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Quantitative Volumetric Study of Brain in Chronic StriatoLenticular Stroke

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A thesis submitted in partial fulfilment of the requirements of Oxford Brookes University for the degree of Master of Philosophy

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I

Abstract

Perforating branches of the middle cerebral artery, namely the striato-lenticular arteries provide the majority of blood supply for the striatum and posterior limb of the internal capsules. Occlusions of these arteries cause a small stroke but have a devastating effect on patients' functions. Previous studies showed that the anterior two thirds of the internal capsule is occupied by the prefrontal tracts with the posterior one third by connection to/from sensorimotor, temporal and posterior parietal cortices. In this study, we aimed to examine the long-term effect of infarction in the striato-capsular region on cerebral cortex thickness and also its association with stroke volume and different functional tests. We hypothesized that because of extensive connections of striatum and internal capsule with the cerebral cortex, infarction of this area results in an extensive cortical thickness degeneration which could in turn cause low fictional measurement scores.

High resolution T1 weighted MRI was obtained from 21 patients with ischemic stroke in the striatum/posterior limb of the internal capsule region. Subjects were carefully selected from a pool of 140 stroke cases recruited for the Northstar Stroke Project. 63 healthy volunteers (30 male), matched for age and gender were also chosen to form the control group from the OASIS database. Patients and normal subjects were right handed except for 3 patients who have the stroke in the left side of the brain. Patients were defined as left-sided stroke and right-sided stroke depending on the side of the stroke in brain. MRI scans were done 6 months to 2 years after the stroke. To measure cortical thickness, we used Freesurfer software. Vertexwise group comparison was carried out using General Linear Models (GLM). With the Significance level set at 0.05.

Population maps of stroke lesions showed that the majority of strokes were located in the striatum and posterior internal capsule. Cortical thickness reduction was greater in the ipsilateral hemisphere. Vertex-wise group comparison between left-sided stroke patients and controls group showed significant reduction in the cortical
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thickness in the dorsal and medial prefrontal, premotor, posterior parietal, precuneus, and temporal cortex which survived after correction for multiple comparison using false discovery rate at Freesurfer. Similar comparison for right-sided stroke showed a similar pattern of cortical thinning, however the extent of cortical thinning was much less than in that of the left-sided stroke patients but the ROI analysis showed the main effect of side was significant (f (1, 19) =6.909, p=0.017), which showed that the left hemisphere stroke side group had a thicker cortex (mean=2.463, sd= 0.020) on average compare to the right hemisphere stroke side (mean=2.372, sd= 0.028). Primary motor cortex was surprisingly spared in both stroke groups. In addition, volume of the corpus callosum increased significantly in the stroke group.

The differences between motor cortex (M1) thickness in left-hemispheric stroke patients versus controls (t=1.24, n=14, p>0.05) and right-hemispheric stroke patients versus controls (t=-0.511, n=7, p>0.05) were not significant. There was a negative correlation between the volume of the stroke lesions and the affected M1 thickness.

There was no correlation between the stroke volume and functional tests in patients and also no correlation between the motor cortex thickness and functional tests in patients. Regarding normal subjects, comparison between two sides of the brain showed that the both hemispheres are symmetrical. In addition, correlation between age and cortical thickness showed a negative significant correlation (1-tailed, p<0.0007, manual correction for multiple comparisons) in M1, superior frontal, lingual cortex at both side of the brain and also negative significant correlation in superior temporal cortex and isthmus cingulated cortex on the left side of brain and supramarginal cortex on the right side of brain but there was no significant difference in cortical thickness between males and females.

The finding from this study suggests that the size of the lesion can be a predictor of further M1 cortex reduction. The correlation of M1 thickness with stroke volume showed that secondary cortical degeneration may be mainly depends on the size of neuronal loss in strital-capsular stroke.

From normal subject study it can be concluded that generally cortical thickness will decrease with ageing but gender does not have an effect on the cortical thickness.

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Furthermore, the lack of behavioural correlation with M1 thickness and stroke volume and also the non significant M1 cortex reduction versus control group may suggest that the long-term functional disability after capsular-striatal stroke may not be entirely dependent on primary motor cortex and secondary motor cortex and primary somatosensory cortex could have an important role as well. These results may help to understand why relatively small subcortical infarcts often cause severe disability that is relatively resistant to recovery in the long term.

III

Presentation relevant to thesis

Oral presentation at Third HEERLEN –Oxford Imagery and Neurological Rehabilitation Conference, May 2009.

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Acknowledgements

Abbreviations

2-D	Two dimensions
3-D	Three dimensions
1.5 T	1.5 Tesla
3T	3 Tesla
AD	Alzheimer's disease
ADL	Activities of daily living
ALIC	Anterior limb of internal capsule
AMFM	Arm motor fugl-meyer
AMAT	Arm Motor Ability Test
AV	Atrio-ventricular
AVM	Ateriovenous malformations
BBT	Box and block test
BET	Brain extraction tool
CFT	Corticofugal Tract
CMA	Centre for morphometric
CNS	Central nervous system
COPM	Canadian occupational performance measure
CT	Computerized tomography
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
FDR	False discovery rate
FIRST	FMRIB's integrated registration and segmentation tool
FMRIB	Oxford centre for functional MRI of the brain
FSL	FMRIB's software library
GLM	General linear model
GSTEST	Grip strength test
IC	Internal Capsule
VI	

ICBM	International consortium for brain mapping
ICD	Implantable cardiovascular defibrillator
ICF	International classification of health conditions
M1	Motor cortex
MCA	Middle cerebral artery
(mm)	Millimetres
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
(ms)	Milliseconds
N	Number
NIHSS	National institutes of health stroke scale
OAISIS	Open access series of imaging studies
PLIC	Posterior limb of internal capsule
PTSD	Post traumatic stress
RF	Radio frequency
ROI	Regions of interest
S/E	shoulder/Elbow
SIENA	Structural brain change analysis
SIS	Stroke impact scale
SIS-QOL	Stroke-specific quality of life scale
TE	Echo time
TR	Repetition time
WD	Wallerian degeneration
WHO	World Health Organization
W/H	Wrist/Hand

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Chapter 1 – Introduction

Introduction

This aim of this study is to explore the long-term effect of a focal chronic stroke (straital-capsular stroke) on the structure of cortical and subcortical regions of the brain as measured by cortical thickness and volume. The hypothesis of this study is that striato-capsular stroke has an effect on the cortical thickness which could reduce functional measurement scores in the tests related to assess the impairment after stroke.

Stroke is the second most common cause of death in the world after heart disease and cancer and the leading cause of long-term disability [1-3]. In the United States, about 750,000 strokes and 150,000 resulting deaths occur annually [1]. The Stroke Association estimated that 150,000 people have a stroke in the UK each year and also there are over 67,000 deaths due to stroke in the UK and approximately 300.000 people in England living with moderate to severe disabilities as a result of stroke [4, 5]. Stroke costs around £7 billion per annum for England and Wales [6] . In fact the direct cost to the NHS is about £2.8 billion a year which is more than the cost of treating coronary heart disease [5].

The common subtypes of stroke are atherothrombotic, cardioembolic, lacunar and hemorrhagic[1]. As the study sets to explore the effect of lacunar stroke on the structure of cortical and subcortical regions, the following debate is focused on lacunar stroke.

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The lacunar infarcts or small subcortical infarcts result from occlusion at a single penetrating artery (size between 2-17 mm) and optionally they are based in the internal capsule and basal ganglia [7]. Hence striatal-capsular stroke is a lacunar stroke with the infarction in striatum and internal capsule. Lacunar infarcts account for one quarter of cerebral infarctions [8]. From radiological diagnosis of cerebral infarction, 32.7% were lacunar infarcts [3], more than other types of cerebral infarctions. On the other hand, because of the difficulties in imaging of small arteries, informative imaging studies are scarce. Also, because of the lower rate of mortality evidence from direct pathological studies is limited [9]. Hypertension and diabetes mellitus are major risk factors for lacunar stroke [10].

Lacunar infarcts show a paradoxical clinical course with favourable results in the short term, a low early mortality and reduced functional disability on hospital discharge, but in the mid- and long term are characterized by increasing risk of death, stroke recurrence and dementia [8, 11, 12]. Therefore it should be considered as a potentially severe condition [8].

Depending on the lesion site, signs and symptoms are different. Symptoms are loss of sensation, movement impairment and speech, sight, balance and coordination difficulties [13]. Hemiparesis with or without ipsilesional hemisensory loss is the most common symptom for lacunar stroke which is involving the blood supply of the striatum and internal capsule [13] [1].
Lesions in the brain stem can also produce hemiplegia [1]. Weakness affecting the face and arm more than the leg suggests a stroke in the middle cerebral artery territory, whereas a deficit mainly involving the legs is characteristic of an anterior cerebral artery lesion [1].

The most important etiologies of stroke in the anterior circulation are internal carotid artery stenosis, cardiac embolism and atherothrombotic disease of the major intracranial branches [1, 14] and small vessel disease of the penetrating

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arteries [1]. Even a small stroke in the internal capsule could obviously have major consequences. After stroke, prognoses vary considerably among patients.

The initial deficit and the degree of motor recovery after ischemic stroke are related to such factors as lesion type and size and also the degree of Wallerian degeneration (WD) is related to the degree of functional recovery [15] . Wallerian degeneration is a process that happens when a nerve fibre is crashed or cut, and then the part of axon separated from the neurons cell body [16].

In previous studies it has been shown that impaired upper limb function is due to reduced cortical control of spinal neurons and Wallerian degeneration of the corticofugal tracts (CFT) [17] and the function of CFT is useful   for predicting functional outcome after stroke. There is a correlation between the degree of WD in CFT and upper limb function [17]. Therefore based on this information this study is going to explore how stiatal-capsular stroke causes corticofugal tract degeneration and following that it affects hand impairments.

Many studies have clarified and measured motor recovery and neuronal plasticity after acute stroke [18, 19] . The recovery varies from a few months to years and most of that occurs in the first three months [20] .
Most understanding of the recovery mechanism is based on animal and imaging studies, which highlights the potential of plastic adjustment in cortical and subcortical structures under specific training or behavioural adaption [21] .

Several mechanism are considered to be involved in the recovery process such as recovery of penumbral tissues, neural plasticity, diaschisis (sudden loss of function in a part of brain which is distance of a damaged area but they are connected by neurons) and behavioural compensation [22].

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Reducing the oedema and reperfusion of the ischemic penumbra during the acute phase after stroke and following that neuronal rearrangements and adaptive responses are the recovery process, which can take many months [23].

It is assumed that the lesion area recovers as a result of tissue repair, while its function is controlled by the cortical or subcortical area either next to or remote from the damaged area [21, 22]. This mechanism requires understanding of re-activation of previous present but functionally inactive neuron connections, axonal and dendritic regeneration, synaptogenesis and denervation hypersensitivity [22]. This is the base of the Von Monakow theory which is known as resolution of diaschisis [21, 24-26]. Resolution diaschisis is reactivation of functionally suppressed areas of brain which is connected to but at a distance from the damaged area [21] [24].

Calautti et al 2001. showed that the brain with subcortical infarction has less over- activation later than at the early time point of the stroke [27], therefore earlier rehabilitation is more useful (discussed in next section).

To explore the effect of brain stroke on the different areas of the brain and also the relevant functional impairment, understanding of the anatomy of the brain and the circulation system are very important. Hence the anatomy and blood circulation of the brain will be explained in the next section.

Anatomy of the basal ganglia and internal capsule

The internal capsule is a continuous sheet of fibres that forms the medial boundary of lenticular nucleus and then continues around posteriorly and inferiorly to partially envelop this nucleus. Inferiorly many of the fibres in the internal capsule funnel down into the central peduncle. Superiorly they all fan

out into the corona radiata, in which they travel through the centrum semiovale to reach their cortical origins or destinations [28].

The lentiform nucleus (putamen and globus pallidus) is part of the basal ganglia which is encapsulated in white matter and the laminae bounding its outer and inner surfaces as the external and internal capsule, respectively. The internal capsule is limited laterally by the lentiform nucleus and medially by thalamus as the posterior limb of internal capsule (PLIC) and head of the caudate as anterior limb of Internal capsule (ALIC) [29] the GENU (Latin for knee) is which joins the two limbs [28].

The striatum is the input nucleus of the basal ganglia, receiving afferent projections from the cerebral cortex. The caudate nucleus, which participates in eye movement control and cognition, the putamen, which participates in control of limb and trunk movements; and nucleus accumbens, which participates in emotions, are the three subnuclei of the striatum [28].There is a path from the striatum to two intrinsic nuclei (the external segment of globus pallidus and the subthalamic nucleus) which comprises the indirect path of the basal ganglia , and inhibits the production of movements [28].

The internal capsule is divided into five regions on the basis of the relationship of each part of the lenticular nucleus. The anterior limb is the portion between the lenticular nucleus and the head of the caudate nucleus [2, 30] The posterior limb is the portion between the lenticular nucleus and the thalamus. The genu is the portion at the junction of the anterior and posterior limbs. The retrolenticular part and the sublentricular parts are the portions posterior and inferior to the lenticular nucleus, respectively [30].

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Functional anatomy

Internal capsule and cortical connections

The large collections of thalamocortical and corticothalamic fibres need a route by which to travel from their origins to their destinations. This route is provided by the internal capsule. Almost all the neural traffic to and from the cerebral cortex passes through the internal capsule [30].

Fibres project from the cerebral cortex through the internal capsule to various parts of the basal ganglia, for example, the putamen and the caudate nucleus. All of these fibres fan out as corona radiata just above the internal capsule and mingle with other fibre bundles interconnecting different cortical areas in the centrum semiovale of each hemisphere [30] .

