Neurocognitive predictors of post-stroke cognitive trajectory

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Abstract

The current thesis examined cognitive trajectories following stroke, and tested potential predictors of cognitive outcome, and trajectories. It used data from two existing databases: the Birmingham Cognitive Screen Study (BUCS) collected in the UK, and the C-BCoS collected in China, and newly collected data as part of the HiPPS-CI study (The role of Hippocampus Pathology in Post-Stroke-Cognitive Impairment). Chapter two aimed to answer the question; does the proportional recovery rule exist in cognition, as it does with motor recovery? We found that 80% of patients showed 40-50% proportional recovery of cognition at nine months post-stroke. This was evident across and within cognitive domains. Recovery was not limited to the first three months following stroke. We further identified two other recovery trajectories, where around 10% of patients showed an accelerated recovery, while around 10% showed decelerated recovery and even decline. We then investigated the predictive value of years of education on post-stroke cognitive outcomes, and recovery rate (Chapter three). We found that education improved cognitive outcomes following stroke, and accelerated recovery in the first year following stroke beyond age. Finally, we explored the predictive value of hippocampal pathology, and the impact of hippocampal pathology on post-stroke cognition. We found that beyond stroke and age, hippocampal pathology predicted cognition within three months post-stroke. This was evident in grey matter volume, mean diffusivity, creatine, choline and N-acetylaspartate. Hippocampus pathology (specifically grey matter volume) interacted with education, age, vascular risk, cortical atrophy and small vessel disease. These factors also predicted cognition. It is concluded that post-stroke cognitive outcomes are affected by pre-stroke clinical, and socio-demographic factors, where education ameliorates the impact of stroke on

cognition potentially by preserving the hippocampus, while neurovascular health potentially aggravates the cognitive impairments.

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List of Abbreviations

MRI	Magnetic Resonance Imaging
CT	Computerised tomography
DTI	Diffusion Tensor Imaging
MR	Magnetic Resonance
^{1}H-MRS	Magnetic Resonance Spectroscopy
MD	Mean Diffusivity
GM	Grey Matter
SVD	Small Vessel Disease
BUCS	Birmingham University Cognitive Study
BCoS	Birmingham University Cognitive Screen
MoCA	Montreal Cognitive Screen
HADs	Hospital Anxiety and Depression Scale
C-BCoS	Cantonese BCoS
HiPPS-CI	The Role of Hippocampal Pathology on Cognitive Impairment Study
tNAA	Total N-acetylaspartate
tCr	Total Creatine
tCh	Total Choline
NIHSS	The National Institute of Health Stroke Scale

Chapter 1: Introduction

1.1 Introduction

1.1.1 Aim of thesis

The aim of this thesis is to investigate neuropathological, and cognitive predictors of post-stroke cognitive trajectory. In this thesis, post-stroke cognition was examined by investigating cognitive profiles and trajectories of recovery. Using profiles of post-stroke cognition, this thesis first describes cognitive trajectories following stroke, then predictors of cognitive outcomes, and trajectories are examined. These predictors include social, demographic, stroke profile, vascular health, and neuropathology.

1.1.2 Background to stroke

Stroke is ranked the second leading cause of death worldwide (Lopez et al., 2006). In total, there are 1.2 million stroke survivors living in the UK, and a further 100,000 strokes occurring per year, with 950,000 stroke survivors in the UK aged 45 and over (ISD Scotland, 2017; Royal College of Physicians, 2016). The World Health Organisation term 'stroke' as a 'rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours, or leading to death, with no apparent cause other than that of vascular origin' (Aho et al., 1980). Around 85% of strokes are ischemic, which are caused by a blockage/blood clot in an artery leading to the brain, or within the vessels deep inside the brain (Intercollegiate Stroke Working Party, 2016). This disruption to the blood flow causes changes in blood flow, oedema, metabolisms, inflammation and diaschisis (Murphy & Corbett, 2009). Haemorrhagic stroke accounts for the remaining 15% of stroke incidence Haemorrhagic stroke is caused when a blood vessel bursts which causes bleeding in the brain, often in haemorrhagic stroke outcomes are more severe, and the risk of dying within three

months of stroke is elevated, when compared with ischemic stroke (Bhalla et al., 2013). In some cases, ischemic stroke can lead to haemorrhagic transformation.

Stroke causes lesions to be formed in the area of the brain that lost blood supply during the ischemic event. Lesions can be formed either the left, right hemisphere, or bilaterally, depending on the side of the artery that was blocked during the stroke. Although it is the second leading cause of death, innovative treatments such as thrombolysis and thrombectomy (Macrae & Allan, 2018), are increasing the number of people that survive ischemic stroke (Feigin et al., 2014), which is approximately 85% (Donkor, 2018). With an increase in survival rates, post-stroke cognitive outcomes, and trajectory are an important factor to be investigated in detail.

1.1.2.1 Socioeconomic impact of stroke

The impact of stroke on the individual, and subsequent loss of function depends on the stroke severity, lesion size and the brain region that was affected. The effects of the stroke can include fatigue, emotional changes, physical impairments, communication problems and cognitive impairment (Stroke Association, 2018). This can have a devastating impact on the individual, those around them and the society as a whole. The cost of stroke to the UK society is approximately £25.6 billion per year, and is expected to rise to £43 billion by the year 2025 (Stroke Association, 2018).
There are global differences in the incidence of stroke, with stroke understood to be a burden of the developed world (Donkor, 2018), however most western European countries witnessed a decline in stroke between 1975 and 2005 (Lopez et al., 2006). While in developing world an increase in the rate of stroke, is reported for Eastern Europe, North Asia, Central Africa and South Pacific (Lopez et al., 2006).

1.1.3 Risk factors of stroke

Many factors impact the incidence of stroke. The risk factors can be divided into two categories; modifiable (risk factors that relate to aspects of an individual's lifestyle, which can be managed and improved) and non-modifiable (risk factors out of the individual's control) (O'Donnell et al., 2016; Stroke Association, 2018). Modifiable risk factors relate to life style, and consist of; high blood pressure, high cholesterol, diabetes (type 2), obesity, smoking, alcohol consumption, drug use and lack of exercise (Sacco, 1995; Stroke Association, 2018). Other risk factors (non-modifiable) consist of, age, ethnicity, gender, family and individual history of heart disease, PFO (hole in heart), diabetes (type 1), atrial fibrillation, and genetic disposition (CADISIL) (Boehme et al., 2017; Sacco, 1995; Stroke Association, 2018; Tan & Markus, 2016). An international study 'Interstroke' found that ten modifiable risk factors account for 90% incidence of stroke (O'Donnell et al., 2016), which included hypertension (high blood pressure) and inactivity. The risk of stroke can be assessed using rating scales, a commonly used scale is the Framingham Stroke Profile (Wolf et al., 1991). The risk calculation includes a combination of modifiable and non-modifiable risk factors (e.g. age, gender, systolic blood pressure, antihypertensive treatment, diabetes, cardiovascular risk, smoking, atrial fibrillation) (Parmar et al., 2015).

1.2 Post-Stroke Cognition

1.2.1 Cognition

Cognition is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses" (Oxford Dictionary, 2019). Its impact on our daily function spans "information processing, mental operation, or intellectual activity such as thinking, reasoning, remembering, imagining, or learning" (Wessinger & Clapham, 2009). However, when exploring the definition of cognition,

we must understand, it is not a straightforward concept, due to its heterogeneous nature (Langhorne et al., 2011). Cognition involves multiple domains, including; attention, executive functioning, visuospatial ability, memory and language (Cumming et al., 2012). Furthermore, it is suggested that these cognitive domains overlap, and are not independent of each other (Cumming et al., 2012).

1.2.2 Cognitive Impairment

Post-stroke cognitive impairment is a common consequence of stroke, with about 20% to 80% of individuals having cognitive impairments following stroke (Sun et al., 2014). The prevalence of cognitive impairment following stroke is related to many factors, one of which is location of stroke lesion. It has been found that cognitive impairments are found in 74% of stroke survivors with cortical stroke lesions, 46% with subcortical stroke lesions, and 43% with infratentorial stroke lesions (Nys et al., 2007). Additionally lesion size, and artery location (Jaillard et al., 2010) also play a role in determining cognitive impairments; these impact the severity of the impairment, and the domains that are specifically affected (Ramsey et al., 2017).

Cognitive impairment in at least one domain is reported in about 83% of stroke patients, and impairment in more than three domains in up to 50% of stroke survivors (Jokinen et al., 2015). Commonly reported cognitive impairments following stroke include; neglect (attention), aphasia (language), and amnesia (memory) (Bickerton et al., 2015; Engelter Stefan et al., 2006; Gottesman & Hillis, 2010; Laska et al., 2001; Nys et al., 2005; Riddoch et al., 1995; Ringman et al., 2004; Tatemichi et al., 1994; Wade et al., 1988).

The relationship between cognitive function and / or impairment and the brain are typically investigated using function- lesion mapping. Early studies were driven by a single patient, or small groups relying on a description of the lesion rather than

statistical tests (Humphreys & Price, 2001; Karnath et al., 2018). For example, it has been repeatedly demonstrated that language function is supported by the left hemisphere. A left middle cerebral artery infarction causing damage within the left posterior, superior temporal gyrus and inferior frontal gyrus, can cause problems with speech production (Broca's aphasia) or speech comprehension (Wernicke's aphasia) (Cumming et al., 2012). In the past few decades the advancement of imaging acquisition, voxel-based analyses studies have become more popular (Chechlacz et al., 2018). To date, with the computational revolution, voxel-based multivariate analysis has replaced traditional mass univariate voxel-based analysis (e.g. (DeMarco & Turkeltaub, 2018; Zhang et al., 2014). However, most of these analyses focus on identifying the association of the lesion with the cognitive deficits, ignoring other neuroanatomical abnormalities often observed in these stroke cohorts.

1.2.3 Cognitive Impairment and interacting factors

Demographic profile contributes to the prevalence of post-stroke cognitive impairments. Differences in cognitive outcomes have been dictated by non-modifiable factors; such as age, with higher rates of cognitive impairment, and worse cognitive outcomes with increased age (Ebrahim et al., 1985; Sun et al., 2014; Wolfe et al., 2011). Sex differences not only exist in contributing to stroke incidence, with age related stroke higher in males, and stroke incidence in general higher in females (Reeves et al., 2008), but also in stroke outcomes (Nys et al., 2005; Petrea et al., 2009). Different rates of cognitive impairment, are observed across males and females, with worse cognitive outcomes observed in the first six months in females (Chen et al., 2016; Petrea et al., 2009).

Cognitive impairment causes lower quality of life post-stroke (Cumming et al., 2014), and can predict level of functional outcome following stroke. Bickerton and colleagues

found that initial severity of cognitive impairments following stroke (at three months), predicted functional outcomes at nine months using the Nottingham Extended Activities of Daily Living. This was found beyond the impact of anxiety, depression, and apathy (Bickerton et al., 2015). This was specifically identified with spatial attention, controlled attention and praxis domains (Bickerton et al., 2015).

Level of mood following stroke interacts with cognitive impairments, often perpetuating deficits. The prevalence of depression after stroke is approximately 29%, and it correlates with cognitive impairments (Ayerbe et al., 2018). Though it is important to note the interaction between post-stroke depression and cognitive function is complex (Lees et al., 2012; Mukherjee et al., 2006; Quinn et al., 2018). Post-stroke depression is reported to affect specific cognitive domains, such as non-verbal problem solving. This however was found in both stroke, and non-stroke populations (Kauhanen et al., 1999), suggesting this type of impairment is the consequence of depression, and not only the cause of stroke.

1.2.4 Methods of cognitive assessment

To understand cognitive impairments, it is crucial to comprehensively assess individuals following stroke. There are two documented approaches to cognitive assessment following stroke; 1) assessment of the stroke survivor when there is concern about a specific cognitive problem, and 2) screen all stroke survivors regardless of clear cognitive impairments (Quinn et al., 2018). Quinn and colleagues further document the global differences that exist on whether we should even conduct cognitive assessments in stroke (Quinn et al., 2018). UK guidelines suggest 'routine screening should be undertaken using standardised measures', similarly the American Heart Association state 'screening for cognitive deficits is recommended for all stroke patients before discharge', in contrast, the European stroke organisation comment 'assessment for

cognitive deficits appear desirable' (Quinn et al., 2018). Given the known impact of cognitive impairment on functional ability, and quality of life (Cumming et al., 2014), it seems vital to appropriately assess cognitive impairments following stroke to enable appropriate rehabilitation and support (Cicerone et al., 2005).

The UK guidelines state that all stroke patients should be screened for cognitive impairment. If deficits are identified, a detailed assessment should be carried out using valid and responsive tools before designing a treatment programme (NICE, 2013). Assessment, or screening of cognitive impairments can be performed by a variety of neuropsychological testing batteries. In post-stroke cognitive assessments, the assessment tool chosen is normally due to the preference of the department or setting (Quinn et al., 2018), and as a result there is a lack of consistency across the UK of what neuropsychological assessment tool is used, and how the results are implemented. Commonly used cognitive assessment tools include; Mini Mental State Examination (MMSE) (Folstein et al., 1983) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), although there are many more. These neuropsychological assessments are used in a variety of clinical populations including stroke and dementia, although their initial purpose was for dementia diagnosis (Folstein et al., 1983). These two assessments cover the main cognitive domains of interest (memory, language, attention), and take about 15 minutes to administer. These test batteries are not stroke specific, and as a result rely upon specific cognitive faculties, for example language ability in order to complete a memory task (Bickerton et al., 2015). Furthermore their sensitivity has come into question, with the MMSE unable to detect impairments in single cognitive domains (Lees et al., 2014), and the MoCA although found to be sensitive, lacked in specificity. It has been suggested that adapting the threshold from <26 cut off to <22 in the MoCA would enable more accurate specificity and sensitivity

when assessing post-stroke cognitive impairments (Carson et al., 2018; Demeyere et al., 2016; Lees et al., 2014).

It is vital to correctly identify those with cognitive impairments, to ensure they get adequate rehabilitation and support (Langhorne et al., 2011), however it is as equally important that we do not overestimate cognitive impairments. A recent example of the overestimation of cognitive impairment was published by Swanson and colleagues, who found high rates of cognitive impairment in government officials, suspecting a 'sonic attack' in Cuba (Swanson et al., 2018). These findings were criticised for demonstrating poor neuropsychology conduct, by using high cut off scores for diagnoses of cognitive impairment (Cortex Editorial, 2018; Della Sala & Cubelli, 2018), which demonstrates the issues surrounding cut off scores. A further issues of neuropsychology assessment tools include, not taking into consideration the individuals baseline cognition (e.g. pre stroke/ pre cognitive impairment) (Elliott et al.; Elliott et al., 2019). It should be noted that the MMSE does not take into account education level, however the MoCA does moderate the overall score for those with less than 12 years education (Nasreddine et al., 2005).

When administering neuropsychological assessments in the stroke population, careful consideration of common stroke deficits should be taken. There are some commonly observed cognitive deficits (e.g. neglect and aphasia) that could potentially impede the conduct of the assessment, and also restrict assessment of some cognitive domains leading to patients not being appropriately assessed (Pendlebury et al., 2015). For example, some patients are untestable with MoCA and MMSE, due to dysphasia, hemiparesis and acute confusion (Pendlebury et al., 2015).

One common cognitive deficit following stroke is aphasia, and it can be a barrier to completion of cognitive assessments that involve comprehension or production of language (Demeyere et al., 2016). Another is neglect, where an individual has an inattention in one side of their visual field, it poses an obvious challenge for the patient to be able to complete cognitive assessments (Demeyere et al., 2016). Neuropsychological assessments specifically designed for stroke have been developed to combat these barriers, these include the Oxford Cognitive Screen and the Birmingham Cognitive Screen (Bickerton et al., 2015; Demeyere et al., 2015; Humphreys et al., 2012). Both assessments are designed to be neglect and aphasia friendly, enabling those with cognitive deficits to be comprehensively assessed across five key cognitive domains (language, memory, attention and executive function, number and praxis). This is done by presenting items along vertical line rather than horizontal line, using large fonts and uncrowded displays, or allowing force choice response that is presented orally and in written formats. The oxford cognitive screen was found to be more sensitive than the MMSE, finding higher frequency of impairments, specifically in those with milder strokes (Mancuso et al., 2018). Pre-existing cognitive impairments due to neurological deficit such as previous stroke or dementia may also impact the rate of post-stroke cognitive impairment, and in turn impedes the ability of individuals to be assessed adequately and receive rehabilitation (Elliott et al., 2019; Kalaria & Ballard, 2001; Longley et al., 2018).

1.2.4.1 Birmingham Cognitive Screen

The Birmingham cognitive screen (BCoS) was validated in 2012 (Humphreys et al., 2012). As previously mentioned this cognitive screen was specifically designed for stroke patients, in an era when cognitive assessments were more often than not based on the assessment of cognitive impairment in dementia (Folstein et al., 1983). Due to the

issues with assessing stroke patients documented in (1.2.4), Humphreys and colleagues designed a neuropsychological assessment tool, accounting for deficits in aphasia and neglect (Bickerton et al., 2015; Humphreys et al., 2012).

The BCoS takes about 1- 2 hours to administer, depending on severity of impairment. It can be divided into two assessment sessions. It includes 23 tasks to assess five key cognitive domains: (a) attention and executive function, (b) language, (c) memory, (d) number, and (e) praxis (Humphreys et al., 2012). In brief, the attention and executive function domain includes five tasks that tap into visuospatial impairment, sustained attention and rule finding. The language domain includes six tasks: picture naming, sentence production reading and writing. The memory domain consists of four tasks that tap into long term memory (orientation), verbal episodic memory (story recall) and non-verbal episodic memory (task recall). The number domain covers reading, writing of numbers and calculation (three tasks). Finally, the praxis domain (five tasks) includes three gesture tasks, copying complex figure and interacting with a real object (assembling a torch) (Massa et al., 2015). The BCoS has been adapted to other languages and cultures including Cantonese and Mandarin (Kong et al., 2017; Pan et al., 2015).

The validation of the English version of the BCoS involved a study called The Birmingham University Cognitive Screen (BUCS). This study involved recruitment of stroke patients between November 2006 and January 2011 from 12 west-midlands hospitals. Inclusion criteria consisted (a) medically stable, within 3 months of their latest stroke, and able to give informed consent; (b) clinical diagnosis of a stroke. Exclusion criteria were (a) insufficient understanding of English; (b) inability to concentrate for 35 min per the clinical judgment of the treatment team and the researcher; and (c) pre- morbid conditions affecting cognition (e.g., dementia). This

information has been taken from Bickerton and colleagues, who fully report the recruitment to the BUCS (Bickerton et al., 2015). In total 908 stroke patients were assessed within three months of stroke, with 826 stroke patients completing 75% of the 23 tasks of the BCoS assessment. Common reasons for failure to complete all tasks were due to lack of time or fatigue. Neuropsychological assessment and lesion information was collected via clinical CT scans, along with basic demographical information (age, sex, education), see Bickerton for full consort diagram (Bickerton et al., 2015). Further information was collected on their mood, and functional ability using the Hospital Anxiety and Depression Scale, and Barthel Index (Mahoney & Barthel, 1965; Zigmond & Snaith, 1983). The Hospital anxiety and depression scale is a mood measure often used in measuring mood levels in clinical populations (Zigmond & Snaith, 1983). The hospital anxiety and depression scale is a mood measure of both depression and anxiety. This measure takes about five minutes to complete, depression and anxiety are calculated separately, and the measure contains seven questions for each. The total out of 21 is calculated, with less than seven on each indicating non-clinically relevant levels, eight- ten represents mild mood levels, 11-14 moderate and 15-21 severe. The Barthel Index (Mahoney & Barthel, 1965), was used to measure functional abilities. This measure focuses on activities of daily living, and includes questions about self-care and mobility. In total 100 points out of 10 questions would indicate complete independence, with lower scores indicating dependence in activities of daily living. In addition to the stroke patients recruited in the BUCS study, 100 healthy aged-matched controls based on the 2001 UK population consensus were also recruited. They underwent the same assessment protocol, and this provided age specific cut-offs at 5th percentile for each test (age 50-64, 65-74 and 75 and above) (Bickerton et al., 2015). In addition, a total of 380 stroke patients were followed-up at nine months,

reasons for not being followed up included refusal, death, and no response, a full list is documented in (Bickerton et al., 2015) (Also See Appendices – 1.2.4.1 for consort diagram).

The utility and predictive value of the BCoS on functional outcomes were assessed by Bickerton and colleagues, using a dataset of the two time points of < three months post-stroke and at nine months post-stroke (n=380) (Bickerton et al., 2015). Bickerton and colleagues report that deficits in executive function and attention, and praxis domains were predictive of functional outcome at nine months above initial functional ability (Bickerton et al., 2015).

The validation of the Cantonese BCoS was conducted in Guangzhou First People's Hospital in China. As reported above, the English version of the BCoS was translated in to Cantonese, and most tasks underwent direct translation. Translation of a handful of tasks in the BCoS were computed from the English version to the Chinese BCoS to ensure that they were both linguistically, and culturally appropriate (Pan et al., 2015). In the picture naming task, some of the pictures used in the English version were changed, for example the colander was removed as this is not used in Chinese cooking, and was replaced by a spatula. In the sentence, and nonword reading tasks, in these tasks appropriate use of words in these sentences, and their orthography, and phonology were assessed, and adapted to be linguistically appropriate. In the gesture production and recognition tasks, some gestures were adapted to fit the Chinese culture and daily habits. For example the gesture of hitchhiking was removed, due to it not being a common activity in the Peoples Republic of China, and replaced by a gesture of rubbing one's thumb and forefinger together to indicate money. In the word writing task, Chinese character writing is an equivalent task to (real) word writing in the English

version of the task. In total 105 stroke patients were recruited (of which 98 stroke patients were recruited between July 2013 and March 2014 are reported by (Pan et al., 2015)), inclusion criteria consisted of (a) age 50 years and above, (b) within two weeks of clinical diagnoses of stroke, with no prior stroke, (c) able to concentrate for 45 minutes, (d) able to consent for participation. Exclusion criteria included (a) past history of cognitive impairment, (b) The presence of chronic heart failure, anaemia, or other diseases that may lead to cognitive impairment. In addition, 343 healthy controls were recruited (of which 133 were reported by (Pan et al., 2015)). Criteria for inclusion required them to be aged 50 years or above, without a history of brain lesion and memory impairment (Pan et al., 2015). The control group provided 5th percentile cut off scores for the patients, for each test (age 50-64, 65-74 and 75 and above). The databases discussed here (BUCS, Mandarin and Cantonese BCoS) will be utilised in chapter two and three of this thesis.

1.3 Post-Stroke cognitive recovery

Stroke is characterised by lack of fresh oxygen to the brain due to disruption of blood flow, causing acute stress of the neurons, and other brains cells. In response to the neuronal stress, cells initiate biological processes aimed to ameliorate the dire consequences of stroke, and facilitate recovery (Allen & Bayraktutan, 2009). The biological recovery from stroke is hypothesised to be divided into three phases which are assumed to overlap to some degree (Cramer, 2008): The first stage consists of the initial impact of the stroke which involves changes in blood flow, oedema, metabolisms, inflammation and diaschisis. The second stage involves the beginning of repair in the first days after stroke which continues for several weeks (Cramer, 2008). Homeostatic mechanisms are activated during this early stage of stroke recovery (1-4 weeks), this occurs to re-establish the function of the stroke affected areas. These mechanisms

operate through the adaptation of structural and functional circuits (Murphy & Corbett, 2009). The third phase is reported to begin weeks to months following stroke, when spontaneous behavioural gains have reached a plateau, this is a stable but modifiable chronic phase (Cramer, 2008). In stage three, any recovery is likely to be driven through explicit targeted rehabilitation and/or personal motivation. However, it should be noted that the above timeline for recovery following stroke (Cramer, 2008; Murphy & Corbett, 2009) is based on animal models, and that the translation of these phases and timelines to human stroke survivors is primarily theoretical (Ward, 2017). Therefore, it is possible that homeostatic repair in humans lasts longer, enabling a longer window for plasticity induced rehabilitation intervention. To date, evidence on the impact of the initiation time of rehabilitation intervention is unclear (Ward, 2017).

Cognitive recovery following stroke is complex. There is a growing consensus that some of the observed cognitive recovery is due to biological plasticity, which occur in the first few weeks and months post-stroke (Ward, 2017). It has been suggested that spontaneous recovery occurs within this plasticity period (the first three months) (Klnsella & Ford, 1980; Wade et al., 1988). This period of heightened plasticity has been the focus of many rehabilitation clinical trials, predominantly in motor recovery (Zeiler et al., 2015) (Biernaskie et al., 2004). However, the three-month recovery window has been challenged by new findings, with recovery documented beyond one-year post-stroke (Ballester et al., 2019; Desmond et al., 1996).

1.3.1 Post-stroke cognitive trajectories

It is hypothesised that recovery trajectories are not the same for all stroke patients (Mijajlović et al., 2017). Firstly, it is important to note that not all stroke patients start at the same pre-stroke baseline cognition, this could be due to different levels of education (Parisi et al., 2012), or pre stroke cognitive impairments (Kovalenko et al., 2017). There

is some evidence suggesting higher rates of pre-stroke cognitive decline in those experiencing stroke compared with stroke free individuals (Pendlebury & Rothwell, 2009; Zheng et al., 2019). It has also been found that global cognition declines faster in stroke patients compared to non-stroke over a median period of six years (Levine et al., 2015). In an examination of self-reported recovery rates, four different rates of recovery patterns were noted: meaningful recovery, cycles of recovery and decline, ongoing disruption, and gradual ongoing decline (Hawkins et al., 2017). These self-reported trajectories seem to follow the suggested model by Mijajlović and colleagues (Mijajlović et al., 2017). They challenge the traditional view that individuals start with no previous cognitive impairments (or dementia), and following stroke either have cognitive impairments which are disabling leading to dementia diagnosis, or have no cognitive impairments (Mijajlović et al., 2017). In Figure 1 we see their suggestion of post-stroke cognitive trajectory, where individuals have varied pre-stroke cognition, and following stroke follow varying cognitive trajectories, with trajectory changes observed with further stroke insult (Mijajlović et al., 2017).

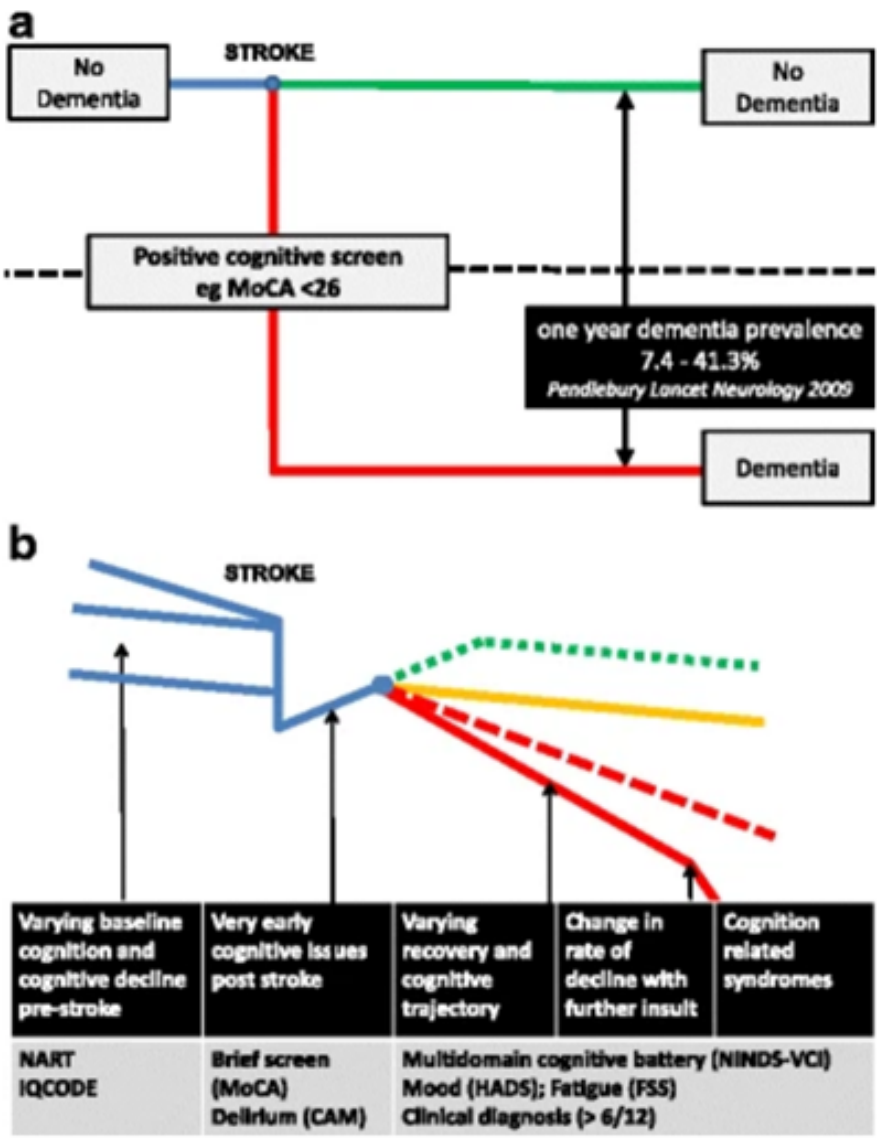


Figure 1. Mijajlović and colleagues 'Cognitive Trajectory in stroke'. A) is the traditional view of post stroke decline, B) is the real-world depiction of cognitive decline (Mijajlović et al., 2017).

There is a debate whether recovery rates differ across cognitive domains. In a ten year cohort study, there were differences in the recovery rate across cognitive domains, global cognition improved, while speed of processing decreased between one year and ten years post-stroke (Elgh & Hu, 2019). The potential for different profiles of cognitive deficits, and their co-existence, gives rise to the hypothesis that recovery rate

is inherently related to the cognitive impairments the stroke patient acquires (Ramsey et al., 2017). It has also been found that recovery rates, are similar across cognitive domains, and relate specifically to biological mechanisms such as brain networks, formation of synapses and genetic activation (Ramsey et al., 2017).

The timing of cognitive assessments when assessing recovery rates is important. It should include at least two time-points to assess change (Hurford et al., 2013). Assessments should not only be carried within the first month post-stroke, as the rate of cognitive impairments are likely to be higher within this period and would not represent the recovery for prolong durations after the stroke (Hurford et al., 2013). The severity of the initial deficit following the stroke also impacts cognitive recovery, suggesting that recovery is proportional to initial deficits (Lazar et al., 2010; Ramsey et al., 2017; Ward, 2017).

The persistence of cognitive impairments has been found to extended beyond the acute stage of stroke, with reports of cognitive impairments in up to 50% of patients > 12 months post-stroke, 22% at five years, and 21% at 14 years post-stroke (Mellon et al., 2015; Nakling et al., 2017; Nys et al., 2005). Beyond this, not only do some stroke patients not recover, and live with persistence cognitive impairments, there is evidence that the persistence of cognitive impairments actually develops into cognitive decline (Elgh & Hu, 2019; Hénon et al., 2006; Levine et al., 2015; Mijajlović et al., 2017; Pendlebury, 2009). We investigate post-stroke cognitive trajectories in chapter two, examining whether individuals recover proportionally to their initial post-stroke deficits, or whether they follow different cognitive trajectories.

1.4 Post-stroke decline

In the past decade large scale epidemiological, retrospective and prospective studies have examined the potential mechanisms that link stroke and dementia (Brainin et al., 2015; Gottesman & Hillis, 2010; Hénon, 2006; Levine et al., 2015; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009; Sahathevan et al., 2012). It is however still debated whether the two are linked causally, or just co-exist due to the similarity of risk factors e.g. vascular disease, history of stroke, metabolic abnormalities, diabetes, inflammation, genetic (APOE4) (Brainin et al., 2015; Hénon, 2006; Sahathevan et al., 2012). Due to the common shared risk factors, dementia patients also have higher risk of stroke (Hennerici, 2009), as with stroke patients being at a higher risk of developing dementia. There is some evidence to suggest that post-stroke dementia (PSD) is more common following left hemisphere stroke (Censori et al., 1996). Though this observation may be an artefact of the cognitive assessment tools which rely on language abilities (Humphreys et al., 2012). Others suggest PSD is more common following cerebral arteries stroke (Desmond et al., 2000), with stroke severity associated with increased risk for PSD (Censori et al., 1996). General brain health has been repeatedly reported to be associated with PSD, such as small vessel disease, leukoarasiosis, and focal neuronal pathology (Corriveau et al., 2016; Grau-Olivares & Arboix, 2009; Kalaria et al., 2016; Pantoni, 2010; Pantoni et al., 2005). Biomarker predictors of PSD have also been noted; such as APOE4 (Mijajlović et al., 2017). However, it has been questioned whether the stroke incidence simply aggravates pre-existing pathology, and thus causes dementia onset (Hénon et al., 2001; Hénon et al., 1997).

1.4.1 Diagnosing dementia

The fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) sets the criteria for diagnoses of dementia and its sub-types. A crucial element of the

diagnosis is the loss of functional independence due to cognitive difficulties. The DSM-IV criteria for Alzheimer's type dementia involves 1) The development of multiple cognitive deficits manifested by both memory impairment and one or more cognitive disturbances in (aphasia, apraxia, agnosia, executive functioning); 2) Criteria one and two lead to impairment in social of occupational functioning; 3) It is characterized by a gradual onset and continued cognitive decline; 4) Cognitive deficits in one are not due to central nervous conditions or systemic conditions; 5) Deficits do not occur exclusively during delirium and 6) The disturbance is not better accounted for by another disorder (American Psychiatric Association, 2000). Similarly, the DSM-IV criteria for vascular dementia includes 1) Memory impairment; 2) One or more cognitive disturbances in (aphasia, apraxia, agnosia, executive functioning); 3) Criteria one and two lead to impairment in social of occupational functioning; 4) Focal neurological signs and symptoms and 5) The deficits do not occur exclusively during delirium (American Psychiatric Association, 2000). Importantly in the diagnoses of vascular dementia using DSM-IV criterion, there is no requirement to measure it as a progressive decline or gradual onset, for example assessment of cognition across more than one time point. Thus, suggesting that vascular dementia can be a diagnoses of stable impairment and not progressive, as a measurement at one time-point is a cognitive outcome.

Importantly, many studies examining post-stroke dementia or decline noted specifically within this thesis will have been published in the era of DSM-IV. The DSM-5 was published in 2013, and some adaptions to the criteria for vascular dementia were made, such as removal of evidence of memory impairment in vascular dementia diagnoses (Sachdev et al., 2019).

Interestingly, in a study examining the differences between DSM-IV and DSM-5, expert clinical diagnosis of dementia using DSM-5 criteria was in line with DSM-IV for 90% of cases. However there was a 127% increase of dementia diagnoses using DSM-5 (Eramudugolla et al., 2017).

There is heated debate over the comorbidity of the two most common dementias; Alzheimer's disease and vascular dementia, in their similarity and difference (de la Torre, 2004). The DSM-5 criterion diagnoses for both overlap heavily. In their purest form, they both have different cause's e.g. Alzheimer's disease with plaque, and vascular dementia with infarctions. But it is suggested that they both sit on a continuum, with overlapping features such as cholinergic deficit (Kalaria, 2002). More recently Alzheimer's disease has been argued to be associated with vascular risk factors, and vascular brain health (Snyder et al., 2015).

Due to the complex aetiology of cognition following stroke, involving both non-vascular neurodegenerative processes, and stroke insult there are a variety of definitions and classifications to describe post-stroke cognitive impairment and post-stroke cognitive decline (Mijajlović et al., 2017). These not exclusively include; mild cognitive impairment (MCI), vascular cognitive impairment (VCI), post-stroke dementia (PSD), and delayed post-stroke dementia (DD). There is still lacking a consensus on terminology that best describes a cognitive impairment following stroke that progressively worsens, and a cognitive impairment that is not progressive. We will briefly describe some different classification labels below.

1.4.1.1 Mild Cognitive Impairment

Mild cognitive impairment is defined as having abnormal memory for age, but an ability to carry out activities of daily living, with no other cognitive domains affected

(Petersen et al., 1999). It is identified as presenting differently to healthy ageing, and as a pre-cursor of Alzheimer's disease. In some cases it marks the beginning of progressive decline in cognition at a faster rate than healthy ageing controls; while in others mild cognitive impairments are reversible or stable (Petersen et al., 1999).

1.4.1.2 Vascular cognitive impairment

Vascular cognitive impairment was previously called multi-infarct dementia (Gorelick et al., 2011), however this term has been coined to describe the spectrum of cognitive disorders that are a result of cerebral vascular brain injury, not stroke in isolation (Gorelick et al., 2011). This is said to include impairment across the spectrum of mild cognitive impairment through to fully developed dementia (Dichgans & Leys, 2017), and often is a label used to identify those who are likely to develop vascular dementia (Petersen et al., 1999).

1.4.1.3 Post-stroke dementia

Mijajlović and colleagues propose the use of PSD for any dementia that develops following a cerebrovascular incident (Mijajlović et al., 2017). Due to the complex neuropathological processes that occur, the term PSD does not align itself to one vascular process, but instead encompasses all vascular insults and also neurodegenerative processes (Biernaskie et al., 2004; Brainin et al., 2015; Mijajlović et al., 2017).

1.4.1.4 Delayed post-stroke dementia

It is suggested that following stroke, an individual presents with a cognitive impairment or dementia which is present immediately following stroke (within three months). However delayed dementia, includes cognitive deficits or cognitive decline which was

not present immediately following stroke. It is classified as a presentation of cognitive decline following stroke beyond three months (Kalaria et al., 2016; Mok et al., 2016).

1.4.2 How prevalent is post-stroke dementia?

It is estimated that around one third of stroke survivors develop dementia (Brainin et al., 2015). The prevalence of dementia in stroke survivors is almost double than that in stroke free individuals (Brainin et al., 2015). Evidence suggests that up to one in three stroke survivors are at risk of developing vascular dementia within five years of stroke (Leys et al., 2005). Although it has been debated that the prevalence of PSD is overestimated, potentially due to the assessment tool used (Rasquin et al., 2005), or the diagnosis and/or definition of post-stroke cognitive impairment or post-stroke dementia (Petersen, 2004). The diagnoses of vascular dementia which is often applied to those experiencing cognitive issues following stroke, would not be an applicable diagnoses classification for stroke survivors. It involves having a loss of occupational ability, which may be due in fact to physical impairments such as hemiparesis following stroke.

1.4.3 Diagnoses of post-stroke cognitive decline

As noted in 1.4.1, most commonly used diagnoses tools are the DSM-IV and DSM-5 for dementia subtypes in clinical practice. The terms taken from these tools are often used interchangeably across research studies, which often leads to confusion as to what type of cognitive impairment, or cognitive decline authors are specifically referring to. Often the MoCA is used to demonstrate post-stroke dementia classification < 26 out of 30 (Mijajlović et al., 2017), however as previously described in 1.2.4, there are many issues surrounding the use of this tool and its sensitivity in stroke populations. The different tools used to diagnose post-stroke cognitive impairment will in turn provide different rates of incidence. It is suggested that using the diagnostic criteria that we use for dementia, may not be applicable to stroke patients experiencing cognitive decline

(Mijajlović et al., 2017), as some of those experiencing cognitive impairment may not experience the limitations of daily activities associated with dementia (Petersen et al., 1999). On the other hand, the diagnostic criteria commonly used for dementia includes loss of occupational function, which is not an appropriate diagnostic criterion for the stroke population, where loss of function is common in this group as a result of hemiparesis, and other motor deficits (Mijajlović et al., 2017). The VASCOG criteria for the diagnoses of vascular cognitive disorders may be more applicable to the stroke population, as it requires neuroimaging evidence, although it bears strong similarities to the DSM-5 (Sachdev et al., 2014; Sachdev et al., 2019). This VASCOG criteria was found to be more sensitive and specific compared with older criteria for vascular dementia (Sachdev et al., 2014; Sachdev et al., 2019).

As mentioned previously, in order to measure trajectories, whether it be in terms of recovery or decline –more than one time-point is required. With only one time point measurement, it is difficult to differentiate progressive cognitive decline, from stable cognitive impairment. The global understanding is that dementia is progressive decline. However, the DSM criterion lacks measurement of change (e.g. no criteria requires repeat assessment at six months interval), suggesting that evidence of cognitive impairment at one time-point is enough to diagnose post-stroke dementia. Mijajlović and colleagues suggest a diagnoses of dementia at six months post-stroke (one time point), and not before is appropriate (Mijajlović et al., 2017). Thus, it seems that those experiencing cognitive impairment at six months would be given a post-stroke dementia diagnoses, regardless of the nature, and expected progression. Based on this criteria it may not be surprising that over a third of stroke patients develop dementia (Brainin et al., 2015), due to the fact that stroke often causes cognitive impairments. Though this diagnosis does not suggest that these patients will keep declining in rates faster than

expected in normal aging. Furthermore, increased rates of dementia following stoke do not take into consideration those already with dementia, estimated to be about 10% (Mijajlović et al., 2017).

DSM philosophy is that diagnoses are based on clinical symptoms. Therefore, DSM criteria for dementia diagnoses does not account for the aetiology root cause of the issue, or the long-term prognosis, only the current cognitive impairment and functionality. Due to this, it does not take into account pre-stroke cognitive condition, which is important to understand the condition and future rehabilitation potential of the patient.

How useful is a post-stroke dementia label for prognosis, and planning of future care? It does not predict whether the cognitive impairment is persistent or progressive. Since providing, and justifying rehabilitation in a time pressured work environment is challenging (Longley et al., 2018), a diagnosis label of dementia may exclude individuals from rehabilitation programs. A further issue regarding diagnoses, not excluding the complex aetiology, is the timing of diagnoses. It is possible that the cerebrovascular incident exasperates previous symptoms, or just simply alerts healthcare professionals to an issue that preceded the ischemic incident (Hénon et al., 2001; Hénon et al., 1997).

In summary, even though many studies have attempted to clarify post-stroke cognition in terms of dementia, the range of classification criteria, and tools out in the field make it difficult to understand and follow. For researchers examining post-stroke cognition, looking at recovery and/ or decline, more consensus on ‘dementia’, and whether it is a stable cognitive impairment or progressive would be useful, not only for replication across studies, but also clinically for the patients themselves.

