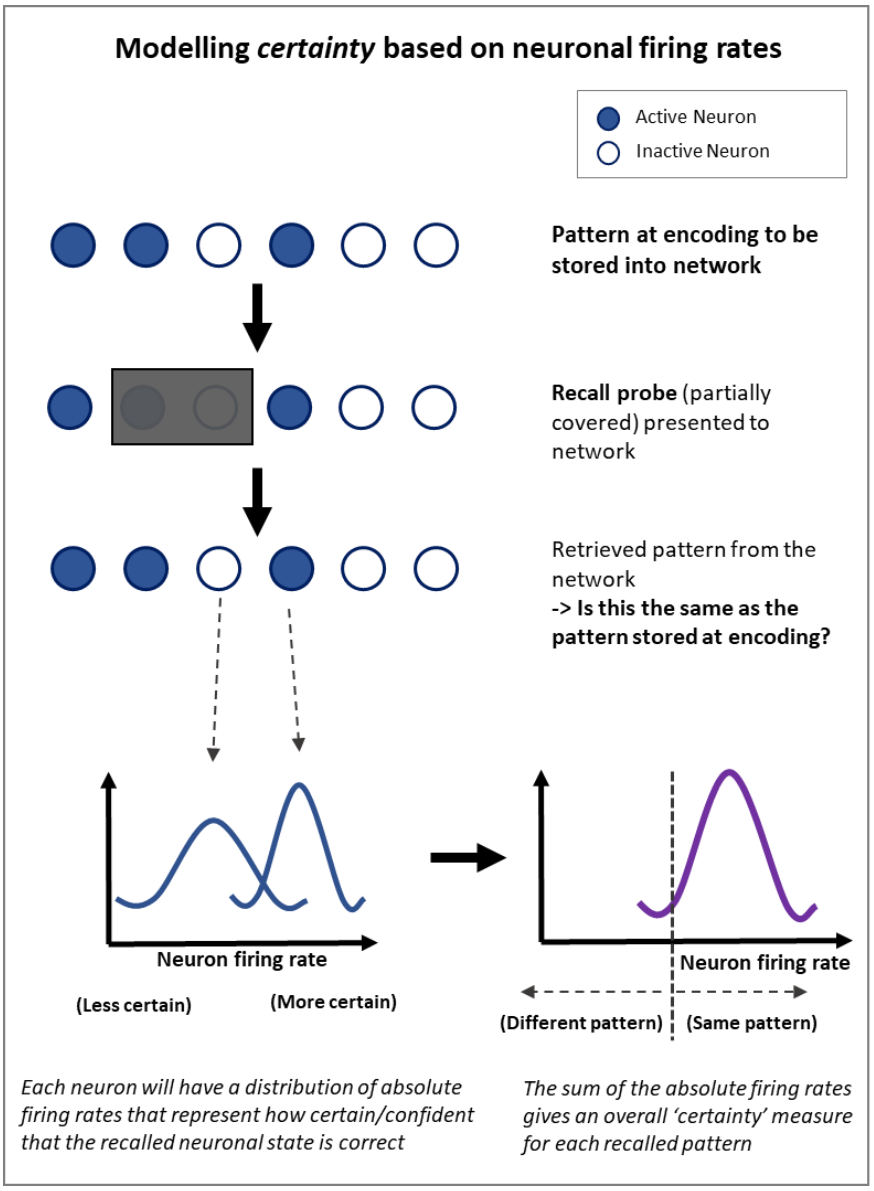


Figure 6-2. "Same" or "different" decision based on model certainty

Patterns are stored in the network at encoding. At a later stage, a recall probe will be presented to the model (partially covered) and the network will retrieve a stored representation. Each neuron involved in this representation has a distribution of absolute firing rates that reflects the model

certainty on whether that neuron was correctly recalled. These firing rates can be combined to give an overall *certainty* measure to decide whether the pattern was “same” or “different”.

6.5 Results

6.5.1 Set size effect

The set size effect, or ‘list-length’, effect is a fundamental principle of both short and long-term memory which is principally demonstrated by a reduction in performance with increasing number of items to be remembered. Behaviourally, this can be reflected by several metrics such as worse accuracy, lower memory precision or higher reaction times across tasks such as visual search and change detection judgements (311–314). Set size effect is commonly thought of in terms of memory capacity, precision or ability to tolerate interference.

To test the set size effect in my neural network, I considered the baseline model architecture with neurons N = 100 (plus 100 context neurons) and tested the network with sets increasing stimuli number from two to 40 stimuli. At recall, the model was given half covered probes and assessed on the accuracy for recreating the covered components. As the set size increased, the accuracy for correctly recalling a hidden neuronal state decreased (Figure 6-3).

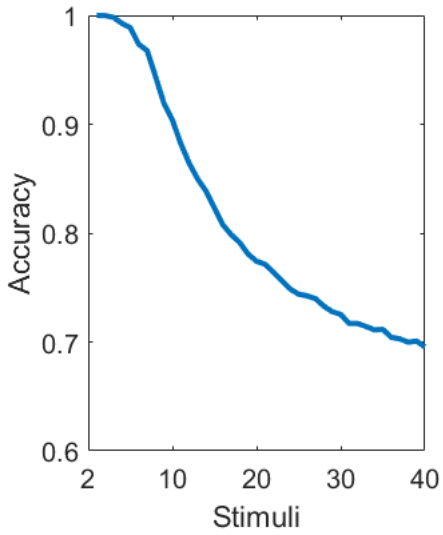


Figure 6-3. Set size effect

Accuracy for recalling the correct probe components decrease with increasing set size.

6.5.2 Reducing the number of neurons in the network

Single-layer feedforward or recurrent neural networks are thought to perform better with more neurons (layer width). This principle applies to Hopfield networks as retrieval errors increase when the number of stored patterns exceeds a proportion of the network size (315). Reducing the number of neurons may be one mechanism to explain changes in performance with disease or ageing.

To examine the effect of network size, I model three different network architectures with N = 200, N = 100 and N = 40 across increasing set sizes (Figure 6-4). Smaller network size was associated with a decrease in model accuracy for a given set size.

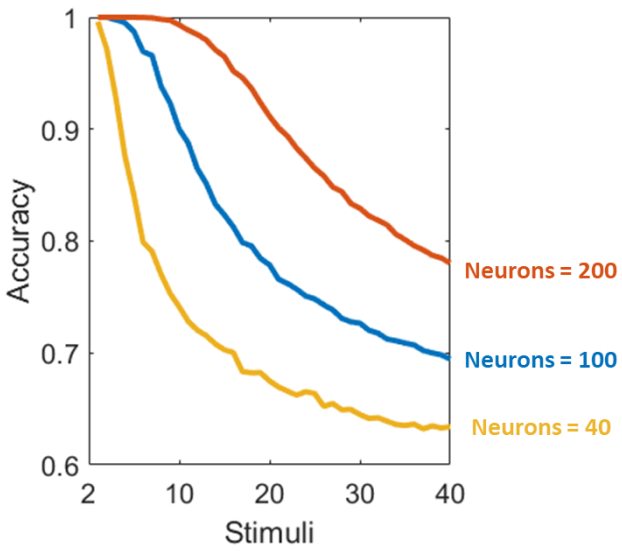


Figure 6-4. Reducing neuron number

Lower number of neurons are associated with lower overall accuracy for a given set size.

6.5.4 Obscuring/ covering neuron activity

In the Memory Pinhole task, I covered stimuli probe so that pattern completion could occur at retrieval. the. To model this, neuron patterns were encoded, or 'learned', by the model as either active or inactive neurons (set to *1* or *0*). These learned representations can be tested by 'obscuring' individual neuronal activity at probe (set to *0.5*) and testing the accuracy for the obscured component of a pattern. Increasing the proportion of neuronal activity which is obscured (from 5% to 50%) at recall is associated with lower model accuracy across a range of (Figure 6-5). This reflects a pattern completion effect whereby partial cues are harder to recall when more obscured.

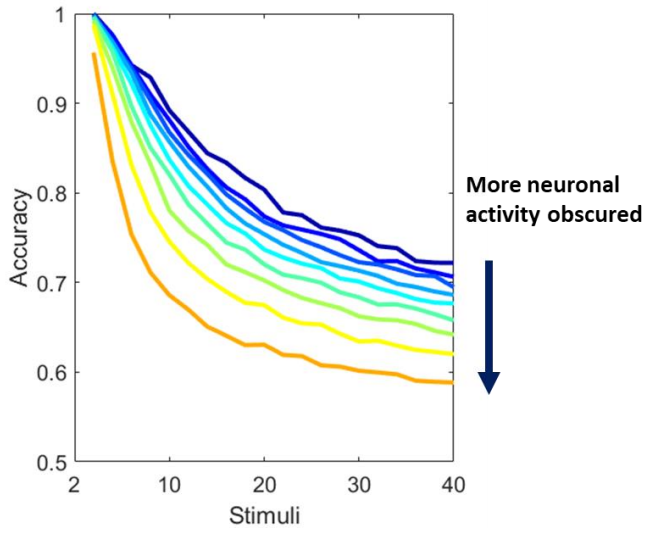


Figure 6-5. Obscuring neuronal activity

During recall, increasing the proportion of obscured neurons (5% - 50% obscured) is associated with reduced model accuracy.

6.5.5 Altering retrieval similarity

Some tasks probe memory using noisy stimuli, rather than simply removing some information at retrieval. To model this, the similarity between encoding stimuli and probe can be parametrically changed by taking the encoding stimuli and flipping the neural activity state of each component of the pattern one at a time (discussed in 6.4 Methods). An encoding stimulus-probe pair which is different by two components will be more similar than an encoding stimulus-pair that is different by 10 components.

Increasing the proportion of the stimulus which is flipped at retrieval is associated with a decrease in model accuracy (Figure 6-6a). Similarly, the model performance for choosing 'different' improves as probes are less similar to the encoding stimuli (Figure 6-6b).