Prefrontal cortex connections have been located within the anterior limb of internal capsule (ALIC) and the anterior part of the posterior limb of internal capsule (PLIC) and also the M1 tract is exactly posterior to the premotor region and it is followed by the S1 tract. Most pathways of the temporal cortex are in the posterior lateral part of the PLIC and the rest are located in the medial border of the ALIC. The occipital cortical connection is within the most posterior part of the PLIC [31].

Brain blood circulation (internal capsule and striatum)

When the blood supply of the brain is suddenly cut off or reduced, ischemic stroke will happen. Depending on which artery has been blocked, ischemic stroke will impact on the area which was fed by that particular artery [13].

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The principal blood supply for the brain comes from two arterial systems that receive blood from different systemic arteries: the anterior circulation (or carotid circulation) fed by the internal carotid artery and the posterior circulation (vertebral-basilar circulation), which receives blood from the vertebral arteries [2].

The middle cerebral artery (MCA) and anterior cerebral artery are the terminal branches of the internal carotid artery and the posterior cerebral artery is separated from the basilar artery [32]. MCA is the largest branch of the internal carotid artery and the cortical area supplied by the middle cerebral artery includes the insula, claustrum, and the lateral portion of the hemisphere which includes the brain motor areas [29]. Figure 1 shows the arterial supply of the cerebral cortex.

The anterior cerebral artery encompasses the frontal lobes, basal ganglia, internal capsule and a major portion of the temporal lobes[1] and the areas which are fed by the posterior or vertebrobasilar artery are the brain stem, cerebellum, thalamus, occipital lobes and medial and inferior temporal lobes [1].

The arterial supply of the thalamus, hypothalamus, basal ganglia and internal capsule derives from both the anterior and posterior circulation. Different parts of the internal capsule are supplied by different principal sources [2].

The superior halves of the anterior and posterior limbs are supplied by branches of the middle cerebral artery. The inferior half of the internal capsule is supplied by the anterior cerebral and anterior choroidal arteries [29].

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Figure 1: This figure shows parts of brain are supplied by different arteries: figure A is the lateral view and Figure B is the medial view of brain. Blue colour: anterior cerebral artery, red colour: middle cerebral artery. Green colour: posterior cerebral artery [13].

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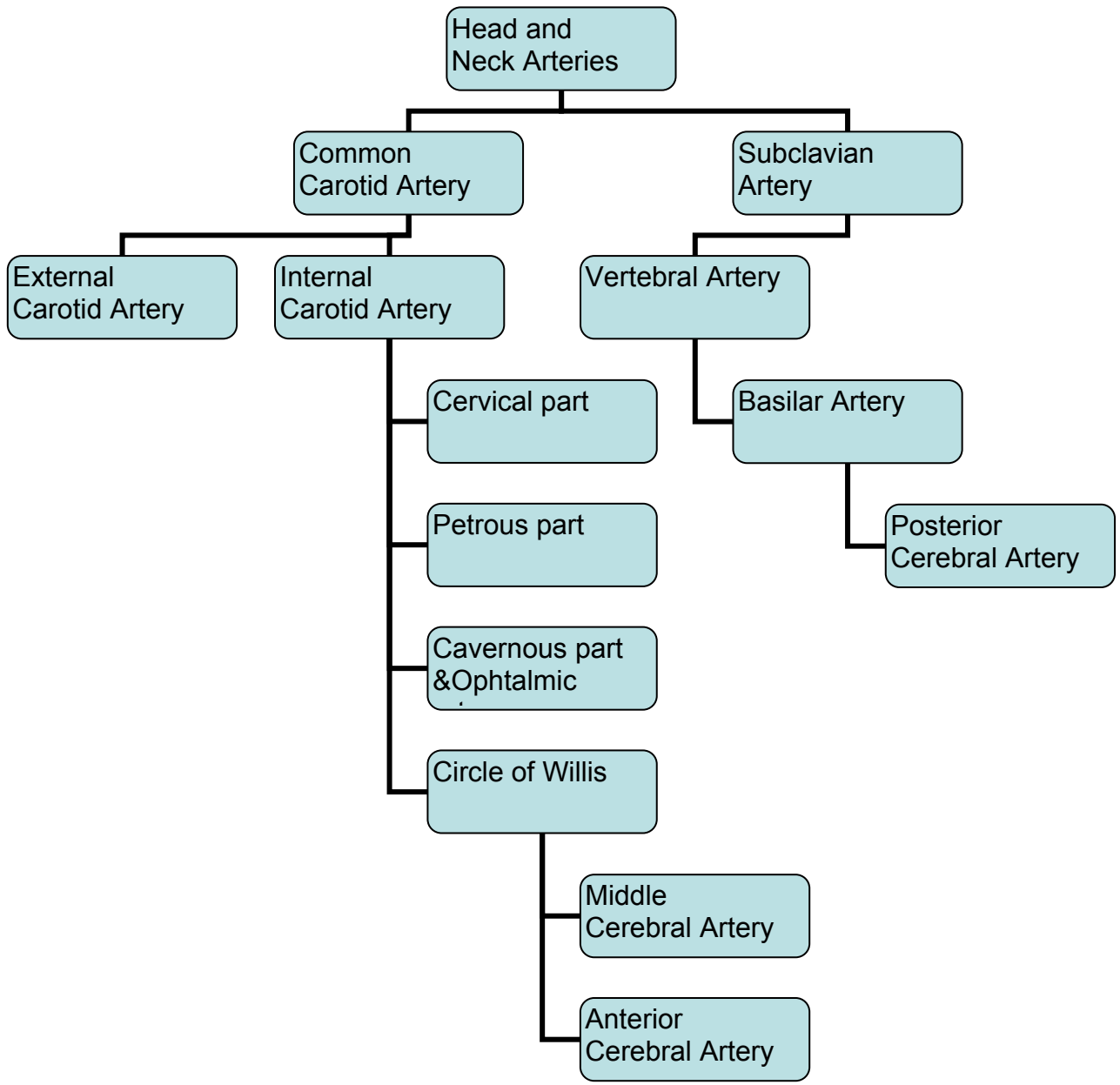
Figure 2: The diagram shows the head and neck arteries with the main branches.

Rehabilitation after stroke

Rehabilitation is an effective process and the most common treatment for reducing the impairment and improving the quality of life after stroke [22, 33]. Rehabilitation after stroke reduces the relative risk of death by 50% and the relative risk of discharge to nursing home by 40% [34].

Rehabilitation does not just involve training disabled people themselves but also their family and community are involved in rehabilitation plans and the aim of this process is to help each patient to achieve the highest possible level of individual physical and psychological performance [22, 35]. The process of rehabilitation is solving a problem in a standard frame of medical practice, such as a treatment for a diagnosed disease [33].

Recovery of motor deficit following stroke is a complex and multifunctional process [23]. To decrease the rate of impairment early rehabilitation (within 24 hours) is suggested, which could vary according to patients' needs including speech and language therapy, physiotherapy or clinical psychology treatment [36, 37]. Rehabilitation after stroke might happen over weeks and months or it can continue for several years after stroke, until maximum recovery is achieved, thus it covers the chronic phase of stroke as well [36, 37]. Studies have shown that exercising the affected hand, especially hand and wrist movement is essential in all levels of the rehabilitation schedule [38], and that has been suggested that higher-intensity training results in better functional outcome [39]. As rehabilitation is expensive, finding the better approach is an important area of research.

To evaluate effectiveness of the rehabilitation after stroke, MRI scans can be used to detect structural changes such as changes in the gray matter in cortex and also, volume changes in different structures [40].

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Neuroimaging studies can provide crucial information regarding tissue injury, such as size, location, and degree of reversibility of ischemic injury and also the presence of haemorrhage [41]. Computerised tomography (CT) and magnetic resonance imaging (MRI) scans are the most non-invasive techniques [41]. CT scanning is quicker than MRI (which needs at least 45 minutes) and the risk to the patients is minimal. On the other hand artefacts may occur at bone and soft tissue interfaces [42], in addition CT is insensitive to detecting small cortical or subcortical infarctions [41].

Thus, to diagnose stroke, MRI became the ideal technique for imaging patients with suspected acute stroke, detecting both infarction and other differential diagnoses [8]. MRI is able to assess three main aspects such as parenchyma, perfusion, and penumbra in acute stroke patients [43].

MRI images are classified according to their signal intensity on T1- and T2-weighted images [44]. High resolution T1 weighted MRI with improved contrast has been used for patients with striato-lenticular stroke more than 6 months prior to data collection. MRI will be used in this study to measure cortical thickness and volume of cerebrum as well as subcortical region volume.

Following the cell body or proximal axon injury, degeneration of axons (distal to the injury) and the myelin sheaths occur which is called Wallerian Degeneration (WD) [45]. WD happens following several conditions but the most common cause is cerebral infarction [46].

WD happens in both the peripheral nervous system (PNS) and central nervous system (CNS).

We hypothesized that because of the extensive connection of the striatum and internal capsule with the cerebral cortex, infarction in this area will result in significant cortical degeneration and also significant negative changes would be expected in functional scores.

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This study aims to clarify differences related to cortical thickness such as: differences in cortical thickness in the affected hemisphere in both left and right sided stroke group versus control group, differences in M1 thickness between right hemispheric stroke and control group and left hemispheric stroke and control group, and also asymmetry in cortical thicknesses in the normal subjects. After this particular study further degeneration and following impairment might be predictable therefore these images might be helpful in future for rehabilitation.

In addition, to explore the importance of the impact of stroke it is necessary to look at the body functions and structure, activity, personal and environmental factors and participation; as the international classification of the functioning model. This will be explained with details in the next chapter.

Chapter 2 – Measurement

Outcome measures

Neurological deficit and motor function

The aim of this chapter is to explain the different methods to measure the functional impairment after stroke and discuss the classic way to approach them. Regarding to the hypothesis it is necessary to choose the best way to measure after stroke impairment and its impact.

In 2001, the World Health Organization (WHO) [47] ratified and published the International Classification of Functioning, Disability and Health (ICF) [48, 49]. ICF explained the measurement and assessment of health and disability concepts [48].

This is an approach to health condition which focuses on disability and impairment and includes different levels, to provide a scientific framework for classification of health conditions [48] [50]. The different levels measured in ICF refer to impairment, individual level activities being related to achieving a task or activity and social level participation in an individual's involvement in life. Furthermore personal and environmental factors influence all these levels [48, 50-52].

Four main measurements are examined in this study, which are related to body function and arm activities, the Fugl-Meyer assessment, arm motor ability test, box and block test and grip strength test. No participation measures were taken in this exploratory experimental study.

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The following diagram is a representation of the model of disability on the basis of ICF [47, 48](Figure1).
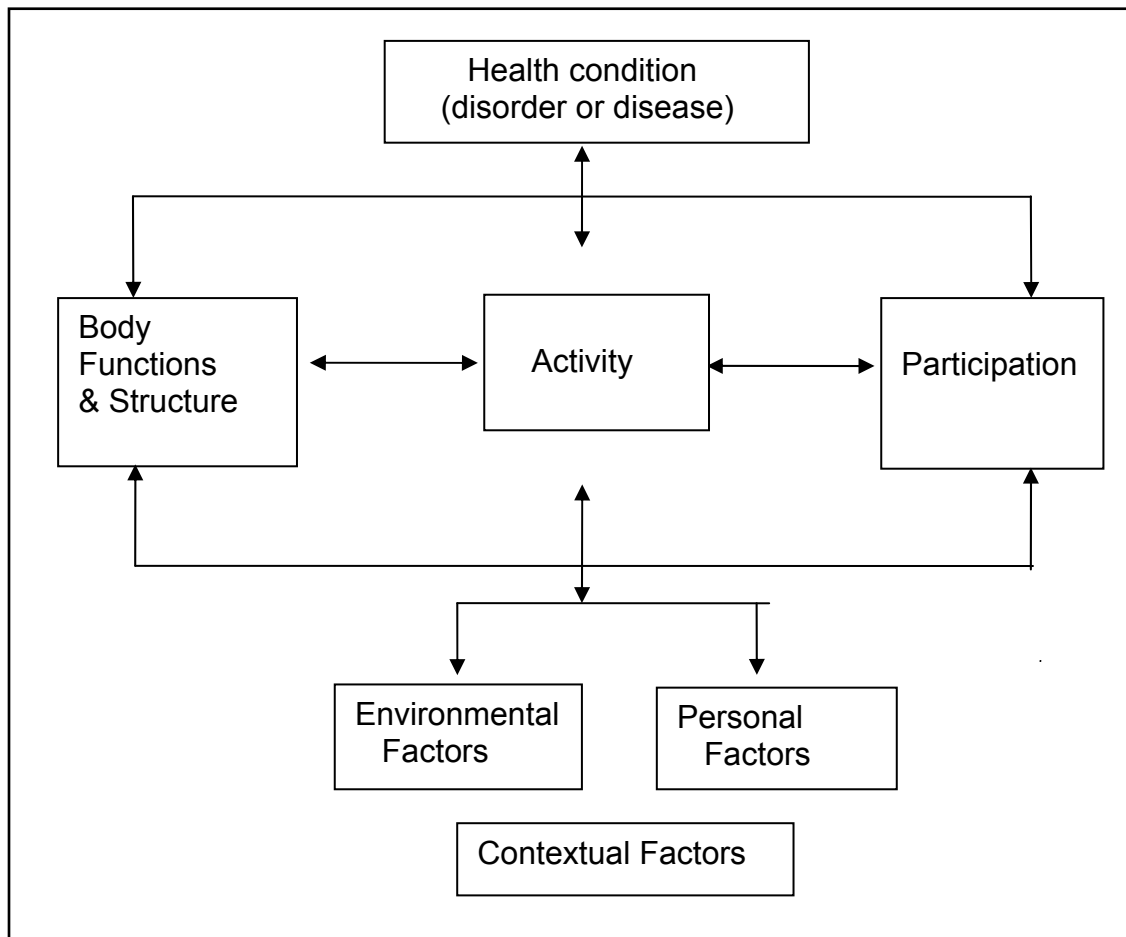
Figure 3: The international classification of the functioning (ICF) mode I[48, 49] .