For the purpose of this thesis cognitive deficit following stroke will be referred to as post-stroke cognitive impairments. When measuring only one time point, the cognitive state will be labelled as post-stroke cognitive outcome. When cognition is measured at two time points, and the difference between these two time points is assessed, it will be described as post-stroke cognitive trajectory. The thesis describes groups of patients that may be experiencing progressive cognitive decline. However, it does not attempt to classify them as having developed vascular or post-stroke dementia.

1.5 Predictors of post-stroke cognitive trajectory

1.5.1 Sociodemographic

1.5.1.1 Demographic

Sociodemographic status typically includes key information about the individuals; such as age, sex, ethnicity, socio-economic status, life style and education level. Sociodemographic profile is inherently related to stroke incidence due to its interaction with our overall health (Kleindorfer, 2009). As a result, it is not surprising that it is has also been found to be a predictor of cognition following stroke. Age has been reported to be an important determining factor for onset of cognitive decline following stroke (Ebrahim et al., 1985; Gorelick et al., 2011; Leys et al., 2005; Sun et al., 2014; Wolfe et al., 2011). And as previously reported (1.2.3), differences are observed in cognitive recovery for females and males, (Levine et al., 2015; Mahon et al., 2017; Nys et al., 2005).

1.5.1.2 Education

A modifiable predictor of cognitive outcome is education level. Lower education level predicts worse outcomes when specifically examining cognitive outcomes (Chaudhari et al., 2014; Chen et al., 2016; Elkins et al., 2006; Leys et al., 2005; Parisi et al., 2012).

The theoretical underpinnings of why higher education of an individual may protect against worse cognitive outcomes, is shrouded in cognitive/ brain reserve (Nunnari et al., 2014). Cognitive brain reserve is a concept that accounts for potential 'resilience' of an individual against cognitive ageing, and ageing related diseases. This concept can be broken down into different aspects of potential resilience, one of which is cognitive reserve, the other is brain reserve. Cognitive reserve refers to 'the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities, or day to day function to brain ageing, pathology, or insult' (Stern et al., 2018). In the current thesis, cognitive reserve would refer to the resilience of the individual brain to neurological insult (stroke), and possible decline. For each individual, cognitive reserve is determined by cognitive and functional brain processes. Of which are both at the influence of individual differences, made up of innate (e.g genetics), and lifetime exposures (e.g education). Stern and colleagues describe cognitive reserve to be a malleable model, of which cognitive and brain processes can be dynamic, and can cope with brain changes or damage (Stern et al., 2018). For example, when examining Alzheimer's disease in post-mortem studies, an observation is made for those with preserved functioning in those with higher education level, but with evidence of severe Alzheimer's pathology (Stern et al., 2018). A second aspect to note is brain reserve. Brain reserve refers specifically to the pathology of the brain, including number of neurons and synapses (Stern et al., 2018). Its individual structural characteristics allow some to cope better with insult, and age-related changes. Brain reserve is a fixed construct; however life experience can add to brain reserve. Stern refers to cognitive reserve as the software, and brain reserve as the hardware (Stern et al., 2018).

In chapter three we examine cognitive reserve using level of education as a measure of cognitive reserve. Education and its influence on ageing and cognitive decline/ dementia

has been well documented (Brayne et al., 2010; Brayne et al., 2006; Brayne & Miller, 2017; Christensen et al., 2007; Farfel et al., 2013; Pinter et al., 2015; Skoog et al., 2017) (Zieren et al., 2013). Additionally it has been found to correlate with post-stroke cognition (Mirza et al., 2016; Sun et al., 2014; Withall et al., 2009). With level of formal education (measured in either level of education, or years), having a positive and 'protective' effect on cognition following stroke, with increased education. Del Ser describes education as a marker of higher socioeconomic status, which in turn related to a more advantaged and health lifestyle, with also less exposure to environmental toxins (Del Ser et al., 1999). This combination may protect individuals at a higher level against brain diseases.

To investigate the effects of cognitive reserve (resilience), on cognitive outcomes following stroke, education was deemed an appropriate, and accessible measure. In chapter three, the cognitive resilience of an individual following an insult (stroke), and the abilities of individuals to overcome this insult was measured by years in formal education. To establish the impact of formal education years on cognitive resilience across three key groups 1) Ageing, 2) Post-stroke outcome, 3) Post-stroke recovery at nine months, and across two countries 1) U.K, 2) China.

1.5.2 Clinical profile

The clinical risk factors of stroke (Boehme et al., 2017; Stroke Association, 2018; Tan & Markus, 2016), are in turn predictors of post-stroke cognitive outcomes. For example, diabetes, hypertension and cholesterol have all been identified as determinants of worse cognitive outcomes, and specifically risk factors for a decline cognitive trajectory following stroke (Censori et al., 1996; Chaudhari et al., 2014; Leys et al., 2005). Additionally, another condition increasing stroke incidence is atrial fibrillation. It has

been identified as a predictor of poor cognitive prognosis, and cognitive trajectory following stroke (Censori et al., 1996; Leys et al., 2005).

1.5.3 Stroke profile

1.5.3.1 Stroke severity

Individual stroke profiles are a reported predictor of cognitive recovery following stroke. Stroke lesion location has been found to be a strong predictor of cognitive outcome (Chaudhari et al., 2014; Leys et al., 2005; Munsch et al., 2016; Pendlebury & Rothwell, 2009). Initial stroke severity as measured by NIHSS, was also a predictor of cognitive outcome (Chaudhari et al., 2014; Leys et al., 2005). And there is evidence that history of previous stroke can further impact cognitive outcome following subsequent ischemic events (Chaudhari et al., 2014; Chen et al., 2016; Leys et al., 2005). Recurrent stroke is also argued to be an important predictor for cognitive recovery trajectories, with a third of those with recurrent stroke being identified as having dementia (Pendlebury & Rothwell, 2009).

1.5.3.2 Lesion severity

Stroke severity is a predictor of outcome and cognitive recovery trajectory, so inherently lesion profile contributes. Evidence of strategic single infarcts to the thalamus, angular gyrus, caudate, globus pallidus, basal forebrain or hippocampus have been found to cause post-stroke dementia, affecting post-stroke cognitive trajectory. Furthermore lesions in this region (subcortical circuit) are associated with rapid cognitive decline (Moorhouse & Rockwood, 2008). Territorial infarct was also identified as an independent predictor of cognitive impairment when measured at one month, six and 12 months following stroke (Rasquin et al., 2004).

1.5.3.3 Lesion location

Lesion location as with lesion severity has been dubbed a window of opportunity to predict cognitive outcomes and recovery. When determining recovery from aphasia, it has been repeatedly reported that lesion location, is as reliable at predicting recovery as lesion volume and severity of impairment (Plowman et al., 2012). Furthermore, lesion location has been used to map recovery trajectories in aphasia, in collaboration with time since stroke and lesion volume (Hope et al., 2013).

1.5.4 Neuropathological

1.5.4.1 Brain Health

Beyond the individual profile of stroke, and its neurological impact on cognitive trajectory, additional neuropathological factors impact cognitive trajectories. Small vessel disease has been found to be an independent predictor of worse cognitive outcomes. In stroke patients with small vessel disease, and lower brain volume, poorer executive function was observed compared to controls (Lawrence et al., 2013). Evidence of small vessel disease in the post-stroke brain, indicates poor brain health, and in turn impacts recovery, putting those with small vessel disease at risk of cognitive decline following stroke insult (Mijajlović et al., 2017; Mok et al., 2016).

Another indicator of poor brain health, or cerebrovascular insult is white matter changes; like small vessel disease, those with white matter changes are at increased risk for cognitive decline following stroke (Hennerici, 2009; Leys et al., 2005).

Global grey matter atrophy has been observed in those with post-stroke cognitive impairments compared to those without cognitive impairments (Stebbins et al., 2008). Specifically, medial temporal lobe atrophy, is a predictor of worse cognitive outcomes in the short-term following stroke, and is also associated with cognitive decline

(Brodtmann et al., 2012; Casolla et al., 2018; Chen et al., 2016; Leys et al., 2005; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009).

1.5.4.2 Methods of magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive method of measuring a multitude of properties within the brain, and can provide detailed information on anatomy, neuronal activity, connectivity and pathologies (Jenkinson, 2018). MRI can be used to capture a wide variety of information, by adjusting the acquisition parameters.

The basis of the acquisition is on atomic nuclei, sometimes referred to as spins, that act as bar magnets, and interact with magnetic fields which allows us to measure, and manipulate the nuclei magnetic state. Specifically in MRI, it is the hydrogen nuclei within the water molecules of the tissue, that are targeted and manipulated. In order to manipulate these molecules, MRI uses coils which are made of electronically conducting wire. When electric currents are passed through a coil, it creates a magnetic field. Shifting these magnetic fields within a coil induces electrical currents, both of which are important in the function of MRI.

The M in MRI stands for magnetic. The strength of MRI is defined by the B_0 field (the filed that is parallel to the tube). The magnetic field (B_0 field) is created from a large superconducting coil, which is always active, and is continually cooled by liquid helium. In MRI there are varying gradients of magnetic strength, which is measured in tesla, and can vary for example from 1T to 7T, with 7 being the strongest. The ability to affect hydrogen nuclei, depends on a strength of magnetic field, where the bar magnets of nuclei will point in the same direction – along the magnetic field. In a none-magnetic environment the sum of the hydrogen magnetic field is nearly zero, where each passes along different angles.

It is common that the magnetic field experiences external interferences, which we call non-uniformities. To control for these uniformities in the B_0 field, we can utilise other

coils; called ‘shimming coils’, which can control for imaging artefacts. These shimming coils are applied at the start of the scanning, and this is called shimming.

The R in MRI stands for resonance, which is the B_1 field. The bar magnets in the hydrogen nuclei when in a strong magnetic field, rotate round the axis of the B_0 field. The frequency of the rotation is proportional to the strength of the magnetic field. This rotation interaction creates oscillating fields- the B_1 fields. We have an ability to detect and externally manipulate these oscillating fields. We refer to this resonance frequency as Lamor frequency.

The I in MRI stands for imaging. So far, we have the MR signal, which originates from contributions from all the nuclei which are identified within the bore of the scanner. To determine the where the MR signal is coming from, we can separate out the difference signal frequencies in order to determine the location of the frequency. Gradient coils are used at this stage to purposefully add extra carefully controlled magnetic fields with varying locations. By adding this extra field during acquisition of signal measurements, it allows us to measure how strong a signal is and also work out where the signal is originating from, and thus enables us to form an image.

The I in MRI allows us to acquire an image, and if we manipulate the MR then we can acquire different types of images. There are characteristics is are similar to the 2D version of pixels. The resolution of the image refers to the voxel size. The voxel size, and number of voxels multiplied together create the field of view (FOV).

When we acquire structural images it shows the anatomy of the brain; optimising the separation of grey matter, white matter and cerebrospinal fluid. Most commonly these are T1-weighted images, in these images the most important principles are proton density, and relaxation processes. For example for T1-weighted images, this is T_1

relaxation constants. These properties are determined by the microscopic environment in the water molecules, and are different within the three tissue properties that can be identified in structural images. The proton density is simply the concentration of water within the molecule. Both the proton density, and relaxation constants allow us to obtain information about different structural properties within the brain.

Reduction in volume of grey matter often correlates with ageing, and cognitive decline (Raz & Rodrigue, 2006). Grey matter volume can be measured with MRI from T1-weighted images (Amiri et al., 2018), as this sequence gives optimal contrast between the three tissue types. Computing a regional volume can be done in two ways. The first is manually delineating a region (e.g. tracing the hippocampus borders) then counting how many voxels are within the traced area.

A second is to use an automated approach to quantifying grey matter volume. These are often combined with standardised atlases to classify tissues types across each brain structure (Amiri et al., 2018; Ashburner & Friston, 2005; Ashburner & Ridgway, 2013). The unified-segmentation algorithm is a common automated approach to classifying tissues within the brain, the approach uses probability maps to determine the probability of the tissue type within each voxel (Whitwell, 2009). The toolbox CAT12 is an improved version of the above algorithm, where the main aim is to study local grey matter volume changes. The output of this procedure is a probability map of grey matter in the normalized space. The intensity of each voxel is weighed by the amount of transformation a region has undergone to fit it to the normalized space. Such that if the hippocampus had to be stretched to better fit the a-priori tissue probability map, then the signal in those stretched voxels will be reduced to represent this deformation. These are called modulated grey matter images. Following the automated method of tissue type quantification, regions of interest (ROI) across all brain regions, can be selected using

automated ROI atlases such as the SPM anatomy toolbox (Eickhoff et al., 2005) defined by the Montreal neurological institute (MNI) (Garrison et al., 2015; Mazziotta et al., 1995).

Both approaches are commonly used to determine grey matter volume. It is important to note that it is yet unclear what the physiological contributors to the grey matter signal measured by MRI are, and consequently what the meaning of the signal intensity in the tissue probability map is (Eriksson et al., 2009). This is because MRI, measures relative level of disturbances to the local magnetic field, and there are many factors that can affect this. In contrast, Computerised Tomography (CT) has a very clear physiological meaning, as CT measures the density of the tissue, but this is the only property that can be measured by CT.

Diffusion MRI (dMRI) also focuses on the water molecules, and specifically their movement (Brownian motion). In dMRI we can measure how much molecules move, and also in which direction and over what time period. Typically water molecules diffuse along the same direction of the axons, and the direction they are orientated. In diffusion imaging there are diffusion-encoding gradients, these gradients change the magnetic field strongly enough in one direction in space. The water molecules that do not mirror this direction, are unaffected by the gradients. Those that do move in the same direction, have their resonant frequency changed, which in turn leads to changes in phase, which is important for the diffusion signal. The more the movement (diffusion) in the same direction as the gradient, the smaller the signal will be. Additionally we can collect information on the timing, and strength of the gradients, which together make the b-value. Diffusion represents displacement of water molecules within a single voxel (Le Bihan et al., 2001). Mean diffusivity of a voxel provides information about the molecular diffusion rate (e.g. how far on average a molecule

travelled in a given time) (Soares et al., 2013). Depending on the tissue type, diffusion rates differ. In grey matter tissue diffusivity is less anisotropic compared to white matter tissue, and in CSF it is isotropic. Fluctuations in values of diffusion often indicate structural changes within the brain, with higher mean diffusivity values indicating damaged or impaired fibres, and loss of directionality in movement of molecules (Soares et al., 2013). Due to a low signal to noise ratio in diffusion weighted imaging, it is vulnerable to motion artefacts, although software can be used to account for this in the data (Andersson & Sotiropoulos, 2016), only in extreme cases would the data need to be removed from the analyses.

MRI can also be used to measured magnetic resonance spectroscopy (^{1}H-MRS). In contrast to most methods of MRI acquisition, spectroscopy does not utilise the water molecules to form the image, instead it uses other molecules, such as NAA, Choline etc. Specifically these molecules have lower concentrations than water (Oz, 2016). This acquisition relies upon a function called chemical shift. Where the signal in each type of molecule causes a shift in the frequency, allowing us to measure the contribution of each molecule and its quantification. The most commonly used approach to this method, is single-voxel spectroscopy (Wilson, Andronesi, et al., 2019). The signal to noise ratio is lower as a result of this, compared with many other MRI methods (Oz, 2016). Spectra of metabolites often overlap each other (Oz, 2016), so to obtain more reliable absolute measurements of metabolites, metabolite ratios are calculated (Wilson, Andronesi, et al., 2019). Different metabolites each provide different information. The metabolites have different concentrations in different tissue types, hence it is important to account for these differences in the analysis (e.g. weight the signal by the amount of grey matter in the voxel). For example, neuronal health can be measured using (N-acetylaspartate), demyelination/increased membrane turnover using (Choline), and

decreased energy metabolism with (N-acetylaspartate and Creatine). This method has historically been used for the identification of tumours (Preul et al., 1996) due to the indication of metabolic changes in abnormal brain tissue. However, more recently it has been used in identification of neurodegeneration (Seo et al., 2012; Tumati et al., 2013), and also temporal changes within brain lesions following stroke (Muñoz Maniega et al., 2008).

1.5.4.3 Hippocampal pathology

The hippocampus is situated within the medial-temporal lobe, its robustness and health is often linked with neurodegeneration. The hippocampus is one of the first areas of the brain to undergo damage with the onset of Alzheimer type dementia. The progression of Alzheimer's, and its subtypes are associated with progressive decrease in hippocampal volume (Vijayakumar & Vijayakumar, 2012).

As documented in section 1.4 we describe the relation between stroke, and onset of cognitive decline, or as some describe it; post-stroke dementia. There is sample of convincing literature on the link between dementia, specifically Alzheimer's and the hippocampus (Casolla et al., 2018; Chen et al., 2016; Kliper et al., 2013; Leys et al., 2005; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009; Schaapsmeerders et al., 2015; Sun et al., 2014). The hippocampus is a known vulnerable structure in the disease of dementia and ageing.

If we want to explore potential drivers of post stroke dementia, then examining the pathology of the hippocampus in the post-stroke brain may provide an insight into the pathological onset of post-stroke dementia. Some studies have implicated the hippocampus as an important structure in post-stroke dementia, with decreased hippocampal volume following stroke evident even within the early stages post-stroke

(Brodtmann et al., 2012; Werden et al., 2017). These studies are described in more detail in Chapter four.

In the post-stroke brain, there has been reported neuronal loss in the hippocampus, causing more severe cognitive outcomes (Kliper et al., 2013; Schaapsmeerders et al., 2015; Sun et al., 2014). Atrophy in this structure has been associated poor cognitive outcomes, and an increased risk of cognitive decline following stroke (Casolla et al., 2018; Chen et al., 2016; Leys et al., 2005; Mijajlović et al., 2017; Pendlebury & Rothwell, 2009). Hippocampal mean diffusivity has been found to predict memory abilities following stroke independent of lesion volume (Hosseini et al., 2017; Kliper et al., 2013). Kliper and colleagues further suggest that mean diffusivity precedes volumetric changes in the hippocampus, making it a potential biomarker for early cognitive decline following stroke (Kliper et al., 2016).

Metabolic changes have been observed in dementia, where N-acetylaspartate (NAA) is found to be lower in Alzheimer's Disease (Kantarci, 2007). Decreased NAA and Cr have been found to predict dementia onset (Metastasio et al., 2006). Specifically in the hippocampus, and there is evidence of lower NAA in Alzheimer 's disease, and subcortical ischemic vascular dementia (Shiino et al., 2012), with increased Ch in the hippocampus in Alzheimer's disease progression compared to healthy controls. Following stroke, Ross and colleagues examined the predictive value of metabolites (NAA/Cr) in the frontal white matter, and found that it predicted cognitive decline in the first 12 months following stroke (Ross et al., 2006). Focusing on the hippocampus of middle cerebral artery stroke patients in the chronic stage, Tang and colleagues show that relative to controls (matched on age and education), patients' hippocampus was reduced in volume, and also the ratio between NAA and creatinine (Tang et al., 2012). Patients with larger hippocampi volume reduction also showed cognitive deficits (Tang

et al., 2012). It is worth noting that the Tang and colleagues did not comment of whether they accounted for volume changes in their spectroscopy analyses (Tang et al., 2012).

In Chapter four, DTI, Spectroscopy, and volumetric measurements were taken using MRI. Please see section 1.5.4.2 for methodological description of the MR modalities used in Chapter four. We investigated hippocampal pathology using these three modalities, allowing us to examine whether hippocampal changes are evident in our stroke cohort, as with other stroke cohorts reported in studies examining hippocampal pathology within three months of stroke (Brodtmann et al., 2012; Haque et al., 2019; Werden et al., 2017). DTI and volumetric measurement of the non- lesioned hippocampus in the post stroke brain has been previously examined. Where decreased volume, and increased levels of mean diffusivity was identified in the post-stroke hippocampus (as discussed above). Additionally, both lowered volume of the hippocampus, and increased mean diffusivity of the hippocampus correlated with lowered cognition. These studies are described in more detail in Chapter four.

We utilised a third MR modality – Magnetic Resonance Spectroscopy (MRS), which has previously focused on chemical levels (metabolites) within the lesion site following stroke. MRS has also been used to examine chemical changes in cognitive decline, with metabolite NAA highly implicated in the process of cognitive decline (Kantarci, 2007; Liang et al., 2017; Targosz-Gajniak et al., 2013). We will mirror the use of this modality as previously done in dementia research, and like the DTI and volumetric measurements, explore whether hippocampal pathology is evident in our stroke cohort, as it is with others in stroke cohorts and in cognitive decline research. The MR modalities are described in more detail in section 1.5.4.2. Using all three modalities provides a detailed profile of hippocampal pathology following stroke.

1.6 Summary

The literature suggests that not all stroke patients recover in the same way, and that some are at risk of cognitive decline. The studies advocating cognitive decline following stroke use varied definitions of what constitutes cognitive decline, with a large number of definitions, and lack of clarity (Mijajlović et al., 2017). A large proportion of studies comment on cognitive decline examining only one cognitive domain, and using a brief cognitive screens (Suzuki et al., 2013). When establishing potential post-stroke cognitive trajectories there is a necessity to assess two or more time-points, in order to establish cognitive change over time. In order to understand the potential cognitive trajectories, it is important to consider all these factors; the whole profile of cognition using detailed cognitive assessments across multiple domains, and measuring change across more than one time point.

The suggested factors affecting recovery trajectories, and influencing cognitive decline following stroke are wide ranging; from socio and clinical demographics, to stroke profile and overall brain health. Epidemiological and longitudinal cohort studies have attempted to answer the impact of these factors on post-stroke cognitive impairment, with only a handful examining their impact on cognitive trajectories using a detailed cognitive profiling approach (Ramsey et al., 2017).

1.7 Outline of thesis

The current thesis aimed to describe cognitive trajectories following stroke, and examine potential predictors of cognitive outcome, and trajectories. It used data from two existing databases: the Birmingham Cognitive Screen Study (BUCS) collected in the UK, and the C-BCoS collected in China. It also reports newly collected data as part of the HiPPS-CI study which aimed to examine the role of hippocampal pathology in

post-stroke cognitive impairment. Stroke cohorts across all three studies represented stroke patients with mild-moderate severity strokes. Recruitment was as inclusive as possible with minimal exclusion criteria to provide a representative sample of these types of survivors. Across all three chapters (two-four), the BCoS was used to provide a detailed cognitive profile of patients within and across cognitive domains.

1.8 Chapter Outline

Chapter two aimed to answer the question; does the proportional recovery rule (recovery of a percentage of deficits proportional to initial post-stroke deficit) exist in cognition, as it does with motor recovery? In other words, can short term cognitive outcomes following stroke be used to predict long term outcome. In motor recovery it has been argued that in the long term, recovery is proportional to initial deficits. We also examined whether all stroke patients follow the proportional recovery rule, and if they do not, what other trajectories of cognitive recovery exist in post-stroke cognition?. In chapter two, Rosanna Laverick (RL) was presented with the BUCS database. The database contained both baseline and follow up cognitive data (n=380), which was somewhat organised. RL further cleaned and organised the data, and additionally computed more details. RL calculated the number of missing data (number of tasks per individual), and consequently extracted only individuals that reached the data inclusion threshold. In those with a small number of missing data, a conservative approach was taken by inputting the group average. RL then calculated the number of intact tasks, and deviation scores for each patient, and deviation scores only for controls. The statistics within the chapter (e.g proportional recovery calculations) were also calculated by RL, and all figurative presentations were also completed by RL. RL wrote the chapter in manuscript format, with draft reviews from supervisors and collaborators. This chapter has been submitted for review: **Laverick R**, A.A Hosseini, W-L Bickerton, N

Demeyere, D Sims And P Rotshtein. Recovery trajectories following stroke: the proportional recovery rule in cognition. *(Submitted)*. Please note that this chapter has been submitted to a journal as a research article, and has been presented at national conferences.

Chapter three investigated the protective factor of education level on cognition across and within cognitive domains. The impact of education on cognition was examined in relation to other clinical-demographic factors such as age, mood and functional independence. The relationship between education and cognition was examined in three different contexts. Firstly, we examined whether education predicted level of cognition in an ageing population across, and within UK and China cohorts. Secondly, we assessed whether years of education can determine cognitive outcomes within three months of stroke across, and within UK and China cohorts. And finally, expand our understanding of the predictive value of level of education on cognitive outcomes at nine months post-stroke, and its impact on recovery rates between three, and nine months post-stroke. In chapter three, Rosanna Laverick (RL) utilised the work computed in chapter two with the BUCS database, with the addition of >500 additional data points of baseline cognition for the UK cohort. As with chapter two, RL calculated the same information for these additional data points. In addition to the data from the BUCS database, data from the C-BCoS was also included. RL organised and translated this database from Cantonese and Mandarin, and organised in accordance with the BUCS database format. Following database cohesion, the same calculations as mentioned above were also computed across the C-BCoS database, with both patients and controls. The statistics within the chapter were also computed by RL, and all figurative presentations were completed by RL. RL wrote the chapter in manuscript format, with draft reviews from supervisors and collaborators. This chapter has been

submitted for review: **Rosanna Laverick,** Haobo Chen, Johnny King Lau, Wai-Ling Bickerton, Akram A. Hosseini, Nele Demeyere, Don Sims, Jin Zhou, Xiaoping Pan, Pia Rotshtein. Education improves short and long-term stroke cognitive outcomes in UK and China. *(Submitted).* Please note that this chapter has been submitted to a journal as a research article, and has been presented at international and national conferences.

Chapter four used neuroimaging methods to assess whether stroke causes abnormal hippocampal pathology in the first three months following stroke. Secondly, we aimed to examine the relationship between abnormal hippocampal pathology, and post-stroke cognition. Neuroimaging methods used for these analyses included; mean diffusivity of the hippocampus using diffusion tensor imaging, grey matter voxel intensity of the hippocampus using T1-weighted images, and metabolite levels using magnetic resonance spectroscopy. Chapter four included a newly collected database from the HiPPS-CI project. The project (HiPPS-CI) presented in chapter four, was initiated in 2015 prior to the start of this PhD. At the start of the PhD project, ethical approval was obtained, and recruitment of participants and their assessments had begun (n=10) at one NHS site. Following the start of the PhD, RL took over responsibility for this project, as trial manager. This included ethical amendments, of which focused on increasing recruitment size. RL successfully assisted in obtaining clinical research network portfolio adoption of the project, and the addition of a second recruiting NHS site. Management of the project involved ethical, recruitment, data management, and assessments of individuals (Cognitive and MRI). Two undergraduate students, and one masters' student assisted with the data collection at different time points in the duration of the project. Data collection, data cleaning, and organisation of data for both cognitive and imaging data by RL. Analysis of imaging and cognitive data was completed RL, and in the case of the imaging data the pre-processing, modelling and statistics. The

writing of this chapter was completed by RL, with reviews by supervisors. Please note that this has been presented in part at national conferences.

Chapter 2: Recovery trajectories following stroke: *the proportional recovery rule in cognition*

2.1 Abstract

2.1.1 Background

There is some evidence that post-stroke recovery is proportional to the initial severity of the impairment. This has been repeatedly reported in post-stroke motor recovery. Though, not all patients with severe motor impairments recover proportionally.

2.1.2 Aims

This chapter aimed to examine whether proportional recovery is observed within and across cognitive domains following stroke; and whether all patients show similar recovery trajectories.

2.1.3 Method

The data of 380 stroke patients from the BUCS study were analysed. Cognitive ability was assessed using the Birmingham Cognitive Screen (BCoS) at baseline (within three months of stroke) and at follow up (nine months post-stroke). The BCoS assessed cognition along five domains: language, memory, praxis, attention and executive function and number. Proportional recovery from baseline to follow up was computed using the number of impaired tasks, as well as domain specific impairments. A formal outlier analysis was used to identify patients that did not follow the proportional recovery rule.

2.1.4 Results

Within the first nine months, 80% of patients recovered 40-50% of their loss of cognitive abilities recorded at post-stroke baseline. This is shown within and across cognitive domains. The outlier analysis identified two groups that did not follow the

proportional recovery rule. 10% of patients showed an accelerated recovery, while around 10% showed a decelerated recovery or decline. In the decline group, 2/3 had severe cognitive impairment at post-stroke baseline, while 1/3 had mild impairments.

2.1.5 Conclusion

The analysis demonstrated proportional recovery of cognition at nine months following stroke, both across and within domains, in 80% of the sample. However, in contrast to the literature examining motor recovery, trajectories of cognition were variable, showing accelerated recovery in some patients and decline even in patients with mild impairments at post-stroke baseline.

2.2 Introduction

A proportional recovery rule in the first three months post-stroke has been well documented in the motor domain (Krakauer, 2006; Krakauer, 2015). The proportional recovery rule in motor recovery predicts that, on average, stroke patients will achieve about 60% of their potential for recovery (Krakauer, 2006; Krakauer, 2015). Potential for recovery is defined as the difference between post-stroke performance, and intact motor ability. However, some patients who have severe motor impairments do not recover as predicted by the proportional recovery rule (Buch et al., 2016; Shyam et al., 2007). These patients are described as 'non-fitters' (Buch et al., 2016; Shyam et al., 2007). The proportional recovery rule is less established for cognition than for motor recovery, although it has been demonstrated in research in specific cognitive domains, such as aphasia (Lazar et al., 2010) and neglect (Marchi et al., 2017). Ramsey and colleagues (Ramsey et al., 2017) examined recovery across cognitive domains, and found that initial deficit predicted outcome, with most recovery occurring within the first three months. In the current chapter, we will re-examine the proportional recovery

rule across and within cognitive domains. We will systematically assess whether individual patients fit the rule.

Research suggests that 80% percent of acute stroke patients have cognitive impairments in at least one cognitive domain (Demeyere et al., 2015; Sun et al., 2014). Cognitive deficits predict patients' ability to function independently (Bickerton et al., 2015) (see 1.2.4.1). There is mixed evidence regarding long-term cognitive outcomes following stroke. While most stroke patients improve their functional and cognitive abilities (Bickerton et al., 2015; Ramsey et al., 2017), one third develop dementia after stroke (Pendlebury, 2009). Most studies reporting on prevalence of dementia following stroke rely on a single time point measure (Barker-Collo & Feigin, 2006; Hénon, 2006; Pendlebury, 2009) (see 1.4.3). Mijajlović and colleagues advocate for a diagnosis of post-stroke dementia, based on presence of cognitive impairment at six months post-stroke (Mijajlović et al., 2017) . The authors acknowledge that their diagnosis cannot differentiate between vascular insult and neurodegeneration aetiology. To be able to distinguish between different causes it is critical to study cognition as a trajectory of an individual's change between at least two time points (Ramsey et al., 2017; Viglieccа, 2017), following stroke (Brainin et al., 2015; Lodder, 2007).

We retrospectively analysed the data obtained from the Birmingham University Cognitive Screen (BUCS) study (Humphreys et al., 2012). The BUCS study was conducted to validate the Birmingham Cognitive Screen (BCoS) in stroke. The BUCS recruited patients up to three months after stroke, for a baseline assessment, and followed them up at nine months. Detailed cognitive, functional and mood assessments were obtained at each time point.

2.3 Methods

2.3.1 Participants

As documented in 1.2.4.1, the BUCS study was designed to validate a cognitive screen. The data was collected between 2006 and 2011. On average, the baseline assessments were conducted four weeks after the stroke, ranging from one to ninety days. No patients were assessed during the hyper-acute stage <12 hours from stroke onset (Table 1). It is worth noting that in 2008, the UK NICE guidelines introduced thrombolysis as an early intervention for hyper-acute stroke. Consequently, it is possible that a small portion of the patients in this study will have received thrombolysis.

The current study only included patients who were followed up at nine months post-stroke (n=380). The demographics and baseline clinical history of this study population is presented in Table 1.

The recruitment criteria were designed to be as inclusive as possible, with minimal exclusion criteria. This was to gain a representative sample of stroke patients who had high chance of survival at nine months. Stroke patients were recruited if they were: (a) medically stable, (b) within three months of clinical diagnosis of stroke, (c) able to give informed consent. They were excluded if they had (a) insufficient understanding of English, (b) inability to concentrate for 35 min (c) and if they failed the BCoS force-choice orientation questions (e.g. what city you are in? what is the year?) suggesting lack of comprehension. Patients who were initially too impaired to participate, were approached to take part, again at a later point within three months. This means that stroke severity negatively correlated with time of testing in the BUCS dataset (Lau et al., 2015).

The original BUCS study included 908 stroke patients, of whom 380 were followed up

at nine months after stroke. Reasons for missing follow up were: (a) incomplete baseline data (20%) (b) refusal (11%), (c) death (8%), (d) inability to contact (17%), (e) hospitalisation or other serious conditions (4%), (f) other reasons (2%). Informed consent was obtained according to the approved ethics protocols by the U.K. National Research Ethics Committee. Please see details of the trial CONSORT flow diagram for recruitment and attritions in Bickerton and colleagues (Bickerton et al., 2015). In the full BUCS dataset, no differences in sex, age and baseline Barthel Index, were reported between patients who were followed up or lost to follow up (Bickerton et al., 2015) (See Appendix 1.2.4.1).

We computed required sample size for chapter two using effect sizes documented in (Lazar et al., 2010) and G*Power. Effect size used to compute required sample size for predicting baseline cognition to follow-up cognition was r=.69 with power at 80% alpha, which required N=15.

Table 1. Clinical and demographic information

	Stroke (n=380)	
	Mean/Ratio	***SD***
Age (years)	69.28	12.87
Sex (Male: Female)	213:167	
Neurological History (History: No History)	127:253	
Type of Stroke (Ischaemic: Haemorrhagic)	358:22	
Stroke incidences from Baseline-Follow Up	19	
Stroke to Baseline Assessment (months)	0.55	1.08
Baseline to Follow Up Assessment (months)	8.75	1.07
Years of Education	11.59	3.03
Baseline Barthel	12.63	5.92
Baseline HADS anxiety	6.46	4.48
Baseline HADS depression	6.23	3.92
Follow up Barthel	17.02	4.02
Follow up HADS anxiety	5.82	4.33
Follow up HADS depression	5.87	3.80

Notes. Std= Standard Deviation, HADs= Hospital Depression and Anxiety scale (higher scores indicate higher severity), Barthel Index (higher scores indicate more functional ability).

2.3.2 Measures

All the data were collected by examiners (psychologists, occupational therapists, or stroke researchers), who were trained, tested and supported by the BCoS team. The database also includes normative data from 100 healthy age-matched and socio-economic matched controls (Humphreys et al., 2012).

The data for each patient included demographic information (Table 1), level of functional independence measured by the Barthel Index (Mahoney & Barthel, 1965), and mood status was assessed by the Hospital anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), (See 1.2.4.1 for description of these measures). Evidence for neurological history (previous stroke, TIA, tumour, dementia, epilepsy, other) was recorded based on the patient's hospital records. Neurological incidents between

baseline and follow up were self-reported by the patients (See 2.4.1 for neurological history breakdown). All patients had at least 80% of the data completed. For each task, less than 5% of the data were missing (incomplete individual tasks, for example due to fatigue, aphasia), and in these instances we adopted a conservative approach and replaced the missing data by the group mean, to ensure this would not affect the regression analyses.

2.3.3 Cognitive measures

The BCoS was used to assess cognition (Humphreys et al., 2012), focusing on domain specific abilities, across five cognitive domains (a) attention and executive function, (b) language, (c) memory, (d) number, and (e) praxis. A full description of the BCoS is documented in section 1.2.4.1.

2.3.4 Dependent measures

Two measures were computed for each patient per task at baseline and follow up: (a) Patients were categorised as 'impaired' or 'not impaired' on the task. Impairment was defined as performance within the 5th percentile of aged matched controls (Humphreys et al., 2012). General cognition was computed by counting the number of tasks in which a patient was classified as impaired. Due to the uneven number of tasks per domain, this measure may be biased toward language abilities, as these were measured using six tasks (as opposed to numerical ability, which was assessed with three tasks). This measure was used as it adheres to common approaches in standardised cognitive tests (e.g. MoCA (Nasreddine et al., 2005), and OCS (Demeyere et al., 2015)); (b) a deviation score from the control data was computed (Z=(meanControl–Patient score)/stdevControl) (Sampanis, 2015). Using Z scores enabled a finer measurement of cognitive ability, accounting for change in deficit severity. Ability within domain was computed by averaging the Z scores of the relevant tasks. General cognitive ability was

computed by averaging across the five domains; hence it was not confounded by the number of tasks per domain.

First, step-wise regression was performed to test whether age, education, previous neurological history, stroke type, time to baseline assessment, time between baseline and follow up assessments, lesion side (left, right or bilateral), and mood measures (HADs) were confounding variables to the relationship of baseline and follow up cognition. This procedure was applied for each of the dependent measures. The only reliable association was found between performance on baseline, education and follow up performances, whereas all other associations were unreliable ($-.1 < \text{partial } r < .1$, $P > .1$). To simplify, the proportional recovery analyses only included the baseline performances as a predictor. To ensure the results were not driven by education or age, we computed linear regression for each cognitive domain and general cognition where we used baseline residuals after accounting for education and age (Table 2).

Table 2. Cognitive domain correlation with residuals after controlling for education

Cognitive Domains	R^2(F)	B
General	.144 (63.83)	.168**
Memory	.097 (40.78)	.290**
Attention and Executive Function	.274 (143.01)	.429**
Language	.352 (205.25)	.442**
Praxis	.117 (49.94)	.263**
Number	.326 (182.70)	.457**

** *Significant at P<001 level*

2.3.5 Analysis

2.3.5.1 Proportional recovery

To calculate the proportional recovery for general cognition (i.e. number (#) of impaired tasks) two regression models were implemented. In both models, the potential for recovery at baseline was used as a predictor. The models differed in their dependent variables. Regression (1) followed the reported formula by (Krakauer, 2006; Lazar et al., 2010). This model was used to predict proportional recovery in the domains of motor abilities and aphasia.

Regression (1):

$$\Delta D = T1 - T0$$

$$\Delta D = \beta 1 * (23 - T0) + \beta 0 ;$$

$$PR = \beta 1 * 100$$

T0 is the number of tasks that were intact at baseline; T1 is the number of tasks that were intact at follow up; ΔD is the difference between the two. 23 is the total number of tasks that were assessed. In regression (1) the dependent variable was the difference between patients' ability at follow up and their ability at baseline. β1 and β0 are

estimated parameters. In this case, β1 reflected the proportion of task that recovered as a function of the initial number of impaired tasks. *PR* is proportional recovery. This model may be confounded by mathematical coupling (Blomqvist, 1977; Hope et al., 2018; Krakauer, 2015). This confound is inflated if the difference in the variability between patients at baseline and follow up is large. We therefore computed proportional recovery using a dependent variable that was completely independent from the baseline measurement.

Regression (2):

$$dT1 = 23 - T1$$

$$dT1 = \beta1 * (23 - T0) + \beta0$$

$$PR = (1 - \beta1) * 100$$

Predicted outcomes (performance at follow up) were computed using the betas obtained in regression 2.

$$\widehat{dT}1 = \beta1 * (23 - T0) + \beta0$$

The difference between the predicted and observed outcomes represented the deviation from the outcome that would have been expected based on the proportional recovery rule. $\widehat{dT}1$ represents the predicted deficit, and Δ represents the difference between predicted and observed.

$$\Delta = \widehat{dT}1 - dT1$$

For the number of impaired tasks, negative delta (Δ) in the formula represented an accelerated recovery (fewer impaired tasks than expected), whereas positive delta

represented a decelerated recovery (more impaired tasks than expected). For the regressions based on the Z scores, negative delta (Δ) represented a decelerated recovery rate (poorer performance than expected), while positive delta represented an accelerated recovery rate (better performance than expected) in comparison to the predicted outcome.

The baseline scores were used for prediction of the actual follow up scores. This is the recommended way to predict recovery, since it reduces the measurement noise confounds, and decouples the predictors from the dependent variables (Cronbach, 1970). In this case, the estimated parameter reflected the proportion of ability that did not recover from baseline (measured as number of tasks or Z score), hence to compute the proportion of impairment that recovered we present it as the difference from 100%.

2.3.5.2 Recovery trajectories: Fitters and non-fitters

To identify non-fitters, outlier analyses in SPSS23 were performed for patients whose recovery did not follow the proportional rule. This was computed for each domain as well as for the measures of general cognition. The SPSS algorithm used the distribution of the data (i.e. the delta) to identify outliers (i.e. non-fitters). Outliers were identified as patients' scores that were outside a conservative range. Specifically, the range was determined by 50% of the population ± 1.5 the interquartile range. The interquartile range was computed as the difference between the highest and the lowest scores of 50% of the sample. Further analyses were done to explore and describe the demographic and cognitive characteristics of the non-fitter patients.

2.3.5.3 Post-stroke recovery time

The extended time window at the baseline assessment (three months) enabled us to test whether in this sample, recovery depended on the time window between baseline and

follow- up assessments. We analysed each individual's proportionate change from baseline to follow up [(baseline-follow up)/baseline] in each of the seven dependent cognitive measures (i.e. number of impaired tasks, Z-scores across and within each of the five domains). The study population was divided into 12 groups based on the week of baseline assessment (number of weeks since stroke). One-way ANOVA was performed to test for reliable differences between the groups. To ensure that the results were not driven by a floor effect, we ran additional separate analyses for patients who were more severely impaired (more than 1.65 from the control mean) and those who were mildly impaired at baseline (>1.65). Linear regression was performed to test for reliable differences between the individual as a function of time from stroke to baseline assessment. To assess whether the evidence supported the alternative (time of testing affected recovery rate) or the null hypothesis (it does not), we computed Bayes factor (BF_{01}) (Jaroz, 2014) applying the conventions that $BF_{01} > 3$ would support the null hypothesis, and $BF_{01} < 1/3$ would support the alternative.

2.4 Results

2.4.1 Demographics and cognitive profile

Table 1 presents a full description of the 380 stroke patients included in these analyses. At baseline, 253 patients had no recorded neurological history; for 99 participants a prior history of stroke/TIA was recorded, four had documented head injury, two were diagnosed with dementia prior to the stroke, and 21 had a history of other neurological conditions (e.g. tumour, epilepsy). Information on one patient was not recorded. At follow up, 19 patients' self-reported recurrent incidence of stroke/TIA, while nine reported new epileptic seizures, for five patients this information was not recorded at follow up. Of the 19 patients who reported a second stroke at follow up, two had decelerated non-fitter pattern, and showed deterioration across all cognitive scores. One

patient performed poorly at baseline (showing deficits on more than 65% of the tasks, with an average severity score of -7.9), the second patient only had a mild impairment at baseline, (showing deficits on ~7% of the tasks, with an average severity of -.92). One patient showed substantially declined performance on attention and executive function (identified as decelerated non-fitter for this domain), while two others had significant improvements in their overall cognitive scores (accelerated non-fitter). Of the nine who reported epilepsy, four had decelerated non-fitter data; only one of them showed deceleration across domain while the three others showed deceleration only in two of the domains. The performance at follow up for the two patients with pre-stroke dementia was predicted by their baseline performances, i.e. their recovery fitted the proportional rule of the group.