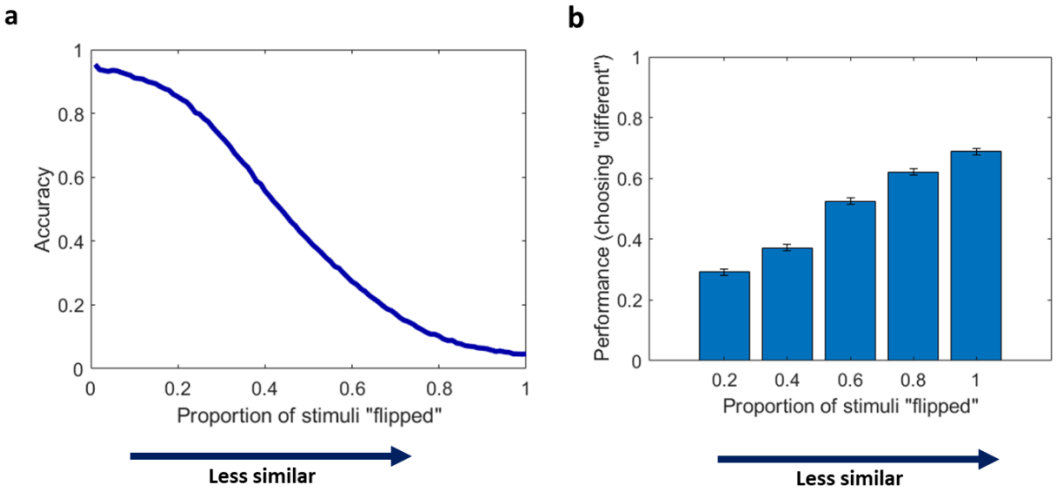


Figure 6-6. Reducing retrieval probe similarity

a The model accuracy decreases as a function of lower similarity between encoding stimuli and retrieval probe. **b** As retrieval probes are less similar than the encoding stimuli, the model is more likely to choose 'different'.

6.5.6 Altering encoding similarity

The behavioural results of the experiment described in section 5.4 indicated that greater similarity between two encoding stimuli leads to greater accuracy compared to less similar encoding stimuli. This was explored further using the network with a stimulus set with high within-pattern stimulus similarity and a set with low intra-stimulus similarity at encoding. It should be noted that a pattern presented to the network at encoding could represent two visual stimuli on the same screen to a human participant. Within each set, the probes were either more or less covered and performance was determined by the model correctly identifying the probe as "same".

The model showed better performance when encoding similarity was higher i.e. high intra-stimulus similarity (Figure 6-7). Regardless of the encoding similarity, the model performed better with probes which were less covered. This reflects a pattern completion effect described above.

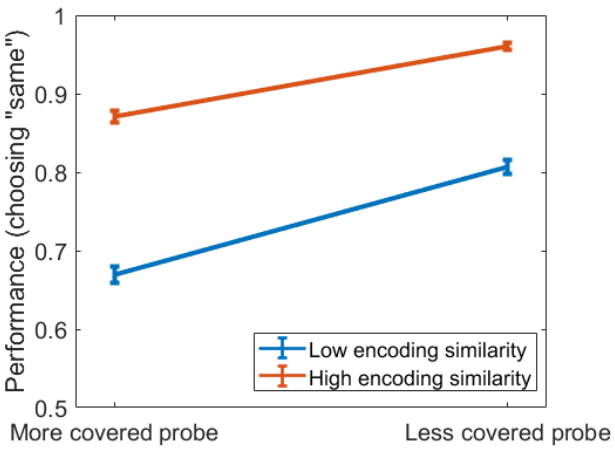


Figure 6-7. Effect of greater similarity between encoding stimuli

Higher encoding similarity was associated with better performance while probes which were more covered were associated with worse performance.

6.5.7 Modelling the Memory Pinhole task

The Memory Pinhole task described in Section 5.6 was simulated here using closely matched parameters. Specifically, 196 stimuli were encoded with corresponding match probes (same as pattern at encoding), more similar non-match probes (25% of the pattern flipped) and less similar non-match probes (50% flipped). All probes were either more covered (50%) or less covered (25%). These conditions were counterbalanced to model the behavioural task. The key output was whether the model considered the probe as being 'same' or 'different' compared to the corresponding encoding stimuli.

Healthy 'young' individuals (baseline)

Using a baseline model architecture (neurons N = 100 with the equal number of context neurons), the model output showed worse performance in match trials for more covered probes and was therefore more 'certain' of a probe being a match when more information was present i.e. less covered probes. This model performance reflects the behavioural results of the memory pinhole task and represents a pattern completion effect (Figure 6-8a).

For non-match trials, model performance was better for probes which were less similar to the encoding stimulus which also reflected behavioural results (Figure 6-8b). Interestingly, the model

predicts that when probes are more covered, they should lead to better performance at choosing "different" for non-match probes. This may be explained by the model having less certainty that the probe is a match when more covered and therefore more likely to choose "different". Behavioural results do not suggest a clear positive or negative effect of the non-match probe being less covered for non-match probes but, based on the model prediction, this may be observed for different task parameters- for example, if there were more contrast between the two probe cover/completeness conditions.

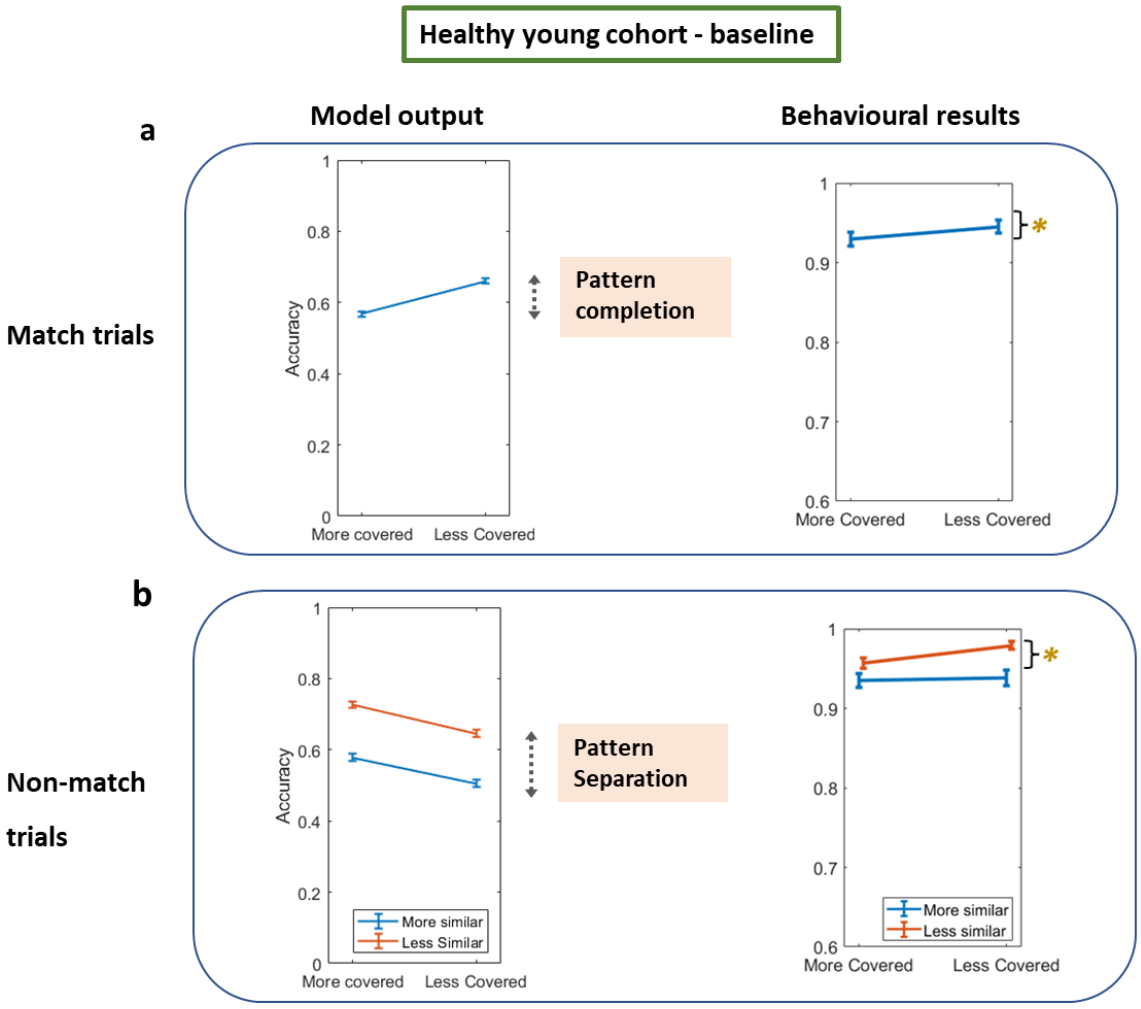


Figure 6-8. Modelling the Memory Pinhole Task: "healthy young" individuals

a Match trial model performance shows higher accuracy for less covered probes compared to more covered probes (Pattern completion effect). This is consistent with behavioural results from the Memory Pinhole Task. **b** For non-match trials, the model performed better for less similar probes reflecting a pattern separation effect which was seen in human participants.

Healthy 'older' individuals (less context neurons)

Reducing the number of context neurons was the model parameter manipulation that best modelled the behavioural results of the healthy older cohort in the Memory Pinhole task. When the number of context neurons was equal to half the task neurons, the model still showed better performance in match trials for less covered probes compared to more covered probes indicating a pattern completion effect. This was also seen in the behavioural results (Figure 6-9a). For non-match trials, however, there was no clear difference in performance for more or less similar probes suggesting no pattern separation effect. Correspondingly, this effect was not present in the behavioural results either (Figure 6-9b). One consideration when comparing the network and behavioural results was that the model output had a lower absolute accuracy for both match and non-match trials compared to behavioural results. This may reflect a different decision threshold in human participants which was kept as a fixed parameter in the model.