Apart from the ICF framework to classify levels of outcomes measures, having a set of criteria to guide the selection of outcome measures is necessary [53]. 413 articles have been examined by the Health Technology Assessment [54] on methodological aspects of the use and development of patient based outcome measures. From their report it is recommended to use eight evaluation criteria, which are listed with definitions in Appendix 1.

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Response to treatment after stroke needs to be measured and it is an important part of clinical assessment after stroke. It can be measured in many ways and the method chosen will depend on the information needed [55]. "Quantification of an observation against a standard" is explained as an outcome measure [56].

Several outcome measures have been involved in this study, such as stroke scales, psychological and cognitive measurements and also quality of life measurements, explained further in the Methods chapter. However regarding the aim of the current study some of the relevant measurements chosen as those measurements have been mentioned in previous articles [57-59] that they are the main and reliable measurements to assess stroke patient impairments.

The main outcome measures for this study were measures of neurological deficit and motor function, the Fugl-Meyer, arm motor ability test, box and block test and grip strength test. Their reliability and validity have been established in many studies [57, 60] [58], [59], [61] and also studies focusing on the Grip strength test as a prognostic indicator [61]. These are explained below.

Arm motor Fugl-Meyer assessment

The Fugl-Meyer (FM) assessment is a quantitative measure for motor impairment after stroke which has been considered by many in the field of stroke rehabilitation and recommended for clinical trials of stroke rehabilitation and also it is the first evaluative tool to measure sensorimotor stroke recovery [62]. This scale is designed to assess hemiplegic patients in the post stroke phase of recovery and the measurement scale is divided into 5 different parts: 1. motor function, 2.sensory function, 3.balance, 4.joint range of motion, and 5.joint pain, and the motor part which includes measuring movement, coordination, and reflex action about the shoulder, elbow, forearm, wrist, hand

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and the motor score from 0 (hemiplegic) to a maximum of 100 points (normal motor performance), which is divided into 66 points for the upper extremity and 34 points for lower extremity [62]. Each function scores from 0 to 2 the level of performance ability (0 = cannot perform, 1 = performs partially, 2 = performs fully) and It takes around 30 minutes to complete a test [62]. Appendix 2 shows all the details of the Fugl-Meyer test [62].

Arm Motor Ability Test [25]

Arm Motor Ability [25] is an instrument for assessing deficits in activities of daily living (ADL) [61]. ADL is an assessment used to assess the deficits in activities of daily living after central nervous system injuries, in addition it is related to several movement parameters, including strength, coordination between muscles and body parts, speed, active and passive range of motion, pain, and spasticity [61]. Its importance is to determine the patient's condition severity and so make it easier to plan a treatment and assess its effectiveness of that [58].

The Arm Motor Ability Test [25] is a functional assessment to measure both quantitative and qualitative aspects of a range of ADL; it is able to assess both quality of movement and time of performance of upper limb movement in chronic stroke patients [58, 63].

The AMAT assesses the effect of intervention in improving ADL function, originally including 16 compound ADL tasks. Each task involves one to three component tasks or movement segments; all components for distal and proximal musculature and each limb are evaluated separately. Each task's compound performed continuously and the examiner can rate each component task according to two scales relevant to recovery of motor function: Functional Ability (i.e., capacity to accomplish the specified motor or behavioural goal) and Quality of Movement (i.e., how well the task movements

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are executed) [58, 63]. All scales were timed separately [58]. Appendix 3 shows the AMAT components.

The AMAT scale provides information about aspects of movement that is difficult to assess quantitatively, especially when studying a broad range of tasks. It has 44 task components according to shoulder/elbow (S/E) or wrist/hand (W/H) movements (Appendix 3) [58] .

Unilateral activities were carried out by the affected arm and bilateral activities were performed using dominant and non-dominant extremities in the roles in which they had usually been employed before the onset of hemiparesis.

Box and Block Test (BBT)

The Box and Block Test measures gross manual dexterity and has been used by occupational therapists and others to evaluate physically handicapped individuals [59, 64]. It is a box with a partition in the centre of the box that divides it into two equal sides. A number of small wooden cubes (blocks) are already in one side of the box and the subjects are asked to use the dominant hand to grasp one block at the same time and transport it to the other side of the partition and release it there [64]. The subject is given one minute to complete the test and the number of cubes transferred to the other side is counted [57]. The test is then repeated with the non-dominant hand [64].

Grip strength test

The strength of voluntary grip is an indicator of arm function recovery after stroke and it can be measured by using a sensitive electronic dynamometer [61]. Normally it is reported by calculating the mean of three maximum grip strength tests.

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In summary in order to explore the impact of stroke on body function Arm motor ability test, Arm motor Fugl-Meyer test, box and block test and grip strength measurements were selected. In this provision study exploring mechanism; participation and activity measures were not explored.

Chapter 3 – Imaging

Magnetic Resonance Imaging (MRI)

This chapter is a general introduction about the concept of physics in MRI and different type of image acquisition such as T1 and T2. In addition, the different methods of analysis which have been used for this study will be discussed.

Since the early 1980s, MRI has been shown to be a sensitive technique to monitor and measure intracranial disease. Structural MRI provides extensive details about the anatomical structure of the brain [65]. It is becoming increasingly important to explore cortical changes associated with the normal aging process or further changes regarding different diseases such as dementia illnesses (Alzheimer's disease (AD)), and it is also very sensitive to cerebral white matter diseases and is the only sensible imaging test for Multiple Sclerosis (MS) . As long as contrast is used it is sensitive to diseases that involve the pial meninges, which could otherwise be easily missed [66].

Furthermore structural MRI is an essential tool for clinical care for patients with brain diseases and it is used for clinical trials to identify response to treatment [66]. Since MRI's introduction into clinical practice in the early 1980s, it is estimated that over 20 million scans are carried out worldwide each year without any problem with safety, so safety is a big advantage for MRI scanning [65].

Although MRI is an extremely safe form of medical imaging there are specific interactions between the scanner and the patient that need to be mentioned as potential safety hazards, which correspond to the static magnetic field produced by scanner, radio-transmitting and receiving coils, which excite and detect the MR signal, and magnetic field gradients, which localize the MRI signals [65, 67].

Physical basics of magnetic resonance

Magnetic resonance imaging relies on spinning motion of the nuclei present in human tissues [68]. Atoms contain three types of particles: protons (positively charged), neutrons (no net charge) together within an atom and electrons (negatively charged) [69].

Different atoms have different nuclear contents and atoms with an odd number of protons and/or neutrons have non-zero 'spin' and are therefore detectable using MRI. For instance hydrogen nuclei have a single proton. Hydrogen is the most abundant atom in the human body, so hydrogen is the most commonly imaged nucleus in MRI [68-70].

As hydrogen has a spin so it can possess electrical charge and spinning of a charged particle like hydrogen nucleus creates a magnetic field around it and it works as a magnet (Figure 2), it has a north and south pole with equal strength. It has a magnetic moment shown by a vector. The direction of that vector shows the direction of magnetic moment and the length of the vector shows the size of the magnetic moment (Figure 4) [68].

In the absence of an external magnetic field the magnetic moments of the hydrogen atoms are oriented randomly but when a magnetic field exists the majority of the magnetic moments of hydrogen nuclei align with the magnetic field (Figure 3) [68, 70]. In the magnetic field the majority of hydrogen proton

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spins align parallel to the magnetic field and create a net magnetization in the direction of the applied field [70].

So in MRI when a radiofrequency [71] pulse is transmitted to the subject, the signal is received from the magnetized spin of proton in the body [71] [70]. In magnetic resonance imaging, the main magnetic field of scanner is often indicated with the symbol B0 [68].

Figure 4: Left: without an external magnetic field a proton rotating around its own axis and generate a magnetic field. Right: The magnetic moment of a hydrogen nucleus, it shows the magnetic vector with the direction and size [70] [68].

Figure 5: Left: random alignment in the absence of an external magnetic field. Right: alignment with the magnetic field that is shown by the large white vector [68].

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T1 and T2 contrast

Different contrast can be generated in the MRI scan which is related to exchanging the energy of hydrogen nuclei [68]. The process by which hydrogen loses energy is called relaxation. In this process individual spins go back to their energy state which is in the direction of the magnetic field. This causes the recovery of magnetic moments of nuclei and causes them to give up energy to the surrounding environment. This process is termed T1 recovery which is the recovery of longitudinal (z) magnetization [68, 70].

There are two important factors that govern the time at which MR images are collected. The first factor is the time interval from the application of one radio frequency (RF) pulse to the application of next RF pulse, which is known as repetition time (TR) and is measured in milliseconds (ms) and the second factor is the time interval from application of one RF and data acquisition, which is known as echo time, or TE and is also measured in ms [68, 69].

TR determines the amount of relaxation that is allowed to be between the end of one RF pulse and the application of the next one [68]. TE determines the amount of decay of transverse magnetization is allowed to occur [68, 70].

By changing the scan TR and TE, the contrast between different tissues types is changed T1-weighted and T2-weighted images are two types of different contrast that are possible to have from MRI. To generate images sensitive to T1 contrast, a pulse sequence with intermediate TR and short TE must be collected and T2 is the "transverse" relaxation time and to generate images sensitive to T2 contrast, a pulse sequence with long TR and intermediate TE must be collected [69].

In the other words TR determines the amount of T1 relaxation that has occurred when the signal is read and TE controls the amount of T2 relaxation that has occurred when signal is read [68]. Figure 6 shows samples of T1- and T2-weighted images.

The most commonly used structural contrast for anatomical images of the brain is T1-weighted images and T2-weighted images are used to detect characteristic pathological changes, for example in Multiple Sclerosis [67].
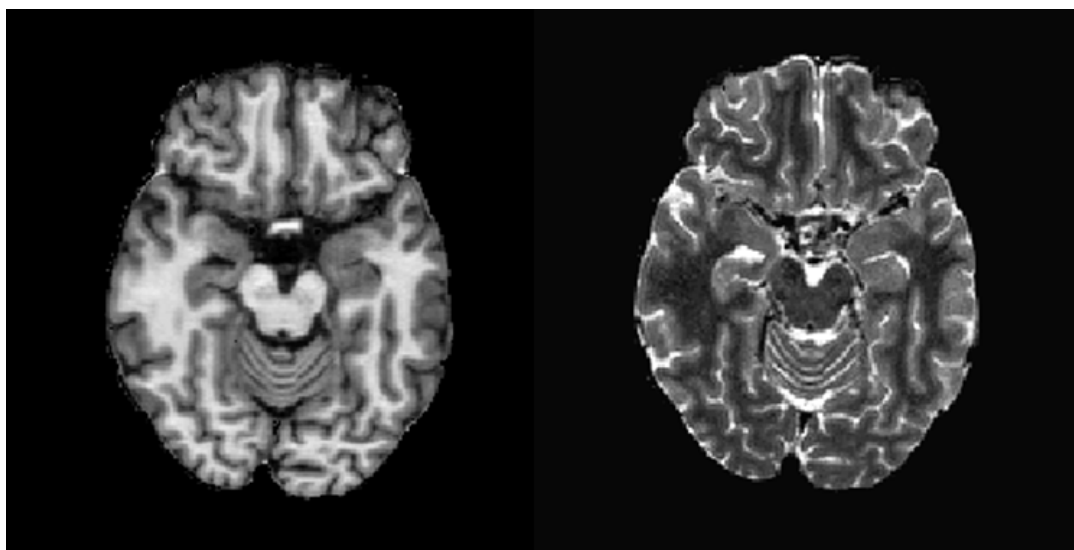
Figure 6: T1-(left) and T2-weighted (right) axial cross-sections for tissue segmentation.

FMRIB's Software Library (FSL)

FSL is a comprehensive library of analysis tools for MRI, functional MRI, and DTI brain imaging data. FSL is written mainly by members of the Analysis Group, FMRIB, and Oxford, UK. FSL runs on Apple, PCs (Linux and Windows) and is very easy to install. Here are the definitions of different FSL tools which have been used for this analysis.

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FIRST (FMRIB's Integrated Registration and Segmentation Tool)

FIRST is a model-based segmentation/registration tool. The shape/appearance models used in FIRST are constructed from manually segmented images provided by the Centre for Morphometric Analysis (CMA), MGH, Boston [74].

FIRST program consists of a series of steps. Initially, the skull is removed from the brain image and affine registration is carried out to standard space (which is MNI152 space at 1mm resolution) [75].

In the next step segmentation is used to segment a single structure then segmentation of all modelled brain structures is carried out based on that first segmentation in the model. FIRST provides model files for the Caudate, Hippocampus, Lateral Ventricules and Amygdala, and it uses Thalamus as a reference [75, 76]. In addition, there is way and easy command to use FIRST which does all of the above, including registration and segmentation of subcortical structure in the models, and producing a summary segmentation image for all structures [75-77].

In addition there is an option in FIRST that helps boundary correction on all the models (structures). It will automatically parallelise the fitting of each structure [75-77].

After these processes it is possible to estimate the volume of each of the segmented areas with FIRST program.

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FREESURFER

The cortex is a highly folded area of brain that is outside of the white matter and it is between 1 to 4.5 mm with an average of 2.5 mm. Therefore cortical thickness measurement carried out in 3-D is important [78, 79].