The cognitive data were not normally distributed and were positively skewed, with more patients showing relatively mild cognitive impairment (Table 3). There was a medium to high correlation between the baseline and the follow up performances. The overall cognition and performances within each domain improved at follow up (Table 3, Figure 2).

Overall functional ability, as measured by the Barthel Index (lower Barthel Index demonstrates a lower functional status), improved across all patients from baseline to follow up, as did their mood measured by the HADs (lower HADs demonstrates a better mood status), in both anxiety and depression.

Table 3. Baseline and Follow Up Cognition

	Baseline		Follow up		BL-FU
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	**T (379)**
Intact cognitive Tasks (Max=23)	15.26 (6.28)	17.00	17.41 (5.26)	19	-9.17**
Overall severity (Z)	-3.01 (3.79)	-1.36	-1.97 (2.94)	-0.935	-6.55**
Domain Severity (Z)					
Language	-4.18 (7.22)	-1.00	-2.47 (5.53)	-0.379	-5.89**
Attention and Executive Function	-2.41 (3.45)	-2.00	-3.53 (4.06)	-9.72	-6.07**
Number	-2.59 (3.79)	-0.69	-1.68 (3.14)	-0.125	-5.68**
Praxis	-2.02 (2.85)	-1.03	-1.32 (2.26)	-0.548	-4.75**
Memory	-2.70 (4.19)	-0.71	-1.98 (3.95)	-0.314	-2.99*

Notes. **Significant at $p < .001$ level (2-tailed), *Significant at $p < .005$ (2-tailed), SD=standard deviation. Domains= five cognitive domains in BCoS, Max intact score= 23 tasks, Z= 0 is not impaired and negative numbers represent the distance from healthy controls

2.4.2 Proportional recovery

Regression model one (a similar procedure to Krakauer and colleagues (Krakauer, 2006; Krakauer, 2015) showed that overall, patients recovered 41% of their lost function at nine months (Table 4), as judged by the number of impaired tasks. Regression model two, which is not confounded by mathematical coupling, showed similar results; baseline deficits linearly predicted performances at nine months follow up (Table 4, Figure 2).

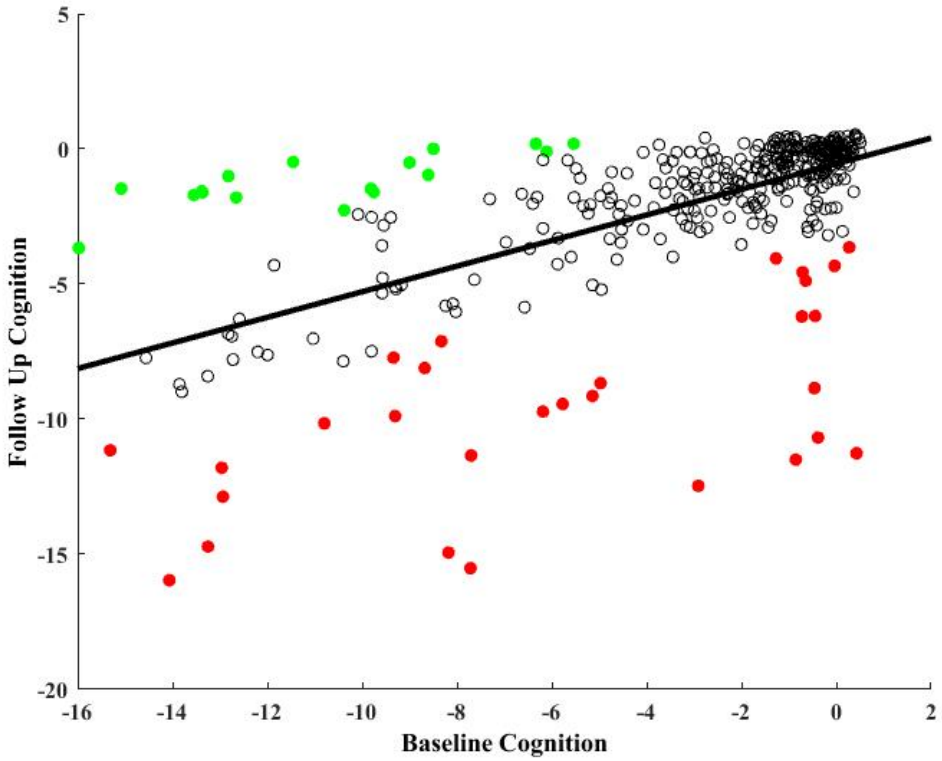


Figure 2. Cognitive recovery is proportional to initial impairment in general cognition (Z score).

Baseline general cognition is represented on the x-axis, and Follow up general cognition is represented on the y-axis. Cognition is measured in Z score, with 0 demonstrating no impairment, and negative numbers representing impairment, and distance from healthy controls. Evidence of accelerating non-fitters (red), and decelerating non-fitters (green).

Table 4. Proportional recovery: Linear Regression Models

Formula	R^2(F)	B1 (CI)	B0 (CI)	Proportional (%)	Outliers Decelerate	Outliers Accelerate
General cognition:						
#T: FU-BL=B1 (max-BL) +B0	0.32 (179.59)	0.41 (0.35:0.47)	-1.05 (-1.65:-1.45)	41%		
#T: FU=B1(max-BL) +B0	0.49 (362.80)	0.59 (0.53:0.65)	1.00 (0.44:1.65)	41%	n=22 Δ#T $\leq$ -6.8	n=6 Δ#T $\geq$ 7.5
Z: FU=B1(BL)+B0	0.37 (222.56)	0.47 (0.41:0.54)	-0.55 (-0.85:0.25)	53%	n=31 ΔZ $\leq$ -2.6	n=18 ΔZ $\geq$ 3.1
Cognitive Domains (Z):						
Memory	0.12 (50.75)	0.32 (0.23:0.41)	-1.10 (-1.56:0.66)	68%	n=47 ΔZ $\leq$ -2.8	n=9 ΔZ $\geq$ 4.3
Attention and Executive Function	0.30 (164.94)	0.47 (0.40:0.54)	-0.75 (-1.14:0.37)	53%	n=34 ΔZ $\leq$ -3.5	n=10 ΔZ $\geq$ 4.3
Language	0.40 (253.32)	0.49 (0.42:0.54)	-0.44 (-0.94:0.06)	51%	n=37 ΔZ $\leq$ -2.0	n=34 ΔZ $\geq$ 2.8
Praxis	0.15 (66.92)	0.31 (0.23:0.38)	-0.70 (-0.95:-0.44)	69%	n=27 ΔZ $\leq$ -2.9	n=3 ΔZ $\geq$ 4.1
Number	0.37 (218.63)	0.50 (0.44:0.57)	-0.38 (-0.69:-0.07)	50%	n=38 ΔZ $\leq$ -2.8	n=18 ΔZ $\geq$ 3.5

Notes. #T= number of tasks; Z,= standardised deviation from healthy controls; FU= follow up; BL= Baseline; B1= the fitted parameters for the baseline data, B0= the fitted parameters for the constant; CI= confidence interval for the fitted parameters.; F test with (1,379) degrees of freedom; n=number of patients classed as outliers. Outliers defined from the SPSS outlier software (described on page 60). ΔZ represents the outlier direction, with negative delta (Δ)representing an accelerated recovery (fewer impaired tasks than expected), whereas positive delta represented a decelerated recovery (more impaired tasks than expected).

When patients' deficit severity was analysed as a continuous measure (Z scores), the expected proportional recovery was larger. Across the five cognitive domains, patients were expected to recover more than 50% of their deficits. The lowest recovery level was observed for numerical abilities (50%) and the highest for praxis abilities (69%) (Table 4).

2.4.3 Recovery trajectory: time from stroke

Figure 3 presents the number of impaired tasks based on the week patients had their baseline assessments. Patients' overall cognitive performance improved at follow up irrespective of the time of assessment. A formal analysis of recovery based on the time of baseline assessment revealed no reliable effects for all the seven dependent measures (for all Fs (20,359) < 1.4, p > .118). To ensure that these null results were not driven by a floor effect (the mild patients), we recomputed the analysis with linear regression using the general cognition separately for patients with mild impairment (n=172, R^2 = .001), P =1.00, BF_{01} < .01), and those who were more severely impaired at baseline (n=208, R^2 = .001, P =1.00, BF_{01} < .01). The analysis showed that the effects were not reliable, in all analyses. Note that the Bayes factor (BF_{01}) in all analyses was smaller than 0.3, meaning the data provide sufficient evidence to support the hypothesis that time of testing post-stroke did not affect the recovery trajectories.

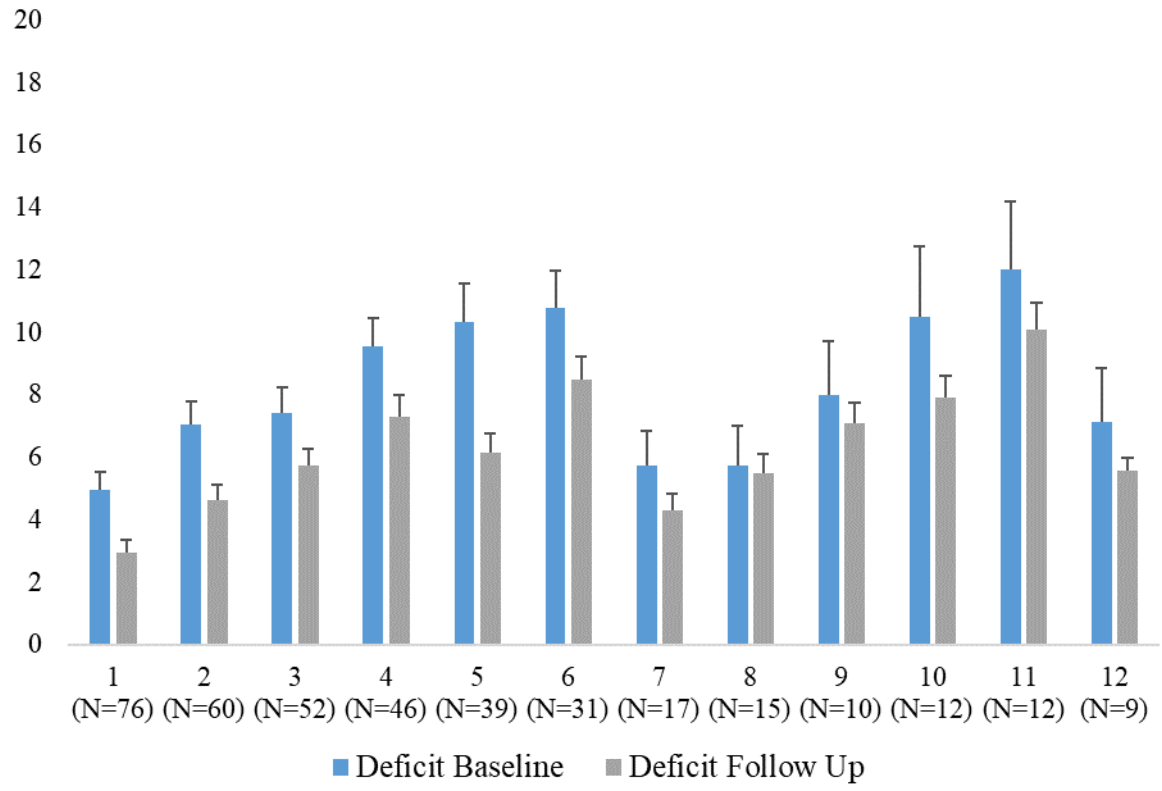


Figure 3. Number of Cognitive Deficits by Time of Baseline Assessment. The x-axis represents the number of weeks from stroke that baseline assessment was completed. N denotes the number of patients assessed at each time point. The y-axis represents the average number of deficits (0-23). Blue represents baseline and grey follow up.

2.4.4 Recovery trajectories: Fitters and non-fitters

The outlier analyses detected two types of non-fitter data for each measure (Table 4, Figure 2). Those with accelerated recovery rates exhibited better than predicted performance at follow up. Non-fitter data characterised by decelerated recovery revealed poorer than expected performance at nine months. There were more decelerated non-fitters than accelerated. When considering the number of impaired tasks, all patients who showed a decelerated recovery (below the regression line, fewer deficits than expected, Figure 2) performed relatively poorly at baseline. However, performances at baseline varied for the decelerated recovery group (above the

regression line, more deficits than expected); some showed severe impairments at baseline, while others showed very mild baseline cognitive impairments. See

Figure ***4***.

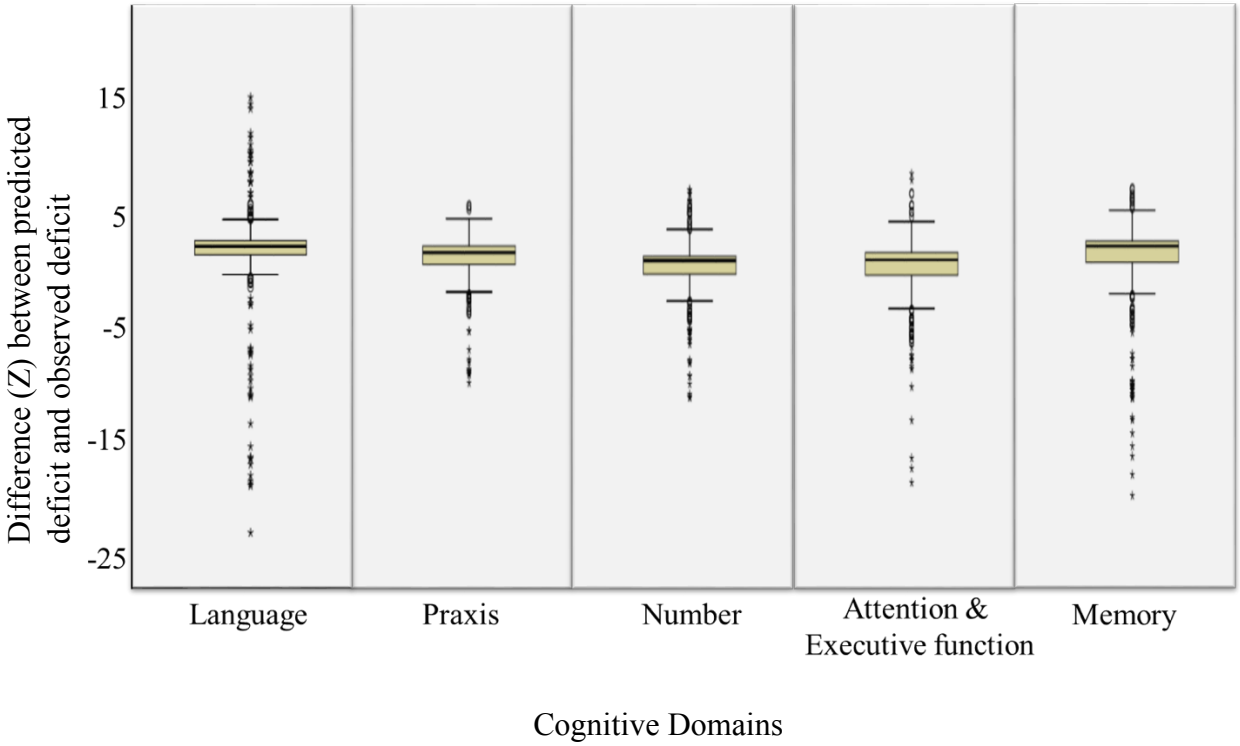


Figure 4. Cognitive domain outlier box-plots. Each cognitive domain is represented by a box-plot. The Y axis plots the difference between the predicted cognitive deficit (Z) at follow-up, as opposed to the observed (Z).

A detailed examination of the outliers who declined at follow up revealed that 6.84% (26/380) of patients showed overall cognitive deceleration (i.e. they were identified as decelerated outliers in more than three domains). A total of 18.15% (69/380) of patients were identified as non-fitters in only one or two domains. In Table 5, we provide descriptive information (demographic, mood, functional and clinical information) for two decelerated groups: 1) those who declined only on one/two cognitive domain(s); 2) those with overall cognitive decline; and 3) for the fitter and accelerated group

combined. The clinical and demographic profile did not differ between any of the groups (see Table 5).

Table 5. Demographic and clinical information of Fitters and non-Fitters

	Accelerated & Fitters	**Decelerated (non-fitter 1-2 domains)**	**Decelerated (non-fitter >2 domains)**
N	**281**	**69**	**26**
Age (years)	69.12	69.86 (13.55)	69.64 (18.32)
Gender (Male: Female)	164:121	34:35	15:11
Neurological History (yes: No History)	98:187	48:21	8:18
Type of Stroke (Ischaemic: Haemorrhagic)	268:13	66:3	24:2
Stroke recurrence from Baseline-Follow Up	16	1	2
Stroke to Baseline Assessment (months)	.52 (1.18)	.62 (.72)	.61 (.75)
Baseline to Follow Up Assessment (months)	8.72 (1.08)	8.79 (1.07)	8.92 (.95)
Years of Education	11.86 (2.96)	11.17 (2.90)	9.78 (3.44)
Baseline Barthel	13.21 (5.84)	10.92 (5.77)	10.74 (6.22)
Baseline HADS anxiety	6.11 (4.30)	7.22 (4.84)	7.97 (4.93)
Baseline HADS depression	5.98 (3.71)	6.64 (4.31)	7.85 (4.69)
Follow up Barthel	17.65 (3.54)	15.68 (4.57)	13.69 (4.97)
Follow up HADS anxiety	5.67 (3.60)	6.42 (4.90)	5.83 (4.05)
Follow up HADS depression	5.50 (3.60)	6.63 (4.23)	7.81 (4.01)

Notes: Mean is represented in the table, with standard deviation noted alongside the mean, HADs= Hospital Depression and Anxiety scale (higher scores indicate higher severity), Barthel Index (higher scores indicate more functional ability).

2.5 Discussion

The present study offers evidence for proportional recovery across the cognitive spectrum at nine months following stroke. A proportional recovery rate of 40% was observed for the number of impaired cognitive tasks. Higher recovery rates were demonstrated when using a continuous measure of severity (50% - 69%), both for overall cognitive performance and for specific cognitive domains. Recovery rate at nine months was not affected by the time of baseline assessment. In other words, patients recovered at similar rates when assessed within one week of the stroke or at three months following stroke. The analysis also identified "non-fitter" patients who did not follow the proportional recovery rule. We identified a small group of patients (<10%), who showed more improvement in cognitive abilities than expected, displaying accelerated recovery. A second group of patients (~10%), presented decelerated recovery. The available clinical and demographic information did not clearly differentiate between the fitters and the decelerated non-fitters.

2.5.1 Recovery up to nine months

This study demonstrated proportional recovery in cognition at nine months following stroke. The cognitive recovery rate within and across domain matches previous reports (Ramsey et al., 2017).

Proportional recovery in previous studies focused on recovery at shorter time scales, between 72 hours to 90 days (Lazar et al., 2010; Marchi et al., 2017), (though see (Ramsey et al., 2017; Winters et al., 2016)). Based on the biological recovery timeline (Cramer, 2008; Murphy & Corbett, 2009), the proportional rule measured in those studies reflected the restoration of functions based on a mixture of homeostatic processes (one to four weeks post-stroke, adapting structural and functional neural

circuits, recovery phase, and 2) and rehabilitation (weeks to months, recovery phase 3). In contrast, in the current chapter, the time scale was much longer (up to nine months), and the observed recovery processes possibly reflected the impact of formal and informal rehabilitation. It is likely that some of the patients in the current analysis had formal rehabilitation between baseline and follow up assessments, especially those with moderate to severe post-stroke deficits. Thus, the observed recovery rates at least partly reflect the benefits of the intervention pathways used at that time (2006-2011) in the UK. The current study highlights that any new intervention needs to take into account the current observed recovery rate for each cognitive domain, and show advantages beyond evidence of proportional recovery.

In the present dataset, the time of baseline assessment and duration between baseline and follow up were not predictors of the follow up performance (Table 1,Figure 3), and did not affect the recovery rates. It is plausible that time by recovery rate interactions were examined as cross-sectional rather than within individuals. Furthermore, the sampling of patients in previous studies (Lazar et al., 2010; Murphy & Corbett, 2009; Winters et al., 2016) might have been biased towards those who could complete the study within days of stroke (Cramer, 2008; Murphy & Corbett, 2009).

The results of the current study suggests a large recovery potential that continues beyond the spontaneous biological repair processes (three months) (Winters et al., 2016). However, as the timeline for post-stroke recovery (Cramer, 2008; Murphy & Corbett, 2009) is based on animal models, the translation of these phases and timelines to human is theoretical (Ward, 2017). It is possible that homeostatic repair in human occurs over a longer period, enabling a larger window for plasticity induced intervention. To date, evidence for the impact of the initiation time of intervention is unclear (Ward, 2017).

2.5.2 Fitters and Non-fitters

In contrast to previously reported studies in proportional recovery for motor deficits, aphasia and neglect (Krakauer, 2015; Lazar et al., 2010; Marchi et al., 2017; Winters et al., 2016), we observed patients who showed *accelerated recovery*. Baseline cognitive impairments for these patients were moderate to severe. The number of patients who showed an accelerated recovery varied depending on the domain (Table 4), but was less than 10% in each. The relatively small proportion of accelerators may explain why these have been missed by previous studies that looked at domain specific recovery (Lazar et al., 2010; Marchi et al., 2017; Wilson, Eriksson, et al., 2019; Winters et al., 2016). Although regression to the mean (Hope et al., 2018) can partly explain these observed results, future research should examine this group in more detail, as they might provide useful insights into mechanisms of successful recovery.

Around 10% of our study population showed decelerated recovery (Table 4, Figure 2). These were identified as non-fitters in specific domains or across overall cognition. In the literature (Krakauer, 2015; Lazar et al., 2010; Marchi et al., 2017; Winters et al., 2016), decelerated recovery is typically reported for patients who show severe impairments at baseline. In contrast, in the current analysis some of our decelerated recovery patients presented only mild impairments at baseline, meaning they actually declined following the stroke incident. This pattern of declined abilities of some mild patients has not been reported before (Krakauer, 2015; Lazar et al., 2010; Marchi et al., 2017; Winters et al., 2016). It is possible that the decline pattern only applies to cognition but not to motor abilities. The relatively small sample of previous studies may have hindered their ability to identify these declined patients. However, in qualitative analyses of self-reported recovery trajectories, four recovery trajectories were identified,

with stroke patients reporting; (a) meaningful recovery, (b) cycles of recovery and decline, (c) ongoing disruption, (d) gradual, ongoing decline (Hawkins et al., 2017).

A trajectory of post-stroke cognitive decline may be a pre-cursor to developing delayed dementia (Snaphaan, 2007; Vigliecca, 2017). The cognitively decelerated group showed slightly lower functioning and mood at baseline and follow up, and fewer years in education (Table 4). However, none of these characteristics reliably differentiated between those who decelerated and those who recovered. Neurological events, age, or type of stroke (ischemic/haemorrhagic) did not distinguish between the decelerated non-fitters and the rest of the patients. Thus, for the current sample, the factors contributing to the deceleration of recovery remains unclear.

2.5.3 Methodological considerations

The BCoS was specifically designed for stroke patients (Humphreys et al., 2012). The broad approach of the BCoS allowed enabled investigation of proportional recovery across and within domains. However, the BCoS requires patients to concentrate for at least 35 minutes, and to have sufficient English comprehension; therefore, the BUCS database is biased towards patients who are sufficiently unimpaired to meet these limiting criteria.

The inclusion criteria used in the BUCS meant that the study population represents mild to moderate stroke patients. Notably, the extended time window from stroke to the baseline meant that patients who were initially too severe to be tested within a few days after stroke, could be assessed later at the rehabilitation phase.

The formula used in proportional recovery in other studies, such as motor recovery (Krakauer, 2015), is likely to be inflated by mathematical coupling because baseline performances form part of the independent and the dependent variables (Blomqvist,

1977; Chiolero et al., 2013; Fisk, 1967; Tu, 2016), as well as ceiling/floor effects of the measurements, and change in the distribution of scores from baseline to follow up (Hope et al., 2018). In the present study, therefore, we calculated proportional recovery using a regression model that does not suffer from the above problems. We demonstrated similar cognitive proportional recovery using both formulas. However, the data were skewed, suggesting potential floor effects, which might lead to overestimation of the recovery rate (Hope et al., 2018). There were a number of patients who had recurrent stroke/TIA, which could be considered a limitation. However, even after removing these patients there was no change in the outcome of the proportional recovery rates.

2.5.4 Conclusions

The study demonstrated that 80% of patients showed 40-50% proportional recovery of cognition at nine months. This was evident across and within cognitive domains. Recovery was not limited to the first three months following stroke. The study also identified that less than 10% showed an accelerated recovery, while around 10% showed decelerated recovery and even decline. This highlights the importance of considering individual cognitive trajectories following stroke exist we should take this into account. Firstly, when conducting rehabilitation trials, and secondly in clinical practice when planning individual rehabilitation. Currently NICE guidelines advise that stroke patients should be followed up in primary care at six months post-stroke, and annually thereafter. In the present study we show that cognitive trajectories may accelerate or decline within nine months, even in those with mild stroke deficits initially. It would be beneficial to have healthcare professional input earlier than six months post-stroke, as it may provide opportunity to identify those on the decline trajectory at an earlier stage. Furthermore, it would be important that the same

healthcare professional carried out the follow up in order to observe potentially subtle symptoms of decline, in the U.K it is often be difficult to see the same healthcare professional in the primary care setting.

Chapter 3: Can education protect cognition? A study in UK and China of healthy ageing and stroke

3.1 Abstract

3.1.1 Background

With an increasing ageing population, the risk for cognitive decline and cognitive associated diseases (e.g. stroke, dementia) increases. In the present chapter we examined the effect of years in education on cognitive abilities in ageing, and stroke populations. In study 1, we tested whether education predicts cognitive ageing. Study 2 tested whether education improves outcomes following stroke, and study 3 tested whether education predicts nine months cognitive outcomes, and recovery rates.

3.1.2 Aims

To examine the predictive value of cognition in an ageing population, across and within UK and China cohorts. To assess whether years of education has an impact on post-stroke cognition within three months of stroke across and within UK and China cohorts. And, to examine the impact of level of education on post-stroke cognitive recovery at nine months across and within a UK cohort.

3.1.3 Methods

A prospective population-based cohort study in two settings: West-Midlands, UK and Guangzhou, China. The analysis included 100 non-stroke and 826 stroke patients from the UK, of which 380 were followed up at nine months; 343 non-stroke and 105 stroke patients from China. Correlational analyses were used to assess the predictive value of years in education on cognitive abilities. Cognitive abilities were measured using the English and Chinese versions of the Birmingham Cognitive Screen (BCoS, C-BCoS). It includes the following domains: language, memory, attention and executive functions,

praxis and number. Analyses were computed within and across cognitive domains for non-stroke participants (Study 1), stroke patients (< three months post-stroke) (Study 2), and stroke recovery at nine months using longitudinal data (< three months) up to nine months post-stroke (Study 3).

3.1.4 Results

Beyond age and setting, education was a reliable predictor of general cognitive ability in non-stroke cognitive ageing (Study 1: r =.187); education predicted cognitive ability in all five domains (r >.134). Following stroke (Study 2), after age and setting were accounted for, education reliably predicted cognitive outcomes (Study 2: r =.090); this effect was primarily related to preservation of the language and number domains. Finally, when accounting for age and baseline assessment (< 3 months), education predicted cognitive recovery at nine months (Study 3: r = .157); as well as recovery rate (r=.260).

3.1.5 Conclusion

In these cohort analyses education was a protective factor of cognitive ageing. Education also improved cognitive outcome following stroke, and accelerated recovery in the first year following stroke beyond age. However, important socioeconomic and other health related known associated factors were not accounted for in these analyses.

3.2 Introduction

With an increasing ageing population, the risk for cognitive decline and cognitive associated diseases (e.g. stroke, dementia) also rises (WHO, 2018). This intensifies financial demands on the economy, and has devastating societal impact (WHO, 2017). As a consequence, international efforts are directed to diminish the impact of ageing on cognition (Brayne & Miller, 2017). In this chapter, we assessed whether increasing the number of years spent in education can protect cognition against age related decline, and disease. In chapter one section 1.5.1.2, we provide a detailed description of the influence of education on cognitive reserve, and the suggested mechanisms behind it.

The impact of education on cognition is reported in the context of cognitive ageing. For example, in both male and female individuals (60-64 years) from Australia, higher years in education correlated with an increase in cognitive ability (Christensen et al., 2007). This is also demonstrated in a sample from Low-Income and Low-Literacy settings (Africa) (Humphreys et al., 2016). A systematic review of six studies reporting data from over 2000 people also confirm that education attainment attenuates the impact of small vessel disease on cognitive abilities (Pinter et al., 2015). Furthermore, education is reported to ameliorate dementia symptoms, at 85 years old, those with diagnosed dementia were less educated than those who did not develop the condition (Skoog et al., 2017). Similar results were reported in a study population from Brazil (Farfel et al., 2013). However, not all studies found this association between education and cognitive ageing (Ramakrishnan et al., 2017).

In the context of stroke, analysis of data from the Rotterdam study (Mirza et al., 2016) suggests that education can also protect against long-term cognitive outcomes following stroke (Mirza et al., 2016; Sun et al., 2014; Withall et al., 2009). A meta-analysis of

2064 stroke patients, report that low levels of education doubled the chances of cognitive impairments following stroke (Pendlebury & Rothwell, 2009).

In the current chapter, we present three studies which examine whether education protects cognition in ageing and stroke populations, in the UK and China. Study 1 examined the impact of education on cognitive abilities in ageing controls participants (UK and China). Study 2 examined the impact of education on post-stroke cognition (UK and China), and Study 3 measured the impact of education on cognitive recovery following stroke.

3.3 Methods

This study is a retrospective analysis of the data obtained by the BUCS study (see 1.2.4.1) (Birmingham University Cognitive Screen, 2006 – 2011), and the China-Birmingham Cognitive Screen study (C-BCoS) (2012 – 2017). The BUCS and C-BCoS studies validated the utility of a cognitive screen for stroke (Birmingham Cognitive Screen (BCoS) (Bickerton et al., 2015; Humphreys et al., 2012), and its Mandarin and Cantonese translated versions (Pan et al., 2015). It is worth noting that there are multiple dialects spoken by people living in and around Guangzhou city. The official language is Mandarin, though as Guangzhou was the capital of Canton, many speak a specific local Yue dialect, known as Cantonese. Participant in the current analysis, were assessed using the version (Mandarin/Cantonese) they felt most comfortable with; the examiners were well versed in both languages.

The studies recruited stroke patients and also control groups of age and demographic matched participants who reported no previous history of neurological or cerebrovascular disorders.

The BUCS was approved by the UK National Research Ethics Committee. The C-BCoS

study was approved by the University of Birmingham, and the Guangzhou First People's Hospital research ethical committees. All participants gave written informed consent.

3.3.1 Participants

3.3.1.1 Study 1: Healthy Ageing

The controls were recruited using an opportunistic sample of individuals of 50 years old and above. The demographics for these controls are presented in Table 6. The UK control participants (n=100) were recruited from the West Midlands, with the purpose that they represent the 2001 UK population census on the distribution of sex and education across the three age groups. The two china control groups included Cantonese speakers (n=156), and mandarin speakers (n=187). We excluded participants who completed less than 75% of cognitive data available. We computed two separate sample size calculations for chapter three. For those in Study 1: Healthy ageing with controls, we used (Kim & Park, 2016) to obtain a reference effect size in an analysis similar to the one presented in chapter three. We used G*Power to calculate required sample size with power at 80% alpha considering multiple comparisons p= .050/6: p=.008 = N=358.

3.3.1.2 Study 2: UK and China Stroke

Recruitment criteria for stroke patients were designed to be as inclusive as possible, with minimal exclusion criteria to gain a representative sample of patients with good survival chances. Demographics are reported in Table 9.

For full description of recruitment and BUCS study please see 1.2.4.1. Please see details of the trial CONSORT flow diagram for recruitment and attritions in Bickerton and colleagues (Bickerton et al., 2015). The initial sample included 908 stroke patients. In this study, a total of 826 stroke patients were included in the final analyses, as we

excluded those who had less than 75% of cognitive data available.

China stroke cohorts were recruited from a neurological department in Guangzhou first people's Hospital. Due to the hospital structure, the sample represented patients who were medically stable with mild to moderate cognitive impairments. See 1.2.4.1 for full description of recruitment. Patients completed the C-BCoS (Wong et al., 2009) in the language that they felt most comfortable with (Mandarin/Cantonese).

Across both samples, assessments were carried out on average within the first month of stroke; UK (29 days), based on 794 participants information, C-China (9 days), based on 91 participants and M-China (5 days), based on 43 participants.

For those in Study 2 and 3: Stroke, we used (Mirza et al., 2016), to obtain a reference effect size in an analysis similar to the one presented in chapter three. Where the authors report the incidence of developing dementia following stroke. Using levels of education (high, intermediate or low) to compare incidence of dementia following stroke. We computed a Chi square based on the data in table 2 of (Mirza et al., 2016). We used G*Power to calculate the required sample size, square of 91.88 = r=.70), N=15.

3.3.1.3 Study 3: UK stroke recovery

The initial sample of stroke patients included 908, of which 380 were followed up at nine months' post- stroke. The assessment at follow up included identical measures as were taken at the initial baseline assessment. No differences in sex, age and baseline Barthel Index is reported between the followed up and non-followed up patients were identified (Bickerton et al., 2015). Please see Bickerton and colleagues for consort diagram for information on loss to follow-up (Bickerton et al., 2015). Average time from baseline to follow up was nine months (See Table 12).

3.3.2 Measures

All the UK data was collected by examiners (psychologists, occupational therapists, or stroke researchers). The China data was collected by medical personnel (e.g. neurologist trainee). All attended training and were assessed, and supported by the same University of Birmingham team.

3.3.2.1 Cognitive measures: BCoS and C-BCoS

The BCoS was used to assess cognition (Bickerton et al., 2015; Humphreys et al., 2012; Pan et al., 2015), focusing on domain specific abilities, across five cognitive domains (a) attention and executive function, (b) language, (c) memory, (d) number, and (e) praxis. A full description of the BCoS and C-BCoS is documented in section 1.2.4.1.

3.3.2.2 Demographic measures

Education was coded as self-reported number of years in formal education. For example, eleven years of education in the UK was recorded to be equivalent to compulsory years in education (high school, GCSE). Thirteen years of education in the UK, and twelve years in China was equivalent to college education (A level or diploma), and above thirteen years was equivalent to University level of education.

For UK stroke patients (study 2) in addition to the cognitive data, further demographic information was collected (Table 9), level of functional independence using the Barthel Index (Mahoney & Barthel, 1965), and mood status using the Hospital anxiety and Depression Scale (Zigmond & Snaith, 1983). Evidence for neurological history (previous stroke, TIA, tumour, dementia, epilepsy, other) was recorded based on the patient's hospital records.

A sub-sample of the china cohort participants were also assessed using the Chinese version of the MoCA (Montreal Cognitive Assessment) (Tan et al., 2015; Wong et al.,

2009)

3.3.3 Analysis

We excluded controls, and patients who had less than 75% of cognitive data available. Missing data was replaced by the average of the group. Analysis was computed with SPSS24.

Demographic, and cognitive characteristics are reported in Table 6, Table 9, and Table 12 . Independent t-tests were used to compare between the three samples. As samples differed in their size, statistics reported assume unequal variance for all analyses. These were corrected for multiple comparisons; using Bonferroni-Holmes correction. Whether significance remained after corrections is noted in each correlation.

To compute summary statistics, individual scores for each task were normalized. The standardised distance from the sample specific control mean was calculated. Thus, for the China and UK control cohorts separately were used to compute Z scores for their corresponding samples of stroke patients. Cut off scores were based on their own cultural and language cut offs. For the control group, we computed Z scores based on their group average and standard deviation scores. For each domain the Z scores were averaged across tasks and for the general cognition score the Z scores were averaged across the five domains (language, attention and executive function, number, praxis and memory).

To assess the relationship between education and cognition (within and across domains), we computed partial correlations accounting for age and setting. This was computed across the three settings and for each setting separately (Study 1 and 2). For study 3, partial correlation also accounted for baseline cognitive abilities.

To further elucidate the relations between education and cognition while accounting

other measures, we used step-wise linear regression including the measures available for each group. For the UK stroke cohort, beyond age it also included the HADs and Barthel Index. Note that in study 3, the baseline, and follow up measures of the HADs and Barthel Index and baseline cognition were included.

The relationship between education and cognition was also assessed using the MoCA in the sub-sample of the China participants.

3.4 Results

3.4.1 Study 1: Heathy ageing

Figure 5 and Table 6, present the demographic data for each cohort. UK cohort median age was 70, M-China was 65 and C-China was 64; UK vs. M-China $t(100.85)=-4.77$, $p<.001$; UK vs. C-China $t(955)=-.908$, $p=.365$; M-China vs. C-China $t(201)=3.42$, $p<.001$ (See Figure 5).

The UK cohort had a median of 11 years in education which is equivalent to modern GCSE (secondary school). The Mandarin speaking China cohort (M-China) had a median of 12 years equivalent to A level education. The UK and M-China groups were not reliably different in their education levels $t(282.06)=.207$, $p=.836$ (See Figure 5)The Cantonese speaking China cohort (C-China) were significantly less educated from both former cohorts, with a median of 9 years C-China vs. UK: $t(251.67)=8.40$, $p <.001$, C-China were less educated than M-China, $t(341)=7.57$, $p<.001$.

Age did not correlate with education in the UK-Cohort ($r=-.083$, $p =.411$). In the M-China cohort age positively correlated with education ($r = .203$, $p =.006$), showing older people were more educated. In the C-China the correlation was negative ($r =-.281$, $p <.001$) as younger people were more educated.

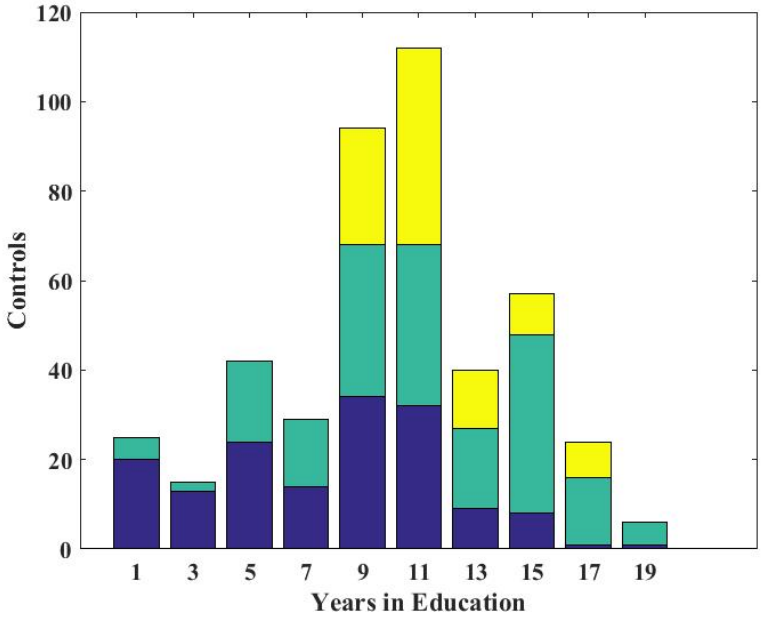
The UK and M-China cohorts had similar ratio of equal representation for both sexes, but C-China cohort was pre-dominantly females. There were sex differences in the level of education in the C-China cohort, male versus female $t(78.33)=2.33$, $p=.022$ equal variances not assumed. There were no sex differences in the level of education in the M-China cohort, $t(184)=-.587$, $p=.558$, or in the UK cohort, $t(98)=.076$, $p=.940$.

Table 6. Demographic and clinical characteristics for Study 1 (Healthy Controls)

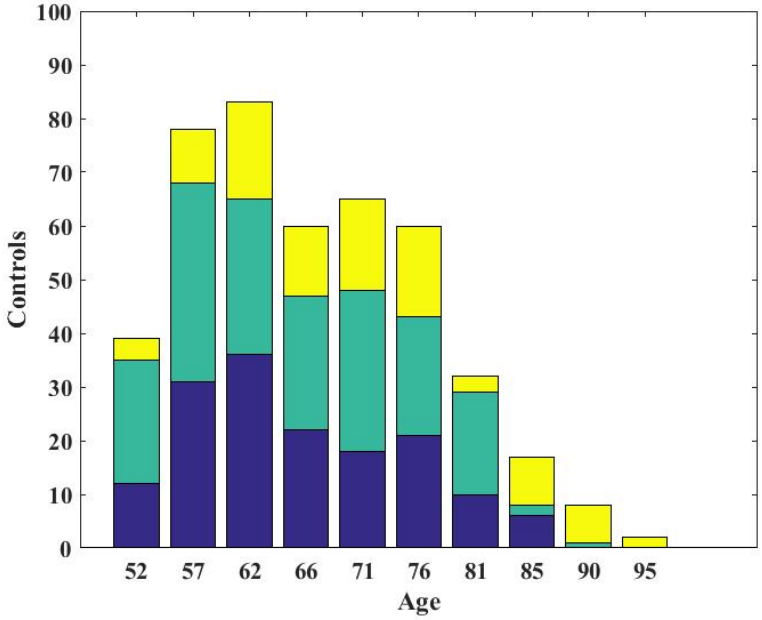
	U.K Controls (n=100)			**Mandarin Controls (n=187)**			**Cantonese Controls (n=156)**		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Age (years)	70.65 (10.43)	69.5	52-97	65.71 (9.38)	65	50-92	65.74 (8.78)	64	50-86
Gender (Male: Female)	54:46			97:92			41:115		
Years of Education	11.78 (2.46)	10.51	9-18	11.69 (4.16)	12	0-20	8.23 (4.26)	9	0-19

Notes. SD: standard deviation. Barthel Index: higher score= more functional ability.

HADs= Hospital Depression and Anxiety scale: higher the score equals higher anxiety and depression level.