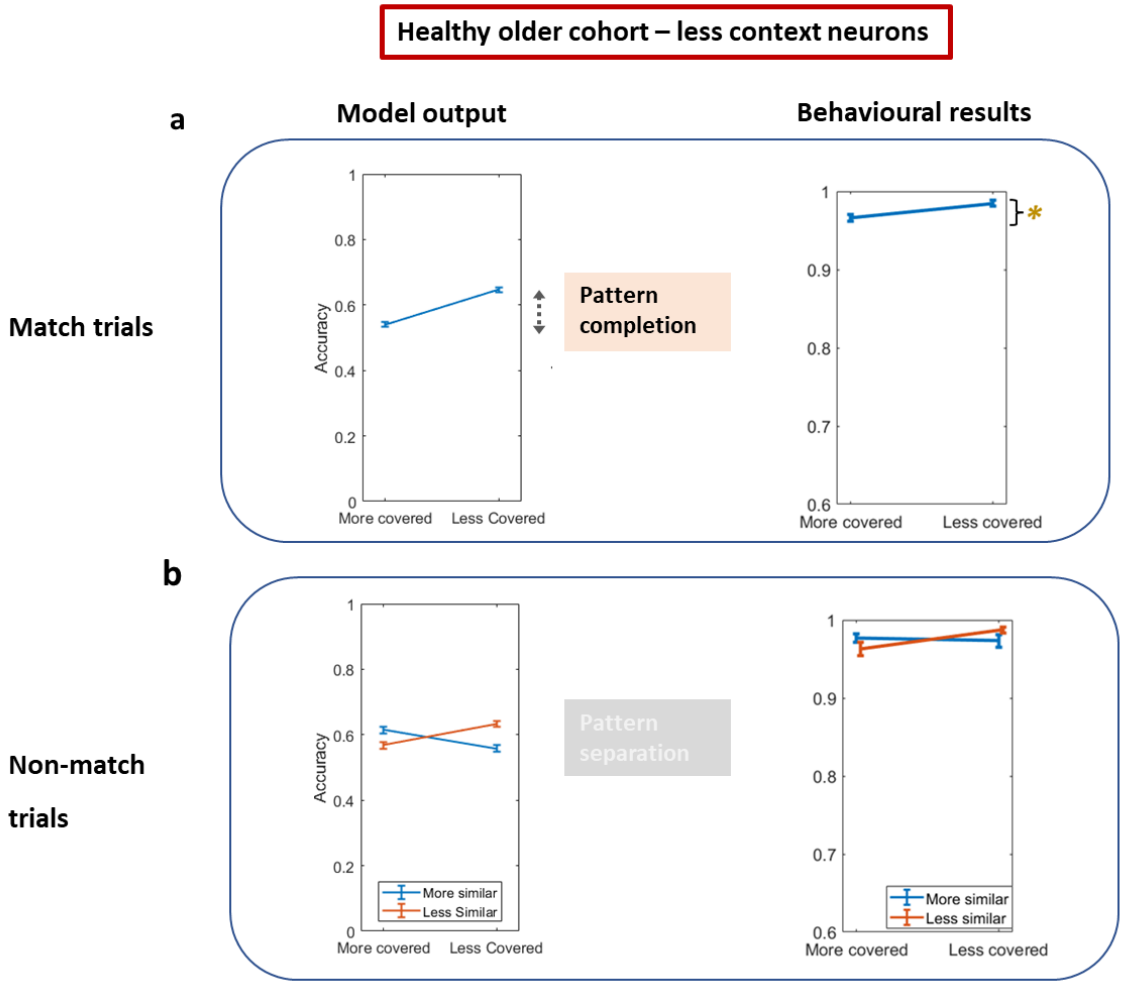


Figure 6-9. Modelling the Memory Pinhole Task: "healthy older" individuals

a Reducing context neurons led to higher match trial model performance for less covered probes compared to more covered probes (pattern completion effect). **b** For non-match trials, different levels of probe similarity was not associated with an overall performance difference or clear pattern separation effect. These model outputs match the behavioural results of the Memory Pinhole Task.

People with Epilepsy (fewer active neurons)

The model was lesioned by reducing the number of task neurons involved in storing information about the encoding stimuli. This best simulated the behavioural results of people with epilepsy. When considering a model with half the number of task neurons, the model maintained better performance for non-match trials with less similar probes representing a pattern separation effect that was observed in people with epilepsy (Figure 6-10a). For match trials, however, the effect of

probe cover was smaller with reduced task neurons as the model was only slightly better at identifying less covered match probes (Figure 6-10b). Interestingly, people with epilepsy had a trend towards better performance with less covered match probes however this was not statistically significant. A larger sample size may be needed to detect this effect which is predicted by the model. The set of simulations outlined in this sub-section show that the auto-associative network can simulate the Memory Pinhole Task and the results from different task cohorts may be explained through lesioning different pools of neurons within the network.

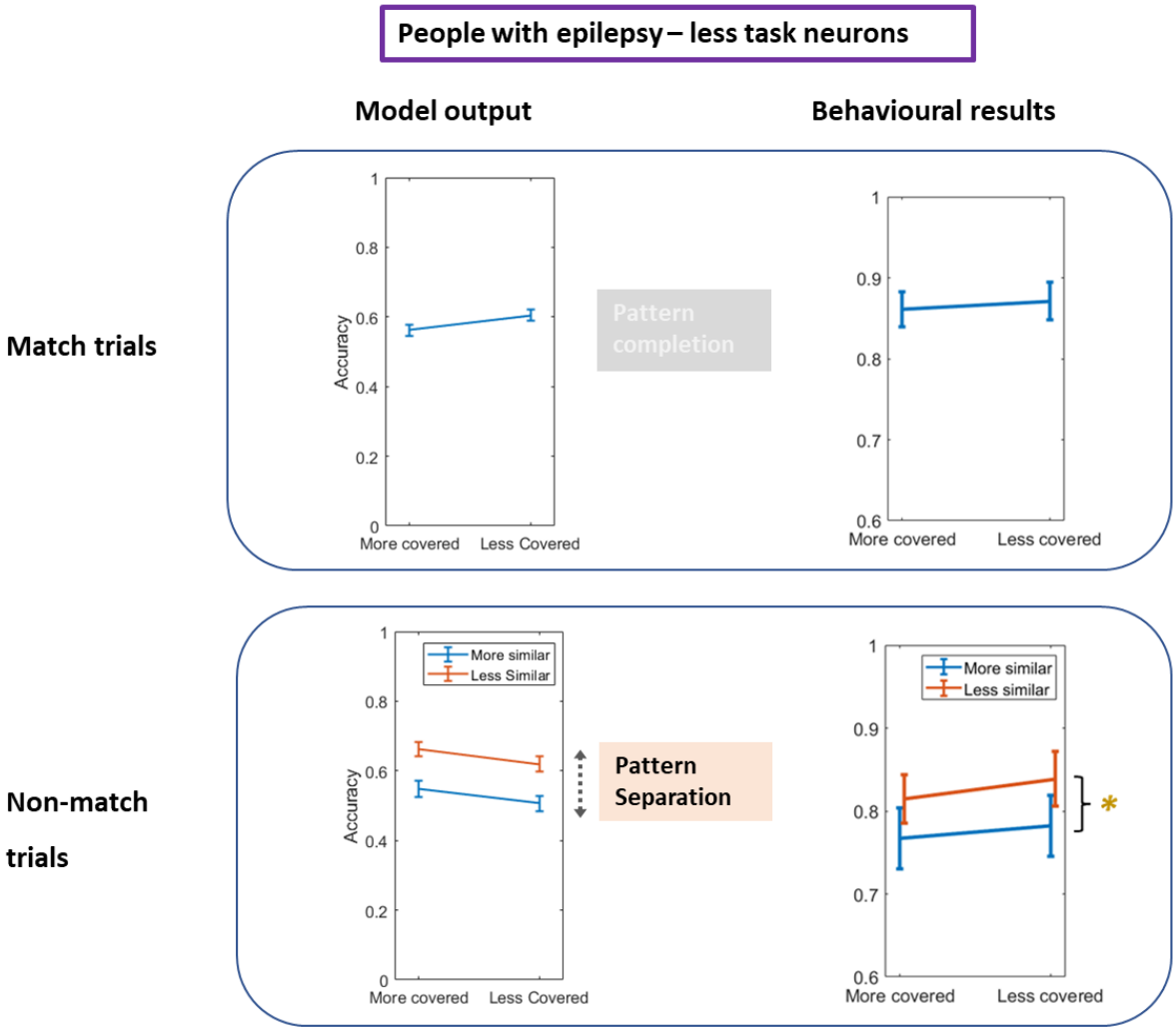


Figure 6-10. Modelling the Memory Pinhole Task: people with epilepsy

a For match trials, reducing task neurons resulted in a smaller pattern completion effect (when performance is better with less covered probes). Correspondingly, behavioural results did not show a significant difference in accuracy between more and less covered match probes. **b** For non-match

trials, better performance was associated with less similar compared to more similar probes. This reflected the behavioural results of the Memory Pinhole Task.

6.5.8 Modelling other pattern separation and pattern completion tasks from the literature

To test the robustness of the autoassociative network to model pattern separation and completion, the network should be able to simulate behavioural paradigms in the literature and gain insight into the results.

Mnemonic similarity task

The mnemonic similarity task is a popular pattern separation paradigm described in the literature (113). Participants are shown a set of stimuli at encoding followed by a set of retrieval probes which are either the same, similar or different. A pattern separation metric termed 'lure discrimination index' reflects how well participants discriminate similar probes from repeat probes. Performance improves as probes become less similar. Overall, younger participants performed better than older participants for all the conditions including repeat and new probes, with older people having a bias to choose 'same'. This difference in performance observed in older individuals was explained as erroneous 'over-completion'. While this interpretation of 'over-completion' may not be correct, the mnemonic similarity task can be simulated with the autoassociative network using matched parameters of similar probes (five different levels from 10% to 50% similar), match probes and completely different (fully flipped) probes.