Traditional measurement of cortical thickness was based on folded 2-D surfaces which was measured by drawing contours from each part on to thin wax sheets and then arrange the sheets in order for viewing [80],

De Yoe et al 1996 used a computerised version of this method for some human neuroimaging data [81] but it is time consuming. The other method is to estimate the thickness of cortical areas manually but it is also time consuming and needs a trained anatomist, and it can still has some errors as the folded cortex in some areas can not be perpendicular to any of the original axes [79]. Therefore an automated and accurate method should be used for cortical thickness measurement.

FreeSurfer is a set of software tools for the study of cortical and subcortical anatomy and also cortical reconstruction and volumetric segmentation [82]. The technique is explained in prior publications [79, 80, and 83] [84, 85].

This surface based analysis includes several stages. First, the volume is registered with the Talairach atlas using an affine registration [86, 87] and the B1 bias field is estimated regarding the variation of white matter intensity measurement and based on the location of white matter in Talairach space and also the intensity of the local neighbourhood areas [82]. Then the skull is stripped and as well as cerebellum and brain stem and the point of cutting is based on the Talairach location of corpus callosum and pons [66, 82, and 83].

In the cortical surface, this software is able to define a boundary between white matter and cortical gray matter and also a boundary between gray matter and CSF at the pial surface [80] (Figure 5). The cortical thickness that it measures is the distance between the gray/white boundary and the pial surface [88]. Cortical and subcortical areas are segmented and both segmentation and labelling use the same basic algorithm [86, 87]. The result of freesurfer software is shown in Figure 6, which shows the volumetric labelling of white matter including several subcortical structures [82].

After this process anatomical measures become possible, including: cortical thickness, surface area, curvature, and surface normal at each point on the cortex. The distance between the white and the pial gives us the thickness at each location of cortex [79].

This software is able to make the surfaces inflated and/or flattened for improved visualization. In addition, a cortical surface-based atlas has been defined based on average folding patterns mapped to a sphere [84].
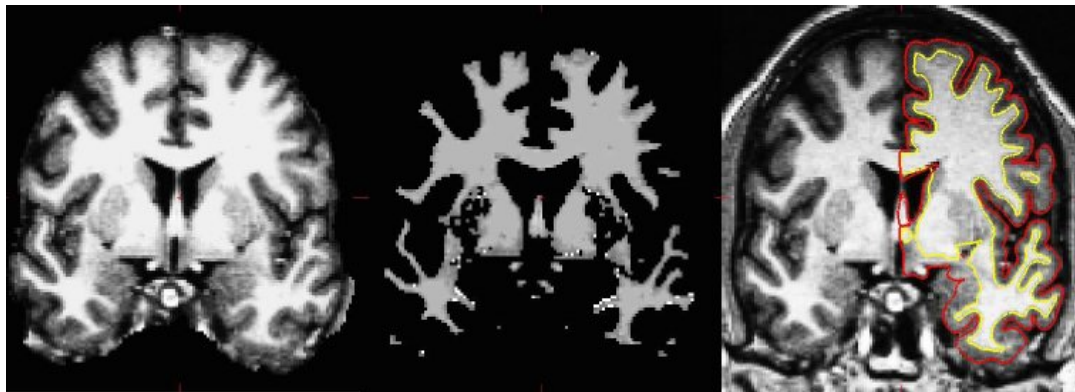
Figure 7: Three stages from the Freesurfer cortical analysis pipeline. Left: skull stripped image. Middle: white matter segmentation. Right: surface between white and gray (yellow line) and between gray and pia (red line) overlaid on the original T1-weighed.

Figure 8: Left: Volume-based labelling. Cortical gray matter and white mater are represented by single classes. There are separate labels for the structures in each hemisphere. Right: Surface-based labelling.

A 3D view of the pial surface is shown in Figure 7, Left. This surface can be inflated to show the areas in the sulci as shown in Figure 7, Right. This surface can then be registered to the spherical atlas based on the folding patterns [89].

Figure 9: Left: Showing the pial surface, Right: showing Sulci in Red colour and Gyri in green colour.

Chapter 4 – Method

Introduction

This chapter is to determine the data (patients and normal subjects) recruitment method such as the necessary different assessments before recruiting and also inclusion and exclusion criteria.

The research was performed on pre-existing data. The Local Institutional Review Boards granted ethical approval for Northwestern University in Chicago (Northstar Neuroscience Protocol V0267: Safety and Effectiveness of Cortical Stimulation in the Treatment of Upper Extremity Hemiparesis).

Protocol

Patients were recruited from a pool of patients known to study personnel (therapists, physiatrists), through direct mailing, radio advertisement with call-in centres, at stroke support groups (study personnel went and gave talks discussing the study), via advertisements on hospital websites, and via flyers posted in hospitals [90].

All participants reviewed and signed an informed consent form before enrolment for inclusion. Each patient was individually screened regarding the inclusion and exclusion criteria, as described later.

All subjects were tested with the Edinburgh handedness test [91] to confirm their handedness and all subjects were right handed except three.

Eligible participants attended for structural brain imaging in three centres by

3-T scanners. Following brain imaging all participants underwent basic medical evaluation including complete medical history, blood tests, electrocardiogram and chest x-ray. Then the following outcome measures were assessed:

Measures of Neurological Deficit and Motor Function
Arm Motor Fugl-Meyer (AMFM)[62]
Box and Block Test [64]
Grip strength [61]

Measures of Activities of Daily Living (ADL) [61]
Arm Motor Ability Test [25]
Canadian Occupational Performance Measure (COPM) [92]

Stroke Scales
National Institutes of Health Stroke Scale (NIHSS) [93]
Stroke Impact Scale (SIS) [94]

Psychological and Cognitive Measures
Mini-Mental Status Examination [95]
Beck Depression Inventory [96]

Measures of Quality of Life
Stroke-Specific Quality of Life scale(SIS-QOL)[97]
Short Form-36-Item (SF-36) Health Survey [98]

Thus the patients who were recruited had ischemic stroke which occurred at least 4 months previously, arm motor Fugl-Meyer score between 20-50 points, active wrist extension of at least 5°, age ≥ 21 years, no history of seizure, no substantial neglect, depression, or sensory deficit. Patients who took

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amphetamine, antiepileptic, anxiolytics, or antidepressants, which could confound the study, had been excluded. Complete inclusion and exclusion criteria are listed below.

Inclusion criteria

1. Subjects must have an ischemic vascular lesion that is:

Cranial computed Tomography or MRI confirmed ischemic stroke above level of brainstem resulting in neurological deficit
Ability to comply with rehabilitation protocol
Stroke lesion Is at least 4 months old, has been documented by computerized tomography (CT) or magnetic resonance imaging (MRI).
This lesion results in the neurologic deficit defined in the study inclusion and exclusion criteria and is considered the "index stroke".

2. The index stroke must be the most recent stroke.

3. Subjects are medically and neurologically stable, as determined by medical history and documented neurological examination.

4. Moderate to moderately severe upper-extremity hemiparesis, defined as an arm motor Fugl-Meyer score between 28 and 50 (inclusive), and either active Wrist extension of at least 5 degrees or ability to perform a repetitive grasping task.

5. Age 21 years or older.

6. For women of childbearing potential, a negative serum BhCG pregnancy test within 2 weeks prior to study entry, and willingness to practice adequate Contraception during the study.

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7. Ability to comply with the study rehabilitation protocol.

Exclusion criteria

Study subjects must not meet any of the following exclusion criteria:

1. Primary hemorrhagic stroke. It is recognized that some ischemic strokes may have a minor amount of hemosiderin in the parenchyma. If this occurs, this is not considered a "hemorrhagic stroke" referred to in this exclusion criterion.

2. Any additional stroke (other than the index stroke) associated with incomplete motor recovery.

3. Any neurologic or physical condition that impairs function of the target extremity.

4. History of seizure disorder or a spontaneous seizure that has occurred one month or longer from index stroke or patients who have had a documented bout of status epilepticus.

5. Neurological condition that would likely reduce the safety of study participation, including central nervous system (CNS) vasculitis, intracranial tumour, intracranial aneurysm, multiple sclerosis [99] or arteriovenous malformations (AVM).

6. Moderate to severe hemispatial neglect and/or anosognosia involving the affected limb.

7. Severe sensory deficit, defined as a score of 2 on part 8 of the NIH Stroke Scale.

8. Inability to understand, cooperates, or complies with the study procedures.

9. Severe spasticity, defined as an Ashworth score of 4 on any upper extremity region.

10. Any medications 6 weeks prior to enrolment or Botox injections in the affected arm 4 months prior to enrolment which cause changes in spasticity.

11. Major active psychiatric illness that may interfere with required study procedures or treatments as determined by the enrolling physician.

12. Untreated or inadequately treated depression defined by a score of 19 or greater (out of 63) on the 21-question version of the Beck Depression Inventory.

13. Modified Rankin Score of 4 or more.

14. A substantial cardiopulmonary or metabolic disorder. This includes a current serum creatinine >3.0 mg/dL, a total serum bilirubin >2.0 mg/dL, or advanced chronic obstructive pulmonary disease.

15. Increased risk for myocardial infarction or other major medical complications of general anaesthesia or surgery. Exclusions include, but are not limited to, subjects with unstable angina, decompensated congestive heart failure, severe cardiac valvular disease, a high-grade atrio-ventricular (AV) block on EKG, or a symptomatic ventricular arrhythmia or a myocardial infarction within 6 months prior to enrolment.

16. Terminal illness associated with survival <12 months.

17. Inability to discontinue antithrombotic therapy (e.g. antiplatelet agents or anticoagulants) preoperatively for device implantation and removal.

18. Introduction in the 2 months prior to enrolment of a potentially confounding central nervous system (CNS) drug (e.g., amphetamines, antiepileptics, anxiolytics, and antidepressants).

19. History of spinal cord injury, traumatic brain injury, or spontaneous subdural or epidural hematoma that has resulted in a neurologic deficit.

20. Current abuse of alcohol or drugs, prescription or otherwise.

21. Contraindication to stimulation system placement surgery.

22. Contraindication to magnetic resonance (MR) imaging. This may include weight incompatible with scanner, metallic devices such as some aneurysm clips or shrapnel, certain eyeliner tattoos, or implanted electrical devices (e.g., cardiac pacemaker, implantable cardioverter defibrillator (ICD), or a spinal cord Stimulator).

23. Nursing a child, pregnancy, or intent to become pregnant during the study.

24. Participation in another drug, device, or biological trial within the 30 days prior to enrolment.

25. Patient has a condition that, in the opinion of the investigators, would interfere with study compliance or safety.

26. Patients who would require diathermy during the study period where an investigational device may be implanted (i.e., through follow-up week 8).

27. Patients who would require an MRI during the study period where an investigational device may be implanted (i.e., through follow-up week 8).

Data selection was performed under the supervision of an experienced neurologist (Dr Mojtaba Zarei). Cases were excluded who had massive damage or had global brain atrophy which was not the current study interest or had a different type of stroke from Striato-capsular stroke. Only patients with stroke affecting the posterior limb of the internal capsule stroke and/or striatum were selected.

Normal subject data

Normal subjects were selected from 416 subjects from Open Access Series of Imaging Studies (OASIS) which will be explained in the next paragraph.

Different information from normal subjects was downloaded such as descriptive data, cortical thickness, and cortical volume. Because the normal subjects were not from the same centres as patients, in some ages it was impossible to get an exact age match. To reduce this bias, for each patient 3 normal subjects that were sex matched and with a similar age were chosen. Thus 63 normal subjects were selected versus 21 patients.

All the normal subjects were right handed but in the patient group there were 3 left handed subjects which were all in the left hemispheric stroke group. The age of both groups is between 30 to 78 years.

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OASIS data

Data from Open Access Series of imaging Studies (OASIS) were used to form the healthy control group.

OASIS is a series of magnetic resonance imaging (MRI) data sets that is publicly available for study and analysis [100]. The initial data set consists of a cross-sectional collection of 416 subjects aged 18 to 96 years with and without dementia which have been selected from a larger database of individuals who had participated in MRI studies at Washington University based on the availability of at least three acquired T1-weighted images, right-hand dominance and a recent clinical evaluation for older adults [100].

One hundred of the included subjects older than 60 years have been clinically diagnosed with very mild to moderate Alzheimer's disease. We have excluded these subjects from the control group. The OASIS database has provided data that would be difficult for individual laboratories to acquire [100]. So providing a normal group in comparison with patients, 63 normal age and sex matched subjects have been selected among the normal subjects from the OASIS data.

For each subject, three or four individual T1-weighted magnetization images were acquired on a 1.5T Vision scanner (Siemens, Erlangen, Germany) in a singe imaging session [100] and for this study just one session scan has been used. The effect of cross-scanner is negligible as it has shown at Xiao Han study [101].

Chapter 5 – MRI analysis

MRI data

This chapter discusses step by step image analysis to define the cortical and subcortical areas. Furthermore calculating the cortical thickness and stroke lesion volume will be explained with the related soft wares.

 Each image was analysed by using the FSL program [73, 102]. FSL included different Tools for different aims of analysis are as follows:

Stage 1: The brain extraction tool [103] [104] was used to delete non-brain tissue from the image of the whole head (Figure 10,11), this process was done for each case. Some images included neck as well; therefore before processing them in Brain extraction tool (BET), neck and extra artefacts had to be removed by hand to have a perfect brain image.

Stage 2: In the next step the stroke lesion of each case was masked manually in FSLVIEW (an interactive display tool for 3D and 4D data) using 3D mode [105], under the supervision of an experienced neurologist.

Stage 3: After masking the lesions, all lesions were overlapped on each other by FSL program to create a population map of all cases, which shows the region of stroke in striatum and posterior limb of internal capsule. Figure 12 shows the population map of the region of interest. In addition the volume of lesion areas have been calculated by FIRST (FMRIB integrated and Registration and Segmentation Tool) [75-77].