(A)



(B)

Figure 5. Dark Blue= Cantonese cohort; Turquoise= Mandarin cohort; Yellow= UK cohort. (A) Control cohorts/ Years of Education. Years in education is presented in the x-axis, and numbers in each cohort is represented in the y-axis. (B) Control cohorts/ Age. Age is presented in the x-axis, and numbers in each cohort is represented in the y-axis.

Table 7. Cognitive profile for participants in Study 1 (Healthy Controls)

	UK Controls (n=100)			**Mandarin Controls (n=187)**			**Cantonese Controls (n=156)**		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Language	-.005 (.59)	.16	-2.77-.59	-.093 (1.09)	.189	-12.03-.45	-.048 (.81)	.19	-5.11-.49
Attention and Executive Function	.001 (.54)	.13	-2.58-.77	-.099 (.813)	.116	-4.19-.52	.013 (.54)	.160	-2.50-.69
Number	-.014 (.72)	.72	-3.02-.42	-.249 (1.37)	.409	-5.96-.41	-.116 (.94)	.914	-3.92-.61
Praxis	-.005 (.56)	.07	-2.13-.71	-.299 (1.31)	.081	-6.63-.50	-.002 (.68)	.200	-4.42-.65
Memory	-.004 (.64)	.19	-2.77-.59	-.161 (.892)	.137	-4.84-.57	.009 (.683)	.141	-4.89-.73
General Cognition	-.006 (.39)	.11	-1.14-.58	-.181 (.890)	.094	-6.35-.45	-.025 (.91)	.151	-3.00-.55
MoCA				26.18 (2.98)	27	14-30	23.87 (3.51)	24	14-30

Notes. SD: Standard Deviation. MoCA= Montreal Cognitive Assessment; Cognition is represented in z scores= standardised deviation from each control cohort.

There were differences in cognitive abilities between the three cohorts, despite the normalization (Table 7). However, these differences did not survive family-wise error correction. The large differences between the median, and average suggest that the distributions were positively skewed (e.g. the averages are often negative, while the medians are positive).

Partial correlation analyses were computed across settings (UK and China). Education positively correlated across the domains (general cognition r=.268, p<.001) (Figure 6), and within each domain (language r=.187, p<.001; memory r=.203, p<.050; attention and executive function r=.248, p<.001; praxis r=.134, <.001 and number r=.282, p<.001).

For each cohort (Table 8), we computed separate partial correlations of education after age had been removed with each cognitive measure. In the UK cohort, education positively correlated with language, praxis and general cognition with effect sizes of (Pearson r) from .233 to .350. Education positively correlated with all cognitive measures in the C-China cohort with effects (Pearson r) ranging from .229 to.531. The pattern was slightly different for the M-China cohorts, where the predictive value of education on cognition ranged from .210 to .258, and all cognitive domains had significant predictive value except language and praxis. General cognition was also assessed using the MoCA in the two China Cohorts, similar to the general cognition of the BCoS. Education correlated performance on the MoCA in both the control cohorts.

Table 8. Correlation and regression models for Study 1 (Healthy Controls)

	Education Correlation	Regression Model	Predictors
UK and China Controls			
Language	.187**^	R^2=.043, F(2,440)=9.89**^	*+Education***-Age**
Memory	.203**^	R^2=.170, F(4,438)=22.15**^	*-Age***+Education***+Group**
Attention and Executive Function	.248***^	R^2=.135, F(4,440)=17.07**^	*-Age***+Education***+Group**
Number	.282**^	R^2=.123, F(4,439)=15.31**^	*+Education***-Age**+Group**
Praxis	.134*^	R^2=.098, F(4,440)=11.78**^	*-Age***+Education***+Group**
General cognition	.268**^	R^2=.165, F(4,438)=21.40**^	*+Education***-Age***+Group**
UK Controls			
Language	.255*^	R^2=.179, F(2,99)=10.58**^	*-Age*** *+Education**
Memory	.162	R^2=.250, F(1,99)=10.25**^	*-Age***
Attention and Executive Function	.141	R^2=.081, F(1,99)=8.87**^	*-Age***
Number	.222	R^2=.096, F(2,99)=5.15**^	*+Education** -Age**
Praxis	.233*^	R^2=.138, F(2,99)=8.91**^	*-Age*** *+Education***
General cognition	.350**^	R^2=.364, F(2,99)=27.77**^	*-Age*** *+Education***
China Controls: Cantonese			
Language	.293**^	R^2=.109, F(1,155)=18.78**^	*+Education***
Memory	.229*^	R^2=.222, F(2,155)=21.79**^	*+Education*** *-Age***
Attention and Executive Function	.489**^	R^2=.314, F(2,155)=7.15**^	*+Education*** *-Age**
Number	.531**^	R^2=.320, F(1,155)=72.59**^	*+Education***
Praxis	.330**^	R^2=.267, F(2,155)=27.84**^	*-Age*** *+Education***

	Education Correlation	Regression Model	Predictors
China Controls: Cantonese			
General cognition	.489**^	R^2=.356, F(2,155)=42.29**^	+*Education*** -*Age***
MOCA	.549**^	R^2=.332, F(1,155)=55.11**^	+*Education* -*Age**
China Controls: Mandarin			
Language	.116	N/A	
Memory	.258**^	R^2=.106 F(2,180)=10.65**^	+*Education*** +*Age***
Attention and Executive Function	.216*^	R^2=.080, F(2,184)=7.96**^	-*Age*** +*Education**
Number	.210*^	R^2=.038, F(1,183)=7.20**^	+*Education***
Praxis	.109	N/A	
General cognition	.217*^	R^2=.063, F(2,182)=6.02*^	+*Education*** -*Age**
MOCA	.252*^	R^2=.063, F(1,147)=9.89*^	+*Education***

Notes. ** Significant at p<.001. * Significant at p<.050. +/- indicates a positive or negative direction. ^ Survived correction for multiple comparison p= .005/6 or .005/7 =.0083/.00071.

In each regression model it contained a number of predictor variables. For the UK stroke cohort, beyond age it also included the HADs and Barthel Index. Only the predictor variables that survived the regression are reported as predictors.

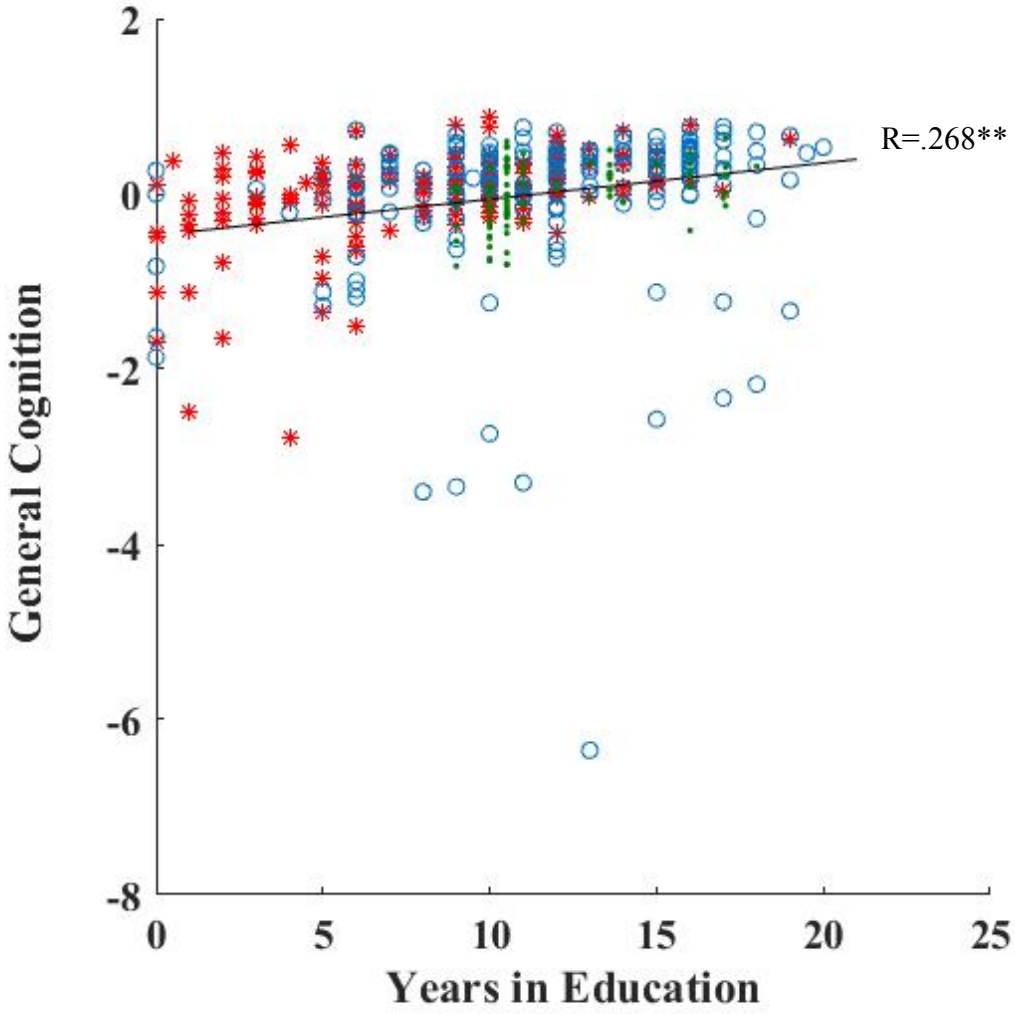


Figure 6. Correlation of general cognition (y-axis) by years in education (x-axis). Three healthy ageing cohorts presented: Dark green circle- UK cohort, Red Star-Mandarin cohort, Blue circle- Cantonese cohort. General cognition is plotted after variability in age and test language were removed.

3.4.2 Study 2: UK and China Stroke

Table 9 reports the demographics of the three stroke cohorts. The UK stroke patients spent a median of 11 years in education, M-China 9 years and C-China 8 years (Figure **7**). The level of education in both the China Stroke patients was lower than the UK. UK vs. M-China were reliably different in their education levels t(80.77)=-3.35 , p <.001. The Cantonese speaking China cohort (C-China) were reliably less educated from both former cohorts, C-China vs. UK: t(154.01)=-11.19, p <.001; C-China vs. M-China, t(203)=-4.66, p<.001.

UK cohort median age was 72, M-China was 63 and C-China was 70; UK were older than. M-China t(100.85)=-4.77, p<.001; but not different to C-China t(955)=-.908, p=.365; M-China were younger than C-China t(201)=3.42, p<.001. Age correlated with education in the UK-Cohort (r= -.281, p <.001), and C-China (r= -.214, p =.014), but not in M-China (r= .030, p =.804).

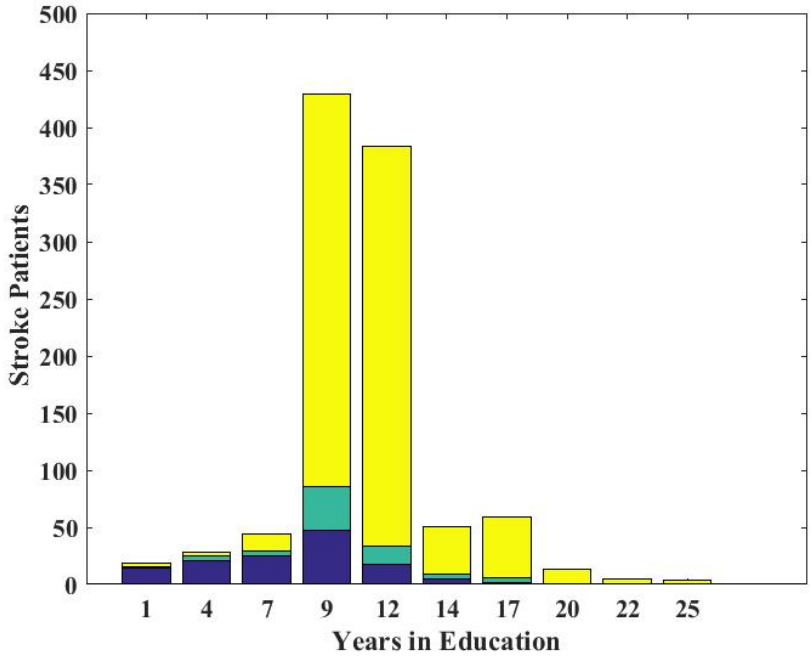
There was an equal representation of female to male stroke patients across all three cohorts. There was a small difference of education between the sexes in the UK cohort (r=.086, p=.013). A minority of UK stroke patients had haemorrhagic stroke (114). Education level did not reliably differ between the stroke types.

Table 9. Demographic and clinical characteristics for Study 2 (Stroke)

	U.K Stroke (n=826)			Mandarin Stroke (n=73)			Cantonese Stroke (n=132)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Age (years)	69.92 (13.73)	72	18:95	64.26 (9.20)	63	41-88	69.03 (9.68)	70	50-94
Years of Education	11.21 (2.69)	11	3-26	9.88 (3.29)	9	0-22	7.45 (3.70)	8	0-17
Gender (Male: Female)	368:458			31:42			79:53		
Stroke to Assessment (days)	29			5			9		
Type of Stroke (Ischemic: Haemorrhagic)	712:114			73:0			132:0		
Neurological History (History: No History)	516:310								
Lesion Side (Left:Right:Bilateral)	251:289:286								
Baseline Barthel Index	13.17 (5.39)	13.25	0-20						
Baseline HADS anxiety	6.44 (4.35)	6.44	0-21						
Baseline HADS depression	6.03 (3.83)	6	0-21						

Notes. SD: standard deviation. Barthel Index: higher score= more functional ability.

HADs= Hospital Depression and Anxiety scale: higher the score equals higher anxiety and depression level.



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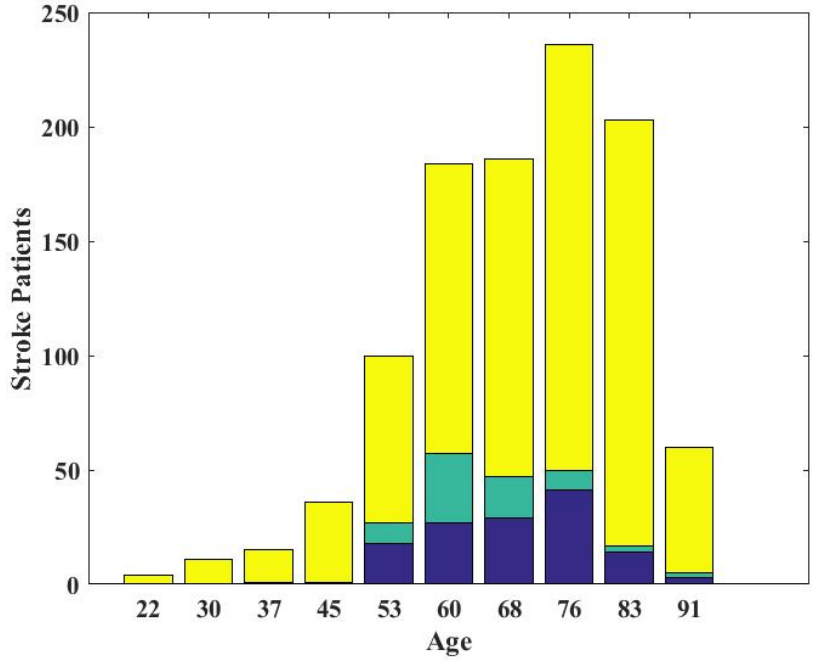

(B)

Figure 7. Dark Blue= Cantonese cohort; Turquoise= Mandarin cohort; Yellow= UK cohort. (B) Stroke cohorts/ Years of Education. Years in education is presented in the x-axis, and numbers in each cohort is represented in the y-axis. (C) Stroke cohorts/ Age. Age is presented in the x-axis, and numbers in cohort is represented in the y-axis.

Levels of cognition differed across the three stroke groups (Table 10). The UK stroke demonstrated more severe post-stroke cognitive abilities, compared to the Chinese stroke cohorts (e.g. for general cognition: UK vs. M-China $t(427.55)=17.80$, $p<.001$; UK vs. C-China $t(736.99)=17.62$, $p<.001$. The two Chinese cohorts demonstrated similar post-stroke cognition (e.g. for general cognition: C-China vs. M-China $t(175.3)=-88$, $p=.339$.

Table 10. Cognitive profiles for participants in Study 2 (Stroke)

	U.K Stroke (n=826)			Mandarin Stroke (n=73)			Cantonese Stroke (n=132)		
Language	-5.73 (8.20)	-2.28	-28.54-.46	-1.15 (2.22)	-.376	-9.10-.45	-.99 (1.96)	-.178	-8.31-.70
Attention and Executive Function	-.584 (6.49)	-3.63	-31.11-.75	-.438 (1.24)	-.117	-8.10-.42	-.647 (1.22)	-.155	-5.21-.63
Number	-3.20 (4.05)	-1.46	-11.30-14.81	-.765 (1.11)	-.441	-398-.41	-.952 (1.61)	-.312	-5.21-.61
Praxis	-2.41 (3.21)	-1.33	-12.28-15.45	-.438 (.94)	-.201	-4.29-.55	-.773 (1.57)	-.211	-7.21-.59
Memory	-4.76 (6.94)	-1.97	-32.01-.62	-.508 (1.16)	.136	-5.29-.57	-.810 (1.51)	-.180	-7.19-.73
General Cognition	-4.93 (4.79)	-2.65	-22.67-1.58	-.660 (1.08)	-.355	-4.96-.47	-.811 (1.33)	-.319	-6.05-.48
MoCA				19.80 (6.47)	20	4-29	20.15 (5.86)	22	4-30

Notes. SD: Standard Deviation. MoCA= Montreal Cognitive Assessment; Cognition is represented in z scores= standardised deviation from each of their own control cohort.

Partial correlation analyses were computed across settings (UK and China) to assess the impact of education on cognition in a stroke population, specifically in the short-term period following stroke. Education positively correlated across domains, general cognition r=.090, p<.050 (Figure 8), and within domains; language r=.103, p<.050 and number r=.101, p<.050. There were no significant correlations for memory, attention and executive function, and praxis.

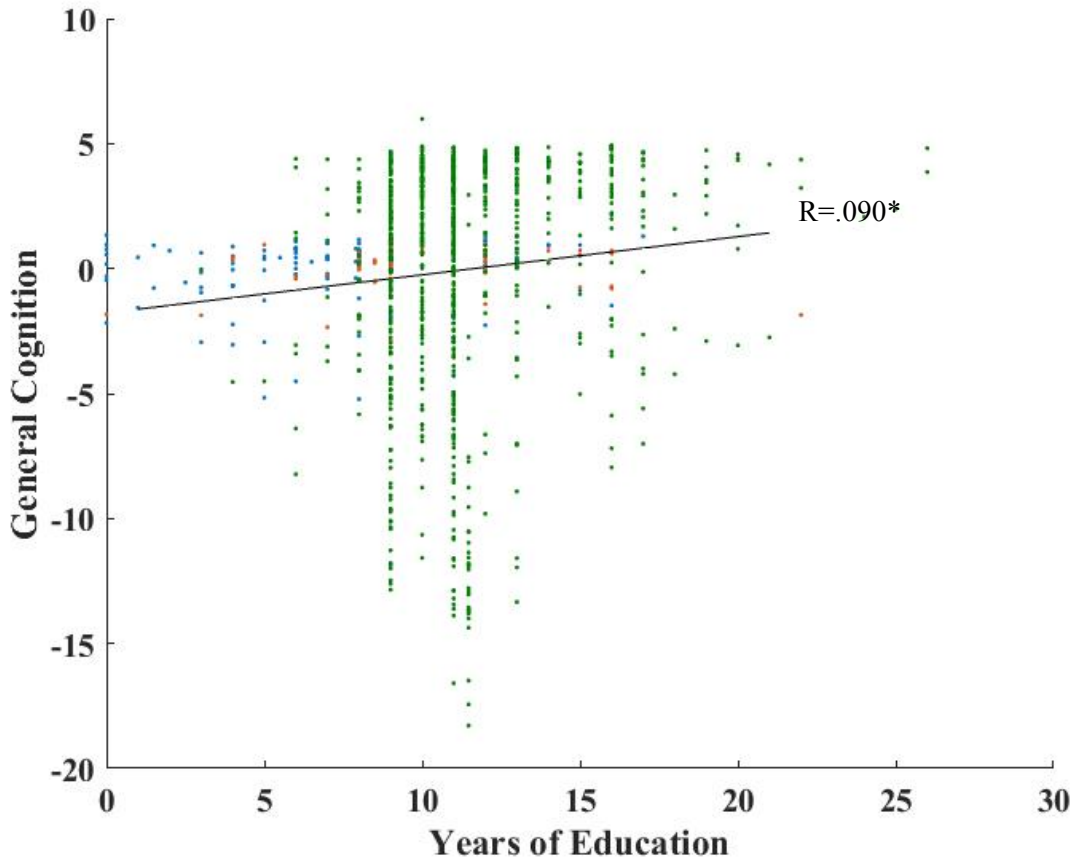

Figure 8. Correlation of general cognition (y-axis) by years in education (x-axis). Three stroke cohorts presented: Dark green circle- UK Stroke, Red Star-Mandarin Stroke, Blue circle- Cantonese Stroke.

Table 11. Correlation and regression models for Study 2 (Stroke)

	Education Correlation	Regression Model	Predictors
UK and China Stroke			
Language	.103*^	R^2=.071, F(2,1027)=39.03**^	*-Group**+Education**
Memory	.055	R^2=.064, F(2,1027)=47.19**^	*-Group**-Age**
Attention and Executive Function	.053	R^2=.143, F(2,1027)=85.32**^	*-Group**-Age**
Number	.101*^	R^2=.093, F(3,1023)=35.05**^	*-Group**-Age**+Education**
Praxis	.050	R^2=.119, F(2,1027)=69.21**^	*-Age**+Group**
General cognition	.090*^	R^2=.102, F(3,1026)=51.99**^	*+Group**-Age**+Education**
UK Stroke			
Language	.111**^	R^2=.038, F(2,821)=16.11**^	*+Baseline Barthel** +Education**
Memory	.056	R^2=.051 F(3,821)=14.53**^	*+Baseline Barthel**-Age**-Baseline Depression**
Attention and Executive Function	.054	R^2=.088, F(3,821)=26.14**^	*+Baseline Barthel**-Age**-Baseline Depression**
Number	.102*^	R^2=.061 F(3,820)=17.84**^	*+Baseline Barthel**-Age**+Education**
Praxis	.069*^	R^2=.126, F(4,820)=29.35**^	*-Age**+Baseline Barthel**-Baseline Depression* +Education**
General cognition	.096*^	R^2=.087, F(4,820)=19.36**^	*+Baseline Barthel**-Age**-Baseline Depression**+Education**
China Stroke: Cantonese			
Language	.167	R^2=.040, F(1,130)=5.33*^	*+Education**
Memory	.192*^	R^2=.049, F(1,130)=6.66*^	*+Education**
Attention and Executive Function	.131	NA	
Number	.162	R^2=.047, F(1,130)=6.30*^	*-Age**
Praxis	-.017	NA	

	Education Correlation	Regression Model	Predictors
China Stroke: Cantonese			
General cognition	.152	R^2=.040, F(1,130)=5.39*^	-*Age**
MOCA	.011	NA	
China Stroke: Mandarin			
Language	.113	NA	
Memory	-.074	NA	
Attention and Executive Function	.101	NA	
Number	.102	NA	
Praxis	-.279*^	R^2=.079, F(1,71)=5.96*^	-*Education**
General cognition	.028	NA	
MOCA	-.019	NA	

Notes. ** Significant at p<.001. * Significant at p<.050. +/- indicates a positive or negative direction. ^ Survived correction for multiple comparison p= .005/6 or .005/7 =.0083/.00071. For the UK stroke cohort, beyond age it also included the HADs and Barthel Index.

For each cohort (Table 11) we computed separate partial correlations of education with each cognitive measure. In the UK cohort education positively correlated with language, number, praxis, and general cognition with effect sizes of Pearson r from .069 to .111. For the C-China cohort the effect sizes (Pearson r) ranged from -.017 (praxis) to .192 (memory), with only memory showing reliable relations. The pattern was slightly different for the M-China cohort, where the impact of education ranged from negative -.279 (praxis) to positive .113 (language), with only praxis (-.279) showing reliable effects. The two China samples included the frequently used MoCA to assess general cognition following stroke. In neither of the cohort education MoCA scores (Table 11). Given the relatively small sample size in this cohort, inferences should be made with caution (see column 2 Table 11).

The UK cohort included measures of functional abilities and mood. Step-wise regression included these variables and age. Education was a reliable predictor of general cognition, as well as praxis, number and language. Not surprisingly functional abilities (Barthel Index), depression levels (HADs), and age also contributed to cognitive outcomes (Table 11).

3.4.3 Study 3: UK stroke recovery

Baseline demographics of this cohort are reported in Table 8. Patients who were followed up presented a similar profile to the one in study 2 UK sample; this was true for age, gender, stroke type, and years of education (Table 12). Functional status, measured by the Barthel Index improved from baseline to follow up, as did mood measured by the HADs.

Table 12. Demographic and clinical characteristics for Study 3 (Follow Up UK Stroke)

	U.K Stroke Follow Up (n=380)		
	Mean (SD)	Median	Range
Age (years)	69.28 (12.87)	71	18-91
Gender (Male: Female)	213:167		
Neurological History (History: No History)	127:253		
Type of Stroke (Ischemic: Haemorrhagic)	358:22:00		
Lesion Side (Left:Right:Bilateral)	110:151:46		
Stroke to Assessment (months)	0.55	0	0:14
Baseline to Follow Up Assessment (months)	8.74	0	0:14
Years of Education	11.62 (2.92)	11	3-24
Baseline Barthel Index	12.63 (5.92)	13	0-20
Baseline HADS anxiety	6.46 (4.48)	6	0-21
Baseline HADS depression	6.23 (3.92)	6	0-20
Follow up Barthel Index	17.02 (4.02)	19	0-20
Follow up HADS anxiety	5.82 (4.33)	5.82	0-21
Follow up HADS depression	5.87 (3.80)	5.87	0-20

Notes. SD: standard deviation. Barthel Index: higher score= more functional ability. HADs= Hospital Depression and Anxiety scale: higher the score equals higher anxiety and depression level.

Table 13. Cognitive profiles for participants in Study 3 (Follow Up UK Stroke)

	U.K Stroke Follow up (n=380)		
	Mean (SD)	**Median**	**Range**
Language	-2.47 (5.53)	-.37	-25.05-.50
Attention and Executive Function	-2.41 (3.45)	-.97	-20.80-.74
Number	-1.68 (3.14)	-.125	-11.27-.44
Praxis	-1.32 (2.62)	-.548	-12.13-.71
Memory	-1.98 (3.95)	-.31	-25.01-.61
General Cognition	-1.97 (.94)	-1.36	-15.96-.54

Notes. SD: Standard Deviation. MoCA= Montreal Cognitive Assessment. Cognition is represented in Z scores= standardised deviation from UK control cohort.

Partial correlation analyses were computed to assess the impact of education on cognition at nine months following stroke (Table 14), controlling for age and baseline cognitive deficits. Education positively correlated across domains, general cognition $r=.157$, $p<.001$(Figure 9), and within domains; language $r=.111$, $p<.005$, number $r=.173$, $p<.001$. There were no significant correlations for memory, praxis and attention and executive function. Step wise regression included cognitive outcomes at baseline, age, functional abilities and mood measures at baseline, and follow up. Education was a reliable predictor of general cognition, attention and executive function, praxis and number domains.

Table 14. Correlation and regression models for Study 3 (Follow Up UK Stroke)

	Education Correlation	Regression Model	Predictors
Baseline			
Language	.204**^	R2=.0.76, F(2,379)=15.43**^	+*Baseline Barthel*****+*Education***
Memory	.172*^	R2=.131, F(3,379)=25.81**^	+*Baseline Barthel*** +*Education*** -*Baseline Depression**
Attention and Executive Function	.081	R2=.139, F(3,379)=20.17**^	+*Baseline Barthel*****-*Age**-*Baseline Depression**
Number	.166*^	R2=.0.80, F(2,379)=16.32**^	+*Baseline Barthel*** +*Education****
Praxis	.115*^	R2=.140, F(4,379)=15.29**^	+*Baseline Barthel*** +*Education**-*Age**-*Baseline Depression**
General cognition	.184**^	R2=.129, F(2,379)=27.97**^	+*Baseline Barthel*** +*Education****
Follow Up			
Language	.111*^	R2=.414, F(2,379)=133.245**^	+*Language Baseline*****-*Follow Up Depression**
Memory	.092*^	R2=.157, F(2,379)=35.00**^	+*Memory Baseline*****+*Follow Up Barthel****
Attention and Executive Function	.173*^	R2=.411, F(4,379)=65.49**^	+*Attention Baseline*****+*Follow Up Barthel ***+*Education*****-*Follow Up Depression****
Number	.173*^	R2=.412, F(3,379)=87.94**^	+*Number Baseline*****+*Follow Up Barthel*****+*Education****
Praxis	.105*^	R2=.201, F(3,379)=31.52**^	+*Praxis Baseline*****+*Follow Up Barthel*****+*Education**
General cognition	.157*^	R2=.432, F(4,379)=71.22**^	+*General Baseline*****+*Follow Up Barthel*****+*Education*****-*Follow Up Depression**

Notes. ** Significant at P<.001. * Significant at <.050. +/- indicates a positive or negative direction ^Survived correction for multiple comparison P = .005/6 =.0083.

For the UK stroke cohort, beyond age it also included the HADs and Barthel Index. Note that in study 3, the baseline, and follow up measures of the HADs and Barthel Index and baseline cognition were included.

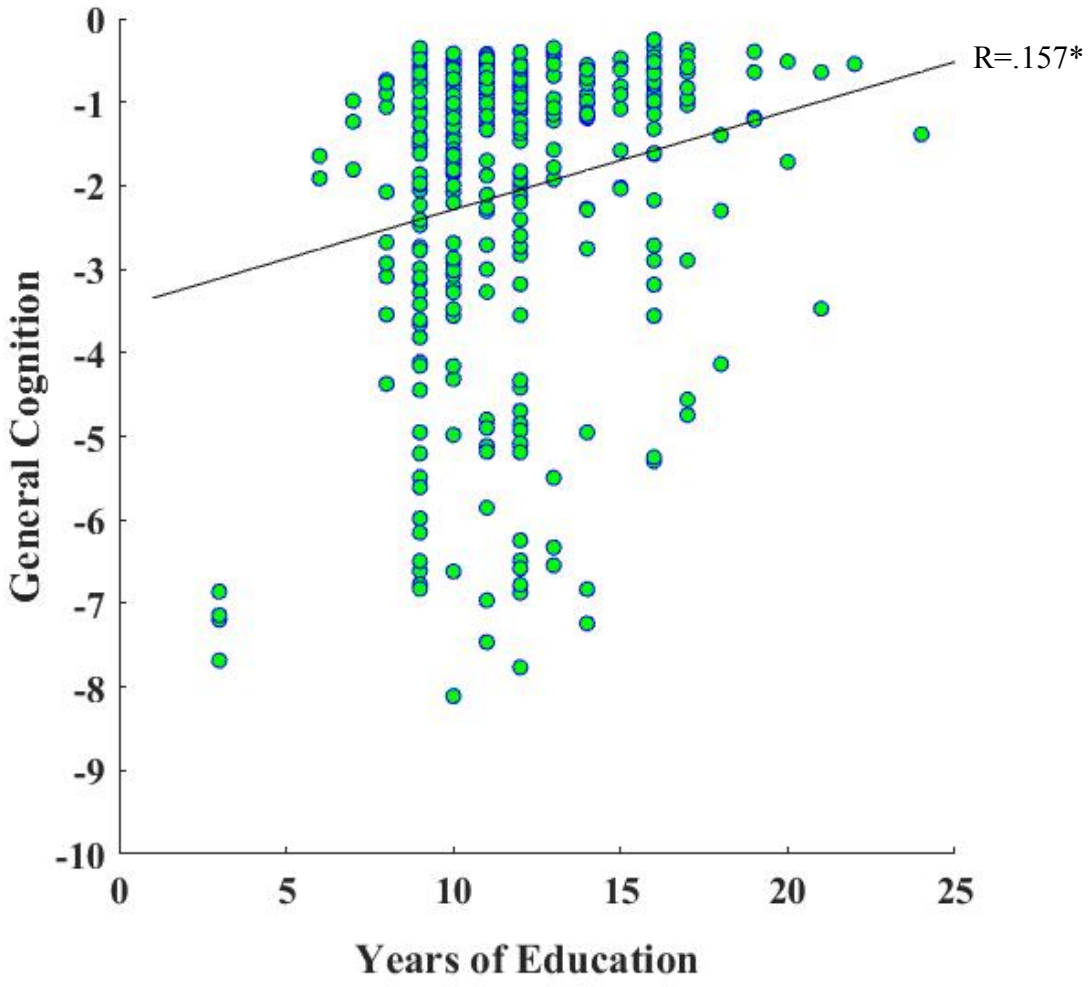

Figure 9. Correlation of UK stroke follow up general cognition (y-axis) by education years (x-axis). General cognition is plotted after variability in age, and baseline cognition were removed.

Beyond education, not surprisingly, general cognition and abilities of memory, attention and executive function, number, and praxis were predicted by cognitive ability at baseline and functional ability (Barthel Index). Language ability at nine months following stroke were not affected by functional abilities. Higher levels of depression at follow up predicted language, attention and executive function and general cognition abilities at nine months post-stroke.

We next explored whether education predicted the rate of change from baseline to follow up. This was calculated by examining the percentage of change from baseline to follow up, relative to baseline. We computed Pearson correlations, and controlled for age, using Bonferroni correction (alpha = .05/12 comparisons, corrected alpha = .0042). Positive correlations indicated that more years in education related to larger recovery rates at nine months post-stroke.

After controlling for age, education linearly predict the cognitive change rate, across domains ($r = .234$), and within the number ($r = .236$), language ($r = .213$) and attention and executive function ($r = .188$) domains, (all uncorrected $p < .001$). Recovery of praxis ($r = .138$, uncorrected $p = .007$), and memory ($r = .144$, uncorrected $p = .005$) only trended toward significance, after applying family wise error correction.

In summary, after controlling for baseline ability, and age, years in education predicted cognitive ability within, and across domains at nine months and it also accelerated recovery rates.

3.5 Discussion

The present chapter examined the impact of education on cognition in three neurological contexts. After age and cultural settings were controlled for, study 1 showed that education interacted with (within and across) cognitive domains. Study 2 demonstrated that education improved cognitive outcome following stroke. Study 3, showed that more years in education improved cognitive outcomes at nine months following stroke, and additionally accelerated the recovery rate.

Study 1, replicated previous findings (Christensen et al., 2007; Farfel et al., 2013; Humphreys et al., 2016; Mirza et al., 2016; Pinter et al., 2015; Skoog et al., 2017) that

show that education positively impacted cognitive abilities in an ageing population. We found that beyond age, in the ageing population, education mediated cognition across general cognition, and across the key five cognitive domains (language, attention and executive function, praxis, memory and number). We show this across three cohorts who differ in ethnicity and language. Though, the relations were more reliable in the two China cohorts (see Table 8), potentially because these were larger cohorts, and they were more variable in their education levels. This effect was observed beyond age, though in most of the tests age was independently found to be a negative predictor; where cognitive ability was lower with increased age. Going beyond previous studies we showed that education affected cognition across different cultural settings, and found that it is primarily driven by the ability to retain language and number abilities.

In study 1, all individuals were self-declared healthy, with no previously diagnosed neurological or cognitive impairment. However, within the C-China and especially the M-China cohort, some (18-30%) presented with lower than expected cognitive abilities for their age, showing less than 24 on the C-MoCA, exhibiting cognitive level akin to mild cognitive impairment and dementia (Tan et al., 2015). This was also evident in their C-BCoS scores, where they scored >4 std below their own group average on all domains.

In study 2, education impacted cognitive outcomes within the first month post-stroke across different languages, and cultural settings. This observation replicates previous reports (Mirza et al., 2016; Sun et al., 2014; Withall et al., 2009). This was demonstrated with general cognition, and across all five cognitive domains, it was preserved beyond age and cultural settings. The effects overall were smaller than observed in study 1. The relations were more reliable in the UK than the China stroke

cohorts. This might have been because the UK stroke cohort was more than 7 folds larger, and the cognitive abilities of the stroke patients were more variable than either of the China cohorts.

As the UK stroke sample included measures of functional independence and mood, we examined the contribution of education beyond these measures. The benefit of increased years in education, was observed after controlling for age, Barthel and HADs. In the C-China, and M-China stroke cohort the effect of education on cognition varied between domains. Beyond age, education affected memory in the C-China, but only praxis in the M-China. Surprisingly, the impact of education on praxis in M-China was reversed, more education lead to poorer post-stroke praxis outcomes. This result is unclear and unexpected. It may reflect social-cultural differences that confound education. A part of the praxis assessment in the C-BCoS relies on gesture tasks. It has been suggested that gestures are used less frequently in China than the westernised culture (So, 2010), suggesting the gestures tasks may not be that reliable in the context of the China cohorts. Furthermore, gestures are more commonly used in one's native language proficiency (Gregersen et al., 2009). Thus, it could be that for some M-China patients, especially those coming from rural regions, where mandarin was their non-native language, led them to be less experienced with mandarin gestures. Finally, in study 3 we demonstrated that beyond age and baseline cognition, education correlated with post-stroke recovery at nine months of general cognition, language, praxis, and number domains. After controlling for depression and functional ability, education also predicted recovery of attention and executive function, but did not predict language recovery. When examining recovery rate, education accelerated recovery rate across domains (general cognition), and within domains. This finding challenges the argument

that education relates only to our cognitive ability and not necessarily the rate in which we decline (Berggren et al., 2018). In the present study we demonstrated that education related to both cognitive ability, and also to rate of decline/recovery.

The mechanisms by which education protects cognition in different neurological contexts is assumed to be driven by an increase in cognitive reserve (Farfel et al., 2013; Stern, 2006; Stern, 2012). Cognitive reserve is a concept that is used to describe the resilience of humans' function in light of adverse neurological events. It is assumed that education, together with other experiences across the life-span contribute to increased resilience. It is still unclear how brain reserve is manifested neurologically. One hypothesis suggests that education is associated with overall reduced grey matter atrophy, white-matter disease (Sun et al., 2014), and lesion load specifically in stroke patients (Umarova, 2017). Others have suggested cognitive reserve is made up of two mechanisms; neural reserve which refers to the brain networks that are less susceptible to neurological disruption, and neural compensation refers to the ability of the individual suffering from neurological disruption to use their brain structures to compensate for the damage (Stern, 2006) (See section – for a more detailed description on cognitive reserve).

Alternatively, education may simply improve the ability of an individual to communicate with medical professionals, and understand their medical conditions (Willems et al., 2005) but see (DeVoe et al., 2009; Francis et al., 1969; Verlinde et al., 2012). This in turn could lead to more effective responses to medical advice both in response to general health, and specifically following stroke.

We note here that cultural differences (UK vs. China), are evident in the present analysis, with differences between healthy controls, time of assessment (number of days since stroke), and severity of post-stroke cognition. To account for these potential cultural/sampling confounds, the cognition scores (Z) of each participant/patient were normalised in respect to their own cultural groups. This normalisation procedure enabled us to combined databases to achieve reasonable power to answer the research questions posed in this chapter. For completeness, I report analyses across cultural groups, as well as within each group separately. We acknowledge the potential affects that these difference may have had on the overall results, hence the separate statistical analyses across the groups are also provided.

An important consideration is the sociodemographic status, general lifestyle and overall health of individuals which inherently relates to their education levels (Mirza et al., 2016).

CAMCOG is a large epidemiological longitudinal study examining the onset of dementia in an ageing cohort, and associated factors. They assessed cognition using the MMSE, and followed up participants in a varying time window (one year to 10 years after initial assessment) between 1990-1991 (Brayne et al., 2006). In a sub analyses of 4,075 ageing individuals, it was reported that sex (women vs men), was directly associated with dementia onset, as was incidence of stroke, and education level trended, however social class did not contribute (Yip et al., 2006). A further study, examined education (and other socioeconomic indicators), and its relation to cognitive decline in 15,594 women nurses, between 1995 and 2000. They found that less cognitive decline was evident in those with a bachelor or graduate degree, compared with those with a

nurse diploma. Their socioeconomic status measures were found to be less related to incidence of decline (Lee et al., 2003).

As previously discussed, the present data is in line with evidence that supports the hypothesis of a positive relationship between education and cognition in both ageing and neurological insult. Previous studies show that these relations are evident even after socio-economic status (Yip et al., 2006), and occupation (Lee et al., 2003) are controlled for. However, as this information was not recorded in the current database, we cannot assess the impact of these factors on the current results. Due to the difficulties in partialing out education level, from socioeconomic status, and occupation these factors should not be excluded as a potential influencing variables, and should be taken into account where possible.

The EClipSE collaboration, was a longitudinal epidemiological study, which collected data on cognition, dementia diagnoses, brain tissue, and other demographical details in 90 individuals (Brayne et al., 2010). They found that education did not protect against accumulation of neurodegenerative, or vascular pathology in the brain, which was measured following death, but it did mitigate pathological burden, and cognitive decline. Those with higher education level, had reduced risk of dementia in older age. This finding supports Stern and the reserve hypotheses (Stern et al., 2018). They conclude that those with less education don't necessarily have greater neurodegeneration than those with higher education, but those with higher education do have 'heavier brains' (higher brain volume), and maintain cognition in situations of pathological burden (Brayne et al., 2010). In the current chapter, we examined cognitive reserve in ageing, and also the reserve of individuals in relation to neurological insult (stroke). The results presented in Chapter three, also support the hypotheses that

cognitive reserve (education) may be the mechanism to which cognition is retained in the face of ageing and stroke. In the present chapter, we do not have further information on the profile of the individuals studied, for example to examine their brain volume, in order to fully comply with the cognitive/ brain reserve hypotheses.

The present study used years of formal education as a marker of cognitive reserve and neurological reliance, which does not account for informal education, such as reading. We did not account for any of these factors. Therefore, we cannot rule out that the current results are potentially driven by any of these factors, rather than by formal education per se. However, the consistent correlations of education with both language and number domains, which are the most practiced domains during formal education, suggest that formal education may have directly impacted cognition in the current studies.