The model predicted better performance at identifying the probe as 'different' as the probe become less similar. This closely simulates the behavioural results of the mnemonic similarity task in terms of the similarity effect (Figure 6-11a). Reproducing the results of the older individuals was not straightforward. One way to achieve this was to lower the threshold at which the model chooses 'same' which matches the fact that older individuals had a bias towards choosing same in this task.

In contrast to modelling the Memory Pinhole Task, this was not achieved by reducing the number of neurons in the model – which on its own, cannot generate a bias. Instead, the threshold was fixed at the value created by the younger cohort parameters and either the number of context neurons were increased or gaussian noise was added to the firing rate to simulate the behavioural results.

One task feature which may explain why a different manipulation was required to simulate the findings was that the mnemonic similarity task used everyday objects whereas the Memory Pinhole Task used randomly generated abstract stimuli. Therefore, it is possible that additional non-task context associated with everyday objects experienced to a greater degree in older individuals compared to younger individuals would negatively affect their performance. These experiences may be represented by addition noise during retrieval.

Memory Image Completion task

A commonly used pattern completion study is the Memory Image Completion task (134). Participants learned several scenes during the encoding phase. During the probe phase, participants were shown scenes which were partially covered to different completeness levels and were asked to identify the scene as one from the encoding phase or a new scene. Accuracy at identifying the scene correctly decreased as a function of probe completeness which was described as a pattern completion effect. Younger individuals performed overall better than older individuals.

When considering decreasing levels of probe completeness, the autoassociative network correctly predicts worse accuracy at completing the probe (Figure 6-11b). Worse performance in older individuals was modelled by reducing the context neuron population within the model.

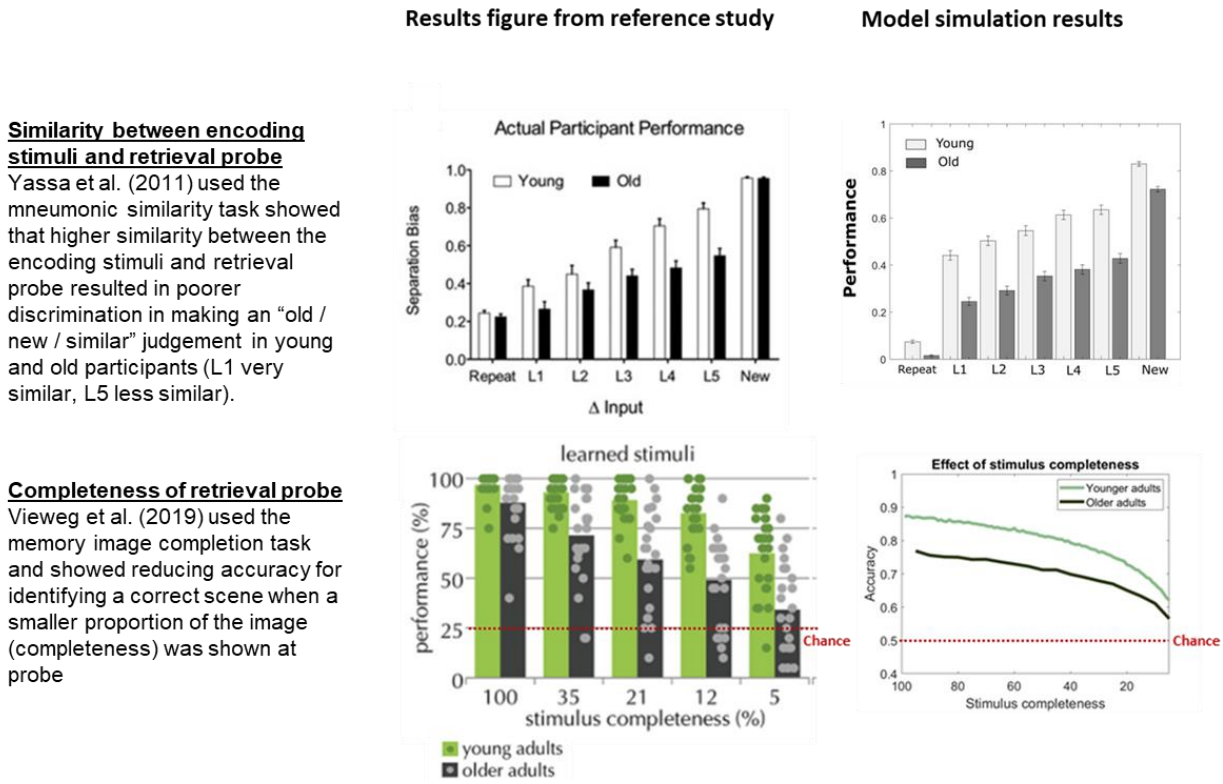


Figure 6-11. Simulating pattern separation and pattern completion tasks from the literature

Using the network to better understand two main behavioural paradigms of pattern separation and pattern completion in the literature

6.6 Discussion

The simulation results demonstrate how a modified Hopfield network can model behavioural findings which reflect both pattern separation and pattern completion. This network demonstrates properties of memory encoding and retrieval such as set size effect on retrieval accuracy while increasing storage capacity is achieved through additional neurons. Similarity and probe completeness could be modelled by flipping neuron activity states and making a neuron's state neutral. The model then predicts behavioural performance through a range of similarity and completeness levels.

A "same"/ "different" decision was derived using the firing rates of the neurons in the network and reflected the model 'certainty'. Better performance in choosing "same" was observed in match

trials when probes were less covered (pattern completion effect) while, in non-match trials, the model performed better in choosing "different" with less similar probes. Changing different parameters led to model outputs that simulated behaviour from healthy older participants (decreasing context neurons) and people with epilepsy (decreasing task neurons). This corresponded with reduced pattern completion in healthy older participants and reduced pattern separation effect in people with epilepsy. These findings suggest that pattern separation and completion are distinct processes in which different neuronal populations are involved.

Interpreting the role or biological relevance of each neuronal pool is not straightforward. Task neurons are directly involved with retrieving stored representations within the model. Reducing or lesioning task neurons may be analogous to disrupting the memory retrieval process which may occur in the epileptogenic CA3 region of the hippocampus. However, one may also argue that task neurons are required to encode stimuli into the model at the first instance. It is likely that both encoding and retrieval are affected in people with epilepsy however the reduced pattern separation effect is more clearly observed in both behavioural results and predicted by the model output.

Changing the context neurons modelled the behaviour of older participants. While not directly involved in the relevant task pattern, context neurons allow better encoding of each pattern by increasing the difference between other patterns in the model. This, in effect, describes a pattern separation effect which is reduced in the behavioural results of older participants. From a computational perspective, the context neurons allow patterns to be stored separately within more distinct basins of attraction within the network. This reduces the chance that one pattern will be confused by another pattern at recall.

The model allows for other predictions through simulating behavioural paradigms of pattern separation and pattern completion from the literature. When examining the mnemonic similarity task, a popular pattern separation task, the effect of different similarity levels were clearly reproduced by this network to reflect pattern separation (113). However, the worse performance in

older individuals which was described as ‘over-completion’ appeared to be a decision bias towards choosing ‘old’. It is unclear whether this can be described as a disruption in pattern completion.

In conclusion, this chapter describes a modified neural network to simulate both pattern separation and pattern completion. Simulation results support the behavioural observations being replicated using a Hebbian learning rule of memory and manipulation of similarity and probe completeness. It allows predictions over a wider parameter space than performed in human participants and modelled the effects of both ageing and epilepsy. Lesioning different populations of neurons reproduced the behavioural results suggesting distinct deficits in encoding and retrieval across the cohorts. Further exploration of these parameters will lead to better understanding of behaviour while application to model neural recordings is also planned for a future study.

7. General discussion

I have investigated the mechanisms of cognitive impairment focusing specifically on the relationship between cardiovascular health, epilepsy, and associated cognitive impairment and risk of developing dementia. I then evaluated specific hippocampal-related functions to understand a potential underlying cognitive mechanism for memory difficulties experienced by people with epilepsy. The first main finding in healthy older individuals, presented in **Chapter 2**, was that cardiovascular risk is significantly associated with poorer executive function which was mediated through widespread changes to fronto-parietal brain networks. This led to questions, addressed in **Chapter 3**, regarding the impact of cardiometabolic multimorbidity on developing dementia in comparison to genetic risk. My results indicated the extent to which cardiovascular health, a modifiable parameter, is associated with the risk of developing dementia. Continuing this line of investigation, in **Chapter 4**, I asked whether people with epilepsy have a higher risk of developing dementia and how this risk compares with other neurological conditions such as stroke. I also investigated whether there may be a synergy between the impact of cardiovascular risk and epileptic impact on cognition and dementia risk. These results suggested that cardiovascular health is an important link between epilepsy and dementia with implications for personalised healthcare of patients and clinical guidelines.

Chapters 5 and **6** explored the hippocampal-related functions of pattern separation and completion, from a cognitive neuroscience perspective, to ask whether both cognitive operations can be measured distinctly in a single behavioural task. This was achieved using a novel paradigm, in which a possible dissociation was found between deficits in pattern separation and pattern completion in people with epilepsy and older healthy individuals. A neural network model was then used to gain a deeper understanding of these results. In the following pages, I present a brief summary of the key findings described in each of the empirical chapters. I then discuss the clinical and scientific

implications of these findings for our understanding on the relationship between epilepsy and cognitive impairment, emphasising important future directions of research in the area.