At the first attempt for analysing MRI data, FMRIB's Integrated Registration and Segmentation Tool (FIRST) [106, 107] were used to register the T1-

weighted structural image. This carried out the affine transformation to standard space to MNI152 space at 1mm resolution and then the subcortical structures were segmented with applying boundaries for each region (Figure 13).
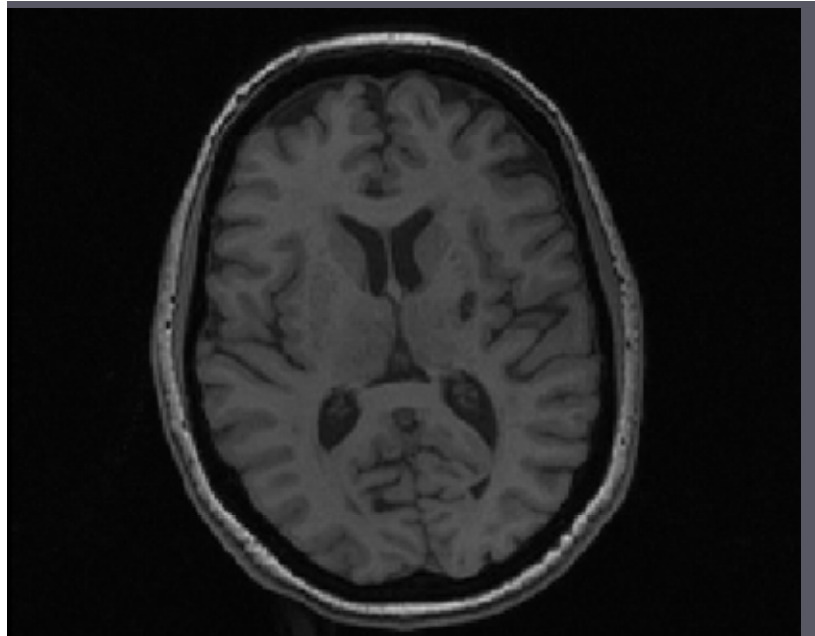
Figure 10: T1 weighted structural MRI: image shows stage 1 before removing the skull.
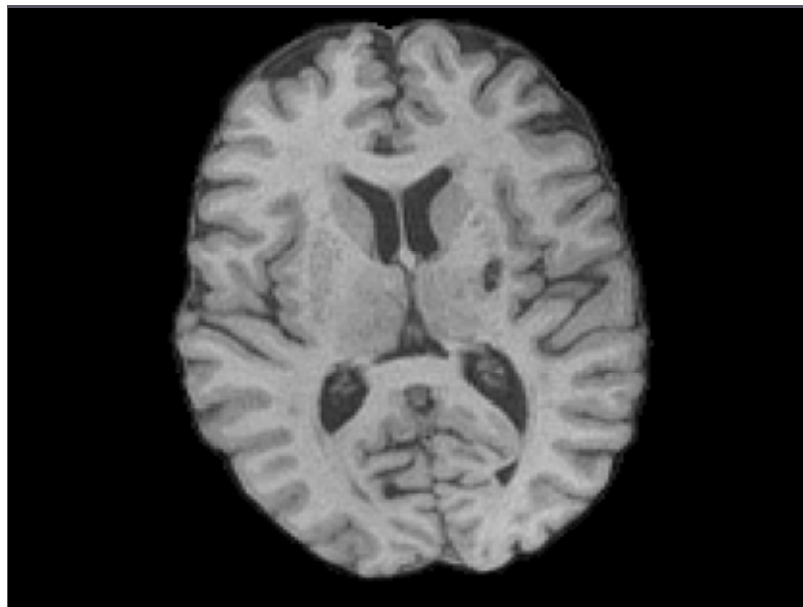
Figure 11:T1 weighted structural MRI: image shows stage 1 after removing the skull.
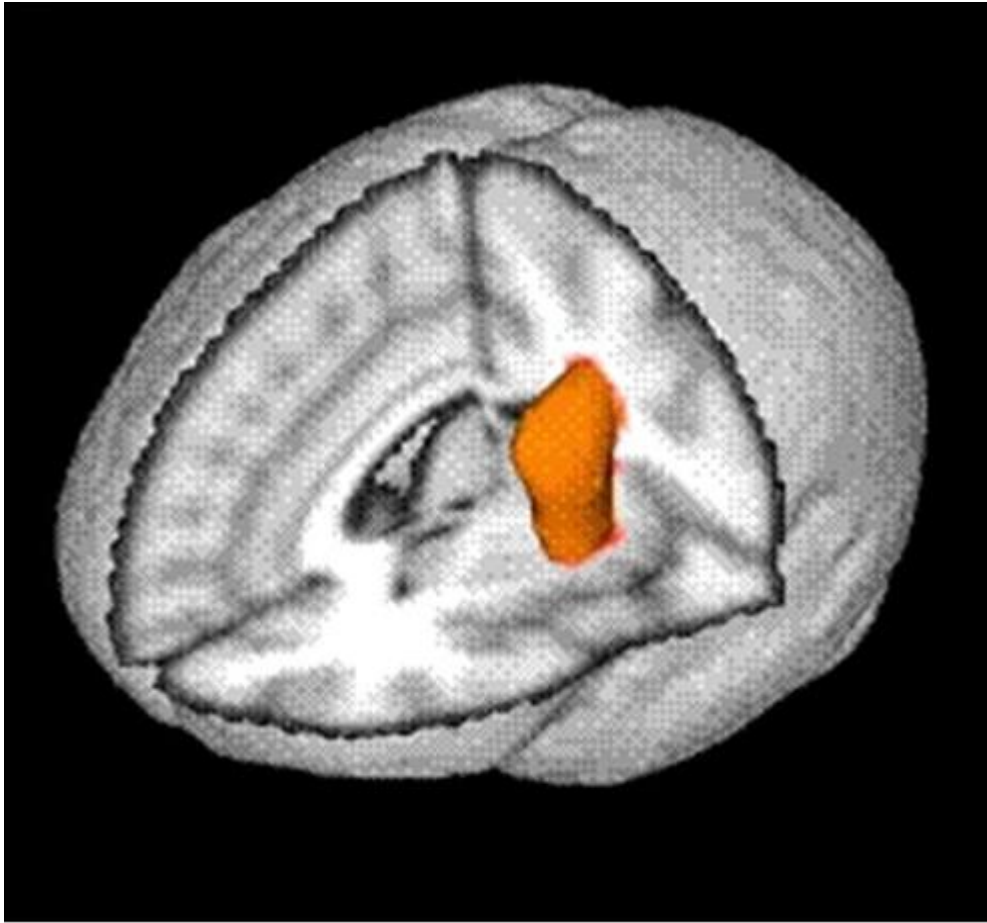
Figures 12: Population map of subcortical stroke lesion sites (in 2D); red colour shows the majority of stroke lesions were located in the striatum and posterior limb of internal capsule, n= 21.
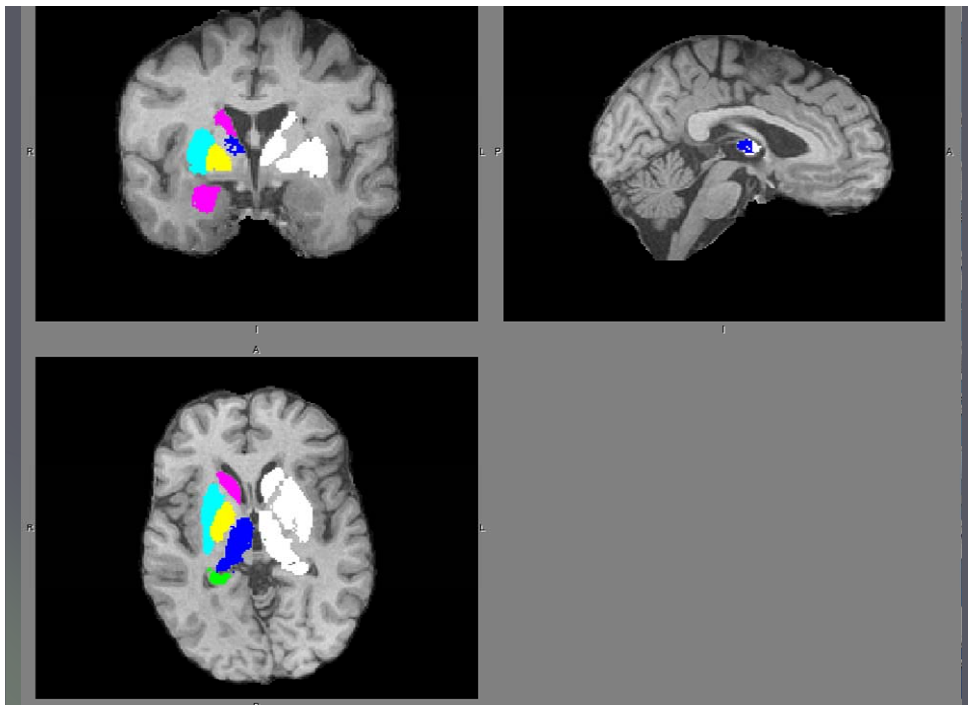
Figure 13: Registered and segmented brain image opened in FSLVIEW. Different areas in left side of brain separated by colour; Light blue: Putamen. Pink: Caudate. Blue: Thalamous. Yellow: Globus Pallidus. Green: Hippocampus. The right side of the brain shows exactly the same areas but has not been coloured.

Constructing contrast matrices to test the hypotheses

Statical analysis of cortical thickness data

Freesurfer was used to define surfaces for all subjects; after all surface reconstruction was completed for all subjects in the study. FreeSurfer's mri_glmfit command was used to perform inter-subject/group averaging and inference on the cortical surface. Mri_glmfit models the data as a linear combination of effects related to variables of interest, confounds and errors, and permits statistical inferences to be made about effects of interest in relation to error variance. It also allows for certain permutation testing and

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other means for correcting for multiple comparisons. For group analysis, this technique fits a general linear model (GLM) at each surface vertex to explain the data from all subjects in the study.

Functional assessment

Four behavioural measurements were utilised in this study, which focused on upper limb function, which have been explained with details in the Introduction and in the early section of the Methods chapter. They are AMAT and FMAT, which are based on some criteria such as activity of daily living and sensorimotor stroke recovery, respectively. BBT was done as a manual dexterity test and Grip strength test measured grip power directly. All the functional assessment was done in the standard protocol order with the SPSS version 16.

Chapter 6 – Results

Introduction

The hypothesis of this study is that striato-capsular stroke has an effect on cortical thickness, and affects the functional measurement scores after stroke. Also, the thickness of cortex could be related to the size of stroke.

As shown in Table 1 age and sex in patient groups is similar to the control group. The patients are in two groups of left-hemisphere stroke and right-hemisphere stroke. The time after stroke is varies with the minimum of 4 months and the maximum of 419 months after stroke and the mean and standard deviation are calculated that is (53.89 ±93.60). The information about the number of months after stroke was available for 19 out of 21 patients.

The regions of interest of this study are the areas related to motor function (motor cortex, premotor cortex, supplementary motor area and somatosensory cortex cortex). These areas were chosen because they are involved in planning and initiation of movement, regulating posture and voluntary movement. Results were considered with a significant level of $p < 0.05$.

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	Hand Dominancy		Female	Male	Age (mean ± SD)
	Right	Left	Female	Male	Age (mean ± SD)
Left-Sided Stroke	11	3	6	8	32-68 (50±9)
Right-Sided Stroke	7	0	3	4	51-78 (60±8)
Control	63	0	33	30	33-78 (54±10)

Table 1: Demographic data

Freesurfer was used to measure cortical thickness in the primary motor cortex (M1) .We used the SIENA tool, which is a package to estimate atrophy (volumetric loss of brain tissue) to quantify stroke volume[102, 108]. The descriptive analysis of the M1 thickness and stroke volume in the left-hemisphere and right-hemisphere stroke groups is shown in Table 2.

Cortical thickness of all cortical areas has been calculated and also the volume of all subcortical and cortical areas, which is addressed respectively in Appendices 4, 5 and 6.

Stroke_side		N	Mean	SD
Left	Stroke Volume	14	1902.7 ml	1557.9 ml
	Contralesional M1 Thickness	14	2.50 mm	0.135 mm
	Ipsilesional M1 Thickness	14	2.44 mm	0.148 mm
Right	Stroke Volume	7	4161.6 ml	3841.2 ml
	Contralesional M1 Thickness	7	2.42 mm	0.163 mm
	Ipsilesional M1 Thickness	7	2.32 mm	0.169 mm

Table 2: Descriptive values of stroke volume and cortical thickness at the affected and unaffected side of brain. Left: left hemispheric stroke group, Right: right hemispheric stroke group.

1. Difference in cortical thickness in the affected hemisphere in both left and right hemispheric stroke groups versus the control group.

Vertex-wise group comparisons with Freesurfer software were carried out between left-hemisphere and right-hemisphere stroke patients and the control group. The left-hemisphere stroke group showed significant reduction compared to controls in the dorsal and medial prefrontal cortex, premotor, posterior parietal, precuneus, and temporal cortex which survived after correction for multiple comparisons using false discovery rate (FDR), Similar comparisons for the right-hemisphere stroke group showed a similar pattern of cortical thinning, however on visual inspection the extent of cortical thinning was much less than that of the left-hemisphere stroke patients (Figures 15 and 16). Primary motor cortex was notably spared in both stroke groups.

To directly compare left and right hemisphere stroke subjects, we performed a ROI analysis on cortical thickness.