3.6 Summary

In these cohort analyses education was found to be a protective factor of cognitive ageing, it improved cognitive outcomes following stroke, and accelerated recovery rate in the first year following stroke. With concerns reported about an ever increasing ageing population (WHO, 2018), and the demands on the economy, increasing the education level of the population could provide a cost-effective way of increasing brain reserve. This may protect cognition against damage caused by stroke and ageing.

Chapter 4: Hippocampal pathology and its impact on post-stroke cognition

4.1 Abstract

4.1.1 Background

It is suggested that the hippocampus is a region in the brain vulnerable to diseases of old age and neurodegenerative damage. In Alzheimer's research, it has been found that the hippocampus is a biomarker of cognitive decline. This suggests a relationship between pathology in the hippocampus and decline of cognition.

4.1.2 Aims

In the present chapter we examined post-stroke hippocampal pathology across three MR measures; ^{1}H-MRS (magnetic resonance spectroscopy, metabolic), diffusion weighted imaging (mean diffusivity) and T1-weighted imaging (volumetric). Based on findings documented thus far for the onset of mild cognitive impairment, and progressive cognitive decline. We aimed to establish whether hippocampal pathology is also present in the stroke population across these three measures. Importantly, in none of the tested patients was the hippocampus directly affected by the ischemic event. To assess whether the association between hippocampus pathology and cognition was affected by stroke, we also recruited non-stroke aged matched control participants. If the incidence of stroke affected hippocampus pathology, we expected to find reliably stronger correlations between hippocampus and cognition in the stroke patients than in control participants.

4.1.3 Method

A total of 42 stroke patients underwent detailed cognitive assessment using the BCoS. Post-stroke cognition was assessed within three months of stroke along five cognitive domains (language, memory, attention and executive function, number and praxis) and across domains (general cognition). Hippocampal pathology was examined using three magnetic resonance imaging methods; diffusion tensor imaging (mean diffusivity), T1-weighted imaging (volumetric) and magnetic resonance spectroscopy (metabolite). In addition to these measures; mood (HADs), function (Barthel Index) and clinical demographics data was collected. An additional 17 healthy age-matched controls underwent the same protocol. To examine the relationship between hippocampal pathology, stroke incidence and post-stroke cognition, correlation analyses was computed. Moderation analysis was computed to establish whether stroke changes the relation between hippocampal pathology, on post-stroke cognition.

4.1.4 Results

Hippocampal pathology predicted language, number and general cognition at three months post-stroke across all three measures, even though it was not directly affected by the stroke. This was evident in grey matter volume, mean diffusivity, creatine, choline and N-acetylaspartate levels. Relationships between ischemic lesion volume, vascular health, small vessel disease, and regional atrophy (temporal lobe) with cognition were identified in the stroke group. Hippocampus pathology also predicted cognition in the healthy control cohort. No differences in the predictive value of hippocampal pathology were found between stroke and control groups.

4.1.5 Conclusion

This chapter finds that hippocampal pathology may be a biomarker for cognitive outcome in stroke, as it is in healthy ageing. Stroke did not moderate the relation between hippocampus pathology and cognition. Taken together the results suggest that hippocampus pathology is an independent risk factor of cognitive outcome in stroke.

4.1.6 Introduction

The hippocampus is a brain structure within the medial temporal lobe. The understanding of the hippocampus, and its impact on human cognition has developed over the years (Robinson et al., 2015). Initially based on the case of HM hippocampus was primarily thought to associate with memory (Scoville & Milner, 1957). More recently it has been suggested that the hippocampus contributes also to; inhibitory control of learned behaviour, spatial information processing, emotionality, memory and neuroendocrine control (Teyler & Discenna, 1984). The connectome network between the hippocampus, and other brain regions implicates its larger role across cognition (Shohamy & Turk-Browne, 2013). Ageing is associated with disturbances to the functions associated with the hippocampus. These can present themselves in deterioration of memory and lack of ability to learn new things (Samson & Barnes, 2013). These disturbances of external functions are correlated with structural and cellular changes in the hippocampus (Bettio et al., 2017).

Biological changes in the hippocampus have been linked to cognitive impairment. A longitudinal community non neurological cohort study observed decreased hippocampal volume over approximately five years, and this was linked to cognitive impairment in attention and executive function, but not memory (Evans et al., 2018).

Abnormal hippocampal pathology is associated with progressive deterioration of cognition, and the transition from mild cognitive impairment to Alzheimer's disease (Mielke et al., 2012; van Uden et al., 2016). It is suggested that ischemic stroke may also cause indirect structural, and cellular changes in the hippocampus, this is because the hippocampus is assumed to be vulnerable to diseases of later life such as ischemia (Wu et al., 2008).

Research has found that reduced grey matter volume in the temporal lobe has been found in those with silent cerebral infarcts compared with control and this was associated with lower cognitive ability as measured by the MoCA (Yang et al., 2015). At six weeks post-stroke those with previous stroke incidence had lower hippocampal volume compared to first time ever stroke patients, and healthy controls (Werden et al., 2017). Pathological changes have been observed in the acute stage following stroke. When examining cortical thickness within two hours of stroke onset, and at three months, Brodtmann and colleagues found a decrease in hippocampal and thalamic volume in stroke patients, compared with no changes observed in healthy controls across this time frame (Brodtmann et al., 2012). As mentioned above Tang and colleagues (2012) reported smaller hippocampal volume in chronic middle cerebral artery stroke patients in comparison to controls (Tang et al., 2012).

Volumetric changes within this brain region and medial temporal lobe atrophy were associated with incidence of post-stroke dementia at three months post stroke (Pohjasvaara et al., 2000).

Like hippocampal volume, mean diffusivity of the hippocampus is suggested to predict cognition (Carlesimo et al., 2010; den Heijer et al., 2012; Kliper et al., 2016). Increase

mean diffusivity in the hippocampus predicted progression of mild cognitive impairment to early Alzheimer's disease (Mielke et al., 2012; van Uden et al., 2016). Compared to healthy controls, those with mild cognitive impairment had higher mean diffusivity in the hippocampus (Palesi et al., 2012), suggesting damage to microstructures within this brain structure. Furthermore, in 18 patients with mild cognitive impairment co-occurring increased left hippocampal mean diffusivity, and lower left hippocampal grey matter volumes were found to impact verbal memory abilities, but this was not found in the right hippocampus (Müller et al., 2005).

This pattern of abnormal hippocampal pathology, and neurodegeneration is also seen in individuals following stroke. Higher mean diffusivity, and reduced volume in the hippocampus were identified as biomarkers for memory impairment in a stroke cohort with carotid artery disease (Hosseini et al., 2017). More recently this was observed longitudinally, over a period of one year (one month, three months and 12 months post-stroke), hippocampal degeneration was measured using MRI in a cohort of nineteen stroke patients, ipsilesional volumes of the hippocampus decreased, and mean diffusivity increased (Haque et al., 2019). Both higher mean diffusivity, and lower grey matter volume in the hippocampus were found to be associated with impaired cognition at six and 12 months post-stroke (Kliper et al., 2016). Conversely, it has been reported in a cohort of stroke patients who were measured over a period of 10 years, that mean diffusivity did not affect memory when hippocampus volume was normal (Schaapsmeerders et al., 2015).

Neuronal metabolites measured using ^{1}H-MRS can also be used as hippocampus pathology biomarkers. In animals, metabolic reduction of N-acetylaspartate (NAA) in the hippocampus was associated with cognitive decline in memory, and learning

alongside decreased hippocampal volume (Liang et al., 2017). In humans, decreased NAA, and increased choline (Ch) in the hippocampus and other brain regions was observed in the progression of Alzheimer's disease, compared to healthy controls (Kantarci, 2007; Targosz-Gajniak et al., 2013). This pattern of metabolic change in the hippocampus identifies those converting from mild cognitive impairment to dementia, at the early stages of decline (Seo et al., 2012; Tumati et al., 2013), with decreased NAA metabolic concentrations suggested to be a possible pre-clinical marker of Alzheimer's disease (Kantarci et al., 2011; Waragai et al., 2017).

In 21 Alzheimer's patients, decreased NAA, and increased Creatine (Cr) in parietal and occipital regions was found, with NAA levels correlating with cognition (MMSE) (Huang et al., 2001). However, the direction of metabolite concentration is not always consistently reported across neurodegenerative diseases (Su et al., 2016), with Ch (Choline) measured in cerebrospinal fluid reported to be higher in those with vascular dementia and multiple infarct dementia, compared with Alzheimer's type dementia, and healthy controls (Tohgi et al., 1996). Thus, metabolite concentrations may vary depending on the process of neurodegeneration occurring (Liu et al., 2013). Alzheimer's disease patients were found to have a correlation between ratios of decreased NAA/myo-insitol in the mesial parieto-occipital lobes and lower scores on MMSE, with the same correlation not observed in vascular dementia patients. (Waldman & Rai, 2003).

Research looking at metabolite concentrations following ischemic injury, often focuses on measuring changes within the lesion. In animal models, metabolic concentrations have been examined following ischemic injury. Following acute middle cerebral artery stroke, concentrations of Ch in the ischemic tissue are reported to increase, and NAA to

decrease, compared to sham (Ruan et al., 2017). In humans, decreased Ch in the early post-stroke stage has been found in abnormal tissue, but recovered at three months, in contrast, reduced Cr in abnormal tissue is reported even at three months post-stroke (Muñoz Maniega et al., 2008). Similarly, NAA within the lesion site was found to be decreased in the acute stage post-stroke (Felber et al., 1992; Graham et al., 1993), and sub-acute phase (Wardlaw et al., 1998), with continued decreased NAA in relation to Ch at the chronic stage (Felber et al., 1992). Reductions in NAA concentrations at the acute phase, are associated with reduction in functional ability, measured by the Barthel Index (Federico et al., 1998). Thus, demonstrating the potential prognostic value of metabolite concentration in the post-stroke brain on outcomes.

Additionally, cortical thickness and metabolic changes have been observed in the chronic stage following stroke, with lower tNAA in the ipsilesional motor cortex, and reduced precentral gyrus thickness (Jones et al., 2016). Furthermore correlations between peri-infract tNAA concentration level, and associated white matter atrophy in the infarcted hemisphere was identified in stroke patients between one and three months post-stroke (Yassi et al., 2016). As seen in mild cognitive impairment and Alzheimer's disease, metabolic concentration levels are associated with impaired post-stroke cognition. As mentioned above, decreased ratio of NAA/Cr and increased ratio of ml/Cr are reported in the hippocampus of chronic stroke survivors relative to controls (Tang et al., 2012).

In acute stroke patients with mild cognitive impairment, hippocampal NAA/Cr ratio was lower compared to those with no cognitive impairments, this was correlated with MoCA scores (Meng et al., 2016). Ross and colleagues suggest metabolite measurements of NAA may be more valid in identifying early cognitive impairment

following stroke than structural measurements, such as volume (Ross et al., 2006). They found that frontal region NAA/Cr concentration predicted cognitive decline over 12 months, and up to three years post-stroke (Ross et al., 2006). Decreased NAA level in stroke patients with cognitive impairment was found, compared to stroke patients with no cognitive impairment, and healthy controls when matched on age, gender, education and time post stroke (Wang, 2017).

To summarise the metabolite literature, NAA is a reliable biomarker for pathological brain tissue, shown in neurodegenerative research. Like all MRI measures, metabolites are also relative measures. Some authors use a ratio of metabolite to creatine (or choline) level to adjust the value. This assumes that creatine (or choline) is not affected by tissue pathology. Though, this assumption can be challenged by the above literature. For example, creatine is suggested to decrease flowing stroke; while choline is reported to decrease in early stages of stroke, but increase in Alzheimer disease. Therefore, in the current analysis the values of the metabolite will be scaled relative to lipid and overall grey matter in the voxel, but not to each other.

4.2 Methods

4.2.1 Participants

Between July 2015 and January 2019, a total of 71 stroke patients were recruited to the Hippocampal pathology of post stroke cognitive impairment study (HiPPS-CI), from two West-Midlands hospitals (Queen Elizabeth Birmingham and Sandwell General Hospital) (See Appendix 4.2.1.1).

The inclusion criteria for the study were (a) recent (less than three months) clinically diagnosed ischemic stroke, (b) age >18 to <90 years, (c) able and willing to provide

informed consent and (d) cognitive impairment (Montreal cognitive assessment MoCA <=26/30) (Nasreddine et al., 2005). Stroke patients were excluded from the study if they (a) had contraindication to have Magnetic resonance imaging (MRI) e.g. metal foreign body (pacemaker, aneurysm clip, possibility of metal fragments in the eye, etc), (b) unfit or unable to tolerate MRI e.g. unable to lie flat due to backache or severe kyphosis, shortness of breath, (c) Severe disabling stroke (m-Rankin Scale > 4) (Fish, 2011), (d) known pre-stroke dementia or cognitive impairment as confirmed by family members or medical documents. Stroke patients were recruited within their hospital admission. At this stage informed consent was taken, and clinical and demographic information recorded. They were invited to attend Birmingham University to take part in a cognitive assessment, and MRI within three months of stroke.

A total of 20 control participants were recruited during the same period, they were recruited as relatives of stroke patients or from the local community. This was an opportunistic sample with the aim to match the stroke patients on age. The control participants were self-declared healthy. Inclusion criteria consisted of (a) no previous history of stroke, dementia or cognitive decline, (b) no contraindication to have MRI e.g. metal foreign body (pacemaker, aneurysm clip, possibility of metal fragments in the eye, etc). Exclusion criteria included (a) unfit or unable to tolerate MRI e.g. unable to lie flat due to backache or severe kyphosis, shortness of breath, and (b) less than 26 on the MoCA. (See Appendix 4.2.1.2)

In the present analyses a total of 42 stroke patients and 17 controls were included. Reasons for participants not taking part in assessments following recruitment included a) withdrawal, b) unable to contact, c) death. Additionally, one participant was excluded as they had a stroke that directly affected bi-lateral hippocampi. Three controls were

excluded because of incidental findings (e.g. enlarged ventricles, silent stroke) or due to mild cognitive impairment as indicated by the MoCA score (<26). Of note, two of the controls that were excluded also reported some cognitive clinical symptoms when they were assessed. Across each MRI measure the number of individuals included varied. Reasons for the variation were due to; (a) not completing the scan, and (b) removal of data due to quality issues such as excessive movement, poor signal to noise. For each analyses the following number of participants were included; Grey matter hippocampal volume, 42 stroke patients and 17 controls; mean diffusivity, 35 stroke patients and 15 controls, and for ^{1}H-MRS, 31 stroke patients and 17 controls. Due to the uneven numbers across the three MR measures, representative demographical and clinical information for both stroke patients and controls were taken from the grey matter volume cohort which was the largest (stroke n=42, control n=17) for descriptive statistics (Table 15). Stroke specific clinical information is reported in Table 16. We note a lower incidence of previous stroke in the sub-sample of mean diffusivity (20%) than in the grey matter volume cohort (16.6%), $t(41)=2.91$, $p=.006$. The ^{1}H-MRS stroke sub-sample group were less educated than the grey matter volumetric cohort $t(59)=2.02$, $p=.048$. No other clinical-demographic variables varied between the sub-samples.

Mean stroke severity as measured by the NIHSS was five, demonstrating a mild stroke severity cohort. Eight of the 42 stroke patients had been thrombolysed. The ischemic lesion characteristics of the cohort consisted of equal distribution of cortical vs subcortical; twice the number of left sided lesions compared with right lesions. There was little overlap between the lesions in the current cohort. Two patients had partial overlap of their right inferior parietal lesions, and two had partial overlap in their right sub-cortical lesion.

Ethical approval was given by the UK Health Research Authority and West Midlands Black Country Research Ethics Committee (15/WM/0209).

4.2.2 Measures

4.2.2.1 Demographic and clinical information

For each stroke patient clinical and demographic data was collected. This included age, sex, and years of education, patient medical history (dementia, stroke, diabetes, hypercholesterolemia, atrial fibrillation, hypertension, ischemic heart disease, myocardial infarction, peripheral vascular disease), medication (anticoagulant, antiplatelet, hypertensive, statins, antidepressant), and cigarette smoking (per week) was collected. Stroke severity was recorded based on the national institute of health stroke scale (NIHSS), (Ortiz & L. Sacco, 2014) assessed on admission to the emergency department. The scoring consists of a scale 0-42, with 42 documenting a severe stroke.

For the control participants demographic data included: age, sex, years of education, medical history, medication, and cigarette smoking. Questionnaires were completed for both groups to assess activities of daily living (Barthel Index score) (Mahoney & Barthel, 1965), with a higher score demonstrating better functional ability. Mood was also assessed (Hospital anxiety and depression scale), with a higher score demonstrating a lower mood (Zigmond & Snaith, 1983).

Table 15. Demographic and clinical information including group differences (HiPPS-CI study)

	Stroke (n=42)			Control (n=17)			
	Mean (Std)	**Median**	**Range**	**Mean (Std)**	**Median**	**Range**	**P value**
Age (years)	63.48 (12.66)	63.50	34:85	62.18 (10.10)	63.00	39:76	.681
Sex (male:female)	32:10			5:12			.000 [a]
Education	11.90 (2.58)	11.00	9:19	14.94 (3.19)	16.00	10:20	.002 [a]
HADs Anxiety	5.88 (4.36)	5.00	0:17	3.00 (1.69)	3.00	0:8	.001[a]
HADs Depression	5.14 (3.65)	4.00	1:14	1.29 (1.40)	1.00	0:6	.000[a]
Barthel Index	17.45 (3.42)	19.00	8:20	19.18 (1.18)	19.00	15:20	.006
Vascular Risk	27.45 (13.47)	28.00	0:64	10.53 (11.76)	27.45	0:35	.000[a]
MoCA	21.00 (4.56)	17.00	9:26	26.41 (1.21)	26.00	25:29	.000[a]
Intracranial Volume mm^3	1495 (128)	1462	1302:1720	1498 (200)	1526	1109:1776	.952
Parietal Lobe Atrophy	0.95 (0.95)	1.00	0:3	1.00 (0.70)	1.00	0:3	.833
Temporal Lobe Atrophy	0.85 (0.95)	1.00	0:4	0.11 (0.33)	0	0:1	.000[a]
Small Vessel Disease	1.35 (0.98)	1.00	0:3	0.88 (0.48)	1.00	0:2	.017

Notes. Std= Standard Deviation, HADs= Hospital Depression and Anxiety scale (higher scores indicate higher severity), Barthel Index (higher scores indicate more functional ability), Vascular risk score from FSRP (higher scores indicate higher vascular risk), MoCA= Montreal Cognitive Assessment (>26 considered healthy cognitive functioning). [a]Bonferonni FME p = .05/12 =.0041.

4.2.2.2 Vascular risk factors

A vascular risk score was calculated for both stroke patients and controls based on the Framingham stroke risk profile (FSRP). FSRP is an estimate of the individuals stroke risk in the next 10 years, and represents a level of vascular health (Wolf et al., 1991). FSRP includes the following risk factors: age, systolic blood pressure (taken at admission to hospital), antihypertensive medication, diabetes, cigarette smoking, history of cardiovascular disease, and atrial fibrillation. In this analysis, risk scores were calculated using different cut offs according to sex. We did not have information on left ventricular hypertrophy, which is traditionally used in this risk calculation. There was missing data for systolic blood pressure for all controls, a percentage vascular risk score was calculated on the available data for each individual. A higher vascular risk score indicated worse prognosis for further stroke incidence, and lower overall vascular health.

4.2.2.3 Cognition measures

Cognition was assessed using the Birmingham Cognitive Screen (Humphreys et al., 2012). The data was pre-processed, and summarised as in previous chapters (2.3.3, 3.3.2.1).

4.2.2.4 MRI acquisition

All images were acquired within three months of stroke on a 3T Philips Achieva Scanner using a 32channel head coil. The protocol consisted of the following sequences: Sagittal T1- weighted image (TR/TE= 8.4/3.8 ms, FOV=175, matrix= 288x232, slice thickness 1mm, voxel dimensions 1x1x1). T1 was used for estimating the local volume of the hippocampus. DTI (TR/TE=7700/57 ms, FOV=86, matrix=224x224, b values= 1000 /mm^2, voxel dimensions 2x2x2, and 32 gradient

directions) used for mean diffusivity analysis. ^{1}H -MRS (TR/TE=2000/37 ms, 2048 complex points, sampling frequency= 2000Hz, averages=12), both water suppressed and water reference data were collected. For the metabolite extraction two voxels of dimensions (20x15x30mm) placed on the left and right hippocampus were planned on T1-weighted anatomical images. The scanner was upgraded about half way through data collection (i.e. 14 of 42 stroke and 8 of 17 were collected before the scanner upgrade) in March 2017, this involved a workstation software upgrade on the Phillips Achieva MRI from release three to five. This upgrade primarily focused on changing of how dicom images were created, saved and stored. For example, image format was changed from Dicom, to the Dicom Enhanced format. Despite the scanner upgrade being a potential confound, we did not expect that this will impact the image quality and analyses. But as a precaution, we accounted for this potential confound in all statistical analyses anyway. The impact of the upgrade was assessed post-hoc, see analysis section below.

4.2.2.5 Ischemic infarct identification, volume and brain health

The presence of acute ischemic infarcts was identified from acute clinical imaging reports. Ischemic infarcts were defined as cortical (if they affected the cortex) or subcortical. Lesion side was defined as left, right or bilateral. Previous infarct (in the cases this was not their first stroke) identification was established via clinical reporting on the acute clinical imaging (see Table 16. Stroke clinical profile).

Quantification of the ischemic lesions was performed manually by two rater's using MRIcroGL. It was guided by clinical imaging reporting. The number of voxels of the lesion site ROI was multiplied by the voxels of the scan (lesion voxels x 0.56 x 0.56 x

1), the lesion was measured in mm^3. The lesion volume is presented as percentage of intracranial volume obtained from CAT12 (see 4.2.3.1).

Table 16. Stroke clinical profile

	Stroke (n=42)		
	Mean (Std)	**Median**	**Range**
NIHSS	5.02 (4.38) 0:20	5.00	0:20
Thrombolysis (yes: no)	8:34		
Lesion Location (Cortical: Subcortical)	23:18		
Lesion Side (Left:Right:Bilateral)	21:13:8		
Lesion Volume mm^3 (%)	0.19 (0.46)	0.04	0:2.40
Previous stroke (yes: no)	7:35		

Notes. Std= Standard Deviation, NIHSS= National Institute of Health Stroke Scale (higher scores indicate higher severity).

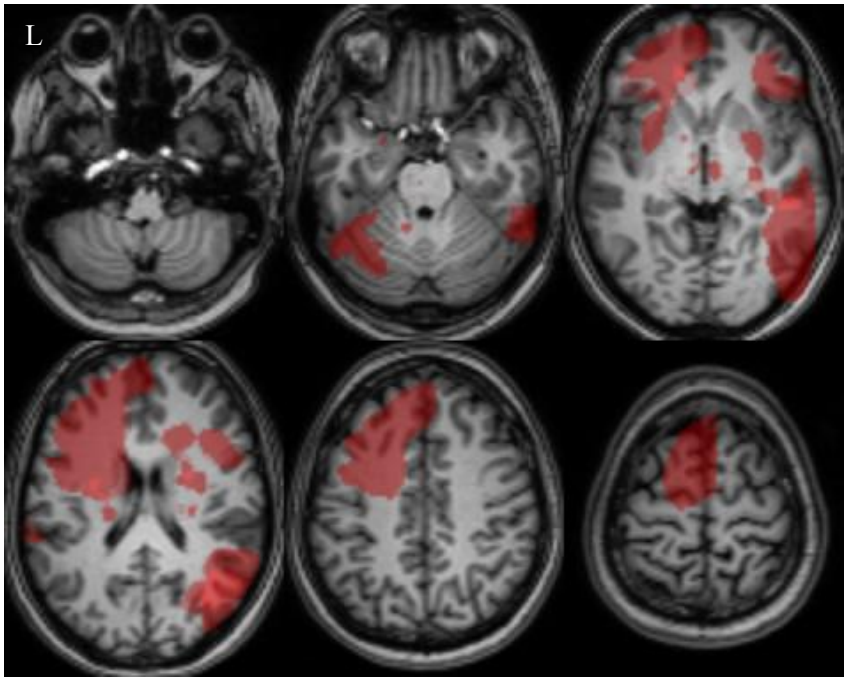

Figure 10. Lesion overlay map

4.2.2.6 Parietal and Medial temporal lobe atrophy

Parietal and temporal regions were graded for atrophy. This was computed for both stroke patients and control participants. Koedam score (parietal atrophy) (Koedam et al., 2011), and MTA visual rating scale (temporal atrophy) (Scheltens et al., 1992) were used to rate the cortical atrophy using T1-Weighted images obtained at time of attendance to the imaging centre (<3 months post-stroke). The scale rated atrophy across a scale from 0-3, with 0 showing no cortical atrophy and 3 demonstrating end stage atrophy. Grading was completed by two rater's, one a clinical radiologist. The ratings were calculated by the two rater's with discussion and in references to guidance of the rating scales. In five stroke patients and four controls, we were unable to complete the grading, and a mean of their respective groups was allocated.

4.2.2.7 Small vessel disease

In both stroke patients and control participants, level of small vessel disease was examined. The Fazekas Scale was used to rate the scale of small vessel disease using FLAIR images obtained at time of attendance to the imaging centre (<3 months post-stroke). The scale rates the level of white matter changes from 0 no small vessel disease to chronic= 3 (Wardlaw et al., 2013). Grading was completed by two rater's, one a clinical radiologist. The ratings were calculated by the two rater's, with discussion and in references to guidance of the rating scales. In five stroke patients and four controls, due to software upgrades, we were unable to complete the grading, and a mean of their respective groups was allocated.

4.2.3 Analyses of MR measures

The effect of the scanner software upgrade was tested using two sample independent t-tests, comparing the signal of all hippocampus measures before and after the upgrade for each measure, across the entire group and for stroke patients alone. No difference was found in the grey matter volume and mean diffusivity hippocampal measures (in the entire group and the stroke group alone, all Ps > .09). The right tNAA's peak was higher after the upgrade compared to before, this was observed in the entire group ($t(46) = 2.31$, $p = .026$) and in the stroke group alone ($t(29) = 2.1$, $p = .045$). Note that this difference did not survive multiple comparison ($P_{corr} = .05/7 = .007$). Nevertheless, we added scanner upgrade as a covariate in all the regression analyses, to ensure that the relations between hippocampal pathology and cognition was not driven by a difference due to scanner upgrade.

4.2.3.1 Volumetric measurement of hippocampi

The volumetric analysis was performed using the T1-weighted images in SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12) and CAT12 toolbox. Each patients' T1-weighted image was warped to the normalized MNI template using the unified segmentation algorithm. This resulted in a tissue probability map for the grey matter. Then each voxel intensity was modulated by the Jacobian deformation map. The modulated segmented images account for changes in local tissue volume, by weighting the value of each voxel by the deformation maps (if the hippocampus was stretched to fit the normalised template then the value of the grey matter voxels in this stretched area is reduced). Therefore, it is assumed that higher values in a voxel tissue probability map indicate larger grey matter volume. From this point forward, we will refer to the modified grey matter tissue probability measure, as grey matter volume. We tested for

each participant the quality of the normalization, and the segmentation by comparing it to SPM standard templates.

The Automatic Anatomical Labelling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) was used to define the left and right hippocampi. To obtain a summary statistic of the voxel's volume within the hippocampus, the VOI toolbox (Eigen variate) of SPM12 was used. This toolbox extracts the first eigen variate that best represents all voxels in the volume of interest (VOI). A higher value indicates more grey matter volume within the hippocampus structure. Intracranial volume was extracted from the CAT12 segmentation tool, which was a value given in mm^3.

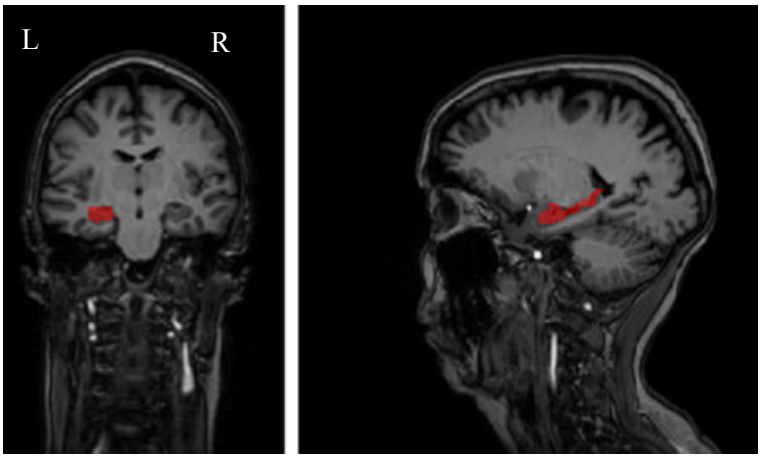

Figure 11. Coronal and sagittal slices of T1-Weighted image.
Left Hippocampus shown in red, selected with AAL toolbox.

4.2.3.2 Mean diffusivity of hippocampi

Mean diffusivity was calculated using both FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki, and SPM (www.fil.ion.ucl.ac.uk/spm/software/spm12). The data was corrected for eddy currents, and motion distortion using eddy correction (Andersson & Sotiropoulos, 2016). Binary masks were created using FMRIB Brain Extraction Tool (BET) (Smith, 2002). Tensors were fitted and eigenvalues estimated (Basser et al., 1994). SPM12 was

used to register individual diffusion maps to T1-Weighed images. Mean diffusivity was extracted using masks from Automatic Anatomical Labelling (AAL) toolbox (Tzourio-Mazoyer et al., 2002) for both the left and right hippocampi. The extracted mean diffusion values were measured as mm^2, and scaled using 10^3 multiplication factor. In healthy brains mean diffusivity values are lower, with higher values demonstrating structurally disorganised, and disintegrated tissue due to water molecules having less restricted diffusion. Therefore, low mean diffusivity is associated with healthier grey matter tissue. Mean diffusivity is expected to negatively correlate with grey matter and with tNAA. When pre-processing the DTI data, we normalised the images prior to the MD extraction. In contrast to the pre-processing of the T1-weighted image, used for measuring the hippocampus volume, we did not modify the DTI signal by the Jacobian deformation map. For functional T2* signal (which is the same signal the DTI is based on), it is not recommended to adjust the signal intensity based on the normalization parameters. As we are focusing only on signal change and not volume, then normalising prior to extraction should not modulate, or cause any changes to the signal we extract. If we were extracting volume then it could cause an issue with values extracted from the images having been normalised (stretched and reduced), and may not represent true values of the individual image.

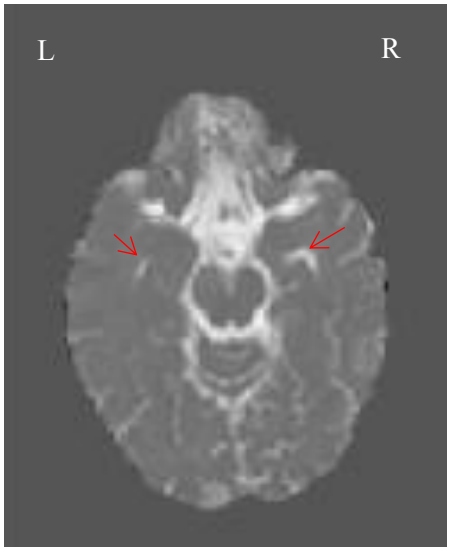

Figure 12. Mean diffusivity map of patient on coronal slice of a single patient. The red arrow points to the hippocampal region. This patient had reduced grey matter volume in their right hippocampus.

4.2.3.3 Magnetic resonance spectroscopy of hippocampi

^{1}H-MRS data was processed using the LC Model analysis software. Absolute metabolite concentrations were calculated by normalising to the water reference acquisition and percentage white matter, grey matter and CSF voxel contributions calculated using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12). Voxel registration, and partial volume metabolite concentration corrections were applied using the 'spant' MRS analysis package for R https://cran.r-project.org/web/packages/spant/index.html. This was processed for both left and right hippocampi. Quality of data was assessed by visually inspecting the spectrum, and examining the signal to noise ratio > 15 (Wilson, Andronesi, et al., 2019). We used a fairly liberal signal-to-noise ratio as the hippocampus is a challenging region to image, since it is in vicinity to the ventricles.

There were consistent issues with the right hippocampus, its spectrum (which was flat), and very low signal to noise ratio (SNR < 5) across most of the participants (>70%). Due to this, the right hippocampus was excluded from the analyses. It is possible that the poor ^{1}H-MRS signal from the right hippocampus was related to a failure in applying the correct shimming, due to a programming bug in the scanner software. In three stroke patients and three controls, SNR was lower than ten but higher than five in the left hippocampus, despite this, they were kept in the analysis as their spectrum showed the expected peaks.

Magnetic resonance imaging (MRS) is a method of MRI that allows us to noninvasively measure alterations in metabolite levels. Deviation from 'normal' levels of metabolites within the brain, can indicate damage or disruption within the brain tissue. Three key metabolites that can reliably be captured by MRS include; N-Acetyl-Aspartate (NAA), Creatine (Cr) and Choline (Cho) (Faghihi et al., 2017). MRS may allow the detection of changes in the brain of post-stroke patients, earlier than volume loss observations.

N-Acetyl-Aspartate (NAA) is one of the most reliable neuronal health markers. Levels of NAA is decreased in situations of neuronal distress, and neuronal loss (Faghihi et al., 2017). Choline is a metabolism marker, and shows a decreased levels in demyelination, and is a marker of breakdown and synthesis of phospholipid membranes (Faghihi et al., 2017).

Creatinine is an energy metabolism marker, rising levels have suggested to be early marker of cognitive decline (Faghihi et al., 2017). In Alzheimer's disease, not surprisingly NAA shows a decreased profile, while ratio of NAA/Cr also show

reduction in temporal regions (Block et al., 2002; Faghihi et al., 2017). Demonstrating both neuronal distress, and decreased energy within the molecules in Alzheimer's disease. Choline does not present with a consistent direction of change however (Faghihi et al., 2017).

The metabolites that were examined included total Choline (tCh), total Creatinine (tCr) and total N-acetylaspartate (tNAA). Calculations for the metabolites consisted of the following; tCh = Glycerophosphocholine (GPC) + Phosphocholine (PCh), tCr = Creatine (Cr) + Phosphocreatine (PCr) and tNAA = N-Acetylaspartate (NAA) + (NAAG) NAA-Glutamic Acid. For tNAA higher values are expected in a healthy brain. It is expected that tNAA will positively correlate with grey matter volume and negatively with age. The expected impact of pathology on the concentration of tCr and tCh is unclear, as the previous reports provide inconsistent pattern. Suggesting changes in Creatine and Choline may differ depending on the disease type and/or progression rather than reflecting general pathology.

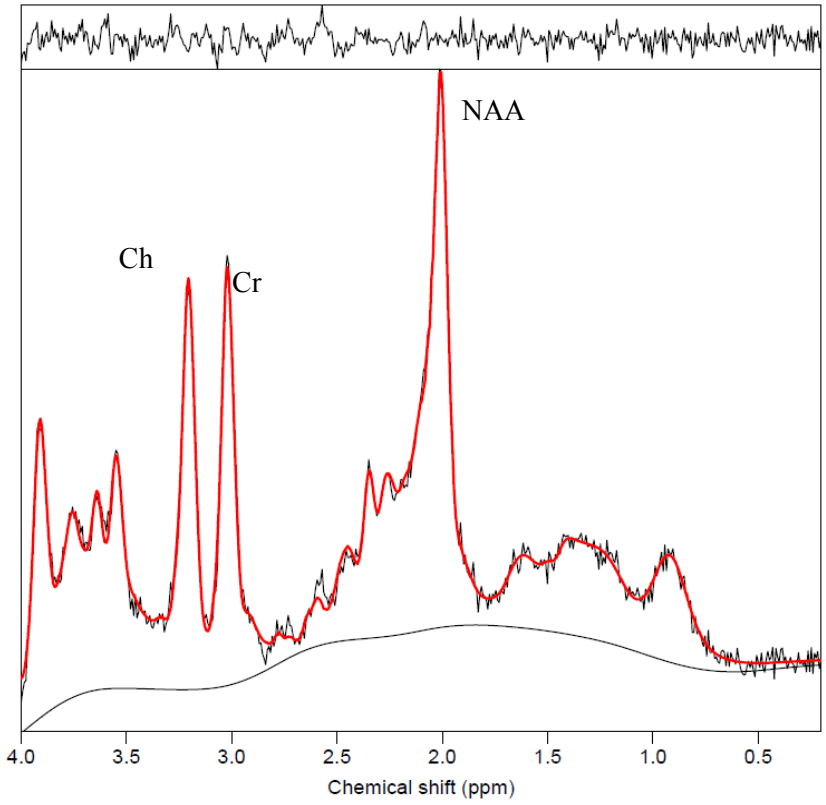

Figure 13. Magnetic resonance spectroscopy spectrum output (example from a stroke patient). Metabolites included in analyses are labelled NAA = N-Acetylaspartate; Cr= Creatine; Ch= Choline.

4.2.3.4 Statistical analyses

SPSS24 was used for all statistical analyses.

Cognitive ability was computed as a deviation score from the controls (Z=(meanControl–Patient score)/stdevControl) (Sampanis, 2015). General cognitive ability was computed by averaging across the five domains. For a full description, see chapter two and three for a full description (2.3.3, 3.3.2.1, 1.2.4.1.).

The differences between the stroke patients and control participants on all clinical, demographic and imaging measures were computed using t-tests, with equal variances not assumed (Chi-square for sex) (Table 15).

To provide an internal validation for the data, the relations between the various measures were assessed. We first looked at the correlation between the demographic and clinical measures. We then correlated those with the hippocampal pathology measures (mean diffusivity, ^{1}H-MRS, and grey matter volume), and then the cognitive domains. Correlations (Pearson r) were firstly computed across a combined group of stroke patients and control participants, and then separately for stroke patients. Due to the some of the variables being dichotomous, and some of the data not being normally distributed Spearman rank was also calculated. We note that the groups had unequal sizes. Hence the correlations in the combined sample were likely to be driven primarily by the largest group (the stroke patients). The control sample was relatively small, and hence was lacking the power to detect the relations between variables on their own (correlations for this group are reported in Appendices 4.6).

The main question of this chapter was to assess whether hippocampus pathology predicts cognitive outcome following stroke, and whether this pattern is different for stroke patients and control participants. We analysed each hippocampal pathology measure independently to the varying number of participants in each measure. Correlation was used to assess the relations of each hippocampus pathology measure, and cognitive domain, this was done for the entire group and each group separately.

To formally test whether the relations between hippocampus pathology, and cognition is affected by stroke incidence we used moderation analyses. This was done by computing

an interaction variable for each of the MRI hippocampal measures and stroke condition. To compute the impact of stroke, we conducted a regression analysis across two models using the combined group of stroke patients and controls. Both models included age, scanner upgrade, and the specific hippocampal measurement as potential predictors of cognition, and differed in the inclusion of the moderated hippocampal variable in the combined group. Beyond the contribution of each variable, these analyses formally assessed whether the two models reliably differed. In other words, did the inclusion of the moderation variable improve the ability to predict the cognition, suggesting that the relations between hippocampal pathology, and cognition were altered following the stroke. As the main interest of this thesis was to examine cognitive outcomes following stroke, we also report a separate regression for the stroke group, to test whether cognition was predicted by the hippocampal pathology after controlling for age and scanner upgrade.

As the correlation analyses (see below) suggested that multiple clinical-demographic variables correlate with cognition, we further assessed whether the relation between cognition and hippocampus pathology in the stroke group is preserved even after controlling in the model for stroke history, lesion volume, stroke severity (NIHSS), vascular risk, and education level. Age was not included in this model, as vascular risk uses age as one of its parameters.

The analysis was run separately for each MR hippocampal measure (i.e. 7 measures). This was due to the high level of correlation between predictors, specifically in small sample size this can lead to spurious findings.

It is important to note that multiple analyses have been conducted on the same set of data, leading to multiple comparisons. As the aim was to explore the data in this new area of research (i.e. not much is yet know about spectroscopy and stroke), a large proportion of the analyses was to establish the internal validity of the measures. We have taken, where possible a hypothesis driven approach, with knowledge gained from other disease areas such as Alzheimer's disease. We took caution with interpreting statistical results that were weak, due to the issues surrounding interpretation of multiple comparisons. In each analysis information is provided of whether significance remained after using Bonferroni-Holmes corrections.

4.3 Results

4.3.1 Demographic and clinical profile

4.3.1.1 Comparison between the controls and the stroke patients

Table 15 presents clinical and demographic data for both stroke patients and control participants. Due to the recruitment criteria, age did not differ between the two groups. Not surprisingly the stroke group were significantly less functionally independent. The rate of vascular risk for stroke was double in the stroke patients, compared with control participants. The stroke patients and controls differed in their representation of sex, with stroke patients predominantly male, and the control group predominantly female. The stroke and control groups were reliably different in their education levels, with the stroke patients having significantly less education years. Mood measured using the HADs, demonstrated significantly higher levels of both anxiety and depression in the stroke patients. The stroke patients scored five points lower than the control group on the MoCA, an effect that is partly driven by the recruitment procedure. Intracranial volume was measured across the two groups; there were no significant differences in volume. The rate of cortical temporal atrophy differed across stroke patients and controls, with stroke patients demonstrating a higher rate of atrophy. In the parietal lobe the stroke patients didn't show increased rate of atrophy, as compared to controls. When examining small vessel disease, we found that stroke patients had a significantly higher rate compared to controls.

4.3.1.2 Associations between the demographic and clinical measures

The relations between the demographic and clinical measures are reported in table (Table 17 and Table 18).

Table 17. Demographic and clinical variable correlations for stroke and controls combined

	1	*2*	*3*	*4*	*5*	*6*	*7*
1 Age	-						
2 Sex	.06	-					
3 Education	-.33*$^{+a}$	-.23	-				
4 HADs A	-.01	-.02	-.15	-			
5 HADs D	.05	.08	-.20^{+a}	.67**$^{++a}$	-		
6 Barthel Index	.09	.08	.05	-.40**$^{+a}$	-.43**$^{+a}$	-	
7 Vascular Risk	.68**$^{++a}$	.15	-.49**$^{++a}$	.17	.27*$^{++a}$	-.13	-

Notes. All N=59, Stroke N=42, Control N=17. Numbers on the X –axis represent the same variables as the Y-axis.

HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression.