7.1 Summary of Experimental Findings

7.1.1 Chapter 2: Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing

In this chapter, I examined the relationship between cardiovascular risk factors and a continuous measure of executive function in healthy older individuals, aged 38-72 years, in the UK Biobank. Several key risk factors were associated with worse cognitive performance including high blood pressure, diabetes and high cholesterol (Table 2-1). Waist-to-hip ratio was no longer significant when other covariates were included in the model. Having an APOE e4 allele was also associated with lower executive function and indicated that genetic risk was an important consideration.

A closer examination of blood pressure revealed a continuous dose-response effect wherein every mmHg pressure increase in blood pressure was associated with lower executive function across the population of non-hypertensive individuals (Figure 2-2). People with known hypertension had overall lower executive function scores but showed a different non-linear pattern where associated cognitive scores were stable within a blood pressure range between 100 to 140 mmHg. Blood pressure measurements above 140 mmHg, however, corresponded with lower executive function. Importantly, this relationship between blood pressure and executive function was seen only in mid-life but not late-life individuals highlighted that blood pressure is an important mid-life risk factor for cognitive impairment.

To better understand which brain measures may best explain the effect of cardiovascular risk factors and executive function, I developed a structural equational model to incorporate the complex relationship between age, cardiovascular risk, fronto-parietal grey and white matter structural brain

networks, white matter hyperintensity lesions and executive function (Figure 2-3). Using a hypothesis-based approach, the model indicates that both white and grey matter fronto-parietal networks mediate the effect of cardiovascular risk factors on cognition. Changes in these networks better explain the relationship between cardiovascular risk and cognition more so than white matter hyperintensity burden, a more conventional metric of vascular damage.

The chapter highlights the importance of cardiovascular health is a risk factor for cognitive decline in older individuals at a population level. There is complexity around each risk factor, as observed with blood pressure management where a single mmHg pressure increase may have a tangible effect on the cognitive health of all older individuals and, furthermore, maintaining blood pressure to a stable window of 100-140 mmHg may be critical to mitigating cognitive effects in those being treated for hypertension.

7.1.2 Chapter 3: Cardiometabolic multimorbidity, genetic risk and dementia: a prospective cohort study

Having explored the relationship between cardiovascular risk factors and cognition. In this chapter, I extended this line of investigation by considering how having multiple cardiovascular or metabolic diseases, i.e. multimorbidity, are related to the risk of developing dementia in older individuals. Most studies of multimorbidity have been poorly powered when considering the outcome of dementia. One previous study showed a multiplicative effect of multimorbidity on mortality rate (167). However, the relationship on developing dementia is largely unexplored. The cohort size and duration of follow-up in the UK Biobank offered a unique opportunity to understand this question. Furthermore, I compared the dementia risk associated with a cardiometabolic disease with that of genetic risk indexed by a comprehensive polygenic risk score for dementia. This angle of inquiry adds to the debate between the contribution of modifiable environmental vs fixed genetic factors when considering dementia risk.

Cardiometabolic multimorbidity, defined as having a history of diabetes, stroke and myocardial infarction, was associated with over a five-fold increase in risk of incident dementia compared to having none of these conditions (Figure 3-1). This reflected a monotonic, additive relationship between having more conditions and dementia risk. Individuals with cardiometabolic multimorbidity were more than three times more likely to develop dementia compared with individuals with high genetic risk (Figure 3-2). Importantly, there was no interaction between dementia risk associated with cardiometabolic multimorbidity and genetic risk.

This chapter expanded the findings of chapter 2 to show how cardiometabolic disease is associated with dementia risk, above and beyond changes to everyday cognition. The magnitude of the associated risk would suggest the critical nature for public heath interventions and risk factor management for all healthy individuals. Furthermore, the potential impact of cardiometabolic multimorbidity being independent and substantially greater than high genetic risk highlights the key message that risk factor modification appears critical for every individual, regardless of pre-determined genetic factors that one may be born with.

7.1.3 Chapter 4: Dementia risk in epilepsy: impact of modifiable cardiovascular risk factors

After exploring the association between cardiovascular risk factors and cognition in healthy individuals, Chapter 4 investigated dementia risk in people with epilepsy and whether cardiovascular risk may be an underlying mechanism between dementia and epilepsy. Previous studies identified cognitive deficits across several domains in people with epilepsy compared with healthy age-matched individuals. It would be useful to put such deficits in context with other non-degenerative neurological disorders. Furthermore, how do cardiovascular risk factors affect epilepsy-related dementia in the absence of stroke (which is a clear risk factor for both seizures and dementia)? Could there be a synergistic effect between the ‘normal’ cardiovascular impact and ‘epileptic impact’ on cognition? This chapter aimed to explore both avenues using data from the UK Biobank.

I first examined executive function, using the measure derived in Chapter 2, in people with epilepsy compared to those with a history of stroke, migraine or none of these conditions (healthy controls). Both epilepsy and stroke were associated with a similar deficit in executive function compared to controls (Figure 4-1) whilst there was no difference in cognitive performance between those with migraine and controls. Crucially, having epilepsy was associated with a high risk of developing dementia, more so than the risk associated with stroke. When divided into cardiovascular risk groups, individuals with epilepsy and a high cardiovascular risk were over 13 times more likely to develop dementia compared to healthy controls with low cardiovascular risk (Figure 4-2). The impact of higher cardiovascular risk on associated dementia risk was greater in the epilepsy cohort compared to stroke or healthy controls.

Secondary analyses in this chapter included changes in brain volume and potential effect of anti-seizure medication on cognition. People with epilepsy had smaller hippocampal and total grey matter volume but no significant difference in white matter hyperintensity burden compared with healthy controls (Figure 4-4). A higher number of anti-seizure medication was associated with worse cognition which likely reflected severity of epilepsy more so than cognitive side-effects of medications. Neither the number of anti-seizure medications or the age of epilepsy onset had a significant effect on dementia risk. This suggests that other unmeasured factors may be driving this effect on dementia risk or there may be a step-function effect of seizure burden rather than a cumulative relationship.

Therefore, this chapter provided context to the level of executive function difficulties reported by people with epilepsy (comparable with stroke) and has highlighted the substantial risk pf epilepsy-related dementia. Targeting modifiable cardiovascular risk factors may be an effective intervention to reduce dementia risk in individuals with epilepsy. This has key implications on clinical practice and personal health practices for people with epilepsy. Importantly, such risk reduction strategies are of

low cost meaning that there is the opportunity for change to be implemented in resource poor, as well as resource privileged, settings.

7.1.4 Chapter 5: Pattern separation and pattern completion in health, ageing and epilepsy

In this chapter, I shifted from the population level analysis examining the impact of cardiovascular health on cognition and dementia risk in people with epilepsy to in-depth behavioural assessment of hippocampal-related functions. Here I used a novel computer-based task to examine a potential cognitive mechanism underlying memory difficulties in epilepsy.

I considered pattern separation and pattern completion together as a useful framework of memory encoding and retrieval which can explain cognitive difficulties at both short and longer timescales-commonly and are commonly described in people with epilepsy. Pattern separation and pattern completion have previously been used to examine hippocampal function in older individuals, people with mild cognitive impairment and other neuropsychiatric conditions. Firstly, I created a behavioural task that could measure pattern separation and pattern completion distinctly (Figure 5-5). Such a task has been lacking in the literature due to the confounding relationship between both cognitive processes. These measures were made possible by manipulating different dimensions of the same stimuli to adjust levels of pattern separation and completion required to complete the task. After several pilot versions of this task, I showed that two distinct measures could be obtained in a cohort of healthy younger individuals (Figure 5-6). Importantly, these measures did not simply reflect overall performance as they were derived from the difference in performance between conditions of separation and completion. I then applied this paradigm, known as the Memory Pinhole Task, to a cohort of healthy older individuals and people with epilepsy who were recruited from the local video telemetry unit.

People with epilepsy performed worse overall, which was expected, with notable deficits in pattern completion. This indicated that difficulties were more pronounced at retrieval. Conversely, older

healthy individuals showed less pattern separation despite performing well overall in the task but intact pattern completion (Figure 5-7). This suggested a potential problem during encoding in older individuals and not retrieval, which contrasts with previous literature that describe erroneous pattern completion activity when unable to correctly identify similar stimuli (lures).

In summary, this chapter demonstrated a novel behavioural task that measures two hippocampal-related functions distinctly and may offer a framework to assess information encoding and retrieval in memory. This framework may be applied to both short- and longer-term memory assessment in health and disease. This work helps to connect two growing fields of pattern separation and pattern completion which are often described together in neuro-anatomical models but are, in reality, often assessed separately by different behavioural paradigms. Furthermore, the results contribute to understanding underlying cognitive mechanisms that may connect memory difficulties seen across epilepsy and dementia.

7.1.5 Chapter 6: A neural network model of pattern separation, pattern completion and disease

The final empirical chapter considered the framework of pattern separation and pattern completion using computational modelling, in the context of neuroanatomical theory. There were two parts to this chapter. Firstly, I hypothesized that pattern separation and pattern completion be modelled using a modified Hopfield neural network. I explored whether such a model could simulate the behavioural results from the Memory Pinhole task in Chapter 5 to gain a more nuanced understanding of the interplay between these two processes.

Consistent with my hypothesis, I developed a modified Hopfield network that implemented a model decision of “same” or “different” based on raw firing outputs of neurons. This approach created a *model certainty* output which contrasts with the traditional approach of thresholding the firing outputs to ‘active’ or ‘inactive’ and then comparing this output with the stimulus originally presented to the model. This new approach had several benefits including the fact that the model

does not need to know the original stimulus (or 'ground truth') in order to provide an output as this would not be biologically feasible.