Within-subject effects

The main effect of hemisphere (ipsilesional and contralesional) was significant ((f (1, 19) = 5.146), p= 0.035). This shows cortical thickness reduction was greater in the ipsilesional hemisphere.

The main effect of area (cortical ROI) was significant (f (9,171) =37.051, p= 0.0001) with thickness varying between cortical regions. Cortical ROI were: caudal anterior cingulate, caudal middle frontal, inferior parietal, paracentral, parsopercularis, posterior cingulate, precentral, superior parietal, superior temporal and postcentral.

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Between-subject effects

The main effect of stroke side was significant (f (1, 19) =6.909, p=0.017), therefore there was a significant difference in cortical thickness between left hemisphere stroke and right hemisphere stroke patients.

Calculating the mean cortical thickness across ROIs revealed that the left hemisphere stroke side group had a thicker cortex on average (mean=2.463, sd= 0.020) compare to the right hemisphere stroke side group (mean=2.372, sd= 0.028).

The small colour bar at the right side of images shows that the higher difference is seen in yellow colour which is considered as a significant difference. The gray colour shows definitely no significant changes.
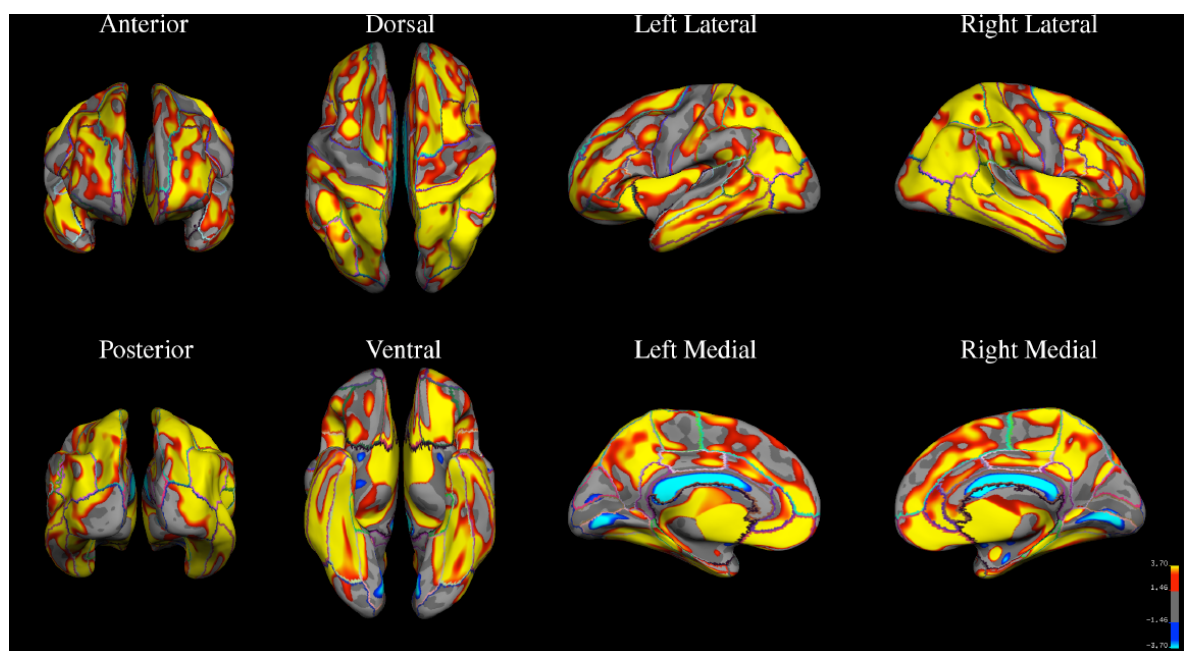
Figure 14: Left-hemisphere stroke results versus control group.
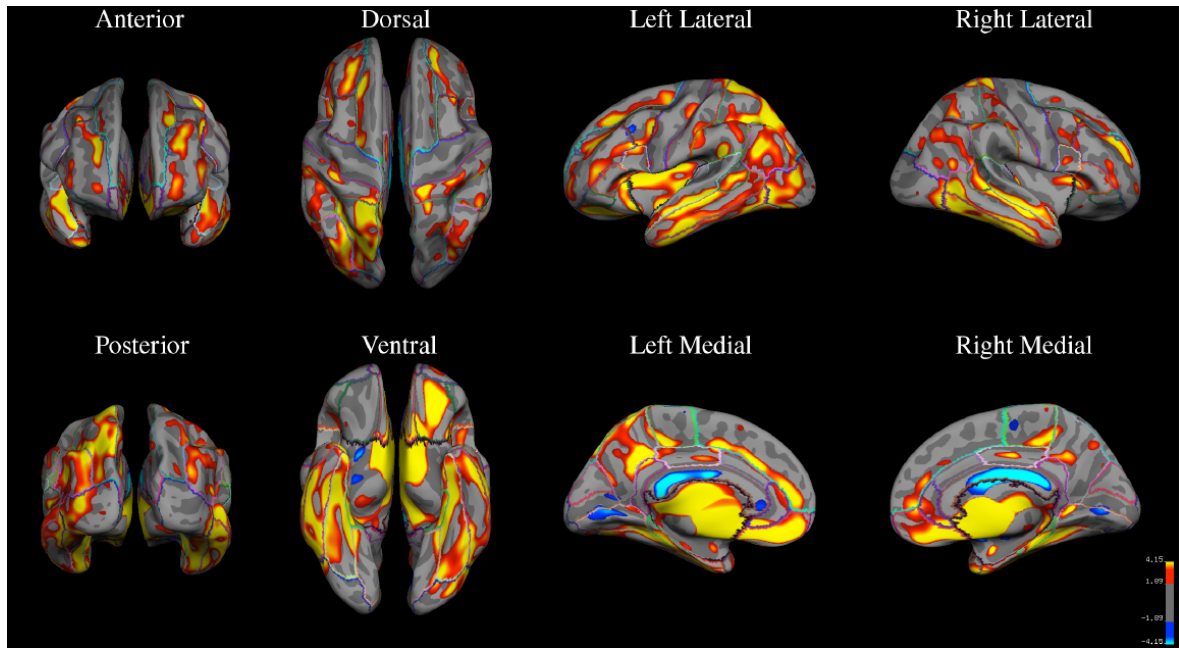
Figure 15: Right-hemisphere stroke results versus control group.

2. Difference in M1 thickness between the right hemispheric stroke and control group and between the left hemispheric stroke group and controls.

An independent sample t_test found that no significant difference in M1 thickness between left hemispheric stroke and control groups (t=1.24, n=14, p>0.05). Similarly, there was no significant difference in M1 thickness between the right hemispheric stroke and controls (t=-0.511, n=7, p>0.05). These results showed that, although the stroke has widespread effects on cortical thickness relative to controls (Figure 10 and 11) thinning was not significant in M1. To test whether variation in M1 thickness correlates with variation of stroke volume, variation of stroke volume in patients was calculated.

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There was a significant negative correlation between M1 thickness on the side of stroke (ipsilisional precenteral cortex) and stroke volume (r = -0.439, n = 21, P=0.023 one-tailed, P< 0.05) Table 3 and Figure 17.

Ipsilesional M1 Thickness	Stroke Volume
Pearson correlation	-0.439
Sig.(1-tailed)	0.023
N	21

Table 3: Correlation Test, correlation between affected M1 thickness and stroke volume.

As it shown in Figure 17 there are some data that seems to be far from the other values, which are called statistical outliers [109] therefore Grubbs' test [110] was performed as a method to determine whether any of the values of data was a significant outlier from the rest or not.

The Grubbs' test calculation for the number of 21 subjects with the significance level of 0.05 (two-sided) clarified that there is no significant outlier data in the list of data entry (M1 thickness and stroke volume).
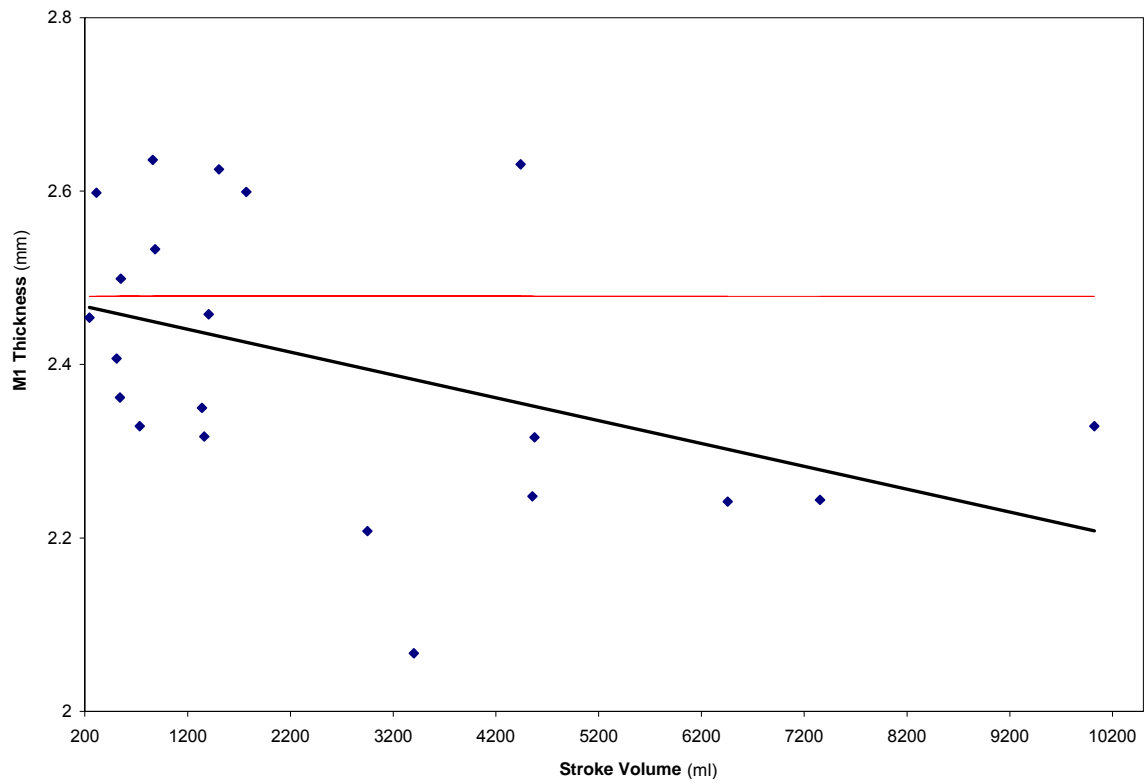
Figure 16: Correlation between ipsilesional M1 thickness (mm) and stroke volume (ml), the red line shows the average of the M1 thickness in control group.

In addition the correlation between the '' time since lesion'' and different functional test were not significant (p>0.05) (Table 4).Also the correlation between the size of lesions (stroke volume) and functional tests were not significant (p>0.05). See Table5.

		GSTEST	AMFM	AMAT	BBT
Time since Lesion	Pearson Correlation	-0.0504	-0.125	-0.265	-0.262
	Sig.(1-tailed)	0.438	0.316	0.144	0.147
	N	12	17	18	18

Table 4: Correlation between the different functional tests and "time since lesion". GSTEST: Grip strength test, AMFT: Arm motor fugl-meyer, AMAT: Arm Motor Ability Test, BBT: Box and Block Test.

		GSTEST	AMFM	AMAT	BBT
Stroke Volume	Pearson Correlation	0.258	0.070	-0.169	-0.077
	Sig.(1-tailed)	0.187	0.388	0.239	0.373
	N	14	19	20	20

Table 5: there is Correlation between different functional tests and stroke volume. GSTEST: Grip strength test, AMFT: Arm motor fugl-meyer, AMAT: Arm Motor Ability Test, BBT: Box and Block Test.

3. Cortical thickness in controls: hemispheric asymmetries and effects of age and sex.

Repeated measures ANOVA, comparing left and right hemispheres in 66 areas in control subjects (63 subjects) showed no significant effect of side ($F_{(1, 62)} = 0.578$, $P > 0.05$).

Bivariate correlation with Pearson's Correlation Coefficient between age and cortical thickness of cortical areas in normal subjects showed negative significant correlation (1-tailed, $p < 0.0007$, manual correction for multiple comparisons) in M1, superior frontal, lingual cortex at both side of the brain and also negative significant correlation in superior temporal cortex and isthmus cingulated cortex on the left side of brain and supramarginal cortex on the right side of brain. Table 4 shows the significant areas with details.

Repeated measurement ANOVA for sex and cortical thickness of brain areas (66 areas) demonstrated no significant differences ($f = 0.393$, $sig = 0.533$) in cortical thickness between female and male, (Male: n=30, Female: n=33, $p > 0.0007$ corrected for multiple comparison).

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List of areas	Correlation between cortex Area and Age	
Left precentral (M1)	Pearson correlation	-0.452
	Sig (1-tailed)	0.00009
Right precentral (M1)	Pearson correlation	-0.437
	Sig (1-tailed)	0.0001
Left superior frontal	Pearson correlation	-0.537
	Sig (1-tailed)	0.000002
Right superior frontal	Pearson correlation	-0.410
	Sig (1-tailed)	0.0004
Left Lingual	Pearson correlation	-0.456
	Sig (1-tailed)	0.00008
Right Lingual	Pearson correlation	-0.412
	Sig (1-tailed)	0.0003
Left superior temporal	Pearson correlation	-0.427
	Sig (1-tailed)	0.0002
Left isthmus cingulate	Pearson correlation	-0.460
	Sig (1-tailed)	0.00007
Right supramarginal	Pearson correlation	-0.505
	Sig (1-tailed)	0.00001

Table 4: Correlation between the thickness of cortical areas (66 areas) and age, $p < 0.0007$.