Vascular Risk= Framingham stroke risk score

- Indicates a negative correlation. Parametric correlation = ** p<.001 * p<.050,

Non-parametric correlation= ^{++}p<.001, ^{+}p<.050. ^{a}Bonferonni FME 0.5/7=0.07

Not surprisingly vascular risk (calculated from medical history) was associated with severity of small vessel disease (estimated from MR scans) in the entire sample, and the sub-sample of stroke. This is evidence of validation of these two clinical measures.

For both groups combined, age positively correlated with vascular risk score, atrophy rate (temporal and parietal), and small vessel disease; this also held in the correlation within the stroke group only. The correlation of age, and vascular risk should be interpreted with cation as age was included as a parameter in the vascular risk calculation. Taken together, as expected age had an adverse effect on overall brain health.

Education level negatively correlated with age, suggesting the older participants were less educated than their younger counterparts, both when considering the entire sample and the subsample of stroke only. Education negatively correlated with vascular risk,

temporal lobe atrophy and small vessel disease across the entire group. When considering the stroke group on their own education negatively correlated with vascular risk, small vessel disease and positively with intracranial volume. Taking together education was an overall protective factor of measures of brain health, though this was potentially confounded by the age differences observed in education level.

As expected sex affected intracranial volume, with males showing large volumes than females, this was true for the entire sample as well as for the sub-sample of stroke patients only. In the entire sample temporal lobe atrophy was different across sex, with higher atrophy rate for male than females. In the stroke group, females showed more severe small vessel disease than males. Education and age were not different between the two sexes in the entire sample and also in the sub-sample of stroke.

Most of the stroke patients and control participants in this sample showed normal level of anxiety and depression; with only a few classing as severe. Only two stroke patients presented with severe anxiety level, six stroke patients with moderate anxiety level, and five with a moderate depression level. As expected, the level of anxiety correlated with the level of depression, for the combined analysis ($r = .67$), and specifically for stroke patients ($r = .61$); the effects were reliable when using Pearson and Spearman tests. Depression positively correlated with increased vascular risk only in the entire group ($r = .27$), as well as with education ($r = -.20$), the latter effect was only reliable in the non-parametric tests. Sex, age, and degree of brain health were not related to level of anxiety or depression.

4.3.1.3 Association of demographic-clinical profiles and stroke specific measures

Age, sex, and anxiety and depression level did not associate with any of the stroke measures (Table 18). Stroke severity (NIHSS) at admission, and history of previous

stroke also did not relate to any of the clinical and demographic measures. Patients with cortical lesions had larger lesion volumes. It worth noting that the correlation with the right parietal atrophy in general, was only reliable when using Pearson test, suggesting this was primarily driven by small number of people. Furthermore, as clinical marking of atrophy is based on the sulci structure it is not directly affected by the presence of a lesion. Lesion side (left, right, bilateral) did not affect any of the clinical-demographic variables (uncorrected $p>.093$). Functional independence was higher in the less anxious ($r = -.32$) and depressed ($r = -.34$) stroke patients. Education was associated with thrombolysis, where those who had thrombolysis had higher education levels, these patients also had less severe small vessel disease, and not surprisingly also had larger intracranial volume. Lesion location and lesion volume did not differ between those who were thrombolysed and those who were not, and there was no difference in stroke severity at admission in this sample.

Table 18. Demographic and clinical variable correlations for stroke group

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
1 Age	-											
2 Sex	-.03	-										
3 Education	-.41**$^{++\,a}$	.17	-									
4 HADs A	-.03	-.27	-.03	-								
5 HADs D	-.01	-.23	.00	.61**$^{++\,a}$	-							
6 Barthel Index	.12	.25	-.06	-.32*^{a}	-.34*$^{+\,a}$	-						
7 Vascular Risk	.73**$^{++\,a}$	-.20	-.37*$^{++\,a}$	-.00	-.00	.03	-					
8 NIHSS	-.02	.07	.18	-.04	.06	-.05	.02	-				
9 Thrombolysis	-.27	.26	.35*^{a}	-.08	-.10	-.15	.-.20	.13	-			
10 Lesion Location	.01	-.13	.02	.09	.01	.04	.12	.20	-.06	-		
11 Lesion Volume	-.08	-.11	.04	.12	.06	.02	-.21	-.09	-.06	.30^{+}	-	
12 Previous stroke	.02	-06	.01	-.03	-.10	.24	.02	.14	.10	.01	-.07	-

Notes. Stroke N=42. Numbers on the X –axis represent the same variables as the Y-axis. HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression. Vascular Risk= Framingham stroke risk score. NIHSS= National Institute of Health Stroke Scale. - Indicates a negative correlation. Parametric correlation = ** p<.001 * p<.050, Non-parametric correlation= ^{++}p<.001, ^{+}p<.050,

[a]Bonferonni FME 0.5/12=0.04.

There were no significant relations between lesion side (left, right, bilateral) and any of the clinical, demographic, cognitive or hippocampal measures, although tNAA trended toward being reliable, $F(2,29)=2.59$. $p=.093$.

4.3.1.4 Summary clinical-demographic profile

The analyses above showed the expected relations between the clinical and demographic measures, providing an internal validity for these measures. In the current sample stroke patients were poorer on all clinical and demographic variables, but age did not differ. The differences observed between groups is important, as it is important to understand when establishing inferences regarding stroke specific effects on cognition and hippocampus pathology.

4.3.2 Cognitive profile

4.3.2.1 Comparison between controls and stroke patients

Cognition was measured using the BCoS across five cognitive domains; language, memory, attention and executive function, number and praxis. A composite cognitive measurement of the five domains was also calculated (general cognition) (Table 19). The cognitive data were not equally distributed, in both stroke patients and control participants. In some cognitive domains this was due to outliers. Overall as expected the stroke group, had significantly lower cognitive ability compared with the controls across the five cognitive domains and general cognition, unequal variances assumed (Table 19).

Table 19. Cognitive profile of stroke and control participants including group differences

Cognitive Domains	Stroke (n=42)			Control (n=17)			
	Mean (Std)	Median	Range	Mean (Std)	Median	Range	P Value
Language	-0.84 (1.40)	-0.56	-6.22:0.46	-0.02 (0.76)	0.33	-1.70:0.45	.006[a]
Memory	-1.19 (2.90)	-0.28	-16.63:0.31	.096 (0.39)	0.19	-0.87:0.41	.007[a]
Attention and Executive Function	-1.70 (3.19)	-0.53	-12.43:2.08	0.34 (.053)	0.46	-0.87:1.10	.000[a]
Number	-2.47 (4.20)	-0.71	-22.85:0.31	-0.85 (0.54)	0.00	-1.46:0.30	.001[a]
Praxis	-1.64 (1.74)	-1.11	-6.13:0.50	-0.01 (0.46)	0.08	-1.14:0.51	.000[a]
General	-1.57 (1.99)	-0.90	-9.07:0.25	0.06 (0.34)	0.11	-0.86:0.46	.000[a]

Notes. Std= Standard Deviation, Cognitive domains from the Birmingham Cognitive Screen, including composite domain (general), Cognitive Domain values are normalized Z scores.

[a]Bonferonni FME 0.5/6=0.08. Stroke N=42.

Table 20. Cognitive Domain correlations for stroke and controls combined and stroke

	1	2	3	4	5	6
1 Language	-	.75**$^{++}$	.53**$^{++}$	.60**$^{++}$	.59**$^{++}$	.86**$^{++}$
2 Memory	.77**$^{++}$ [a]	-	.50**$^{++}$	.36**$^{++}$	.37**$^{++}$	.75**$^{++}$
3 Attention and Executive Function	.52**$^{++}$	.43**$^{++}$	-	.36**$^{++}$	.47**$^{++}$	.75**$^{++}$
4 Number	.58**$^{++}$	.31*$^{++}$	.30^{++}	-	.44**	78**$^{++}$
5 Praxis	.54**$^{+}$	.31*	.39*	.36*	-	.69**$^{++}$
6 General	.87**$^{++}$	.74**$^{++}$	.72**$^{++}$	.75**$^{++}$	.62**$^{+}$	-

Notes. All N=59, Stroke N=42, Control N=17.Stroke data presented in the lower half of the matrix, and control and stroke combined data presented in the upper half. - Indicates a negative correlation. Numbers on the X –axis represent the same variables as the Y-axis.Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= ^{++}p<.001, ^{+}p<.050.

[a]Bonferonni FME 0.5/6=0.08 (all correlations in this matrix survived multiple comparisons corrections).

4.3.2.2 Association between cognitive measures and clinical demographic measures

In the combined sample (stroke and controls) the five cognitive domains correlated with each other. Similar effects were seen in correlations across all cognitive domains only in the stroke group (Table 20). The relationship between cognition and demographic/clinical variables were examined across the two groups combined (Table 21) and for stroke specific (Table 22).

Across the entire sample, general cognitive ability reduced linearly with age, participants who were less educated, had higher vascular risk, more severe small vessel disease, larger degree of atrophy in the temporal, and parietal lobes and higher intracranial volume. In the stroke sample only, age showed a similar effect size on cognition but was not reliable, potentially due to the small sample size. Education, vascular risk, and small vessel disease did not affect general cognition, but level of parietal and temporal atrophy, and overall intracranial volume affected general cognition. This potentially reflects the dominant impact of the lesion on general cognition, see below. It also suggests that the correlation of cognition, with vascular risk, and education in the entire sample was confounded by the difference in this variable, between the stroke patients and control participants.

Not surprisingly participants with higher levels of atrophy in temporal, and parietal regions performed poorly on all cognitive domains. Education, intracranial volume, and vascular risk only affected praxis and number related abilities. Age positively correlated with number abilities.

Specifically, in the stroke patients, like in the entire sample, parietal atrophy impaired performance on all cognitive domains; while temporal lobe atrophy affected performances on memory and number. Reduced intracranial volume was associated with poor abilities in language, numbers and praxis. Education, vascular risk, lesion side and small vessel disease did not relate to abilities on any of the cognitive domains.

Table 21. Demographic, clinical and imaging variables correlations for stroke and controls combined

	1	*2*	*3*	*4*	*5*	*6*	*7*
1 Age	-						
2 Sex	.06	-					
3 Education	-.33*$^{+}$	-.23	-				
4 HADs A	-.01	-.02	-.15	-			
5 HADs D	.05	.08	-.20^{+}	.67**$^{++a}$	-		
6 Barthel Index	.09	.08	.05	-.40**$^{+a}$	-.43**$^{+a}$	-	
7 Vascular Risk	.68**$^{++a}$	.15	-.49**$^{++a}$	.17	.27*$^{++}$	-.13	-
8 Parietal Lobe Atrophy	.36**$^{++a}$	.15	-.13	-.18	-.11	.08	.12
9 Temporal Lobe Atrophy	.48**$^{++a}$	.27*$^{+}$	-.40**$^{++a}$	.05	.05	-.02	.42**^{a}
10 Small Vessel Disease	.51**$^{++a}$	-.091	-.46*$^{++}$	.11	.11	-.09	.56**$^{++a}$
11 Left GM Volume	-.52**$^{++a}$	.20	.45**^{a}	-.17	-.15	.09	-.47**$^{++a}$
12 Right GM Volume	-.51**$^{++a}$	.16	.47**^{a}	-.18	-.26*$^{+}$	.15^{+}	-.45**$^{++a}$
13 Left MD	.26	-.15	-.05	-.16	.03	-.03	.14
14 Right MD	.25	-.19	-.04	-.20	.10	-.09	.13
15 tNAA	-.24	-.10	.01	.02	-.11	.15	-.23
16 tCh	-.14	-.14	-.05	.07	-.04	.12	-.11
17 tCr	-.03	-.15	.06	.05	-.17	.21	-.15

Notes. HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression. Vascular Risk= Framingham stroke risk score. GM= Grey matter.MD= Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$ p<.001, $^{+}$p<.050. ^{a}Bonferonni FME 0.5/17=0.02. GM; Stroke N=42, Control=17, MD; Stroke=36, Control=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, Cr=Total Creatine; Stroke N=31, Control=17. Note that with a binary categorical variable, Pearson correlation is mathematically equivalent to independent two sample t-test (e.g. sex).

Table 22. Demographic, clinical and imaging variables correlations for stroke group

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
1 Age	-										
2 Sex	-.03	-									
3 Education	-.41**[a]	.17	-								
4 HADs A	-.03	-.27	-.03	-							
5 HADs D	.01	-.23	.00	.61**[a]	-						
6 Barthel Index	.12	.25	-.06	-.32*	-.34*[+]	-					
7 Vascular Risk	.73**[++a]	-.20	-.37*[++]	-.00	-.00	.03	-				
8 NIHSS	.02	-.07	.18	-.04	.06	-.05	.02	-			
9 Thrombolysis	-.27	.26	.35*	-.08	-.10	-.15	-.20	.13	-		
10 Lesion Volume	-.08	-.11	.04	.12	.06	-.02	-.21	-.09	-.06	-	
11 Previous stroke	.02	-06	.01	-.03	-.10	.24	.02	.14	.10	-.07	-
12 Parietal Lobe Atrophy	.41**[++a]	.25	-.27	-.20	-.14	.08	.18	.10	-.04	.32*	-.04
13 Temporal Lobe Atrophy	.54**[++a]	.06	-.34	-.08	-.17	.08	.29[+]	-.01	-.24	.19	.06
14 Small Vessel Disease	.51**[++a]	-.39**[+a]	-.51**[+a]	.03	-.01	-.04	.59**[++a]	-.13	-.36*	-.14	-.16
15 Left GM Volume	-.64**[++a]	.37*[++]	.43**[+a]	-.16	-.12	.07	-.57**[++a]	.04	.37*	.03	.09
16 Right GM Volume	-.63**[++a]	.35*[++]	.43**[+a]	-.12	-.18	.09	-.49**[++a]	.07	.39*	-.13	.11
17 Left MD	.34*[+]	-.16	-.02	-.20	.10	-.08	.27	.08	-.11	-.08	.09
18 Right MD	.32	-.22	-.02	-.23	.19	-.14	.24	.16	-.17	-.12	.16
19 tNAA	-.32	.00	-.05	.09	-.05	.16	-.26	.22	.20	-.36*	-.09
20 tCh	-.34	-.28	-.08	.10	-.08	.21	-.33	.11	-.05	-.31	-.02
21 tCr	-.16	-.21	-.05	.11	-.14	.19	-.18	.07	-.00	-.30	-.11

Notes. GM; Stroke N=42. MD; Stroke=36. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine; Stroke N=31. HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression. Vascular Risk= Framingham stroke risk score. NIHSS= National Institute Stroke Scale. GM= Grey matter. MD=

Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$ p<.001, $^{+}$p<.050. [a]Bonferonni FME 0.5/21=0.02. Note that with a binary categorical variable, Pearson correlation is mathematically equivalent to independent two sample t-test (e.g. sex, previous stroke). Numbers on the X –axis represent the same variables as the Y-axis.

4.3.2.3 Summary of cognitive profiles

The analyses above showed that while the stroke patients were more impaired cognitively, the relations between brain health (cortical atrophy) and cognition were preserved. The variability of general cognitive ability (averaged abilities across all five domains) was most robustly associated with the clinical demographic variables, in the current sample.

4.3.3 Hippocampal pathology profile

4.3.3.1 Comparison between control and patients

Table 23. Hippocampal brain measures of stroke and control participants including group differences

	Stroke			**Control**			
	Mean (Std)	**Median**	**Range**	**Mean (std)**	**Median**	**Range**	**P Value**
Left Hippocampal Volume mm^3	0.63 (0.09)	0.61	0.44:0.86	0.65 (0.50)	0.65	0.57:0.78	.284
Right Hippocampal Volume mm^3	0.63 (0.08)	0.63	0.59:0.81	0.67 (0.05)	0.67	0.59:0.81	.059
Left Hippocampal Mean diffusivity mm^3	1.00 (0.32)	1.00	0.40:1.01	1.04 (0.35)	1.10	0.20:1.80	.684
Right Hippocampal Mean diffusivity mm^3	0.98 (0.38)	1.00	0.20:1.80	1.02 (0.30)	1.00	0.30:1.60	.740
Total NAA	10.52 (3.29)	10.89	0:15.46	11.56 (1.29)	11.56	8.90:13.80	.219
Total Choline	3.41 (1.21)	3.51	.03:6.26	3.58 (0.98)	3.73	0.49:5.52	.607
Total Creatine	10.70 (3.98)	10.57	0:21.19	11.89 (2.15)	11.05	9.01:16.56	.189

Notes: Std= Standard Deviation. [a]Bonferonni FME $p = .05/6 = .008$

Group differences across the hippocampal pathology measures were examined. There were no significant differences between stroke patients and control participants for intracranial volume (Table 15), or any of the other brain imaging measures (Table 23). Reduced grey matter volume of the right hippocampus in patients compare to controls trended toward significance, but this was not corrected for the multiple comparisons.

4.3.3.2 Validation of Hippocampal measures

As a validation of the brain measures, we examined the interrelation between them. Across stroke patients and control participants combined, left and right hippocampal grey matter volume, as well as left and right hippocampus mean diffusivity were highly correlated with each other (Table 24). The metabolites were positively correlated with each other. The same pattern was observed for the stroke only group.

Table 24. Imaging measures correlations for stroke and controls combined and stroke only group

	1	2	3	4	5	6	7	8	9	10	11
1 Intracranial volume	-	.02	.16	-.14	.47**$^{++\,a}$	.47*^{a}	-.07	-.07	.04	.00	.06
2 Parietal lobe atrophy	.09	-	.38**^{a}	.09	-.30*	-.30*	.08	.11	-.30*	-.33*	-.24
3 Temporal lobe atrophy	.15	.48**$^{+a}$	-	.40**	-.39**$^{+a}$	-.45^{++}**	.06	.09	-.18	.00	.07
4 Small Vessel Disease	-.31*$^{+}$	.07	.36*$^{+}$	-	-.52**$^{++a}$	-.54**$^{++a}$	.20	.13	-.07	.10	.26
5 Left GM Volume	.48**$^{+a}$	-.30*	-.45**$^{++a}$	-.55**$^{++a}$	-	.90**$^{++\,a}$	-.26	-.22	.42**$^{\,a}$	.28	.23
6 Right GM Volume	.44**$^{++a}$	-.32*	-.49**$^{++a}$	-.54**$^{++a}$	.92**$^{++\,a}$	-	-.28	-.26	.46**^{a}	.28*	.25
7 Left MD	.02	.12	.22^{+}	.27	-.19	-.31	-	.85**$^{++\,a}$	-.37*	-.17	-.18
8 Right MD	.02	.14	.21	.16	-.16	-.27	.83**$^{++\,a}$	-	-.43**^{a}	-.26	-.18
9 tNAA	.05	-.33	-.15	-.00	.45*	.49**$^{\,a}$	-.45*	-.47*	-	.70**$^{++\,a}$	.69**$^{++\,a}$
10 tCh	-.10	-.48**^{a}	.01	.10	.31	.35	-.22	-.30	.79**$^{++\,a}$	-	.71**$^{++\,a}$
11 tCr	-.07	-.37*	.14	.25	.21	.26	-.21	-.23	.79**$^{++\,a}$	.88**$^{++}$	-

Notes. Top half of matrix is stroke and controls combined, below half of matrix is stroke group only. GM; Stroke N=42, Control=17, MD; Stroke=36, Control=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine; Stroke N=31, Control=17. GM= Grey matter. MD= Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$ p<.001,

$^{+}$p<.050. ^{a}Bonferonni FME 0.5/11=0.04.

As expected tNAA positively correlated with left and right hippocampal grey matter volume, and negatively correlated with left and right mean diffusivity.

In the entire sample, and the stroke specific sample, intracranial volume positively correlated with left and right grey matter volume, suggesting that the correction of grey matter signal intensity, by CAT12 was done based on local structures size as intended (Ashburner & Friston, 2005), (www.fil.ion.ucl.ac.uk/spm/software/spm12). Intracranial volume did not correlate with mean diffusivity, or any of the metabolites.

Not surprisingly, in the entire sample as well as in the stroke specific, the rating of atrophy severity in the temporal (and parietal) lobes negatively correlated with grey matter volume in the left and right hippocampus, but not with mean diffusivity. Demonstrating an increase in severity of atrophy, was associated with lower grey matter volume in the hippocampus. The parietal lobe atrophy, but not the temporal negatively correlated with tNAA and tCh in the combined group, and in the stroke group parietal lobe atrophy correlated negatively with tCh and tCr (Table 24). The correlation of parietal atrophy, and tNAA was not reliable in the stroke only group, but the effect size was similar to the ones observed in the combined group analysis. Higher rates of small vessel disease correlated with lower left and right hippocampal grey matter volume, but not with mean diffusivity or any of the metabolites.

4.3.3.3 Hippocampal measures and clinical-demographic data

Bivariate correlations were computed to examine interactions between hippocampal measures, and demographic variables (Table 21, Table 22). In the combined sample (stroke and control participants), left and right hippocampal grey matter volume negatively interacted with age, and vascular risk, atrophy and small vessel disease, and

positively correlated with education. Hippocampal mean diffusivity, and metabolites did not correlate with any of the clinical or demographic variables.

In the stroke group alone, age negatively correlated with left and right hippocampal grey matter volume, and positively with left hippocampal mean diffusivity. Education positively correlated with left and right hippocampal grey matter volume, but not with mean diffusivity or any of the metabolites. Sex impacted left and right hippocampal grey matter volume, males had larger volume than female.

4.3.3.4 Association of hippocampus pathology profiles and stroke specific measures

Stroke severity at admission, lesion side, and history of previous stroke did not affect any of the measures of hippocampus pathology. Patients who were thrombolysed had larger left, and right hippocampal grey matter volume, than those who were not. Lesion volume negatively correlated with tNAA.

4.3.3.5 Summary of hippocampus pathology profile

The analysis above showed the expected correlation between the various hippocampal measures. In the context of the metabolites, variability in the tNAA was mostly related to the other MRI measures. Grey matter volume was more related to the clinical and demographic variables, than mean diffusivity and metabolites. This provides an internal validity of these measures, specifically for the grey matter volume, and tNAA.

Stroke patients and control participants did not reliably differ on any of the hippocampal pathology measures. The relations between hippocampal measures, and the clinical demographic variables appeared to be unaffected by stroke.

Next, the relation of each MRI measure and cognition will be examined separately in more detail, as this is the main focus on the current chapter.

4.3.3.6 Hippocampal grey matter volume and cognition

Hippocampal grey matter was examined looking at voxel density within both the left and right hippocampi. We were able to obtain hippocampal volume values in 42 stroke patients and 17 controls. To understand the relationship between hippocampal volume and cognition, we firstly computed correlations across these two cohorts combined (Table 25). Across the combined sample, this revealed strong associations between level of left and right hippocampal volume general cognition and all cognitive domains (apart from an unreliable correlation between the left hippocampus volume and attention & executive function). Similar pattern was observed in the analysis that included the stroke patients only (Table 26). Left and right hippocampus volume positively correlated with general cognition, and number abilities, and right hippocampal grey matter volume with general cognition, number and language abilities.

(A) (B) (C)

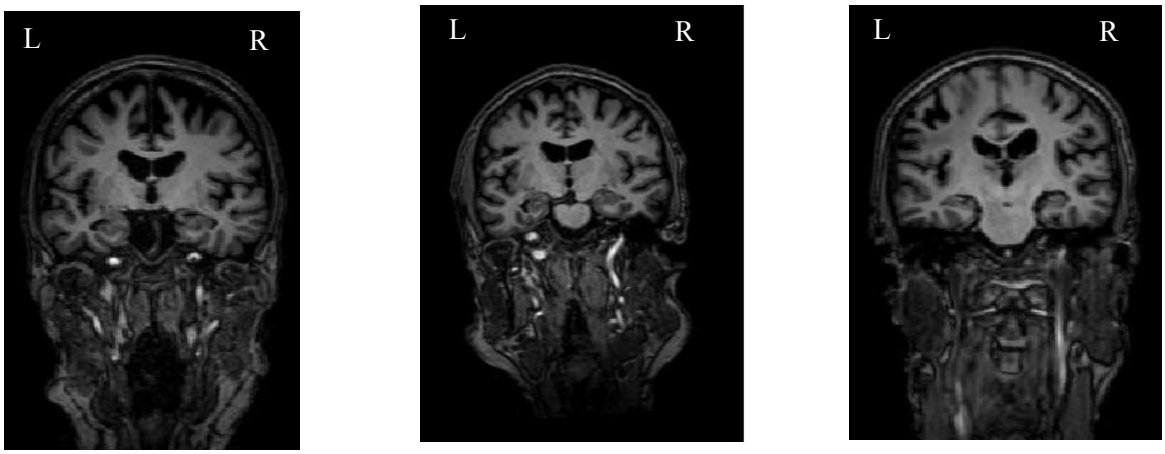

Figure 14. Coronal slices of T1-Weighted images showing Hippocampi. A) Control participant, B) Stroke patient with no impairment in general cognition, C) Stroke patient with impairment in general cognition.

To formally test whether the observed relation between the left and right hippocampal grey matter measures and cognition were different in stroke and control, we used moderation analysis, separately for each side and each cognitive domain. This was followed by the analysis of only the control groups.

Table 25. Cognition, clinical, demographic and imaging variables correlations for stroke and controls combined

	Language	Memory	Attention and Executive Function	Number	Praxis	General
Age	-.15	-.03	-.08	.34**[a]	-.15	-.21[++]
Education	-.19	.20	.24	.21[++]	.24[++]	.29*
Vascular Risk	-.63	.03	-.06	-.35**[a]	-.31**[++a]	-.23[++]
Intracranial volume	.18	.03	.04	.19[++]	.35[+]	.14[++]
Parietal lobe atrophy	-.40**[a]	-.42**[a]	-.36**[a]	-.26*	-.25*	-.43*[++]
Temporal lobe atrophy	-.34**[+a]	-.38**[++a]	-.25[++]	-.41**[a]	-.25*	-.48**[++]
Small Vessel Disease	-.12[+]	-.03	-.18	-.22	-.14	-.19[+]
Left GM Volume	.29*[++]	.14[++]	.12	.45**[++a]	.25*[++]	.35*[++]
Right GM Volume	.40**[++a]	.29*[++]	.25*[+]	.56**[++a]	.29*[++]	.49**[++a]
Left MD	-.26	-.15	-.21	-.35*	-.25	-.34*
Right MD	-.25	-.03	-.20	-.33*	-.23	-.30*
tNAA	.34*	.09	.45**[a]	.52**	.31*	.46**[a]
tCh	.23	.08	.34*	.32*	.20	.30
tCr	.37**[a]	.12	.39**[a]	.34*	.36*[+]	.38**[a]

Notes. GM; Stroke N=42, Control=17, MD; Stroke=36, Control=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine; Stroke N=31, Control=17.Vascular Risk= Framingham stroke risk score. GM= Grey matter. MD= Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= [++] p<.001, [+]p<.050. [a]Bonferonni FME 0.5/14=0.03.

Table 26. Cognition, clinical, demographic and imaging variables correlations for stroke

	Language	Memory	Attention and Executive Function	Number	Praxis	General
Age	-.12	-.01	-.07	-.33*	-.18	-.22
Education	.03	.12	.12	.11	.07	.14
Vascular Risk	.04	.23	.15	-.25	-.12	-.00
NIHSS	-.07	-.02	.06	.22	-.01	.09
Thrombolysis	.22	.02	.17	.20^{+}	.03	.18
Lesion Volume	-.39**^{a}	-.58**^{a}	-.31*	.02	-.08	-.33*
Previous stroke	.10	.15	-.07	-.03	-.10	.00
Intracranial volume	.13^{+}	.02	.07	.27^{++}	.06^{++}	.17^{++}
Parietal lobe atrophy	-.49**$^{+a}$	-.48**^{a}	-.45**$^{++a}$	-.30*	-.34*	-.54**$^{+a}$
Temporal lobe atrophy	-.29	-.33*	-.15	-.35*	-.12	-.35*$^{+}$
Small Vessel Disease	-.04	.01	-.12	-.16	-.05	-.12
Left GM Volume	.25	.12^{++}	.10^{+}	.47**$^{++a}$	.21	.34*$^{++}$
Right GM Volume	.36*	.28^{++}	.22^{+}	.58**$^{++a}$	.21	.48**$^{++a}$
Left MD	-.31	-.24	-.28	-.46**	-.33*	-.47**^{a}
Right MD	-.27	-.06	-.25	-.40*	-.27	-.38*
tNAA	.41*	.02	.45**^{a}	.53**^{a}	.29	.47**^{a}
tCh	.39*	.08	.41*	.39*	.24	.39*
tCr	.41*	.09	.37*	.34*	.32	.38*

Notes. GM; Stroke N=42. MD; Stroke=36. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine; Stroke N=31. HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression. Vascular Risk= Framingham stroke risk score. NIHSS= National Institute stroke scale. GM= Grey matter. MD=

Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$p<.001, $^{+}$p<.050. [a]Bonferonni FME 0.5/14=0.03.

4.3.3.6.1 General Cognition

General cognition was reliably ($F(4,54)=5.97$, $p =.001$, $R^2=.30$) predicted by stroke (standardised β (sβ) = -.39, p = .001), left hippocampal volume (sβ =.28, p = .037), and scanner upgrade trended (sβ =.21, p = .078), age was included in the model but was not a reliable predictor. The relations between left hippocampal volume and general cognition, were not affected by stroke condition (i.e. there was no difference between the basic model - without the moderation and the model that included the moderation variable).

When considering the stroke group alone, general cognition was ($F(3,38)=2.87$, $p =.049$, $R^2=.19$) predicted by left hippocampal volume (sβ =.40, p = .048), and it trended with scanner upgrade (sβ = -.26, p = .086), but not with age. After controlling for clinical and demographic variables (e.g. education, vascular risk, NIHSS, lesion volume and previous stroke), left hippocampal volume was still a reliable predictor (sβ =.53, p = .008), as was lesion volume (sβ = -29, p = .050).

Similarly, to the left hippocampus, general cognition was reliably ($F(4,54)=8.79$, $p <.001$, $R^2=.39$) predicted by the right hippocampal volume (sβ =.47, p = .001), stroke condition (sβ = -.33, p = .004), and scanner upgrade (sβ =.24, p = .034) age was also included in the model but was not a reliable predictor. The relations between right hippocampus volume and general cognition were not affected by the stroke. See Figure 15.

When considering the stroke group alone, general cognition was predicted ($F(3,38) =7.00$, $p = .001$, $R^2=.36$) by right hippocampal volume (sβ =.68, p <.001), and scanner upgrade (sβ =.33, p=.019), age was included in the model but was not reliable. After

controlling for the effects of demographic and stroke specific variables the right hippocampus volume remained a reliable predictor of general cognition (sβ =.70, p < .001), as did scanner upgrade (sβ =.32, p =.024).

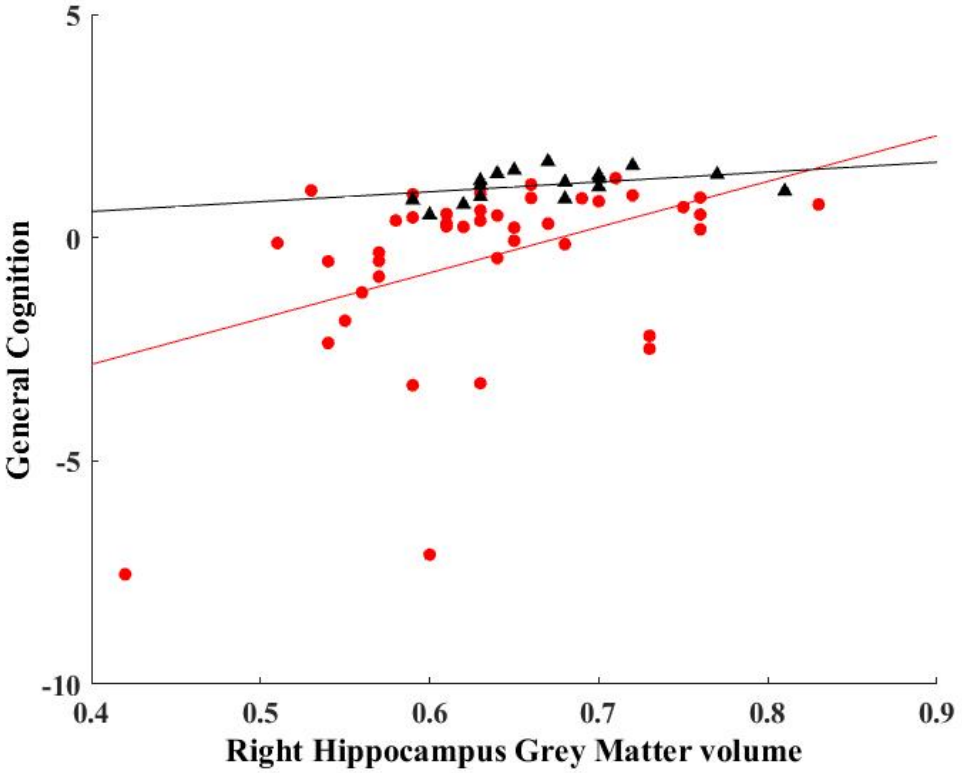

Figure 15. Right hippocampal grey matter volume/ General cognition (after controlling for age). Control participants, N= 17 (black triangle), Stroke patients, N=42 (Red circles).

Taken together, the results suggest that beyond the stroke and age, general cognition was predicted by left and right hippocampal volume. However, stroke did not affect the relations between hippocampal pathology and general cognition, in this case. In the stroke group, beyond clinical and demographic variables, left and right hippocampal volume predicted post-stroke general cognition.

4.3.3.6.2 Language

Language was reliably ($F(4,54)=2.89$, $p =.031$, $R^2=.11$) predicted by stroke ($s\beta = -.28$, $p = .033$), the left hippocampal volume trended ($s\beta =.27$, $p = .075$), age and scanner upgrade were also included in the model but was not a reliable predictor. The relations between left hippocampus volume and language were not affected by the stroke.

When considering the stroke group alone, language was not predicted by left hippocampus volume, age or scanner upgrade. When controlling for clinical-demographic variables the model trended ($F(7,34)=2.08$, $p =.072$, $R^2=.30$), with left hippocampal volume ($s\beta =.42$, $p = .035$), and lesion volume ($s\beta =-.38$, $p = .016$), reliably predicting post-stroke language abilities.

Language was reliably ($F(4,54)=4.30$, $p =.004$, $R^2=.24$) predicted by right hippocampal volume ($s\beta =.41$, $p = .006$), and stroke condition trended ($s\beta =-.22$, $p = .074$), but age and scanner upgrade were not a reliable predictors. The relations between right hippocampus volume and language were not affected by stroke.

When considering the stroke group alone, language was predicted ($F(3,38) =3.20$, $p = .034$, $R^2=.20$) by right hippocampal volume ($s\beta =.54$, $p = .008$), age and scanner upgrade were included in the model but were not reliable. After controlling for clinical and demographic variables the right hippocampus volume remained a reliable predictor of post-stroke language ability ($s\beta = .50$, $p = .009$), and lesion volume trended ($s\beta = -.28$, $p = .063$).

The results suggest that, beyond the stroke and age, language was predicted by the right hippocampal volume and to lesser degree by the left hippocampus. In the stroke group, lesion volume also contributed to post-stroke language abilities. Furthermore, stroke

condition did not affect the relations between hippocampal pathology and language ability.

4.3.3.6.3 Memory

Memory was not reliably predicted by left hippocampal volume, furthermore the relations between left hippocampus volume, and memory were not affected by the stroke condition.

When considering the stroke group alone, memory ability was not predicted by left hippocampal volume. In the model with clinical and demographic predictors ($F(7,34)=4.46$, $p=.001$, $R^2=.48$), memory was predicted by lesion volume ($s\beta=-.53$, $p<.001$), and vascular risk trended ($s\beta=.31$, $p=.057$).

Memory trended toward being reliably predicted ($F(4,54)=2.45$, $p=.057$, $R^2=.15$), by right hippocampal volume ($s\beta=.35$, $p=.023$), stroke condition, scanner upgrade and age were included in the model but were not reliable predictors. The relations between right hippocampus volume and memory were not affected by stroke.

When considering the stroke group alone, memory trended towards bring predicted by right hippocampal volume ($F(3,38)=2.67$, $p=.061$, $R^2=.17$), ($s\beta=.52$, $p=.011$). When clinical and demographic variables were controlled for, right hippocampal volume still predicted memory ($s\beta=.37$, $p=.025$), as did lesion volume ($s\beta=-.47$, $p=.001$), and vascular risk ($s\beta=.34$, $p=.031$).

Taken together, the results suggest that beyond the stroke and age, memory was predicted by the right hippocampal volume and but not the left hippocampus. In the stroke group, lesion volume, and vascular risk status also contributed to post-stroke

memory ability. Stroke incidence did not affect the relations between hippocampus volume and memory abilities.

4.3.3.6.4 Attention and executive function

Attention and executive function was predicted ($F(4,54)=3.10$, $p=.022$, $R^2=.19$), by stroke ($s\beta=-.35$, $p=.007$), and scanner upgrade ($s\beta=.29$, $p=.034$), but not left hippocampal volume or age. Furthermore, the relations between left hippocampal volume, and attention and executive function were not affected by the stroke condition.

When considering the stroke group alone, attention and executive function was not predicted by left hippocampus volume, age or any of the other clinical-demographic factors.

The right hippocampus volume ($F(3,54)=3.89$, $p=.008$, $R^2=.16$), did not reliably predict attention and executive function although it trended ($s\beta=.25$, $p=.093$), however stroke reliably predicted attention and executive function ($s\beta=-.31$, $p=.015$), as did scanner upgrade ($s\beta=.29$, $p=.023$). The relations between right hippocampus volume and attention and executive function were not affected by stroke via moderated variable.

When considering the stroke group alone, attention and executive function was predicted ($F(3,38)=3.14$, $p=.036$, $R^2=.19$), by right hippocampal volume ($s\beta=.41$, $p=.039$), and scanner upgrade ($s\beta=.38$, $p=.015$), but not age. When controlling for clinical-demographic variables right hippocampal volume still predicted attention and executive function ($s\beta=.43$, $p=.028$), as did scanner upgrade ($s\beta=.34$, $p=.031$).

Taken together, the results suggest that attention and executive function was not reliably predicted by left or right hippocampal volume. However, stroke did predict attention in the right hippocampal volume model.

4.3.3.6.5 Number

Number was reliably ($F(4,54)=5.20$, $p < .001$, $R^2=.28$) predicted by stroke ($s\beta = -.24$ $p = .045$) and left hippocampal volume ($s\beta = .36$, $p = .010$), age and scanner upgrade were also included in the model but were not reliable predictors. The relations between left hippocampus volume and number were not affected by the stroke.

When considering the stroke group alone, number was predicted ($F(3,38) = 3.79$, $p = .018$, $R^2=.23$) by the left hippocampal volume ($s\beta = .43$, $p = .026$), age and scanner upgrade were included in the model but were not reliable. After controlling for clinical and demographic variables, left hippocampal volume remained a reliable predictor of number ($s\beta = .55$, $p = .006$).

Similarly, to the left hippocampus, number was reliably ($F(4,54)=7.32$, $p < .001$, $R^2=.35$) predicted by right hippocampal volume ($s\beta = .49$, $p < .001$). Stroke, age, and scanner upgrade were included in the model but were not reliable predictors. The relations between right hippocampus volume, and language were marginally affected by stroke. The stroke by right hippocampal volume moderator variable trended towards significance ($s\beta = -.23$, $p = .056$). This demonstrates that the relation between number ability, and right hippocampus volumes were stronger in the stroke than the control group.

When considering the stroke group alone, number was predicted ($F(3,38) = 6.58$, $p = .001$, $R^2=.29$) by the right hippocampal volume ($s\beta = .62$, $p = .001$) age and scanner upgrade were included in the model but were not reliable. After controlling for clinical and demographic variables, the right hippocampal volume remained a reliable predictor

of number abilities (sβ = .75, p <.001). And stroke severity (NIHSS) trended (sβ =.25, p =.070), as did education (sβ =-.26, p =.099).

Taken together, the results suggest that beyond the stroke and age, number was predicted by the left and right hippocampal volume. In the stroke group, lesion volume and stroke severity also contributed to post-stroke number abilities. Interestingly stroke moderated relations between the right hippocampus and number abilities, suggesting that following stroke those with larger volume in the hippocampus performed better on the number tasks.

4.3.3.6.6 Praxis

Praxis was reliably ($F(4,54)=3.10$, $p =.022$, $R^2=.19$) predicted by stroke (sβ = -.35, p = .007), and scanner upgrade (sβ =.27, p = .034), but not the left hippocampal volume, or age was also included in the model but was not a reliable predictor. The relations between left hippocampus volume and number were not affected by the stroke.

When considering the stroke group alone, praxis was not predicted by the left hippocampal volume, but only scanner upgrade ($F(3,38)=6.97$, $p =.001$, $R^2=.36$), (sβ = .56, p<.001). When controlling for clinical-demographic variables, left hippocampal volume was a predictor of praxis ($F(7,34)=3.05$, $p =.013$, $R^2=.39$), (sβ =.36, p=.047), as was scanner upgrade (sβ =.58, p<.001).

Similarly, to the left hippocampus, number was reliably ($F(4,54)=3.89$, $p =.008$, $R^2=.24$) predicted by stroke (sβ = -.31, p =.015), and scanner upgrade (sβ =.29, p =.023), but not right hippocampal volume although it trended (sβ =.25, p =.093), age was also included in the model but was not a reliable predictor. The relations between right hippocampus volume and praxis were not affected by the stroke.

When considering the stroke group alone, praxis was not predicted by right hippocampal volume or age, but only scanner upgrade ($F(3,38)=7.52$, $p <.001$, $R^2=.37$), ($s\beta =.58$, $p<.001$), with right hippocampal volume trending ($s\beta =.32$, $p=.066$). When controlling for clinical-demographic variables, right hippocampal volume was a predictor of praxis ($F(7,34)=3.35$, $p =.008$, $R^2=.41$), ($s\beta =.42$, $p=.023$), as was scanner upgrade ($s\beta =.62$, $p<.001$).

Taken together, the results suggest that beyond the stroke and age, praxis was not predicted by the right or left hippocampal volume. However, in the stroke group, when controlling for clinical and demographic variables, left and right hippocampal volume was a predictor of post-stroke praxis ability.