This network was able to simulate the behavioural results of the Memory Pinhole task in all three cohorts. Specifically, the performance of healthy older individuals and people with epilepsy were recreated by lesioning different neuronal populations within the model. When modelling epilepsy, disrupting task-specific neurons appeared to be important and may represent an abnormal epileptogenic CA3 region of the hippocampus (Figure 6-10). Older individuals were modelled by lesioning context neurons which may be more important to accurately encoding information in memory (Figure 6-9). While this is largely speculative, these findings do offer predictions that may be tested in specific experiments. Interestingly, performance in older individuals could also be simulated with a higher bias for choosing "same". This shift in bias may explain the 'over-completion' results described in the literature.

To test generalisability, this neural network was shown to simulate findings from two commonly used pattern separation and pattern completion tasks described in the literature (Figure 6-11). Furthermore, these simulations offered additional insights on reported results, such as the 'over-pattern completion' phenomena, which adds to our understanding of the current literature.

In sum, this chapter described a neural network that can provide a computational grounding for pattern separation and pattern completion measured distinctly in the Memory Pinhole task. Combined with behavioural testing, this can be used to model information encoding and retrieval in memory and test predictions in a wider parameter space and simulate disease.

7.2 Mechanisms of cognitive impairment in epilepsy

Descriptions of epileptic fits can be found throughout history including a 4000-year-old Akkadian tablet found in Mesopotamia (316); with an inscription of a person reading: "his neck turning left, hands and feet are tense, and his eyes wide open, and from his mouth froth is flowing without him having any consciousness". Historical descriptions of the cognitive burden of epilepsy can be found more recently. Dr Manley wrote in an 1800s Journal of Mental Science article (317) that temporal lobe epilepsy was a condition '*where the mind has never been developed and we have the idiot whose course is generally cut short in early life'* or where '*some considerable amount of intelligence has been developed, but is afterwards destroyed by successive convulsive attacks*'.

Cognitive difficulties are evident in epilepsy. Altered mental status and awareness are well documented during a seizure and may persistent post-seizure (or post-ictally) for hours to days. Increasingly, it is accepted that more subtle cognitive deficits are present in people with chronic epilepsy (120,121). However, it has been difficult to parse the specific nature of these difficulties while discounting the confounding effects of co-morbidities, such as head injuries and depression. Furthermore, the potential progressive nature of cognitive deficits in epilepsy remains a topic for debate, especially if seizures did not begin during developmental years of life or do not occur frequently (34). Specifically, is epilepsy associated with a progressive dementia as individuals grow older?

These are difficult questions to answer for several reasons. Epilepsy is not a single condition but an umbrella term that represents numerous causes, both genetic and acquired. When considering acquired epilepsy alone, some forms are more closely associated with memory deficits such as temporal lobe epilepsy or specific lesions of the brain (21,318). Epilepsy which begins in older age, however, are usually the acquired, focal type and more homogenous in aetiology relating to a vascular risk (14). While temporal lobe epilepsy is the most common focal epilepsy associated with

cognitive difficulties, other forms may involve temporal lobe structures such as the hippocampus through widespread abnormal networks, even if the seizures do not originate there (96,97).

Managing cognitive symptoms in epilepsy is difficult and there is no specific guidance to mitigate the potential risk of dementia. In view of the peak incidence of epilepsy occurring in older individuals and the ageing nature of the existing epilepsy population, understanding the relationship between epilepsy and cognition as well as developing strategies to mitigate dementia risk is crucial. Conversely, understanding this relationship may also provide insights into treating cognitive dysfunction in people with dementia which is a condition which is lacking in both symptomatic and disease-modifying treatment options.

7.2.1 Cardiovascular disease as a link between epilepsy and dementia

"What is good for the heart is also good for the brain" is an adage that is increasingly used. This may be doubly important when considering cognitive dysfunction in epilepsy. Cerebrovascular stroke is the most common cause of epilepsy in older individuals (13) while cerebrovascular disease is closely linked to vascular dementia (78). An interesting line of questioning is to consider what is the exact relationship and magnitude of impact of cardiovascular disease on cognition and risk of developing dementia? Furthermore, could the impact of cardiovascular disease on cognition and dementia risk be magnified in epilepsy?

The investigations described in this thesis delineated how cardiovascular risk factors are intimately linked to both cognition and dementia risk, often, with a nuanced relationship. These findings have important implications for medical management and public health initiatives. Take blood pressure, for example; a continuous linear association between blood pressure and executive function indicated that even a single mmHg rise may impact cognition in healthy individuals in the UK Biobank. This relationship was non-linear in hypertensive individuals in that controlling blood pressure below 140 mmHg systolic did not reflect additional benefit on cognitive performance. This result reinforces the importance of tight blood pressure control but not overly-aggressive treatment

which may risk dangerous side-effects of medication. Furthermore, the findings reported here appear to be relevant in mid-life individuals but not late-life which indicates that any public health interventions should be aimed at an earlier age.

The statistical structural equation model of the complex relationship between cardiovascular risk and cognition, described in Chapter 2, showed the importance of considering wider brain structural networks when considering the true effects of cardiovascular disease. This has practical implications on using white matter hyperintensity lesions as the main index of vascular disease, which is often the case in the clinical setting, and furthers our understanding of the underlying neurobiology. The involvement of white and grey matter networks which include the temporal lobe may also explain why vascular disease is closely linked to developing temporal lobe seizures, regardless of the location of the vascular burden (100,319).

When considering people with epilepsy, the work in this thesis delineates a substantial impact of modifiable cardiovascular risk factors on epilepsy-related dementia. The finding that epilepsy was associated with a higher risk of dementia than even a previous stroke is paradoxically both surprising and understandable when considering the growing literature on cognitive difficulties in epilepsy and the hints of increased dementia risk from smaller studies and personal experience with patients. The findings from the UK Biobank offer a strong argument that managing cardiovascular risk should be a part of every management plan with our epilepsy patients with supportive guidance from national bodies. Furthermore, such risk reduction strategies are of low cost meaning that there is the opportunity for change to be implemented in resource poor, as well as resource privileged, settings.

7.2.2 Why is cardiovascular health important in epilepsy?

Unravelling the processes which underpin cardiovascular health as a mechanism connecting epilepsy with dementia will advance our scientific understanding of two key chronic diseases. Specifically, could there be a synergy between the “normal” cardiovascular impact on cognition and the seizure-specific impact on cognition?

Exposure to cardiovascular risk factors may lead to cerebrovascular small vessel disease and subsequent cognitive deficits through numerous and complex processes including cerebral hypoperfusion, emboli or infarcts. At a cellular level, studies identify associated impairment of vascular endothelial function and disrupted molecular cascades within the neurovascular unit, i.e. interplay between the cerebral blood vessels and brain tissue (320). This manifests in several ways ranging from blood-brain barrier dysfunction, abnormal inflammatory cell trafficking into the central nervous system and, ultimately, cerebral hypoxia. Larger studies have shown that globally reduced cerebral brain perfusion across ageing may be one the earliest imaging changes in people with dementia (321). Other investigations have focused on the angiogenic processes which are associated with seizures leading to immature, leaky blood vessels (81,83) and potentially seizure-generating arteriovenous malformations (80).

Cerebrovascular circulatory defects are also associated with abnormal protein deposition including amyloid β-peptide aggregates within the brain parenchyma (amyloid plaques) and walls of the small brain arteries leading to cerebral amyloid angiopathy (322). The association between amyloid and small vessel disease has also been shown through PET-amyloid imaging (323) and amyloid deposition has been related to poor clearance due to vascular dysfunction (324). Evidence also links neurovascular pathology with perivascular neurofibrillary tau accumulation and toxicity which leads to further vascular endothelial damage and vessel-astrocyte dysfunction (325). This is an emerging area of investigation as a recent study described that pathological and imaging markers of small vessel disease were associated with a higher burden of tau neurofibrillary tangles and proteomic tau levels but not with amyloid-β levels (326).

Small vessel disease is therefore closely linked with classic pathological protein accumulation of Alzheimer's disease and may be one explanation why cardiovascular health is important for dementia risk in epilepsy. Cerebrovascular disease and overt stroke (70) are risk factors for developing focal epilepsy which, in turn, has also been linked to accumulation of pathological tau

protein (15,88). It is therefore possible that small vessel disease may accelerate any pathological tau process in epilepsy as the mechanistic link with cognitive impairment and dementia. The alternate possibility is that small vessel disease simply provides an additional burden on the brain which is already physiologically vulnerable from the effects of epilepsy. While further studies are required to delineate the exact role that cardiovascular risk factors may play, the findings in this thesis support intervention strategies around cardiovascular risk reduction to mitigate cognitive decline and dementia risk in both healthy and people with epilepsy.

7.2.3 Can we really prevent or mitigate dementia risk?

In the spirit of scientific discussion, I will present two opposite views that argue against the merits of cardiovascular health interventions discussed in the previous sub-sections.

Exploring the impact of cardiovascular risk factors on cognition and magnitude of association with dementia has yielded several interesting findings. However, is this a meaningful line of questioning? Will the obvious outcome be to advise individuals to exercise more and to eat healthier diets which is sensible advice to begin with? I would argue, yes, the findings are very meaningful.

Modifying cardiovascular risk is one of the several lifestyle and risk factor management strategies described to prevent incident dementia. The recent Lancet commission on Dementia prevention concluded that up to 35% of dementia cases could be prevented through a broad prevention strategy (166). Further calculations describe that a 20% reduction across the cardiovascular risk factors and improvement of educational attainment would lead to 15% smaller dementia prevalence by 2050 (327). The magnitude of these effects are substantial for the general public and would have a greater impact for those with epilepsy. This is especially important in view of the paucity of disease-modifying therapy for dementia. While recent reports of anti-amyloid therapy for Alzheimer's disease are welcomed findings by the dementia community, results have been modest

at best by shifting clinical ratings a few percentage points with Lecanumab (328) or statistically inconsistent between phase-III trials with Aducanumab (329) for early Alzheimer's disease.