4. Correlation between stroke volume and functional tests

Bivariate correlation with Pearson's Correlation Coefficient with SPSS 16, demonstrated no significant correlation between different functional tests (Grip Strength Test, Arm Motor Ability Test, Arm Motor Fugel Mayer Test and Box and Block Test) and stroke volume. Table 6 shows the descriptive analysis of different functional tests.

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Descriptive analysis of functional test shows in Table 6. The results illustrate that stroke volume does not relate with the score of the functional tests (Table 7). As it has assumed that the sample size was not enough for this correlation, the sample size for the power of 80% has calculated. It has been named as Estimated sample size described in Table 6, that calculated by sample power *2* program (SPSS16's product) (Table 6).

Descriptive Analysis

	N	Mean	STD.Deviation
GSTEST	14	16.55	13.30
AMFM	19	35.97	6.05
AMAT	20	3.12	0.70
BBT	20	19.50	13.17

Table 5: Descriptive analysis of functional test. GSTEST: Grip Strength Test, AMFM: Arm Motor Fugel Meyer Test, AMAT: Arm Ability Test, BBT: Box and Block test.

Correlation Test

		Stroke Volume
GSTEST	Pearson Correlation	0.258
	Sig. (2-tailed)	0.373
	N	14
	Estimated sample size	110
AMFM	Pearson Correlation	0.070
	Sig. (2-tailed)	0.776
	N	19
	Estimated sample size	1600
AMAT	Pearson Correlation	-0.169
	Sig. (2-tailed)	0.477
	N	20
	Estimated sample size	266
BBT	Pearson Correlation	-0.077
	Sig. (2-tailed)	0.746
	N	20
	Estimated sample size	1221

Table 6: Correlation between Stroke Volume and Functional Tests, GSTEST: Grip Strength Test, AMFM: Arm Motor Fugel Meyer Test, AMAT: Arm Ability Test, BBT: Box and Block test. Estimated sample size is a sample size which is able to show the correlation with the power of 80% and $\alpha = 0.05$.

5. Correlation between the precentral cortex (Motor Cortex) and functional tests

Bivariate correlation with Pearson's Correlation Coefficient with SPSS16 was carried out. There was no significant correlation between the functional tests

and motor cortex thickness. In other words the thickness of the precentral cortex on the side of stroke does not have any effect on the functional score tests (Table 7). Sample size also has been calculated by *Sample Power 2* program for the power of 80%, to show if the current study sample size is enough to calculate the correlation or not. The estimated   required sample size is higher than the current sample size for all correlation tests (Table 7).

Correlation Test		Ipsilesional M1 Thickness
GSTEST	Pearson Correlation	-0.194
	Sig. (2-tailed)	0.507
	N	14
	Estimated sample size	214
AMFM	Pearson Correlation	0.116
	Sig. (2-tailed)	0.636
	N	19
	Estimated sample size	545
AMAT	Pearson Correlation	0.200
	Sig. (2-tailed)	0.398
	N	20
	Estimated sample size	190
BBT	Pearson Correlation	0.126
	Sig. (2-tailed)	0.597
	N	20
	Estimated sample size	460

Table 7: GSTEST: Grip Strength Test, AMFM: Arm Motor Fugel Meyer Test, AMAT: Arm Ability Test, BBT: Box and Block test. Estimated sample size is a sample size which is able to show the correlation with the power of 80%.

Chapter 7 – Discussion

Patient group

The study demonstrated cortical thickness changes in striatolenticular chronic stroke patients which included individuals with right and left hemispheric stroke with moderate to moderately severe upper-extremity hemiparesis.

Voxel-based comparison of cortical thickness measures observed reduced thickness in most areas of the cortex in left hemisphere stroke patients compared to a control group, similar results were observed in right hemisphere stroke patients although the results suggest less extensive reductions in cortical thickness in the right hemisphere stroke group compared to controls.

This result could perhaps be explained by the smaller number of right hemisphere stroke patients (n=7) compared to left hemisphere stroke patients (n=14) which would result in lower power for comparisons between right hemisphere stroke patients and controls. These apparent differences in thickness reduction between the left and right hemisphere groups were not tested statistically in the voxel-based analysis.This is because it is not possible to directly compare the left and right hemisphere stroke group with a voxel-wise analysis (without first flipping the brains so that all stroke appear in the same hemisphere) and so direct comparisons between groups were

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instead performed with a region of interest analysis. A direct comparison between stroke groups using a region of interest analysis showed that side of stroke did have a significant effect on the brain cortical thickness reduction: the left hemisphere stroke group had a thicker cortex than the right hemisphere stroke group.

This finding was surprising given the results of the voxel-wise analysis showing particularly prominent thickness reductions in the left hemisphere stroke group. The thicker cortex in the left hemisphere stroke group suggested by the regions of interest analysis could be due to the fact that majority of patients were right handed; perhaps a stroke to the dominant hemisphere has less severe effects on cortical thickness. Another interpretation of this result is that it is due to the stroke volumes being larger on average for the right hemisphere stroke group.

The current study tested the role of the side of stroke which has previously received limited research interest. One article, by Kwon and colleagues, established that the main control of bilateral upper limb motor control is based on the dominant hemisphere [14] but in the current study the influence of hemisphere dominancy related to cortical thickness changes was not directly tested as we did not have enough left handed subjects to compare dominant versus non dominant hemispheres.

Against our expectation the primary motor cortex was surprisingly spared in both stroke groups. One possibility is that this absence of effect is due to methodological features of the voxel-based MRI analysis in which there could be some biases or errors in steps such as registration, segmentation and parcellation and area masking. Therefore an ROI analysis also performed, which would not suffer from all these potential biases, but it confirmed that there was no difference in MI thickness in the left hemispheric stroke group or the right hemispheric stroke group compared to the control group. Another possible factor can be some mild stroke cases, or in other words those with

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better function, for instance who had Fugl-Meyer scores closer to 50 could have better hand movement than others so it could be the reason for no changes in M1 detected. Also another interpretation for this is that M1 thickness varies substantially between patients, so that the patient groups as a whole do not differ from controls.

There are some articles that investigated cortical thickness changes in different diseases. For instance, Janssen et al showed volumetric decreases of gyral and sulcal cortical structures in adolescents with first episode early-onset psychosis [111] and another study in schizophrenia patients showed greater cortical thinning in temporal-prefrontal cortex [99] and also in PTSD [112], but our findings are in stroke patients, which have not been tested in this way before.

A particularly interesting result from this study was the negative correlation between M1 thicknesses on the side of stroke and volume of stroke, such that larger stroke volumes were associated with lower cortical thickness on the side of stroke. This suggests that the degree of secondary degeneration of motor cortex depends on the size of the original lesion.

Schaechter et al studied structural plasticity in the somatosensory cortex in chronic stroke patients and showed a significant increase in somatosensory cortex after stroke [113] which could be related to compensation, but the current study showed cortical decrease after chronic stroke in motor areas and its correlation with stroke volume .

Healthy population

This study also generated findings on patterns of cortical thickness in the healthy brain. In particular, the study demonstrated that there is symmetry in cortical thickness in all areas of the cortex. This means that there is no difference in cortical thicknesses of each cortical area between the left and right hemisphere in the normal population. By contrast, previous studies reported structural asymmetries in many areas of brain. For instance, it has been proved in the frontal lobe, that the right side is thicker than left side whereas in the occipital lobe also, the left side is thicker than the right side [114].

In addition, a generally higher cortical thickness in the left hemisphere has been reported [115]. It is worthwhile mentioning that in previous studies subjects have been recruited between 18-44 years [114] or approximately 20 – 30 years [115] which is different from our study, in which subjects were 30-78 years, therefore the difference in result could be reasonable because of the higher range of ages.

Previous studies of cortical thickness have focused on structural plasticity in the sensorimotor cortical areas that exhibit functional plasticity [113] or on sex and age differences in cortical thicknesses in healthy subjects [116] [115, 117]. Studies of the effect of gender on cortical thickness showed thicker cortex in women on the posterior temporal and inferior parietal cortex and this effect is stable across the life span [116].

From different studies it has been proven that the frontal cortex (near by primary motor cortex), premotor cortex, part of temporal cortex , parahippocampus and calcarine cortex (near to primary visual cortex) are the areas which degenerate more significantly by aging [88].

The effect of age on cortical thickness has also tested and a negative correlation has been found in most areas of both hemispheres between cortical thickness and age, with increasing age cortical thickness will decrease. This is consistent with previous studies, for example Preul et al. showed a significant decrease in cortical thickness in the same area as this study with aging [118].

In the current study the results show widespread cortical changes with aging in M1, part of the parietal cortex and the lingual cortex and the superior frontal and lingual cortex in both side of the brain and also a negative significant correlation in superior temporal cortex and isthmus cingulate cortex on the left side of brain and supramarginal cortex on the right side of brain. Table 4 shows the significant areas with details.

This difference can be interpreted by the difference of range of ages of subjects which was in a wide range (18-93 y) in the Salat study [88]

Other possible discussion related to present study is that no difference was found between the male and female in cortical thicknesses, but previous studies showed some differences in cortical thickness regarding to gender. For instance, one study showed women have generally thicker cortex than men [118] and another study of age and brain volume in 18 men and women matched showed thicker cortex in temporal and parietal cortex in females [116].

This difference could arise again because of the different method of analysis. They transformed the images into standard international consortium for brain mapping (ICBM) space [119] whereas we used MNI space. There was also a difference in number of subjects, which was 36 in the previous study [116] but we had 63 subjects which might provide greater sensitivity to change. Similarly, the range of age was 18-40 years in previous studies [118] but our study age range was two times more than the previous one, therefore this

greater variety of age in the present study could account for the different results.

Previous imaging studies of cortical thickness have tended to test for effects of factors such as age and sex on thickness in the healthy population [116, 120, 121] and none of the previous studies mentioned the cortical differences between two hemispheres in the normal population.

A number of studies have tested effects of hand dominance by including left- or right-handed subjects [27, 122, 123]. However, Schaechter et al recruited 10 cases for their study which all were right-handed except for one left-handed case [124]. This is similar to our study in which we had only three left-handed among 21 subjects. Therefore we were unable to test directly for effects of handedness but, given the small number of left-handed subjects hand dominance is not expected to have any major effect on the results.

Functional measurements

Some studies showed that functional tests are a valuable marker to measure recovery after stroke or recommended them as a clinical and research tool for evaluating changes in motor impairment following stroke such as the grip strength test and arm fugl meyer test [61, 62, 125, 126].

This study explored correlations between cortical thickness and functional tests. This study aimed to assess weather performance in such tests depends on stroke volume or on cortical degeneration, therefore, correlation of M1 thickness and lesion size (stroke volume) tested which was between all left- and right-hemispheric stroke cases together versus the functional tests that assessed Neurological deficit and arm motor function included AMAT, AMFM, BBT and Grip strength Test.

The correlation between different functional behavioural tests and changes in M1 thicknesses and stroke volume was tested. As shown in the results chapter no significant correlation was found between different functional tests and stroke volume. This suggests that stroke volume does not contribute significantly to performance. It is likely that other factors, such as the location of the stroke, or the extent to which it damages specific structures, determine functional performance. As we know about data collecting standardization and sensitivity people from one site travelled to each site and trained them on the clinical ratings for behavioural measures, and also for the imaging procedure each site performed a similar motor task and used somewhat similar anatomic protocols but not exact.

In reviewing the literature, no data was found on the association between stroke volume in relation to cortical thickness and functional tests. Some studies have shown an association between damage to different levels of the corticofugal tract related to long-term hand motor recovery in one year post stroke patients or the importance of lesion location on upper limb motor recovery after stroke [127].However no previous study has attempted to relate changes in behavioural tests to cortical thickness changes following stroke.

There are several possible explanations for the absence of correlations between behavioural test scores and thickness measures in the present study. Firstly to detect significant correlations with functional tests 21 cases might not be enough. Secondly, this type of stroke, which is lacunar, has a very small volume (although the effect on arm impairment is serious), so the variation in stroke volume is small and finally cortical thickness variation is also small.

Study limitations

As this study aimed to analyse pre-existing imaging data there was no opportunity to change the original study design. In addition, some types of imaging data were not available. For instance It has been established that the thickness reductions have a linear relationship with initial hypoperfusion [128]. If there were acute DWI images or CT perfusion scans available for the patients studied in this thesis it could be tested whether the left hemispheric stroke patients have more severe hypoperfusion at the acute time than the right hemispheric stroke patients, so this could explain their greater grey matter reduction.

The organization, from which we obtained data had some limitations to access patient images as patients were recruited around 5 years ago and from 3 different centres with 3-T scanner all over the US and further data was impossible to access.

Regarding the field strength, Hen et al found that the variability of local thickness measurement with 1.5 T and 3T is low and slightly biased[101], which was another concern of this study. All the analysis was done in one centre at FMRIB centre (Oxford Centre for Functional MRI of The brain) including brain registration, parcellation and all the other processes.

The other data access limitation concerned the functional tests; there was not access to all subjects' scores of Grip strength and there was some missing data which has been excluded in data analyses. So, this could cause some biases on the results because of the low number of the cases for functional tests.

Finally, our control data was chosen from the OASIS database, thus the control group was not recruited at the same time as the patients, with identical

scanner or centres ,as it has mentioned previously it has been shown to have a negligible effect on the result [101].

Chapter 8 – Conclusion

The finding from this study suggests that the size of the lesion can be a predictor of further M1 cortex reduction. The correlation of M1 thickness with stroke volume showed that secondary cortical degeneration may be mainly driven by the size of axonal loss in capsular-striatal stroke.

From normal subject study it can be concluded that generally cortical thickness will decrease by aging but gender does not have an effect on the cortical thickness.