4.3.3.6.7 Summary of hippocampal volume and cognition

On the whole cognition was predicted by the grey matter volume of the left and right hippocampi. This was observed beyond the stroke condition and age. The relations were more robust with the right than the left hippocampus; and were mostly pronounced when considering general cognition, the language, number and memory domains.

With respect to the main research question, stroke only moderated the relations between hippocampus volume and number ability, this association was stronger in the stroke than the control group.

4.3.3.7 Hippocampal mean diffusivity and cognition

In addition to hippocampal grey matter, mean diffusivity of both the left and right hippocampus was examined in relation to cognition. We obtained hippocampal mean diffusivity data in 35 stroke patients and 15 controls. We firstly computed correlations across these two cohorts combined (Table 25). Surprisingly, left and right mean

diffusivity predicted only the ability on the number and general cognition. Similar and stronger correlations were observed for the stroke patients group only (Table 26), with number praxis and general cognition domains.

4.3.3.7.1 General Cognition

General cognition was reliably ($F(4,45)=6.45$, $p <.001$, $R^2=.37$) predicted by stroke ($s\beta = -.44$, $p = .001$), and the left hippocampus mean diffusivity ($s\beta =-.32$, $p = .013$), age was also included in the model but was not a reliable predictor, although it trended ($s\beta =-.22$, $p = .077$), scanner upgrade was not a reliable predictor. The relations between left hippocampus mean diffusivity and general cognition, were not moderated by the stroke condition.

When considering the stroke group alone, general cognition was predicted by ($F(3,31)=3.75$, $p <.021$, $R^2=.27$) left hippocampus mean diffusivity ($s\beta = -.41$, $p = .019$), but not age and scanner upgrade. When controlling for clinical-demographic variables this relation did not survive.

Similarly, to the left hippocampus, general cognition was reliably ($F(4,45)=5.74$, $p <.001$, $R^2=.34$) predicted by stroke ($s\beta = -.44$, $p = .001$), and the right hippocampus mean diffusivity ($s\beta =-.27$, $p = .038$), age was also included in the model but was not a reliable predictor, although it trended ($s\beta =-.24$, $p = .066$). Scanner upgrade was not a reliable predictor. The relation between right hippocampus mean diffusivity and general cognition were not affected by the stroke. See Figure 16.

When considering the stroke group alone, general cognition was not predicted by any of the predictors. Although it trended ($F(3,31) = 2.70$, $p = .063$, $R^2=.20$) with right mean diffusivity ($s\beta = -.31$, $p = .075$). After controlling for clinical and demographic

variables, right hippocampal mean diffusivity predicted general cognition (sβ = -.40, p = .040), although the full model was not significant (F(7,27) = 1.07, p = .448, R^2=.20).

Taken together, the results suggest that beyond the stroke and age, general cognition was predicted by the left and right hippocampal mean diffusivity. However, stroke did not affect the relations between left and right hippocampus and general cognition.

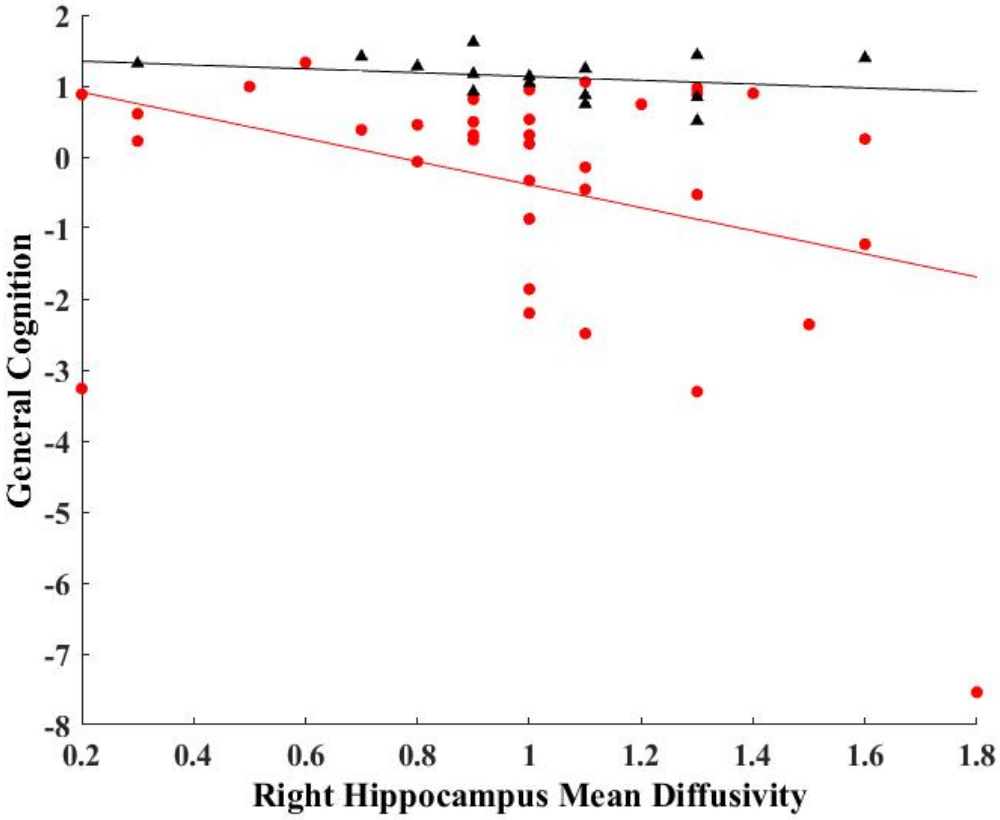

Figure 16. Right hippocampal mean diffusivity/ General cognition (after controlling for age). Control participants, N= 15 (black triangle), Stroke patients, N=36 (Red circles).

4.3.3.7.2 Language

Language was reliably (F(4,45)=2.66, p = .045, R^2=.19) predicted by stroke (sβ = -.30, p = .033), and the left hippocampus mean diffusivity trended towards reliability (sβ =-.23,

p = .096), age and scanner upgrade were also included in the model but were not reliable predictors. The relations between left hippocampus volume and language were not affected by the stroke.

When considering the stroke group alone, language was not predicted by left hippocampus mean diffusivity, age or scanner upgrade. Furthermore, clinical and demographic variables did not mediate this relationship.

Language trended towards being reliably ($F(4,45)=2.53$, $p =.053$, $R^2=.18$) predicted by stroke ($s\beta =-.289$, $p = .035$), but not right hippocampal mean diffusivity, age or scanner upgrade. The relations between right hippocampus volume, and language were not moderated by stroke condition.

When considering the stroke group alone, language was not predicted by right hippocampus mean diffusivity, age, or scanner upgrade. Furthermore, clinical and demographic variables did not mediate this relationship.

Taken together, the results suggest that beyond age, language was predicted by stroke condition alone. Although stroke predicted language, it did not moderate the relations between hippocampal mean diffusivity and language ability. Furthermore, in the stroke group language ability was not predicted by hippocampal mean diffusivity.

4.3.3.7.3 Memory

Memory was not predicted by left hippocampal mean diffusivity, or by age or scanner upgrade.

When considering the stroke group alone, memory was not predicted by left hippocampus mean diffusivity or age or scanner upgrade. Furthermore, clinical and demographic variables did not mediate this relationship.

Memory was not predicted by right hippocampal mean diffusivity, or by age or scanner upgrade.

Similarly, to left hippocampus mean diffusivity, in the stroke group alone, memory was not predicted by right hippocampus mean diffusivity, age or scanner upgrade. Furthermore, clinical and demographic variables did not mediate this relationship.

Memory domain ability was not predicted by mean diffusivity in the left or right hippocampus, and this was the case for stroke and control groups combined and for stroke specifically. Due to the known association of memory and mean diffusivity in the hippocampus (Hosseini et al., 2017), these findings were surprising. We specifically the immediate recall recognition task from the memory domain, as task which tests verbal memory abilities. However, we also found no predictive value of left or right mean diffusivity on this memory task.

4.3.3.7.4 Attention and executive function

Attention and executive function ($F(4,45)=3.16$, $p =.022$, $R^2=.22$) was not reliably predicted by left hippocampal mean diffusivity, although it trended ($s\beta =-.25$, $p = .081$), but was by stroke condition ($s\beta =-.38$, $p = .007$), with scanner upgrade also trending ($s\beta =.25$, $p = .073$). Furthermore, the relations between left hippocampus mean diffusivity, and attention and executive function were not moderated by the stroke.

When considering the stroke group alone, attention and executive function was not predicted by left hippocampus mean diffusivity, age or any of the other clinical and demographic variables.

Similarly, the right hippocampus mean diffusivity, did not reliably predict attention and executive function, however stroke reliably predicted ($F(3,36)=2.80$, $p =.050$, $R^2=.16$), ($s\beta =-.33$, $p = .019$). The relations between right hippocampus volume, and attention and executive function were not affected by stroke via the moderated variable.

When considering the stroke group alone, attention and executive function was not predicted by right hippocampal mean diffusivity, age, or any of the other clinical or demographic variables.

Taken together, the results suggest that attention and executive function was not reliably predicted by left or right hippocampal volume. However, stroke did predict attention and executive function in the left and right hippocampal mean diffusivity models. However, attention and executive function was not moderated by stroke. Furthermore, hippocampal mean diffusivity did not predict post-stroke attention and executive function.

4.3.3.7.5 Number

Number was reliably ($F(4,45)=4.36$, $p =.005$, $R^2=.28$) predicted by left hippocampal mean diffusivity ($s\beta =-.29$, $p = .030$, and stroke ($s\beta = -.29$, $p = .032$), age trended towards predicting number ability ($s\beta = -.24$ $p = .087$). The relations between left hippocampus mean diffusivity and number trended towards being moderated by stroke ($s\beta = .79$, $p = .064$).

When considering the stroke group alone, number ability was predicted ($F(3,31) = 3.98$, $p = .016$, $R^2=.28$) by left hippocampus mean diffusivity ($s\beta =-.39$, $p = .023$), age and scanner upgrade were included in the model but were not reliable. After controlling for the clinical and demographic variables the left hippocampus mean diffusivity remained a reliable predictor of number ($s\beta = -.44$, $p = .013$), but the full model was not significant ($F(7,27) = 2.00$, $p = .091$, $R^2=.34$) .

Similarly, to the left hippocampus, number was reliably ($F(4,45)=4.11$, $p =.006$, $R^2=.268$) predicted by right hippocampal mean diffusivity ($s\beta =-.27$, $p =.045$), stroke condition also predicted number ability ($s\beta =-.28$, $p =.037$), and age trended towards being reliable ($s\beta =-.24$, $p =.080$). However, the relations between right hippocampal mean diffusivity and number were not affected by the stroke.

When considering the stroke group alone, number was predicted ($F(2,34) = 3.16$, $p =.038$, $R^2=.23$) by the right hippocampus mean diffusivity ($s\beta =-.32$, $p =.066$) which trended towards significance, age and scanner upgrade were included in the model but were not reliable. After controlling for the clinical and demographic variables, the right hippocampus mean diffusivity remained a reliable predictor of post-stroke number abilities ($s\beta =-.40$, $p =028$). Although stroke severity (NIHSS) trended towards significance ($s\beta = .32$, $p =.068$), but the full model was not significant ($F(7,27) =1.71$, $p =.149$, $R^2=.31$).

Taken together, the results suggest, number abilities were predicted by the left and right hippocampal mean diffusivity. Interestingly stroke increased the relations between the mean diffusivity in the left hippocampus and number abilities. In the stroke group,

beyond clinical and demographic variables, mean diffusivity predicted post-stroke number abilities.

4.3.3.7.6 Praxis

Praxis was reliably ($F(3,45)=10.26$, $p <.001$, $R^2=.47$) predicted by stroke ($s\beta = -.51$ $p < .001$), and left hippocampus mean diffusivity ($s\beta = -.26$, $p = .027$), age ($s\beta = -.26$, $p = .025$), and scanner upgrade ($s\beta = .44$, $p <.001$). The relations between left hippocampus volume and praxis were not affected by the stroke.

In the stroke group alone, number was reliably ($F(3,31)=6.13$, $p =.002$, $R^2=.37$) predicted by scanner upgrade only ($s\beta = .46$, $p =.003$), and age trended ($s\beta = -.26$, $p = .097$), but left hippocampus mean diffusivity was not reliable. When clinical and demographic variables were controlled for, left mean diffusivity was still not a reliable predictor.

Similarly, to the left hippocampus, number was reliably ($F(4,45)=9.65$, $p <.001$, $R^2=.47$) predicted by stroke ($s\beta = -.50$, $p < .001$), right hippocampus mean diffusivity ($s\beta = -.22$, $p =.058$), age ($s\beta = -.28$, $p = .022$), and scanner upgrade ($s\beta =.44$, $p<.001$). The relations between right hippocampus volume and praxis were not affected by the stroke.

In the stroke group alone, number was reliably ($F(3,31)=5.72$, $p =.003$, $R^2=.36$) predicted by scanner upgrade only ($s\beta = .46$, $p =.003$), and age trended ($s\beta = -.28$, $p = .076$). When clinical and demographic variables were controlled for, right mean diffusivity was still not a reliable predictor, though scanner upgrade was ($s\beta = .46$, $p = .007$), and vascular risk trended ($s\beta = -.31$, $p = .081$), despite the full model only trending ($F(7,27)=2.52$, $p =.061$, $R^2=.37$) .

Taken together, the results suggest that beyond the stroke and age, praxis was predicted by the left or right hippocampal mean diffusivity, although this was not moderated by stroke. In the stroke group specifically though this did not translate, mean diffusivity did not predict post-stroke praxis abilities.

4.3.3.7.7 Summary of hippocampal mean diffusivity and cognition

On the whole cognition was not reliably predicted by the mean diffusivity of the left and right hippocampi. Although for number, praxis and general cognition domains mean diffusivity did predict abilities. With respect to the main research question, stroke did not moderate the relations between hippocampus mean diffusivity and cognition.

4.3.3.8 Hippocampal magnetic resonance spectroscopy and cognition

Finally, we examined metabolic regulation in the left hippocampus using ^{1}H-MRS, across three metabolites tNAA, tCh and tCr. To understand their relationship with cognition, we first computed correlations across the two cohorts combined (Table 25, Table 26). We had data for 31 stroke patients and 17 controls. For tNAA, it correlated with language, number, praxis and general cognition abilities. In the stroke only tNAA correlated with language, attention and executive function, number, and general cognitive abilities. tCh correlated with number, and attention and executive function abilities. In the stroke group it correlated with abilities in language attention and executive function, number and general cognition.

tCr positively correlated with language, attention and executive function, number, praxis, and general cognition abilities. In the stroke group tCr, also correlated with cognitive abilities in language, attention and executive function, number, and general cognition abilities.

We next explored using regression, the predictive value of these metabolites of cognition at three months post-stroke while considering the moderator effect of stroke and controlling for other relevant confounds.

4.3.3.8.1 General cognition

General cognition was reliably ($F(4,43)= 12.38$, $p <.001$, $R^2=.54$) predicted by stroke ($s\beta = -.49$, $p <.001$), tNAA ($s\beta = .38$, $p =.001$), age ($s\beta = -.45$, $p <.001$), and scanner upgrade ($s\beta = .38$, $p =.004$). The relations between tNAA and general cognition were not affected by the condition of stroke.

When considering the stroke group alone ($F(3,27)=8.26$, $p<.001$, $R^2=.48$) , general cognition was predicted by age ($s\beta = -.46$, $p = .005$), tNAA ($s\beta = .48$, $p = .004$), and scanner upgrade ($s\beta = .42$, $p = .011$). When controlling for other clinical-demographic variables tNAA was still a reliable predictor of general cognition ($s\beta = .68$, $p = .002$). See Figure 17.

General cognition was reliably ($F(4,43)=8.95$, $p <.001$, $R^2=.40$) predicted by stroke ($s\beta = -.48$, $p < .001$), age ($s\beta = -.47$, $p =.001$), tCh ($s\beta = -.23$, $p =.052$), and scanner upgrade ($s\beta = .29$, $p =.032$). The relations between tCh and general cognition were not affected by the stroke.

When considering the stroke group alone ($F(3,27)=5.03$, $p =.007$, $R^2=.36$) , general cognition was predicted by age ($s\beta = -.48$, $p = .010$), but not tCh. When controlling for other clinical demographic variables tCh was a reliable predictor of general cognition ($s\beta =.41$, $p = .053$),

General cognition was reliably ($F(4,43)=9.65$, $p <.001$, $R^2=.42$) predicted by stroke ($s\beta = -.47$, $p <.001$), age ($s\beta = -.48$, $p <.001$), and tCr,($s\beta = .27$, $p = .022$). The relations between tCr and general cognition were not affected by the stroke.

When considering the stroke group alone ($F(3,27)=5.58$, $p =.004$, $R^2=.38$) , general cognition was predicted by age ($s\beta = -.51$, $p = .004$), and tCr trended towards significance ($s\beta = .30$, $p = .057$), but scanner upgrade was not reliable. When controlling for clinical demographic variables, tCr reliably predicted post-stroke general cognition ($s\beta = .40$, $p = .045$),

Taken together, the results suggest that beyond the stroke and age, general cognition was predicted by tNAA, tCr, and tCh, although the relationship between general

cognition and hippocampal tNAA, tCh, and tCr was not moderated by stroke. Specifically, in the stroke group, tNAA was a reliable predictor of post-stroke general cognition, for tCh and tCr this was true after controlling for clinical-demographic predictors. Scanner upgrade also contributed to predicting post-stroke general cognition, which suggests bias of cognitive severity before and after scanner upgrade.

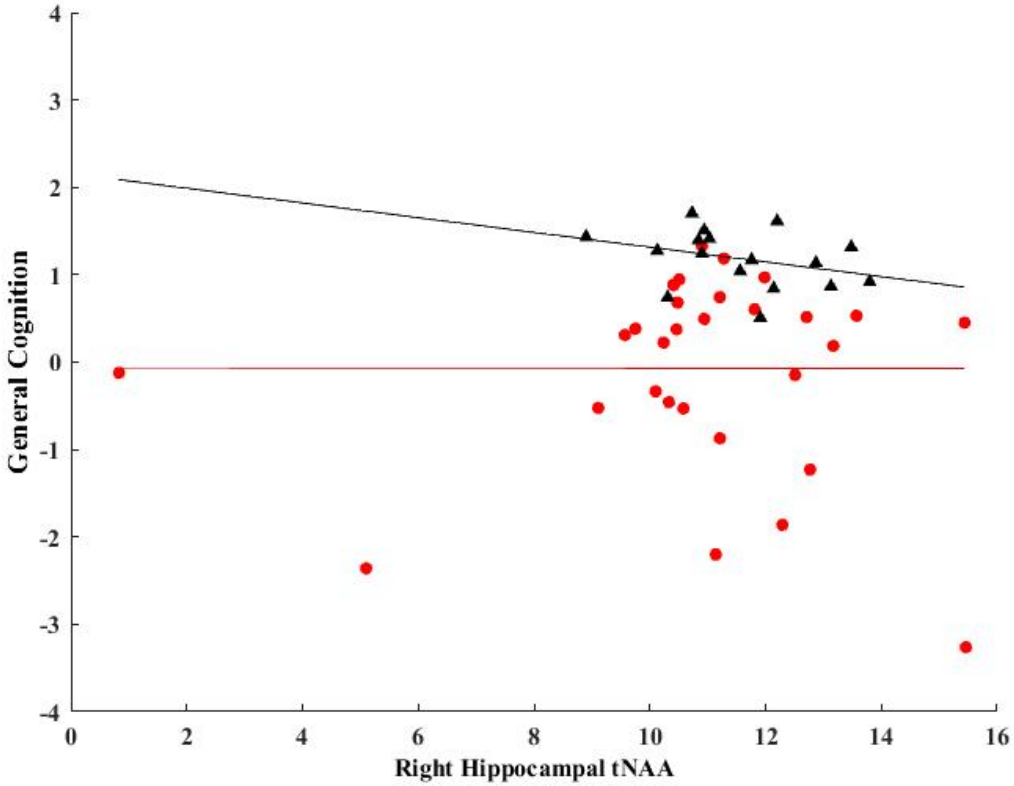

Figure 17. Right hippocampal tNAA/ General cognition (after controlling for age). Control participants, N= 17 (black triangle), Stroke patients, N=31 (Red circles).

4.3.3.8.2 Language

Language was reliably ($F(4,43)=4.90$, $p=.002$, $R^2=.31$) predicted by stroke ($s\beta = -.36$, $p = .011$), age ($s\beta = -.38$, $p = .010$), tNAA ($s\beta = .28$, $p = .045$), and scanner upgrade ($s\beta = .30$, $p = .052$). Though the relations between tNAA, and language were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=3.81$, $p=.021$, $R^2=.30$) language was predicted by tNAA ($s\beta = .42$, $p = .027$), but not age, or scanner upgrade. When controlling for clinical demographic variables, tNAA was still a reliable predictor of post-stroke language abilities ($s\beta = .65$, $p = .004$).

Language was reliably ($F(4,43)= 4.04$, $p=.007$, $R^2=.27$) predicted by stroke ($s\beta = -.38$, $p = .010$), age ($s\beta = -.40$, $p = .009$), but not tCh, or scanner upgrade. The relations between tCh, and language were not moderated by stroke condition.

When considering the stroke group alone language was not predicted by age or tCh.

Language was reliably ($F(4,43)=5.17$, $p=.003$, $R^2=.32$) predicted by stroke ($s\beta = -.32$, $p = .024$), age ($s\beta = -.39$, $p = .008$), and tCr ($s\beta = .29$, $p = .029$). The relations between tCr and language were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=3.61$, $p=.026$, $R^2=.29$) language was predicted by age ($s\beta = -.36$, $p = .052$), and tCr ($s\beta =.36$, $p = .035$). When clinical-demographic variables were controlled for tCr was predictive of post-stroke language ($s\beta = .49$, $p = .014$).

The results suggest that tNAA, and tCr were reliable predictors of language ability, beyond age and stroke. When clinical demographic variables were controlled for, tNAA and tCr were both predictors of post-stroke language abilities.

4.3.3.8.3 Memory

Memory was reliably ($F(4,43)= 3.16$, $p =.023$, $R^2=28$) predicted by stroke ($s\beta = -.41$, $p = .006$), and age ($s\beta = -.36$, $p = .021$), but not tNAA or scanner upgrade. The relations between tNAA and memory were not moderated by stroke condition.

When considering the stroke group alone tNAA did not predict post-stroke memory abilities.

Memory was reliably ($F(4,43)= 3.16$, $p =.023$, $R^2=.23$) predicted by stroke ($s\beta = -.41$, $p = .006$), and age ($s\beta = -.36$, $p = .022$), but not tCh, or scanner upgrade. The relations between tCh and memory were not moderated by stroke condition.

When considering the stroke group alone memory ability was not predicted by age, tCh or scanner upgrade.

Memory was reliably ($F(4,43)=3.17$, $p =.023$, $R^2=.23$) predicted by stroke ($s\beta = -.41$, $p = .008$), age ($s\beta = -.39$, $p = .022$), but not tCr, or scanner upgrade. The relations between tCr and memory were not moderated by stroke condition.

When considering the stroke group alone memory was not predicted by age or tCr.

No metabolites predicted memory ability, at the combined group level, or in the stroke specific group.

4.3.3.8.4 Attention and executive function

Attention and executive function was reliably ($F(4,43)=9.45$, $p =.000$, $R^2=47$) predicted by stroke ($s\beta = -.45$, $p < .001$), age ($s\beta = -.40$, $p = .002$), tNAA ($s\beta =.38$, $p = .003$), and scanner upgrade ($s\beta =.34$, $p = .015$). The relations between tNAA and attention and executive function were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=6.21$, $p=.002$, $R^2=.41$), attention and executive function was reliably predicted by tNAA ($s\beta=.45$, $p=.011$), age ($s\beta=-.43$, $p=.014$), and scanner upgrade ($s\beta=.35$, $p=.042$). When controlling for clinical demographic variables, tNAA still reliably predicted post-stroke attention and executive function ($s\beta=.58$, $p=.009$).

Similarly to tNAA, attention and executive function was reliably ($F(4,43)=7.57$, $p=.000$, $R^2=.41$) predicted by stroke ($s\beta=-.47$, $p<.001$), age ($s\beta=-.42$, $p=.002$), and tCh ($s\beta=.27$, $p=.028$), but not scanner upgrade. The relations between tCh and attention and executive function were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=4.31$, $p=.013$, $R^2=.32$), attention and executive function was not predicted by tCh or scanner upgrade, but only by age ($s\beta=-.42$, $p=.024$).

Attention and executive function was reliably ($F(4,43)=7.96$, $p<.001$, $R^2=.42$) predicted by stroke ($s\beta=-.42$, $p=.002$), age ($s\beta=-.42$, $p=.002$), and tCr ($s\beta=.29$, $p=.017$), but not scanner upgrade. The relations between tCr and attention and executive function were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=4.53$, $p=.011$, $R^2=.34$) attention and executive function was predicted by age ($s\beta=-.48$, $p=.009$), but not tCr, although it trended ($s\beta=.39$, $p=.066$).

Taken together, the results suggest that beyond the stroke and age, attention and executive function was predicted by tNAA, tCr and tCh, although this relationship was not moderated by stroke. Specifically, in the stroke group, tNAA was a reliable

predictor of post-stroke attention and executive function even after controlling for clinical-demographic predictors.

4.3.3.8.5 Number

Number was reliably ($F(4,43)= 10.51$, $p <.001$, $R^2=45$) predicted by stroke ($s\beta = -.38$, $p = .004$), age ($s\beta = -.42$, $p = .001$), tNAA ($s\beta =.45$, $p < .001$), and scanner upgrade ($s\beta =.29$, $p=.034$). The relations between tNAA and number were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=7.73$, $p =.001$, $R^2=.46$), number was reliably predicted by tNAA ($s\beta =.51$, $p = .003$), and age ($s\beta =-.42$, $p = .012$). When controlling for clinical demographic variables, tNAA still reliably predicted post-stroke number ability, tNAA ($s\beta =.65$, $p = .002$).

Similarly to tNAA, number was reliably ($F(4,43)=6.49$, $p =.000$, $R^2=.38$) predicted by stroke ($s\beta = -.39$, $p = .005$), age ($s\beta = -.46$, $p = .005$), and tCh ($s\beta = .25$, $p = .049$). The relations between tCh and number were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=4.14$, $p =.015$, $R^2=.32$), number was not predicted by tCh, but only by age ($s\beta = -.44$, $p = .020$).

Number was reliably ($F(4,43)=6.65$, $p <.001$, $R^2=.38$) predicted by stroke ($s\beta = -.34$, $p = .013$), age ($s\beta = -.46$, $p = .001$), and tCr ($s\beta =.26$, $p = .039$). The relations between tCr and number function were not moderated by stroke condition.

When considering the stroke group alone ($F(3,27)=4.29$, $p =.013$, $R^2=.32$) number was predicted by age ($s\beta =-.48$, $p = .008$), but not tCr,

Taken together, the results suggest that beyond the stroke and age, number ability was predicted by tNAA and tCr. Although this relationship was not moderated by stroke. Specifically, in the stroke group, tNAA was a reliable predictor of post-stroke number ability even after controlling for clinical-demographic predictors.

4.3.3.8.6 Praxis

Praxis was reliably ($F(4,43)=10.09$, $p <.001$, $R^2=48$) predicted by stroke ($s\beta = -.59$, $p <.001$), tNAA ($s\beta =.32$, $p = .009$), age ($s\beta =-.25$, $p = .046$), and scanner upgrade ($s\beta =.54$, $p <.001$). The relations between tNAA and praxis were not moderated by stroke condition.

When considering the stroke group alone praxis was predicted by ($F(3,27)=7.71$, $p <.001$, $R^2=.46$), tNAA ($s\beta =.45$, $p =.007$), and scanner upgrade ($s\beta = 67$, $p =.00$). When controlling for clinical and demographic variables tNAA still predicted post-stroke praxis, as did lesion volume ($s\beta =.32$, $p =.045$).

Praxis was reliably ($F(4,43)=7.71$, $p <.001$, $R^2=.42$) predicted by stroke ($s\beta = -.62$, $p < .001$), age ($s\beta = -.28$, $p =.037$), but not tCh. The relations between tCh and number were not moderated by stroke condition.

When considering the stroke group alone praxis was not predicted by age or tCh, but was by scanner upgrade.

Number was reliably ($F(4,43)=8.53$, $p <.001$, $R^2=.44$) predicted by stroke ($s\beta = -.58$, $p <.001$), and age ($s\beta = -.28$, $p =.037$), with tCr trending ($s\beta =.23$, $p = .060$). The relations between tCr and praxis were not moderated by stroke condition.

When considering the stroke group alone praxis was not predicted by age or tCr, but was by scanner upgrade.

Taken together, the results suggest that beyond the stroke and age, tNAA was the only predictor of praxis abilities. Although this relationship was not moderated by stroke. Specifically, in the stroke group, tNAA predicting post-stroke praxis abilities.

4.3.3.8.7 Summary of hippocampal metabolites and cognition

On the whole cognition was reliably predicted by hippocampal metabolites. Specifically, tNAA was a predictor of cognition across both groups, in general cognition, language, attention and executive function and number. In the stroke group the same pattern was observed, with the addition of tNAA predicting praxis. tCh did predict abilities in general cognition, number and attention and executive function, similarly tCr predicted abilities in general cognition, number, attention and executive function, language and praxis. With respect to the main research question, stroke did not moderate the relations between hippocampus metabolites and cognition.

4.4 Discussion

In the current chapter we investigated the relation of hippocampal pathology with cognition at three months post-stroke, and in age matched controls. We examined hippocampal pathology in three ways; volumetric measurement looking at grey matter integrity, mean diffusivity, and metabolic measurement of tNAA, tCr and tCh. We also collected detailed clinical and demographic information, including both neurovascular and overall brain health.

We demonstrated high internal validity for all the hippocampal pathology measures by replicating expected relations between them. These relations were observed in the entire sample (both groups combined), and in the stroke group alone.

In relation to the research question, there were no significant differences between the stroke patients, and control participants across any of the hippocampal pathology measures. There were however significant differences between the two groups in cognitive ability, across the five cognitive domains and within general cognition.

Hippocampal pathology determined by three MRI measurements, predicted cognition in the combined sample (stroke and control participants), as well as independently in the stroke group. The moderation analyses showed that across all MRI measures the relation between hippocampus pathology, and cognition was not affected by stroke (Table 27). This suggests that at three months post stroke, hippocampus pathology contributes to cognition beyond, and independent to the incidence of stroke. The relations were most pronounced when considering the general cognition measures; but were most robust in the number domain.

There was no difference in hippocampal volume between the stroke patients and control group. Hippocampal volume reduced with age, and increased with education. As expected we found hippocampal grey matter volume predicted cognition. Hippocampus volume predicted language, memory, and number abilities, as well as the composite general cognition domain. This in agreement with previous literature, showing the importance of hippocampus to cognition (Mielke et al., 2012; van Uden et al., 2016). The strong relation between hippocampal volume, and number domain was not expected.

Table 27. Hippocampal imaging measures summary table

Hippocampal measure	Effect	General Cognition	Language	Memory	Attention & Executive function	Number	praxis
Left GM Volume	**Stroke + Control[a]**	√√	X√$	XX	XX	√√	XX
	Moderation	X	X	X	X	X	X
	Stroke[b]	√ √√	XX√$	XXX	XXX	√√√	XX√
Right GM volume	**Stroke + Control[a]**	√√	√√	√$X	√$X	√√	√$X
	Moderation	X	X	X	X	√$	X
	Stroke[b]	√√√	√√√	√√√	√√√	√√√	√$X√
Left MD	**Stroke + Control[a]**	√√	X√$	XX	√$X	√√	√√
	Moderation	X	X	X	X	X	X
	Stroke[b]	√√X	XXX	XXX	XXX	√√$	XXX
Right MD	**Stroke + Control[a]**	√√	XX	XX	XX	√√	X√$
	Moderation	X	X	X	X	X	X
	Stroke[b]	√$ XX	XXX	XXX	XXX	√$√$√$	XXX
tNAA	**Stroke + Control[a]**	√√	√√	XX	√√	√√	X√$
	Moderation	X	X	X	X	X	X
	Stroke[b]	√√√	√√√	XXX	√√√	√√√	√√√
tCh	**Stroke + Control[a]**	√√	XX	XX	√√	√√	√X
	Moderation	X	X	X	X	X	X
	Stroke[b]	XX√$	XX	XXX	XXX	XXX	XXX
tCr	**Stroke + Control[a]**	√√	√√	XX	√√	√√	√√$
	Moderation	X	X	X	X	X	X
	Stroke[b]	X√$√	√√√	XXX	√√$	XXX	XXX

Notes. Stroke + Control[a] . The significance reported in combined analysis of the stroke and control groups (i) the reliability of correlation between the hippocampus pathology measure and the cognitive domain (first mark), and (ii) whether the relations remain reliable after controlling for age, stroke condition, and scanner upgrade (second mark). Moderation effect reports whether the addition of the stroke-by-hippocampus moderation predictor improved the model. Stroke[b]. The significance reported in the stroke

only tests, (i) the correlation cognition and hippocampus measure (first mark), (ii) the significance of the relations after controlling for age and scanner upgrade (middle mark), (ii) the significance after controlling for clinical-demographic variables. √, $p < .05$; √^{s}, $p < .1$; X $p > .1$ n.s. MD= mean diffusivity. GM=Grey matter.

We did not find significant differences between stroke patients, and controls in hippocampal volume as reported in the literature (Brodtmann et al., 2012; Tang et al., 2012). However others have also struggled to find these differences three to six months after the ischemic event (Sachdev et al., 2007). It could be possible that it is too early in the post-stroke trajectory to observe hippocampal changes, with some reporting changes at 12 months, and three years' post-stroke (Ross et al., 2006). The data did not suggest that stroke ignited hippocampal volume loss within three months of stroke.

Hippocampus volume predicted cognition in the combined, and the stroke group alone. Stroke condition did not moderate the relations between hippocampus volume and cognition. It could be that sub-clinical hippocampus pathology, and cognitive deficiency were present in some stroke patients before the ischemic event (Yang et al., 2015). This supports the idea that pre-stroke brain health (including hippocampal pathology), specifically vascular pathology contributes to cognitive ability, and preservation of cognition following stroke (Debette et al., 2011).

Significant correlations between vascular risk, and grey matter volume of left and right hippocampi were found in the stroke patients. Hippocampus volume also correlated with other measures of brain health, such as level of atrophy, and small vessel disease. Similar to previous studies, overall brain health caused by vascular disease impacted cognition in this stroke cohort, furthermore the current cohort had significantly overall lower brain health (small vessel disease and regional atrophy) than the healthy controls

(Hennerici, 2009; Lawrence et al., 2013; Leys et al., 2005). This suggests that in some stroke individuals the hippocampus is vulnerable, due to low vascular and general brain health pre-dating the stroke. Though in the current study hippocampus pathology predicted cognition, beyond other measures of brain health and clinical and demographics.

Stroke incidences may accelerate the damage, and in turn affect cognition (Werden et al., 2017), though we did not find evidence for an acceleration hippocampus pathology following stroke within three months. The relation between hippocampus volume, and cognition were similar for the control and the stroke group.

A similar but less reliable relation was found between hippocampal mean diffusivity and cognition, in comparison to the predictive hippocampal grey matter volume. This is contrary to previous literature that reported mean diffusivity to be more predictive of cognitive ability than hippocampal grey matter volume (Carlesimo et al., 2010; den Heijer et al., 2012; Kliper et al., 2016). Although there have been studies that show no difference in cognition, in those with high mean diffusivity compared to low (Schaapsmeerders et al., 2015). The internal validity analysis showed an expected pattern, with left and right hippocampal mean diffusivity correlating with each other, and mean diffusivity was negatively associated within tNAA. This suggests that lack of reliable effects is unlikely to be driven by poor data quality.

There was no significant difference in mean diffusivity between stroke patients and control participants. Left and right hippocampal mean diffusivity predicted only number abilities and general cognition. These relations were not moderated by stroke. We did not observe effects of mean diffusivity on memory as reported before (Hosseini et al.,

2017). It is difficult to account for this discrepancy. It is possible that the current study lacked the power to detect the findings of previous studies.

Finally, all three metabolites (tNAA, tCr and tCh) predicted cognition with the most reliable effects observed for tNAA. Like the other hippocampal pathology measures, stroke did not reliably affect hippocampus pathology; neither did it affect the relations between hippocampus pathology and cognition. There is relatively limited literature in the area of stroke and spectroscopy, although decreased NAA in the hippocampus has been found in those with cognitive impairment following stroke (Wang, 2017), and a decrease in hippocampal NAA/Cr ratio was reported for chronic stroke relative to controls (Tang et al., 2012).

Despite the lack of significant difference between stroke and control participants, the pattern of metabolite rate in tNAA for both cohorts, fits with previous literature examining cognitive impairment and dementia; with lower tNAA in people with poorer brain health, and lower cognition. The literature is less consistent with respect to Cr and Ch as biomarkers for pathology. The positive correlation of tCr and tCh, with tNAA, and the positive correlation of tCh with grey matter volume in the right hippocampus give some validation in the measures of these two metabolites. Like the tNAA, tCh and tCr showed positive relation with cognition, primarily when considering the two groups combined. The current data suggests that a decrease in Cr and Ch concentration in the hippocampus may mark malfunctioning of the hippocampus in the stroke and ageing population.

As previously mentioned, in the current chapter, the relation between hippocampus pathology, and cognition was not reliably different between the stroke and the control

group. Weak trends for moderation effects were observed for number abilities, when considering right hippocampal volume, and left hippocampal mean diffusivity. These trends can also be seen in the plots of general cognition and the hippocampal pathology measures (Figure 15, Figure 16, Figure 17). We see that hippocampal pathology appears to be a better prediction of cognition in stroke, than controls. Hence it is possible that following stroke, hippocampus health can serve as a protective factor against cognitive impairment caused by stroke. In the current cohort, education correlated with grey matter volume of the hippocampus. It could be possible, mechanism that protects against the impact of stroke on cognition, as described in chapter three, through its association with hippocampal pathology.

4.4.1.1 Findings outside the main research question

Beyond the original research question, we encountered some interesting findings worth noting. Although, we should mention that findings outside the main research question should be interpreted with caution due to the relatively small sample size and heterogeneous sample of stroke patients.

We observed a correlation between thrombolysis and level of education. The eight patients who were thrombolysed, had a higher education level than those that were not Although our sample is small, and only 20% of the patients had thrombolysis, our findings concur with previous literature that report this relationship (Stecksén et al., 2014). This finding demonstrates the importance of education. As it is likely that educated individuals are more aware of the clinical symptoms of stroke, and the potential time constrains associated with various treatments, leading them to seek medical advice earlier. This suggests that education may provide two routes of improving outcomes and recovery; 1) through direct impact at neuronal level, or 2)

simply at a level comprehension of information. In both cases level of education can have a positive impact on stroke treatment, and stroke outcomes.

When examining the stroke group, we find more temporal lobe atrophy compared to the control participants. The association of temporal lobe atrophy following stroke and neurodegeneration onset is well documented. This is an interesting finding, and fits with previous literature. We also find more severe small vessel disease, and lower vascular health in this stroke cohort. Again, it is well documented within the stroke population that small vessel disease is a prominent feature. The brain health of individuals who had stroke was overall lower than those who did not. This again raises the question of whether the stroke incident, and its impact on cognition should be viewed in isolation of other measures of brain health. While stroke has an abrupt effect on the brain, it may be one spike on lifelong trajectory of poor brain health.

Interestingly, in the stroke group small vessel disease was highly linked to grey matter volume in the hippocampus, with higher levels of small vessel disease leading to lower grey matter volume in this brain region. This supports a potential common physiological cause for both grey matter loss disease (like Alzheimer's disease), and vascular based diseases (small vessel disease).

Spectroscopy is well documented in terms of measuring abnormal tissue within the brain, and it has also been used to examine neurodegeneration. Little research has used spectroscopy to measure neurodegeneration in the stroke population. In this chapter we find that it may be a reliable measure of post-stroke cognition. It would be interesting to examine its predictive value in post-stroke cognitive trajectory, when measuring more than one time-point. We observed strong positive correlations between all three

metabolites in the stroke cohort, suggesting that in fact they all decrease along with each other. As mentioned in (1.5.4.3), tNAA level decreases in neurodegeneration, but the reports of tCh and tCr are not as consistent. However, it is suggested that tCh and tCr are decreased within brain tissue following an ischemic event, although this relates to tissue affected by the ischemia and not a neurodegenerative process.

As mentioned in the introduction, the hippocampus is mainly associated with memory function and learning, although some suggest a wider role of the hippocampus within different cognitive functions. In the current analyses, we observe very weak associations with memory ability and hippocampal measures, but strong associations with number ability. We can only hypothesise why this may have occurred, as number has not been documented in the literature as being associated with the hippocampus. The tasks that make up the number domain, include writing prices which involve symbols; this could be a potential link to the hippocampus. It seems that there is a link between number ability and hippocampal pathology, across both control participants and stroke, and needs further investigation.

4.4.1.2 Methodological consideration and limitations

The MRI data presented in the current study was internally valid, which suggests evidence of good quality of data. Internal validity was examined by examining the level to which the hippocampal pathology measures correlated. We found that that measures of homologues regions highly correlate. Furthermore, as expected grey matter volume positively correlated with tNAA.

As discussed in the methods, there are some limitations with the measure of spectroscopy in the hippocampus. Low signal to noise ratio meant that we had to

exclude the right hippocampus from this measure. Even though the method of spectroscopy is continuing to develop, there are known limitations with its reliability (Wilson, Andronesi, et al., 2019).

We accounted for the potential impact of the scanner upgrade in all statistical analyses. The upgrade had a weak correlation to one of the MRS measurements, however this did not survive Bonferroni corrections. The scanner upgrade interacted with some of the cognitive measurements in the regression models, however it is important to note that we observe a recruitment bias from before and after the scanner upgrade, with patients having more severe cognitive deficits before scanner upgrade. It is also important to note that across the hippocampal measurements, they represent slightly different patient and control cohorts, due to the difference in numbers in each group (See Page 127). We conclude that this is interacting with the scanner upgrade, and it is not due to any technical differences with the MRI acquisition.