The second argument against being overly optimistic for cardiovascular risk reduction stems from our incomplete causal understanding around the complex relationship between cardiovascular risk factors and dementia. Population level observational data has identified a strong link between cardiovascular risk factors, cognitive decline and dementia while animal and cellular models have delineated potential pathological and cellular pathways. However, randomized control trials (RCTs) have not provided high-quality evidence that improving cardiovascular risk will lead to clear benefit on cognition and dementia risk at an individual level.

The main large, multi-domain trials which were designed to prevent dementia have shown modest results, at best, including the Multidomain Alzheimer Preventative Trial (MAPT) (330), the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (331) and the Dutch Prevention of Dementia by Intensive Vascular Care (PreDIVA) (332). For example, FINGER was a large 2-year double-blind randomized control trial which combined vascular risk monitoring together with healthy diet, exercise and cognitive training in older adults at risk of dementia. Both the intervention and control group, who received usual care, showed improvement in cognitive metrics which resulted in a relatively small effect size difference between groups (Cohen's d = 0.13). The improvement in the control group was not expected and raised questions around the utility of repeat cognitive testing, and potential practice effects, but also whether regular monitoring in itself could have a positive impact on the lifestyle. The MAPT did not show significant group differences from lifestyle interventions and omega-3 supplementation on measures of episodic memory. However, participants were generally older and more frail at baseline.

Attempts to reconcile the differences between observational findings and RCTs speaks to the complex process underlying cardiovascular risk and dementia. Going forward, there are ongoing larger lifestyle intervention studies that may help our understanding, such as the World Wide Finger

initiative (333), as well as other methodology which delineate where each risk factor lies on the causal pathway for dementia, such as Mendelian randomization (334).

Overall, the evidence does suggest the utility of preventative strategies for dementia and even relatively small reductions in incidence might have a dramatic effect on public health at the population level. Furthermore, many of these lifestyle interventions proposed have benefits beyond cognition and dementia. They are relatively inexpensive with minimal adverse effects and, importantly, can be deployed at scale with relatively minimal training of health care workers.

7.2.4 Pattern separation and pattern completion are behaviourally dissociable cognitive processes

While large dataset exploration is useful to gain insight into the nature of complex disease factors (such as cardiovascular risk) and understand the magnitude of the question, the next few subsections will focus on understanding the precise role that the hippocampus may play in epilepsy-related cognitive dysfunction. Specifically, I asked whether we could obtain distinct measures of pattern separation and pattern completion from a single task and showed that this is possible using a novel task. This is important for three main reasons. Firstly, from a basic cognitive neuroscience perspective, this should be possible based on neuroanatomical models of pattern separation and pattern completion (108,165). Different parts of the hippocampus have been hypothesized to perform each process. This would also mean that specific conditions, including situations of selective damage, that would lead to deficits in both processes and this should be testable.

Secondly, current tasks in the literature do not have separable measures for each process. This question has recently been raised but the proposed solution used a two-task approach and correlated measures from different tasks (158). Conversely, popular pattern separation paradigms suggest that doing well in identifying similar ‘lures’ reflects pattern separation whereas incorrectly identifying lures as ‘old’ (or same as a previous stimuli) is considered erroneous over-completion (114,115,149,156). While pattern separation and pattern completion are closely related, they should

not simply be considered to be opposite ends of a unitary cognitive spectrum. Therefore, if it is possible to get distinct measures of pattern separation and pattern completion, this would question the validity of how we interpret previous results. Lacy et al. (2011) describe that older individuals show more erroneous pattern completion compared to healthy controls as a result of choosing 'same' when faced with similar lures (114). These errors may be due to other reasons such as incorrect encoding of the memory or subsequent guessing at retrieval rather than purely due to pattern completion. Modelling this task using a neural network suggested that one explanation for worse discrimination of similar lures may be a bias in older individuals to choose 'same' which may not be related to pattern completion.

The final reason arguing in favour of a task to delineate pattern separation and completion measures is the potential use as a mechanistic framework to understand cognitive symptoms in health and disease. Reduced pattern separation and, potentially, 'over'-pattern completion has been proposed to occur in older individuals (112–114), those with mild cognitive impairment (115), psychiatric conditions such as depression and anxiety (335), as well as epilepsy (117). This may well be the case for all these conditions, however, there should be a way to show these distinct changes to both pattern separation and pattern completion rather than rely a single measure to infer changes to both processes. One might also argue that it is strange that an individual with any neurological or psychiatric condition would perform better on any cognitive metric although some biological reasons have been proposed, including a lack of hippocampal neurogenesis in depression leading to immature dentate gyrus cells and a higher chance of pattern completion (336).

The results from the Memory Pinhole task described in Chapter 5 suggested a dissociation between pattern separation and pattern completion deficits exists in people with epilepsy and older healthy individuals. The design of the Memory Pinhole task allowed us to tease apart relative deficits in these processes. People with epilepsy demonstrated difficulty completing memory probes more so than discriminating similar objects whereas older individuals were good at completing probes but

worse at discriminating objects. Importantly, this task allowed for worse performance in both pattern separation and pattern completion and these indices did not simply reflect overall task performance. With these distinct measures, we can now try to understand why this may be the case in epilepsy and I will explore this in the next sub-section. Additionally, this same approach can now be applied to other conditions of interest to verify or update existing ideas.

7.2.4 Beyond pattern separation and completion: the role of the epileptic interictal spike

Results from the Memory Pinhole Task, described in chapter 5, showed that people with epilepsy had a reduced pattern completion index, which may reflect difficulties at retrieval, while having a relatively preserved pattern separation index, a reflection of the encoding process. This would be consistent with reports that people with epilepsy struggle with memory retrieval of autobiographical events (337). Why might this be the case?

Interictal spikes

One biological reason for specific retrieval and encoding deficits are subclinical, interictal epileptic phenomena, specifically interictal epileptic spikes. These electrographically characterised as brief large amplitude epileptic waveform discharges followed by a slow wave (338). Interictal spikes occurs transiently in focal epilepsy in the absence of overt seizures. Therefore, individuals who experience such interictal activity may show no alteration in awareness but may have difficulties if tested with a sensitive cognitive paradigm.

Interictal spikes are more prevalent than previously thought as this epileptic activity occurs frequently in structures deep in the brain, such as the hippocampus, and are not easily observed by scalp EEG (339). Indeed, one study identified that only around 10% of interictal spikes recorded from intracranial depth electrodes were detected at the scalp level (340).

What does this mean for cognition? Two recent intracranial investigations on the cognitive effects of interictal spikes showed a time-specific effect on performance with interictal spikes occurring at the

encoding or retrieval phase of a delayed free recall word task but not during maintenance or distractions (341,342). Over 140 people with epilepsy arising aetiologies were included across both studies including temporal and extra-temporal lobe epilepsy patients. Interictal spikes during encoding which occurred within left temporal brain regions, such as the hippocampus, adversely affected performance. Interestingly, Ung et al. found that interictal spike activity occurring in any brain location, both temporal and extra-temporal, and in either hemisphere disrupted memory retrieval (342). In fact, this report suggested that during retrieval inter-ictal spikes which were outside the seizure-onset zone had a greater impact on performance compared to spikes occurring within the seizure onset zone. Furthermore, worse performances correlated with spiking activity during retrieval more so than spikes during encoding.

Putting these findings together, it appears that the retrieval phase of these memory tasks are more vulnerable to wide-spread inter-ictal spike activity whereas spikes in specific left temporal lobe regions were required to disrupt encoding. While there are important limitations of these studies, including the variable location of intracranial recordings across patients and correlational nature of the findings, one might speculate that this may be consistent with impairment of pattern completion identified in people with epilepsy who performed the Memory Pinhole task, described in chapter 5, more so than deficits in pattern separation. Linking this to neuroanatomy, the CA3 region of the hippocampus is thought to be the main region of pattern completion and has numerous recurrent collateral connections between CA3 neurons. One might also speculate that these highly connected neurons are more sensitive to the direct effect of an interictal spike or distant effects via aberrant epileptogenic networks compared with neurons of the dentate gyrus which are linked to pattern separation. This would require further confirmatory investigation.

Additional work, not reported in this thesis, that I have performed, examined the effect of interictal spikes. I studied data from a visual working memory task in nine epilepsy patients undergoing intracranial recording in Bielefeld, Germany. Results indicated that interictal spike activity during

retrieval led to worse performance, which is consistent with the literature, but spikes during encoding did not significantly affect performance. This work was limited by a small sample size and is ongoing with the aim of recruiting more participants, however, the preliminary may also be consistent with a specific retrieval deficit identified in the Memory Pinhole task. I should note that scalp EEG recordings were obtained with the Memory Pinhole task and event-related potential (ERP) analysis was performed but interictal spikes were not seen frequently enough to correlate with behavioural performance.

Disruption of larger networks

The effect of extra-temporal as well as temporal interictal spikes affecting memory may be explained by disruption of larger networks involved in cognition. While epilepsy is often considered a model for hyperexcitable brain networks, how could discrete interictal spikes affect these networks? In the unpublished work from Bielefeld epilepsy patients, I performed a dynamic network connectivity analysis, applying principles of graph theory, to show increased global efficiency across all electrodes in trials with a high spike count which was evident mainly during encoding and retrieval periods of the task. Similar work has shown increase network global efficiency in epilepsy which is thought to represent hyper-active epileptogenic networks (343). The time-specific nature of the interictal spike to affect these larger networks during encoding and retrieval phase was a new finding.

The reason for briefly discussing network disruption is the fact that interictal spike activity is difficult to record from scalp electrodes but perhaps a more global measure of brain activity, such as a network efficiency metric, may be a surrogate marker for underlying epileptic activity. This may help to identify people with epilepsy who have a greater burden of interictal epileptic activity and who many benefit from intervention.