In addition, the lack of behavioural correlation with M1 thickness and stroke volume and also the non significant M1 cortex reduction versus control group may suggest that the long-term functional disability after capsular-striatal stroke may not be entirely dependent on primary motor cortex and secondary motor cortex and primary somatosensory cortex could have an important role as well. Further research in this area would be well advised to investigate the other cortical areas and with larger sample size.

Further studies on the current topic are therefore recommended by using FMRI or DTI and checking the same hypothesis with those measurements. DTI is able to show the tracts that have been lost after stroke. The lack of functionality of areas of brain can be assessed by FMRI. Furthermore a more thorough and complete behavioural functional test, including grip strength testing of all participants, is required.

Appendix 4: Descriptive analysis of cortical thickness.

66 areas of brain is listed and specified by the side of stroke in brain as Ipsilesional and Contralesional.

Areas	N	Mean	Std. Deviation
Ipsilesional_caudalanteriorcingulate_Thickness	21	2.61419	.366026
Ipsilesional_caudalmiddlefrontal_Thickness	21	2.48586	.301934
Ipsilesional_corpuscallosum_Thickness	21	.05876	.128947
Ipsilesional_cuneus_Thickness	21	1.81710	.091526
Ipsilesional_entorhinal_Thickness	21	3.32671	.132611
Ipsilesional_fusiform_Thickness	21	2.61605	.365036
Ipsilesional_inferiorparietal_Thickness	21	2.46171	.180428
Ipsilesional_inferiortemporal_Thickness	21	2.76376	.113960
Ipsilesional_isthmuscingulate_Thickness	21	2.44610	.203208
Ipsilesional_lateraloccipital_Thickness	21	2.17576	.200523
Ipsilesional_lateralorbitofrontal_Thickness	21	2.50681	.148373
Ipsilesional_lingual_Thickness	21	1.96443	.148690
Ipsilesional_medialorbitofrontal_Thickness	21	2.39733	.147623
Ipsilesional_middletemporal_Thickness	21	2.80681	.205781
Ipsilesional_parahippo_Thickness	21	2.54981	.142932
Ipsilesional_paracentral_Thickness	21	2.32133	.256578
Ipsilesional_parsopercularis_Thickness	21	2.46043	.145898
Ipsilesional_parsorbitalis_Thickness	21	2.55624	.129122
Ipsilesional_parstriangularis_Thickness	21	2.38186	.215916
Ipsilesional_pericalcarine_Thickness	21	1.57281	.143345
Ipsilesional_postcentral_Thickness	21	2.11786	.160465
Ipsilesional_posteriorcingulate_Thickness	21	2.40400	.104449
Ipsilesional_precentral_Thickness	21	2.40248	.143366

Ipsilesional_precuneus_Thickness	21	2.32205	.149833
Ipsilesional_rostralanteriorcingulate_Thickness	21	2.80952	.190225
Ipsilesional_rostralmiddlefrontal_Thickness	21	2.33871	.222656
Ipsilesional_superiorfrontal_Thickness	21	2.65871	.128613
Ipsilesional_superiorparietal_Thickness	21	2.23110	.148526
Ipsilesional_superiortemporal_Thickness	21	2.65114	.110076
Ipsilesional_supramarginal_Thickness	21	2.48657	.155321
Ipsilesional_frontalpole_Thickness	21	2.76981	.106099
Ipsilesional_Temporalpole_Thickness	21	3.54486	.236154
Ipsilesional_Transversetemporal_Thickness	21	2.28900	.336019
Contralesional_caudalanteriorcingulate_Thickness	21	2.49705	.232182
Contralesional_caudalmiddlefrontal_Thickness	21	2.54924	.203054
Contralesional_corpuscallosum_Thickness	21	.06429	.168258
Contralesional_cuneus_Thickness	21	1.86133	.021692
Contralesional_entorhinal_Thickness	21	3.30190	.158847
Contralesional_fusiform_Thickness	21	2.67495	.433546
Contralesional_inferiorparietal_Thickness	21	2.52267	.184897
Contralesional_inferiortemporal_Thickness	21	2.79286	.141161
Contralesional_isthmuscingulate_Thickness	21	2.51710	.248358
Contralesional_lateraloccipital_Thickness	21	2.26690	.237706
Contralesional_lateralorbitofrontal_Thickness	21	2.53124	.184920
Contralesional_lingual_Thickness	21	1.94581	.163232
Contralesional_medialorbitofrontal_Thickness	21	2.37005	.139480
Contralesional_middletemporal_Thickness	21	2.89010	.186151
Contralesional_parahippo_Thickness	21	2.61800	.170327
Contralesional_paracentral_Thickness	21	2.33895	.230117
Contralesional_parsopercularis_Thickness	21	2.49500	.165569
Contralesional_parsorbitalis_Thickness	21	2.58829	.176504
Contralesional_parstriangularis_Thickness	21	2.40629	.191727
Contralesional_pericalcarine_Thickness	21	1.54895	.148035
Contralesional_postcentral_Thickness	21	2.17933	.076138

Contralesional_posteriorcingulate_Thickness	21	2.44348	.194405
Contralesional_precentral_Thickness	21	2.47862	.187049
Contralesional_precuneus_Thickness	21	2.34233	.167902
Contralesional_rostralanteriorcingulate_Thickness	21	2.74410	.196277
Contralesional_rostralmiddlefrontal_Thickness	21	2.34233	.212363
Contralesional_superiorfrontal_Thickness	21	2.67810	.150581
Contralesional_superiorparietal_Thickness	21	2.28367	.178553
Contralesional_superiortemporal_Thickness	21	2.72381	.146395
Contralesional_supramarginal_Thickness	21	2.56962	.118800
Contralesional_frontalpole_Thickness	21	2.70552	.128604
Contralesional_Temporalpole_Thickness	21	3.5403	.213237
Contralesional_Transversetemporal_Thickness	21	2.27052	.184170

Appendix 5: Calculation the volume of subcortical areas of brain.

The volume of area is corrected regarding to the brain volume. Areas specified the side of stroke in brain as Ipsilesional and Contralesional.

Areas	N	Mean	Std. Deviation
Ipsilesional_CerebralWhiteMatter	21	2.225E5	2.241E4
Ipsilesional_CerebralCortex	21	2.358E5	1.772E4
Ipsilesional_CerebellumWhiteMatter	21	1.606E4	3.425E3
Ipsilesional_CerebellumCortex	21	4.800E4	7.283E3
Ipsilesional_ThalamusProper	21	6.155E3	1.001E3

Ipsilesional_Caudate	21	3.901E3	7.646E2
Ipsilesional_Putamen	21	4.815E3	7.690E2
Ipsilesional_Pallidum	21	1.261E3	3.254E2
Ipsilesional_Hippocampus	21	4.136E3	3.856E2
Ipsilesional_Amygdala	21	1.679E3	2.552E2
Ipsilesional_Accumbensarea	21	5.132E2	1.043E2
Contralesional_CerebralWhiteMatter	21	2.270E5	1.960E4
Contralesional_CerebralCortex	21	2.404E5	1.909E4
Contralesional_CerebellumWhiteMatter	21	1.547E4	2.569E3
Contralesional_CerebellumCortex	21	4.740E4	7.514E3
Contralesional_ThalamusProper	21	6.618E3	8.012E2
Contralesional_Caudate	21	3.753E3	5.129E2
Contralesional_Putamen	21	5.082E3	5.100E2
Contralesional_Pallidum	21	1.284E3	3.732E2
Contralesional_Hippocampus	21	4.164E3	3.980E2
Contralesiona;_Amygdala	21	1.701E3	1.453E2
Contralesional_Accumbensarea	21	5.565E2	1.448E2
Corpus callosum_Posterior	21	9.282E2	1.762E2
Corpus callosum _Mid_Posterior	21	4.111E2	1.024E2
Corpus callosum _Central	21	4.306E2	9.239E1
Corpus callosum _Mid_Anterior	21	4.798E2	1.237E2
Corpus callosum _Anterior	21	8.463E2	1.2663E2

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Appendix 6: calculation of cortical volume of brain.

Areas are specified by the side of stroke in brain as Ipsilesional and Contralesional.

Areas	N	Mean	Std. Deviation
Ipsilesional_caudalanteriorcingulate_VOLUME	21	2.004E3	4.338E2
Ipsilesional_caudalmiddlefrontal_VOLUME	21	6.160E3	1.165E3
Ipsilesional_corpuscallosum_VOLUME	21	1.254E2	5.602E1
Ipsilesional_cuneus_VOLUME	21	3.121E3	8.818E2
Ipsilesional_entorhinal_VOLUME	21	1.716E3	3.596E2
Ipsilesional_fusiform_VOLUME	21	8.639E3	1.394E3
Ipsilesional_inferiorparietal_VOLUME	21	1.230E4	2.600E3
Ipsilesional_inferiortemporal_VOLUME	21	1.002E4	1.914E3
Ipsilesional_isthmuscingulate_VOLUME	21	2.124E3	4.720E2
Ipsilesional_lateraloccipital_VOLUME	21	1.270E4	2.004E3
Ipsilesional_lateralorbitofrontal_VOLUME	21	7.220E3	8.036E2
Ipsilesional_lingual_VOLUME	21	6.667E3	1.139E3
Ipsilesional_medialorbitofrontal_VOLUME	21	4.543E3	6.868E2
Ipsilesional_middletemporal_VOLUME	21	1.093E4	2.103E3
Ipsilesional_parahippocampal_VOLUME	21	1.850E3	3.072E2
Ipsilesional_paracentral_VOLUME	21	3.468E3	6.146E2
Ipsilesional_parsopercularis_VOLUME	21	4.164E3	1.310E3
Ipsilesional_parsorbitalis_VOLUME	21	2.246E3	4.367E2
Ipsilesional_parstriangularis_VOLUME	21	3.692E3	6.723E2
Ipsilesional_pericalcarine_VOLUME	21	2.227E3	5.625E2
Ipsilesional_postcentral_VOLUME	21	9.312E3	1.458E3
Ipsilesional_posteriorcingulate_VOLUME	21	3.223E3	5.329E2
Ipsilesional_precentral_VOLUME	21	1.256E4	1.618E3
Ipsilesional_precuneus_VOLUME	21	8.949E3	1.807E3
Ipsilesional_rostralanteriorcingulate_VOLUME	21	2.111E3	5.515E2
Ipsilesional_rostralmiddlefrontal_VOLUME	21	1.487E4	1.805E3
Ipsilesional_superiorfrontal_VOLUME	21	2.197E4	2.721E3
Ipsilesional_superiorparietal_VOLUME	21	1.250E4	1.921E3
Ipsilesional_superiortemporal_VOLUME	21	1.165E4	1.945E3
Ipsilesional_supramarginal_VOLUME	21	9.483E3	1.444E3

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Ipsilesional_frontalpole_VOLUME	21	9.075E2	2.004E2
Ipsilesional_temporalpole_VOLUME	21	2.364E3	3.737E2
Ipsilesional_transversetemporal_VOLUME	21	1.034E3	2.954E2
Contralesional_caudalanteriorcingulate_VOLUME	21	2.019E3	5.988E2
Contralesional_caudalmiddlefrontal_VOLUME	21	6.376E3	1.412E3
Contralesional_corpuscallosum_VOLUME	21	1.130E2	7.599E1
Contralesional_cuneus_VOLUME	21	3.343E3	1.022E3
Contralesional_entorhinal_VOLUME	21	1.815E3	3.954E2
Contralesional_fusiform_VOLUME	21	8.500E3	1.520E3
Contralesional_inferiorparietal_VOLUME	21	1.392E4	3.283E3
Contralesional_inferiortemporal_VOLUME	21	9.846E3	2.320E3
Contralesional_isthmuscingulate_VOLUME	21	1.976E3	3.217E2
Contralesional_lateraloccipital_VOLUME	21	1.266E4	2.768E3
Contralesional_lateralorbitofrontal_VOLUME	21	7.228E3	9.515E2
Contralesional_lingual_VOLUME	21	6.490E3	1.367E3
Contralesional_medialorbitofrontal_VOLUME	21	4.624E3	6.829E2
Contralesional_middletemporal_VOLUME	21	1.160E4	1.708E3
Contralesional_parahippocampal_VOLUME	21	1.941E3	5.083E2
Contralesional_paracentral_VOLUME	21	3.890E3	9.374E2
Contralesional_parsopercularis_VOLUME	21	3.981E3	9.139E2
Contralesional_parsorbitalis_VOLUME	21	2.591E3	5.553E2
Contralesional_parstriangularis_VOLUME	21	3.934E3	8.536E2
Contralesional_pericalcarine_VOLUME	21	2.231E3	6.674E2

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Contralesional_postcentral_VOLUME	21	1.002E4	1.923E3
Contralesional_posteriorcingulate_VOLUME	21	3.324E3	7.497E2
Contralesional_precentral_VOLUME	21	1.350E4	1.657E3
Contralesional_precuneus_VOLUME	21	9.301E3	1.416E3
Contralesional_rostralanteriorcingulate_VOLUME	21	2.042E3	6.834E2
Contralesional_rostralmiddlefrontal_VOLUME	21	1.565E4	3.053E3
Contralesional_superiorfrontal_VOLUME	21	2.206E4	2.397E3
Contralesional_superiorparietal_VOLUME	21	1.257E4	1.942E3
Contralesional_superiortemporal_VOLUME	21	1.158E4	1.289E3
Contralesional_supramarginal_VOLUME	21	9.825E3	1.631E3
Contralesional_frontalpole_VOLUME	21	8.925E2	1.868E2
Contralesional_temporalpole_VOLUME	21	2.339E3	5.117E2
Contralesional_transversetemporal_VOLUME	21	9.518E2	2.118E2

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