The distribution of the data was not normal for almost all measures used, evident by the differences observed between the mean and the median. This was true for both the stroke patients and the control participants. Abnormal distribution is a violation of the assumptions of parametric statistics, leading to potential spurious statistical tests. To partly account for this, we computed non-parametric correlations to verify that our results are not driven by outliers. Though it is typically considered that for sample size above 40 this is of minimal concern (Ghasemi & Zahediasl, 2012). The multiple analyses across the same dataset presented in the current chapter is at risk of type 1 error. We took caution with interpreting statistical results that were weak, due to the issues surrounding interpretation of multiple comparisons. In each analysis information is provided of whether significance remained after using Bonferroni-Holmes

corrections. In the majority of the analyses presented in this chapter, significance remained after correcting for multiple comparisons.

There were lots of clinical and demographic differences observed between the stroke patients, and the control participants which were not directly related to the stroke incidence. The control participants overall were more educated, with overall good health status (lower vascular risk), better brain health (less small vessel disease and atrophy), and were pre-dominantly female. Thus, it is difficult to attribute any effects of stroke incidence on cognition to the stroke alone. It is therefore interesting that despite this recruitment bias (cognitive severity and software upgrade), the relations between hippocampal pathology, and cognition were not affected by the stroke condition.

A subject that is debated when researching cognition is the use of healthy controls. In our sample we attempted to recruit controls that were age matched, and considered appropriate in terms of health, and lack of cognitive impairment and/or decline. We must consider however that within an ageing cohort, there will in turn be ageing consequences in health and cognition. Although we excluded cases where this was too severe to be considered healthy, we observe that our control group present with similar atrophy in the parietal region as the stroke patients.

The current sample was very heterogeneous (e.g. there was little overlap of lesions, and high variability of cognition ability). This was an advantage, as most of the analyses relied on variability between individuals (i.e. correlation and regression), but the downside of this, was that the data had a large proportion of unexplained variability which reduced the overall power of the analysis. The sample size was also fairly small, especially in the control group, which again hindered the study power. The lack of reliable differences between the groups may have been potentially masked by the high

variability, and the small sample size. Hence, interpretation of null results should be made with caution, and they require further investigation.

4.4.1.3 Conclusion

Hippocampus pathology predicted cognitive outcome, though the relation between hippocampus pathology, and cognition were not affected by stroke.

The data suggests that some stroke patients may be on a linear trajectory of cognitive decline. And in these cases, the ischemic incident is one time-point on their trajectory, with vascular health, prior cognitive level (education), and brain pathology (hippocampal) all contributing to this trajectory. Though importantly, this was not true for all patients. Thus, hippocampus pathology may serve as a marker of decline trajectory, in similar way that it is used to predict transition from MCI to dementia.

Chapter 5: Discussion

5.1 Summary

This thesis aimed to establish neurocognitive predictors of post-stroke cognitive outcome and trajectories, using neuropsychological, demographical, and brain imaging data (DTI, ^{1}H-MRS, grey matter volume). Through this investigation, we found that, (a) there are three distinct cognitive recovery trajectories that occur following stroke. Most stroke patients recovered around 50% of their cognitive deficits at nine months, while a small proportion of stroke patients showed a declined or accelerated recovery, (b) trajectory of cognitive recovery following stroke can be predicted by modifiable factors such as education. Education improved cognition in ageing, and beyond age it improved post-stroke cognitive outcomes, and accelerated recovery, and finally (c) beyond stroke and age, hippocampal pathology, and overall brain health impacted cognitive ability following stroke. Furthermore, hippocampal pathology represented by grey matter volume interacted with education and age. This suggests that hippocampus pathology may be one contributing factor to cognitive recovery following stroke. We conclude that pre-stroke factors modulate cognitive outcomes, and especially the potential for recovery post-stroke.

Table 28. Summary of chapters

Chapter	Title	Questions	Data	Method	Independent Variable	Dependent Variable	Outcome	Conclusions
Chapter two	Recovery trajectories following stroke: *the proportional recovery rule in cognition*	1. Does proportional recovery exist in cognition? 2. Do all stroke patients follow the proportional recovery rule?	COGNITION: Cognitive data collected using the BCoS Includes: General cognition, memory, language, number, praxis, attention and executive function Stroke population=380	Proportional change calculation using regression for rate of change between IV and DV	COGNITION at 9 months post stroke	COGNITION at <3 months post stroke	1. 80% of patients showed proportional recovery of 40-50% of COGNITION at 9 months 2. 10% of patients showed accelerated recovery and 10% showed decelerated recovery at 9 months	**The proportional recovery rule exists in cognition, across five cognitive domains, and extends beyond 6 months post stroke**

Chapter	Title	Questions	Data	Method	Independent Variable	Dependent Variable	Outcome	Conclusions
Chapter three	Can education protect against age related cognitive decline? A study of UK and Chinese healthy and stroke adults.	Predictive value of years in education on: 1. COGNITON in healthy ageing 2. Post stroke COGNITION <3 months 3. COGNITION and recovery rate at 9 months post-stroke	**COGNITION** (as chapter two) 1. Healthy ageing population UK=100 China= 344 2. Stroke population UK=826 China=205 3. Stroke population UK=380	Linear regression and correlation analyses between IV and DV 1. Collapsed across cohort (UK & China) 2. For UK and China separately	1. COGNITON in healthy ageing 2. Post stroke COGNITION <3 months 3. COGNITION and recovery rate at 9 months post-stroke	Years in Education	1. Education predicted COGNITION in healthy ageing 2. Education predicted cognitive outcome <3 months post stroke in general, language and number 3. Education predicted cognitive outcome at 9 months and recovery rate	**Education was a protective factor of cognitive ageing, improved cognitive outcomes, and accelerated cognitive recovery following stroke**

Chapter	Title	Questions	Data	Method	Independent Variable	Dependent Variable	Outcome	Conclusions
Chapter four	Hippocampal pathology and its impact on post-stroke cognition	1. Does stroke incidence affect hippocampal pathology? 2. Does hippocampal pathology affect COGNITON	**COGNTION** <3 months post stroke **Neuroimaging** <3 months post stroke 1. DTI = mean diffusivity 2. T1 weighted image= grey matter volume 3. Magnetic resonance spectroscopy= metabolites	Linear regression and correlation analyses between IV and DV 1. Collapsed across Stroke patients and control participants 2. For Stroke patients separately	COGNITON within three months post stroke	Hippocampal pathology 1. Mean diffusivity of left and right hippocampi 2. Grey matter volume of left and right hippocampi 3. Metabolites in left hippocampi -NAA -Ch -Cr	1. There were no differences between stroke patients and controls in hippocampal pathology 2. Hippocampal pathology did predict cognition across stroke patients and control participants 2. This effect was stronger in the stroke group	**Hippocampal pathology did predict cognition.** **Hippocampal pathology may be a viable marker for neurodegeneration following stroke**

5.2 Going beyond existing literature

Chapter two examined whether the proportional recovery rule applies for cognition in a heterogeneous sample of 380 stroke patients.

Replication: In line with previous reports of motor recovery (Krakauer, 2006; Krakauer, 2015), aphasia (language) (Lazar et al., 2010), neglect (spatial attention) (Marchi et al., 2017), and across cognitive domains (Ramsey et al., 2017) we found that cognitive recovery after stroke is proportional to the initial deficit.

We also identify 'non-fitter's' as reported in the motor-recovery literature (Buch et al., 2016; Shyam et al., 2007), who do not recover as expected, showing a decelerated recovery. In the motor recovery literature, the non-fitters, were those who were initially severely impaired. In contrast, in this thesis cognition decelerated recovery was independent of initial severity, and was observed in patients who initially were mildly impaired, as well as in those who were severely impaired.

Going beyond: We used analysis methods that were not susceptible to mathematical coupling, and spurious results (Hope, 2018). We showed that when considering performance along a continuum rather than using cut-offs, the proportion of recovery is larger (40% vs. 50%). Improvement in cognitive abilities (i.e. a positive recovery trajectory) were observed from one month till at least nine months post stroke (previous research examined recovery along shorter time scales from three to 90 days (Krakauer & Marshall, 2015; Lazar et al., 2010; Ward, 2017). Comparing across domains, recovery of language abilities was most variable; with the largest recovery seen for the memory and praxis domains. We identified two groups of non-fitters, patients who showed accelerated, and decelerated recovery relative to what is expected. This variable

pattern in recovery is consistent with subjective self-reports of recovery trajectories (Hawkins et al., 2017).

Future research should aim to replicate the observation of the two non-fitter groups, and focus on identifying factors that can predict individual trajectories. Understanding the mechanisms that boost, or hinder recovery can potentially lead to improved care pathways, and rehabilitation procedures following stroke.

To understand further why stroke patients, recover at different rates, chapter three examined the role of prior cognitive ability, in the form of education level using two databases (UK and China)

Replication: In line with previous literature we showed that beyond age, education level predicted general cognitive ability. This is consistent with many previous reports (Pinter et al., 2015). We also showed that education improves general cognitive outcomes following stroke, as suggested by previous meta-analyses (e.g. (Chaudhari et al., 2014; Chen et al., 2016; Elkins et al., 2006; Leys et al., 2005; Parisi et al., 2012; Pendlebury, 2009)).

Going beyond: We showed a similar pattern of results across three versions of the same cognitive screen (English-BCoS, mandarin-BCoS, and Cantonese-BCoS). We showed that the effect of education on general cognition is most driven by the language and numerical domains, stressing a potential direct role of formal education in post-stroke recovery. The data suggested that the impact of education on cognition drops (effect size, $r < .1$) at early stages following stroke (around one month), but returns to effect sizes seen in ageing ($r \sim .15$-$.2$) at nine months post stroke. Finally, we showed that education accelerated recovery rate following stroke.

Future research should aim to examine the neurocognitive mechanisms that mediate the impact of education on cognition. This should include measures regarding life-style and socio-economic status which are associated with education.

Finally, we investigated the impact of brain health on post-stroke cognition. We specifically focused on the hippocampus, as it is a key brain region involved in cognitive decline and ageing (i.e. Alzheimer). We used DTI to establish mean diffusivity, T1-weighted imaging to obtain grey matter volume, and ^{1}H-MRS to measure metabolites (tNAA, tCh and tCr) in the hippocampus, within three months of ischemic stroke (Table 27).

Replication: In contrast to previous literature (Brodtmann et al., 2012; Haque et al., 2019; Ross et al., 2006; Tang et al., 2012; Wang, 2017; Yang et al., 2015) we did not find differences in hippocampal pathology between stroke patients, and control participants (lack of difference was reported before: (Sachdev et al., 2007).

In line with some previous literature we did find that hippocampus pathology predicted general cognition. Replicating effects observed in grey matter volume in aging (Mielke et al., 2012; van Uden et al., 2016) and specifically in stroke (Kliper et al., 2016; Pohjasvaara et al., 2000; Yang et al., 2015). Similarly mean diffusivity in the hippocampus was associated with poorer cognition as reported in ageing studies (Carlesimo et al., 2010; den Heijer et al., 2012; Kliper et al., 2016), and specifically in stroke (Kliper et al., 2016). The current study replicated the positive association between NAA concentrations in the hippocampus and cognition, observed in ageing research (e.g. (Kantarci, 2007; Targosz-Gajniak et al., 2013).

In contrast to previous literature (e.g. (Hosseini et al., 2017), we did not find robust relations between hippocampus pathology and the memory domain. Only the right hippocampus volume reliably related to memory abilities in the combined group.

Going Beyond previous studies, we used advanced neuroimaging methods to characterise hippocampus pathology, and added valuable data to sparse literature on hippocampus pathology, and cognition following stroke. We used a combination of MR measures (local grey matter volume, mean diffusivity, metabolites) to assess hippocampus pathology, and provided converging evidence across these various methods. We showed that at three months post-stroke, the stroke event did not affect the relationship between hippocampus pathology and cognition. This suggests that hippocampus pathology should be viewed as an independent contributor to post-stroke cognition.

The data demonstrated that hippocampus pathology, specifically grey matter volume correlated with education. The association between general cognition, and hippocampus pathology was primarily driven by the number, and then the language domain. These observations suggest that hippocampal health may be one mechanism by which education reduces cognitive impairment following stroke.

Future research should aim to replicate the current study with larger sample size. It should additionally focus on examining the potential of pre-stroke markers of brain health, beyond the hippocampus as predictor of recovery following stroke.

5.3 Post-stroke cognitive trajectory

The current thesis suggests that cognitive trajectory is affected by three factors: the severity of your cognitive impairment following stroke, your pre-stroke demographic status (age and education), and your hippocampal pathology (brain health).

In the introduction we discuss research that focuses on post-stroke cognitive trajectories, and factors that have been found to impact these trajectories. An important review by Mijajlović and colleagues suggest that not all patients follow the same recovery trajectory (Mijajlović et al., 2017), see Figure 1. In this thesis, we provide empirical data that supports the existence of different recovery trajectories. Going beyond this, we specifically show three potential cognitive trajectories; improved abilities in proportional to initial deficits as expected, accelerated recovery trajectory and declined trajectory (see Figure 18). Additionally Mijajlović and colleagues suggest that individuals have different cognitive states, and abilities prior to stroke (Mijajlović et al., 2017). Data provided in chapter three and four, supports this statement, showing that eductaion and age are associated with cognition in ageing, and also in stroke (potentially reflecting pre-stroke cognitive ability). Going beyond the proposed model (Figure 1), we showed that cognitive outcomes at one to three months post stroke depend on patients pre-stroke demographic (age and education), and brain health (hippocampus pathology, small vessel disease, cortical atrophy, vascular risk factors) which are indepepndet contributors to the stroke event itself (stroke severity, lesion volume). This demonstrates that not all stroke patients begin with the same cognitive impairment severity. While initial severity dictates a proportional recovery trajectory for majority of patients (80%), chapter two showed that independent of initial severity 10%

of pateints fail to recover as expected, and even decline, while some patients who initially showed severe cognitive imparments had an accelerated recovery.

The time scale proposed in the Mijajlović model (Mijajlović et al., 2017), is not fully supported by the current data. Specifically, Mijajlović and colleages suggest that cognition deficits stabalise, and reach their peak recovery potential at six months. In contrast the data in chapter two suggests that all three cognitive trajectories are dynamic at least up to nine months post-stroke, and the majority (more than 90% of patients) showed improved cognition at nine months compared with baseline ablities. Due to the fact that we only measured two time points, we do not know exactly when/whether these recovery trajectories will have become stable, but we do know that they were present at nine months post-stroke (see Figure 18), and were independent of the baseline assessment timing (three to 90 days).

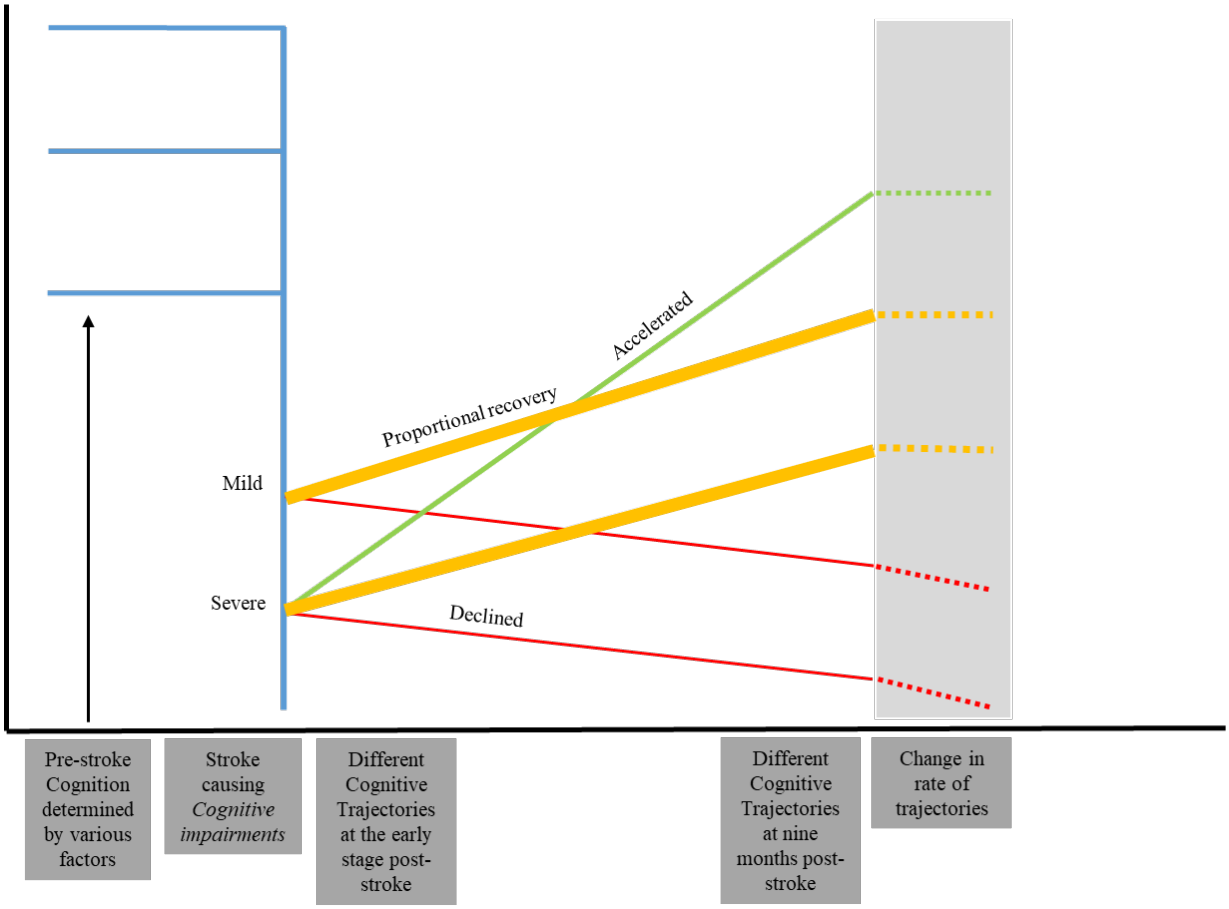

Figure 18. Proposed cognitive trajectories following stroke.

5.4 Post-stroke cognitive trajectory and neurocognitive predictors

How does pre-stroke cognition contribute to post-stroke outcome and recovery? A review on stroke and traumatic brain injury suggest that one possibility is through cognitive reserve, which is assumed to be boosted by education level (Nunnari et al., 2014). Cognitive reserve may protect individual's cognitive impairment following stroke. In previous research into vascular cognitive impairment, those with severe MRI changes were able to utilise their cognitive reserve (level of education) to protect themselves from neuronal damage (Zieren et al., 2013). As documented above, we found the protective factor of education on both post stroke cognition, and recovery trajectories.

As with our findings in chapter two, with initial severity not always predicting cognitive trajectory, in chapter four, stroke severity measured by the NIHSS did not play an important role in predicting cognitive outcomes, previously it has been reported as being a significant predictor of outcomes (Chaudhari et al., 2014; Leys et al., 2005). Other factors did play a role in predicting cognitive outcomes, such as lesion volume. This may relate to the model of cognitive reserve proposed by (Stern, 2012), the larger the lesion the more it impacts both brain structure and in turn brain networks (Alstott et al., 2009), without the cognitive reserve to bolster the disruption, the impact on cognitive outcomes are worse. Additionally, in the measurement of metabolites, age did play a role in predicting cognitive outcomes at three months post-stroke alongside tNAA and tCr, which was previously documented (Wang, 2017).

In chapter two, we identify different recovery rates for number and language domains, which is also evident in chapter three, where level of education was a strong predictor of

language and number cognitive outcomes and ability at nine months post-stroke. In chapter four, we see a strong relationship between hippocampal pathology and post-stroke number abilities. This common theme across all three chapters, demonstrates the impact of these predictors on post-stroke cognition, and the potential interaction between education and hippocampal pathology.

As mentioned above, we identified hippocampal pathology as a predictor of post-stroke cognition, and this was found beyond the impact of age (Stebbins et al., 2008). We further found that small vessel disease, and generalised atrophy in temporal region had an impact on post-stroke cognition, demonstrating that overall brain health is an important predictor of post-stroke cognition as previously reported (Ebrahim et al., 1985; Gorelick et al., 2011; Hennerici, 2009; Lawrence et al., 2013; Leys et al., 2005; Mijajlović et al., 2017; Mok et al., 2016; Sun et al., 2014; Wolfe et al., 2011).

Research focusing on post-stroke cognition, and recovery often look to the lesion location as a predictor of outcome and trajectory (Chechlacz et al., 2012; Hope et al., 2013). In the current study, we did not look at lesion location, only lesion side of which we found zero predictive value. Looking at the lesion location only restricts us to a 'topological' perspective, when a 'hodological' perspective is proposed to be of more use, allowing us to examine networks across wide ranging cortical regions, compared to cortical areas in isolation (Bartolomeo, 2011; Catani, 2007). This allows us to consider the whole brain and unaffected areas as predictors, as we did with the hippocampus. With this approach, we were able to establish the predictive value of hippocampal pathology in post-stroke cognition.

5.5 Strengths and limitations

The strengths of the research presented in this thesis, is that it uses a detailed cognitive assessment tool which is validated specifically for stroke. Many research studies examining cognitive recovery following stroke use short, and limited cognitive assessment tools, not designed specifically for stroke (Lees et al., 2014). We used a comprehensive cognitive assessment tool (Humphreys et al., 2012), that provides a complete cognitive profile of stroke patients across five key cognitive domains. Although due to the depth of the assessment, it can be too cognitively taxing for some, and recruitment can be limited to those who are able to complete it (concentration > 35 minutes). Additionally, there are further potential limitations when collecting large cognitive databases, specifically with the consistency of administration of cognitive assessments. Despite these databases being administered by healthcare professionals who had been centrally trained on the BCoS, there is room for measurement biases in the data coming from both administration and scoring of assessments.

Despite the benefits of detailing cognition across multiple domains, we found that our composite domain (general cognition), which is calculated using the scores across all five cognitive domains, to be more reliably associated with hippocampal pathology, than the five cognitive domains individually. This may suggest that the same approach neuropsychological tests take by calculating an overall cognition score, may enable stronger associations with brain measures, by accounting for all areas of cognition, rather than focusing on specific cognitive abilities. Due to the fact we were not computing function-lesion mapping, in this case general cognition was a useful measure.

This thesis benefited from the large amount of data collected in the BUCS study (Bickerton et al., 2015; Humphreys et al., 2012). Not only did this provide large sample size to work with (chapter two and three), but it was also was an example of efficient use of resources. Although due to the nature of working with pre-existing databases, we were limited to asking questions of the available data. We were lacking important clinical information about the stroke cohorts presented in chapter two and three. Specifically, we did not know about prior cognitive impairment. We report the incidence of previous stroke, but we do not know levels of cognitive impairment prior to data collected for these studies. In chapter four, stroke patients were recruited with known previous stroke, but no previous cognitive impairment or clinically diagnosed dementia. However in all three chapters, we do not know exactly their individual cognitive trajectories, and any underlying cognitive impairment that we were not made aware of (Elliott et al., 2019; Mijajlović et al., 2017).

As the literature suggests, there are many factors that contribute to cognitive trajectories. In chapter two we lack potentially important information that would be useful to factor into calculating recovery trajectories. We collected some information such as; previous stroke, and some basic information about lesion location, however this is relatively limited in terms of individual stroke profiles. It would have been useful to know more information such as lesion size, and previous cognitive impairment as a result of pervious stroke, or by other pathology. For the categorisation of previous neurological history, which included previous stroke, dementia etc, we relied upon self-reported information, which is limits our data to information that the patient is aware of. Using this self-report approach, we are potentially unaware of early stages of neurodegeneration, which we cannot account for in this dataset.

Across all three chapters we did not have information on rehabilitation (formal or informal), which is likely to contribute to individual cognitive recovery trajectories (Cumming et al., 2012). In chapter two, this limits the degree to which we can conclude about proportional recovery in cognition, as we are unable to partial out the effects of rehabilitation on the recovery, especially as the two time point measurements were taken in the key period where rehabilitation was likely to occur.

In chapter three we were fortunate to work with a large cross-cultural database; however this suffers from similar issues as documented with chapter two in terms of interpretation of cognitive assessments, and scoring by healthcare professionals. The china database was collected by personnel that were of similar healthcare background to the UK, and were trained by the same team as the UK. However, we cannot exclude potential differences between healthcare professionals, and also differences between cultures in interpretation of scoring, and execution of assessment. Furthermore, as discussed in chapter three, we found that there were significant differences in the cognitive abilities within the UK stroke cohort, demonstrating more variable and overall more severe cognitive deficits than the two China cohorts. In relation to this, conclusions cross -culturally should be taken with caution. Although despite these differences, even when we examined the role of education on cognitive outcomes following stroke separately across the groups, we see the consistent positive effect of education on cognitive outcomes.

We document that defining controls for neuropsychological, and clinical research is difficult, especially when using age matched controls. Inherently ageing processes will affect control cohorts, which is evident within this thesis, in chapter three and four. In chapter three specifically, we observe the effects of ageing on controls. In this chapter

both of the China cohorts demonstrated lower than expected cognition, with up to 30% presenting with less than 24 on the C-MoCA, which could be diagnoses as cognitive impairment. Furthermore, they scored > 4 std below their own group(s) on the C-BCoS. This may be due to the fact some controls would have been from rural communities, and less familiar, and practiced at cognitive style testing (in comparison to the UK cohort). It could be debated that these participants are not appropriate controls, however to exclude them would also lead to excluding a true representation of control participants for the Chinese stroke patients. In chapter four, we also observed the reality of recruiting, and assessing control participants from the community. We excluded two controls due to incidental findings on their imaging (enlarged ventricles, and silent stroke), and one demonstrated a lower than expected MoCA score indicating mild cognitive impairment. Although we excluded these individuals based on findings, we cannot exclude the possibility that other control participants in chapter four may have confounding profiles, which was not detected through the assessments we conducted. We did observe that the control cohort in chapter four demonstrated similar levels of parietal atrophy as the stroke patients. However, as previously stated, we believe that it is important to include true control recruits from the community, and exclude only those that clearly cannot be included for analyses.

In chapter two and three, the data represents recruitment with little restrictions on inclusivity, which allowed us work with data which represents the heterogeneous nature of stroke data, and work with large databases. Furthermore, it gave us the opportunity for generalisability to the stroke population. Despite the heterogeneous nature of the data, and size of dataset there were biased distribution which led to ceiling/ floor effects

in the measurements (for example in chapter two when investigation proportional recovery) (Hope et al., 2018).

The biased distributions in the dataset which caused ceiling/ floor effects may have inflated the conclusions of proportional recovery, that were made within this chapter. This should be taken into consideration when making conclusions about proportional recovery in cognition.

The exploratory nature of chapter four allowed us to utilise three different MRI modalities, in an investigation into post-stroke pathology of the hippocampus. However we did encounter issues with some of the MR measurements.' In chapter four, when examining hippocampal pathology we only had one time-point measurement which meant we could not specifically comment on cognitive recovery trajectory, but cognitive outcomes only (Hurford et al., 2013). Furthermore, we were unable to find hippocampal changes relating to stroke incidence, or hippocampal pathology relating to cognitive impairment only in the stroke cohort (Sachdev et al., 2007). It is possible that our measurement of the hippocampus was to early post-stroke (three months) to detect pathological changes, and a later measurement would reveal detectable changes.

Finally, in chapter four low signal to noise ratio led to exclusion of the right hippocampus in the measurement of metabolites. There are known limitations with its reliability (Wilson, Andronesi, et al., 2019), with susceptibility to hardware and software issues. Furthermore we were unable to replicate previous findings of higher hippocampal mean diffusivity in the stroke cohort (Kliper et al., 2016). The measurement of a small brain structure such as the hippocampus, near to the ventricles

poses issues with specificity of voxel placement and identification, causing noise in the data.

In chapter four the sample size of both the control participants, and stroke patients were average for an MRI study in stroke, however due to the nature of the chapter, being in the main exploratory, we did enter into the issue of type 1 error due to multiple comparisons. We calculated Bonferroni correction for all statistics, which in the majority of cases allowed us to conclude that the findings were significant even after controlling for multiple comparisons.

As documented in chapter four, we underwent a scanner upgrade during the data acquisition, even though there were some marginal impact on some of the MR measures (not surviving multiple comparisons). We concluded that actually, we experienced less impact on our analyses from the scanner upgrade itself, and specifically a recruitment bias of severity of stroke patients recruited pre and post scanner upgrade.
Finally, although no stroke patients lesions to the hippocampai, (one patient was excluded due to this), we are aware that lesions in the surrounding area in some patients may have impacted the MR measurements of observed pathology (e.g hippocampal volume). It may be useful in future to have more stringent criteria for recruitment in terms of lesion location, to avoid any potential confounds of lesions near to the area of measurement (in this case the hippocampus).

5.6 Future directions

We observed the impact of hippocampal pathology on post-stroke cognition, however we were unable to replicate previous findings that found hippocampal pathology to be different in stroke patients compared with healthy controls, even in the early stages

post-stroke (three months) (Brodtmann et al., 2012). The hippocampus should be further investigated and its predictive value of post-stroke cognitive recovery, we suggest that two or more time points should be acquired to sufficiently measure post-stroke hippocampal pathological changes, and its impact on post-stroke cognitive recovery.

Studies examining post-stroke cognitive recovery should look to use a wider range of MR measures, such as ^{1}H-MRS. In this thesis, we demonstrate its predictive value in post-stroke cognition. It may provide insight into pathological changes at an earlier stage than grey matter volume, and able to detect those that are cognitively declining following stroke.

We discovered the strength of education level on cognitive recovery following stroke. This provides a window of opportunity for a cost-effective way to impact a modifiable risk factor of cognitive decline following stroke, by increasing cognitive reserve allowing networks and structure to be more robust when neurological disruption (stroke) occurs.

Now we have a greater understanding of cognitive trajectories following stroke, and the factors that may predict recovery, those in high stroke risk groups should be under a higher level of monitoring. Examining their modifiable and non-modifiable risk factors, their cognition, and brains (health, networks, structure). Not only will this facilitate a finer grained understanding of their cognitive trajectories, prior to stroke, but in the event of a stroke, this information would be vital to predicting their recovery, and the best approach to assist in achieving the best outcomes for them as individuals. The monitoring of individuals after stroke is also important. As we showed not all of individuals that declined initially had severe stroke symptoms (cognitive deficits). As a

result, it may be important to monitor post-stroke individuals, not focused solely on their stroke deficits (which may be mild) but to also examine their cognitive and health history, which combined could lead them down a cognitive decline trajectory. This thesis also demonstrates that those with seemingly 'good' health, should also be championing for their own monitoring. In chapter four alone, we observed pathological findings without cognitive symptoms in healthy controls. Which leads us to suggest that future research in stroke, should aim where possible to obtain a control sample that is matched on health profile and age, in order to mediate any potential confounding variables in the control sample. In clinical trials this is often common practice, but not as stringent in observational studies.

5.6 Conclusions

The data presented in the current thesis suggested find that not one rule fits all regarding post-stroke cognitive recovery trajectories. While the majority recover proportionally to their initial deficits, there is a minority who present an accelerated, or declined recovery trajectory. Pre-stroke socio-clinical-demographic (age, education, vascular risk), and brain health factors (hippocampus health, small vessel disease and cortical atrophy), potentially affect pre-stroke cognition, modulating post-stroke cognitive outcomes, and recovery rate, beyond the stroke itself. These findings support the hypothesis that brain (cognitive) reserve can be utilised to protect the adverse effect of neurological insult (stroke). The data suggests that the hippocampus may play an important role in post-stroke recovery, through its association with education and age. The multiple factors demonstrated as contributing to post-stroke cognitive outcomes, suggest that there is not one defining factor that determines an individual's post-stroke cognitive trajectory, but a combination. Thus, the heterogeneous nature of stroke, and its varying cognitive

outcomes, are due to the different profile each individual present with prior to the stroke, and immediately following it. The thesis raises the additional intriguing possibility that the stroke can be viewed as a spike (that can often be predicted), along an individual cognitive trajectory which is determined by pre-stroke socio-clinical-demographic factors. In this case post-stroke cognitive trajectory (as measured by change rate) would follow the direction of the initial trajectory a person was on. This thesis demonstrated the utility of re-analysing large existing databases of observational studies, combined with collection of new data in answering questions regarding post-stroke cognitive outcomes. A question that has been the top priority for research for many stroke patients and their carers (Krishnan et al., 2017; Pollock et al., 2012).

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Appendices

1.2.4.1 Bickerton et al 2015 Consort Diagram for recruitment and follow up

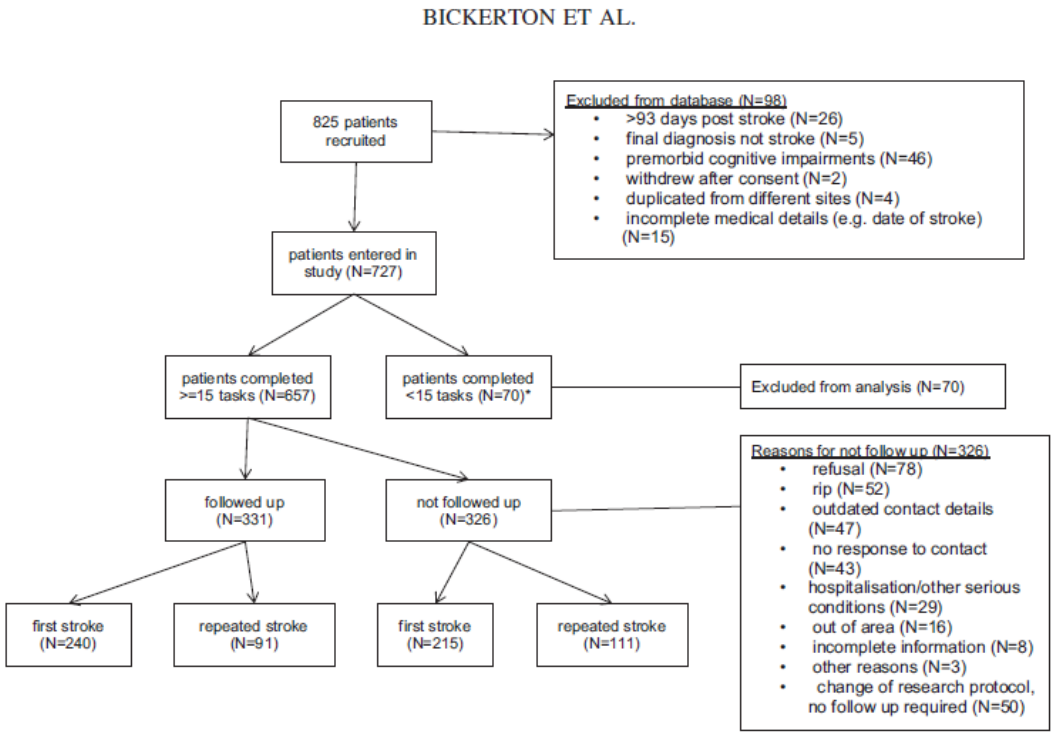

Figure 1. Flowchart of patient cohort at baseline and follow-up.

4.2.1.1 HiPPS-CI Patient Consent form

PATIENT CONSENT FORM (V4.1, 7th October 2017)

Title of Study: The role of hippocampal pathology in post-stroke cognitive impairment

REC ref: 15/WM/0209

Name of Researchers: Dr A. Hosseini, Prof D. Auer, Dr S. Ispoglou, Dr Rotshtein, Dr T. Hayton, Dr V. Sawlani,,Miss R. Laverick, Dr Don Sims, Dr Kurdow Nader.

Name of Participant: **Please initial box**

Project Identifier – ID **Initials/DOB**

1. I confirm that I have read and understand the information sheet (Version 4, 23rd February 2017) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the research group, regulatory authorities or from the NHS Trust where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

4.2.1.2 HiPPS-CI Control Consent form

HEALTHY VOLUNTEER CONSENT FORM 2 (V4, 23rd February 2017)

Title of Study: The role of hippocampal pathology in post-stroke cognitive impairment

REC ref: 15/WM/0209

Name of Researchers: Dr A. Hosseini, Prof D. Auer, Dr S. Ispoglou, Dr Rotshtein, Dr T. Hayton, Dr V. Sawlani, Miss. R Laverick, Dr Don Sims

Name of Participant: **Please initial box**

Project Identifier – ID **Initials/DOB**

1. I confirm that I have read and understand the information sheet (Version 6, 23rd February 2017) and MRI general information sheet (Version 2.2, November 2011) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that I will have memory tests using pen and paper as part of this study. I give permission for these individuals to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I give permission to retain my anonymised scans for use in future research by joining the volunteer panel of the School of Psychology (University of Birmingham). ☐

5. I agree to take part in the above study. ☐

Name of Participant Date Signature

Name of Person taking consent Date Signature

4.6.1 Demographic and clinical variable correlations for controls

	1	*2*	*3*	*4*	*5*	*6*	*7*
1 Age	-						
2 Sex	.27	-					
3 Education	-.19	-.40	-				
4 HADs A	.01	.07	.17	-			
5 HADs D	.19	.05	.07	.70**[a]	-		
6 Barthel Index	.85	.23	-.17	-.77**[a]	-.86**[+a]	-	
7 Vascular Risk	.86**[++a]	,12	-.27	.09	.35	-.26	-

Notes. N=17. HADs= Hospital Anxiety and Depression scale, A= Anxiety, D=Depression.

Vascular Risk= Framingham stroke risk score. GM= Grey matter. MD= Mean diffusivity.

- Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050,

Non-parametric correlation= [++] p<.001, [+]p<.050. [a]Bonferonni FME 0.5/7=0.07

4.6.2 Demographic and clinical variable correlations for controls

	1	*2*	*3*	*4*	*5*	*6*	*7*
1 Age	-						
2 Sex	.27	-					
3 Education	-.19	-.40	-				
4 HADs A	.01	.07	.17	-			
5 HADs D	.19	.05	.07	.70**[a]	-		
6 Barthel Index	-.05	.23	-.17	-.77**[a]	-.86**[+a]	-	
7 Vascular Risk	.86**[++a]	.12	-.27	.09	.35	-.26	-
8 Parietal Lobe Atrophy	.15	.00	.13	-.05	.06	.07	.08
9 Temporal Lobe Atrophy	.29	.56*[+]	-.17	-.11	.05	.10	.31
10 Small Vessel Disease	.59*[+]	.43	-.12	.07	.05	.14	.23
11 Left GM Volume	.07	.07	.57*[+]	.02	.04	-.05	.05
12 Right GM Volume	.01	.18	.46	-.13	-.20	.19	-.01
13 Left MD	.07	-.09	-.20	.01	-.15	.15	.04
14Right MD	.02	-.14	-.16	-.00	-.26	.22	-.05
15 tNAA	.19	-.18	.49	.20	.41	-.55*	.34
16 tCh	.48*[+]	-.21	-.08	.17	.45	-.49*	.53*[++]
17 tCr	.52*[++]	-.29	.17	.22	.24	.04[+]	.32

Notes. GM, N=17, MD, N=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine, N=17.

Vascular Risk= Framingham stroke risk score. GM= Grey matter. MD= Mean diffusivity. - Indicates a negative correlation.

Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= [++] p<.001, [+]p<.050. [a]Bonferonni FME 0.5/17=0.02.

4.6.3 Demographic and clinical variable correlations for controls

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
1 Intracranial volume	-										
2 Parietal lobe atrophy	-.15	-									
3 Temporal lobe atrophy	.52*$^{+}$	.00	-								
4 Small Vessel Disease	.31	.36	.09	-							
5 Left GM Volume	.60*$^{++}$	-.33	.43	-.21	-						
6 Right GM Volume	.67**$^{++a}$	-.27	.40	-.32	.80^{**++a}	-					
7 Left MD	-.20	-.02	-.74**$^{+a}$	.07	-.55*$^{+}$	-.28	-				
8 Right MD	-.29	.00	-.69**$^{+a}$	.10	-.53*$^{+}$	-.30	.94**$^{++a}$	-			
9 tNAA	.01	-.45	.44	-.26	.10	.08	-.25	-.38	-		
10 tCho	.15	.01	.18	.21	.12	.02	-.10	-.17	.35	-	
11 tCr	.38	.14	.24	.66**	.25	.02	-.12	-.02	-.22	.01	-

Notes. GM, N=17, MD, N=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine, N=17.

GM= Grey matter. MD= Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$p<.001, $^{+}$p<.050. ^{a}Bonferonni FME 0.5/11=0.04.

4.6.4 Demographic and clinical variable correlations for controls

	1	*2*	*3*	*4*	*5*	*6*
1 Language	-					
2 Memory	.06	-				
3 Attention and Executive Function	-.03	-.09	-			
4 Number	.53*	.52*	.05	-		
5 Praxis	.61**$^{+a}$	.24	.19	.13	-	
6 General	.79**$^{++a}$	.47	.34	.73**$^{+a}$	.70**$^{++a}$	-

Notes. N=17. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050,

Non-parametric correlation= ^{++}p<.001, ^{+}p<.050. ^{a}Bonferonni FME 0.5/6=0.08

4.6.5 Demographic and clinical variable correlations for controls

	Language	Memory	Attention and Executive Function	Number	Praxis	General
Age	-.29	-.19	-.09	.61**[a]	.20	-.34
Education	.22	.29	.23	.07	.39	.37
Vascular Risk	-.34	-.37	-.07	-.72**[a]	.01	-.49
Intracranial volume	.42	.13	-.17	.04	.77**[++a]	.39
Parietal lobe atrophy	-.03	-.22	.48*[+]	-.23	.11	.03
Temporal lobe atrophy	.21	-.49*[+]	.10	-.17	.25	.04
Small Vessel Disease	-.17	-.01	.26	-.18	.24	.01
Left GM Volume	.41[+]	.11	-.07	.11	.60*[+]	.39
Right GM Volume	.43[+]	.13	-.16	.18	.53*[+]	.37
Left MD	-.22	.20	-.24	-.02	-.38	-.24
Right MD	-.26	.13	-.17	.06	-.50[+]	-.26
tNAA	-.51*	.08	-.14	-.36	-.17	-.42
tCho	-.40	-.14	-.02	-.51*	-.13	-.42
tCr	-.08	-.17	.32	-.25	.39	.04

Notes. GM, N=17, MD, N=15. t=Total, tNAA= Total N-Acetylaspartate, tCho= Total Choline, tCr=Total Creatine, N=17.

GM= Grey matter. MD= Mean diffusivity. - Indicates a negative correlation. Parametric correlation = ** p<.001, *p<.050, Non-parametric correlation= $^{++}$p<.001, $^{+}$p<.050. [a]Bonferonni FME 0.5/14=0.03.