The premise that interictal spikes can affect the retrieval phase of memory has potential clinical application. The next step would be to examine this effect in epilepsy patients on and off anti-seizure medication to investigate whether anti-seizure medication could improve interictal spike

burden and, potentially, memory performance. This would require accurate assessment of interictal spike burden. One possibility to do this would be on an intracranial video-telemetry unit where patients are admitted to investigate seizure-onset zone pre-surgery. This often involves stopping and later restarting anti-seizure medication and such a study is currently being discussed with the epilepsy unit at Bielefeld.

The other avenue is to use either a scalp EEG surrogate marker of interictal spiking activity, as described above, or a behavioural paradigm that may be more sensitive to these retrieval specific deficits. The design of the Memory Pinhole task may achieve this, firstly because the two distinct measures reflect encoding- and retrieval-specific processes. Secondly, because the pattern separation and pattern completion indices are not solely dependent on overall accuracy and reflect the difference between two conditions. This is a critical point for such a task as most people with epilepsy will do worse than their healthy age-matched counterparts in any memory task. The Memory Pinhole task should first be performed with concurrent intracranial EEG recording to show the retrieval effect of interictal spikes corresponds to the pattern completion metric. While several steps need to align before this would be possible, this may be a non-invasive but specific measure of cognition in epilepsy that may guide clinical management.

7.2.5 Through the lens of Alzheimer's disease and other dementias

The discussion in the previous sub-sections have examined hippocampal-related cognitive processes a potential neurobiological process of disruption in people with epilepsy. The same may apply to Alzheimer's disease and related dementias. A recent investigation identified hippocampal interictal epileptic spikes using intracranial foramen ovale electrodes in two patients with Alzheimer's disease who did not have a history of seizures and did not have scalp EEG evidence of epileptiform activity (344). The rate of interictal spikes was recorded at over 400 per hour in one patient while both experienced more spiking activity whilst asleep. One patient in the study had a history of previous

confusional spells while the other patient did not. Such hidden epileptic phenomenon may therefore underpin some hippocampal dysfunction, potentially involving pattern separation deficits, that is seen in Alzheimer's disease in addition to the traditional explanation of hippocampal atrophy.

This mechanistic view adds to the growing debate in the literature on whether temporal lobe epilepsy could be used as a model of cognitive dysfunction in Alzheimer's disease (16,345,346). Thus far, there has only been this single case study with two Alzheimer's disease patients showing interictal epileptiform activity from intracranial recordings. Another investigation using prolonged scalp EEG recording combined with magnetoencephalopgraphy (MEG) identified that a greater proportion of patients with Alzheimer's disease had some form of subclinical epileptiform activity compared with healthy controls (347). This study could only conclude presence or absence or interictal epileptic activity and was likely to be an underestimation of the true burden. Epileptiform activity did not correlate with worse cognitive performance but was associated with a faster decline in cognitive scores over a five-year follow-up period (347). These findings are supported by older transgenic animal models of Alzheimer's disease showing frequent seizure activity (348) and has been further explored to identify sub-clinical interictal spikes of different morphology (349).

A natural next question would be whether treatment of such sub-clinical epileptiform activity could offer symptomatic improvement in Alzheimer's disease and other dementias. This is relevant given the earlier discussion on the lack of effective disease-modifying therapy in dementia. Addressing epileptiform activity may impact an intermediate step along the pathway from underlying pathology to clinical manifestation of dementia.

To this effect, during my DPhil, I was a sub-investigator in An Investigation of Levetiracetam in Alzheimer's Disease (ILiAD): a double-blind, placebo-controlled, randomised crossover proof of concept study (127). This investigation planned to recruit 30 patients with mild-to-moderate Alzheimer's disease with no history of seizures and administer Levetiracetam to assess for improvement in cognitive scores. Unfortunately, the study was stopped early during the COVID-19

pandemic owing to compromised recruitment. We achieved the initial proof of concept aim and demonstrated no unexpected adverse events with a dose of 500 mg twice a day of levetiracetam in the 8 study subjects. Cognitive outcomes, currently unpublished, did not show a significant within-subject effect of levetiracetam compared to placebo. However, few participants completed the cross-over phase. There was no group difference between those who started on levetiracetam or placebo. Interestingly, one participant showed a clear lower cognitive profile and demonstrated some improvement with levetiracetam also had potential epileptiform activity recorded on a baseline EEG. This alone is difficult to interpret, however, may suggest the relevance of targeting interictal epileptic activity.

One other study, published after the start of the ILiAD investigation, has also addressed whether levetiracetam could improve executive function in patients with Alzheimer's disease (126). Here 28 Alzheimer's disease patients underwent a similar study design with a much lower dose of levetiracetam 125 mg twice a day. No difference in cognitive outcomes were detected with levetiracetam compared to controls. However, nine patients who had detectable epileptiform activity on their baseline EEG showed a small improvement on a Stroop test subscale and virtual route learning test at the group level. This supports the hypothesis that certain individuals with Alzheimer's disease may have a higher burden of epileptiform activity, such as interictal spikes, and would benefit from targeted anti-seizure medication. I speculate that better patient selection, either with more sensitive EEG recordings or specific cognitive measures, may lead to a more successful trial outcome and effective use of anti-seizure medication in Alzheimer's disease. The concept of hippocampal dysfunction as a cognitive mechanism for the effects of interictal epileptiform activity is depicted in Figure 7-1 which shows an expanded schematic diagram of the mechanistic links between epilepsy and dementia from Chapter 1.

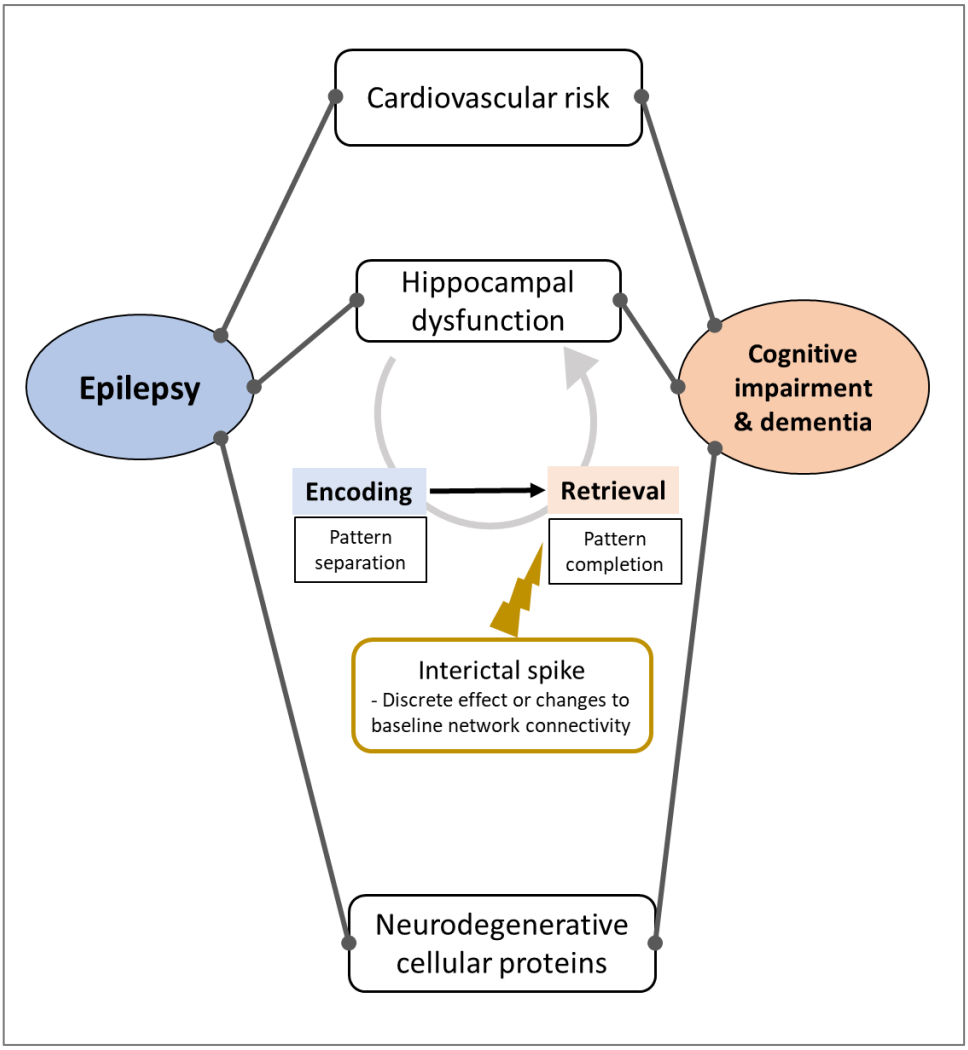


Figure 7-1. Expanding the schematic diagram depicting three mechanistic links between epilepsy and dementia

Hippocampal dysfunction in epilepsy and dementia can be considered in the framework of pattern separation and pattern completion. Memory deficits are associated with interictal epileptiform activity occurring during the retrieval phase of behavioural tasks more so than at encoding. This may be reflected by specific pattern completion deficits in the Memory Pinhole Task. Cardiovascular risk leading to cerebrovascular pathology is related to the accumulation of neurodegenerative proteins tau and beta-amyloid and is observed in both epilepsy and dementia.

7.2.5 Concluding remarks

In this thesis I have outlined and demonstrated evidence for two mechanistic links between epilepsy and cognitive impairment. Cardiovascular health is a key risk factor for developing cognitive impairment and dementia in healthy older individuals. The effect of modifiable cardiovascular risk on dementia risk appears accentuated in people with epilepsy and this finding has important implications on clinical guidance to mitigate the risk of dementia in this patient population. Consideration of hippocampal-related functions of pattern separation and pattern completion may offer a potential framework for understanding such memory difficulties in people with epilepsy. As our ability to measure these cognitive processes improve, we may be able to apply this framework towards identifying the cognitive effects of specific epilepsy phenomena such as interictal spike activity which is also present in dementia. As we look to the future, integrating specific cognitive frameworks using behavioural and computational approaches should help shape our understanding of memory in epilepsy.

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