ATTENTION-CONTROL DEFICITS AND THEIR IMPACT UPON MOTOR DEFICITS IN STROKE

PAUL EDMUND RINNE

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

SUPERVISORS:
DR PAUL BENTLEY
DR DAVID SOTO

DEPARTMENT OF MEDICINE
IMPERIAL COLLEGE LONDON

AUGUST 2015
ABSTRACT

Background: Motor impairment and attention deficits are common in stroke. Little is known about how a patient’s attentional capacity influences their motor function, motor-learning and recovery. This relationship may present a target for rehabilitation. This thesis aimed to: 1) survey the prevalence of attention deficits following stroke; 2) investigate the relationship between attention deficits and motor performance; 3) assess how the attention and motor profile of patients related to lesion location and disruption of functional brain networks; and 4) to develop and test a practical tool that allows for measurement and rehabilitation of attention-motor deficits in combination.

Methods: Study 1: Anatomically-unselected stroke patients performed the Attention Network Task, a sensitive measure of attention, with performance related to lesion anatomy. Study 2: Stroke patients and controls were tested on a novel visuomotor tracking task, with variable distractors, using a commercially available hand-grip controller. Relationships between motor-tracking performance and distractibility were determined, as were the dependency of these behavioural measures on lesion location and functional network integrity. Study 3: A separate group of subjects performed a visuomotor tracking task while functional MRI was obtained. Performance and motor-learning was related to changes in resting-state networks before and after the task. Study 4: A novel portable hand-grip and variant of the visuomotor tracking task were designed and developed for bedside assessment and rehabilitation. The novel system was tested on hemiparetic patients, and its accessibility was compared with existing mobile gaming technologies.

Results: Study 1: A majority of stroke patients showed attention deficits, especially attention-control deficits; even though a far smaller proportion showed attentional-neglect on standard bedside tests. Attention-control impairments were seen equally with lesions to subcortical, premotor and prefrontal cortices. Study 2: Motor performance was closely related to attention-control performance. This was dependent upon lesion location and interference with both attention-control and motor network connectivity. Study 3: The visuomotor task influenced changes in connectivity of visuo-spatial, sensorimotor and cerebellar resting-state networks. These differed between patient and controls, and related to motor-learning. Study 4: A significantly greater proportion of hemiparetic patients – particularly those with a severe motor deficit - could engage with our novel attention-motor trainer than existing technologies.

Conclusions: This work provides evidence that attention deficits frequently accompany stroke and have a significant effect on a patient’s motor ability and recovery potential. Variability in patients’ motor function can be accounted for by lesions that damage both corticospinal and attention-control systems. A novel portable electronic device, designed as part of the PhD, allows for both testing and training of motor stroke patients, for both their motor and related attention deficits.
The work presented in this thesis is original and my own. Information derived from other sources has been appropriately acknowledged and referenced.

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.
ACKNOWLEDGEMENTS

First and foremost I would like to thank my supervisor, Dr Paul Bentley; his support and mentorship throughout the past four years has been invaluable to me. I am truly indebted to him.

I would also like to thank my co-supervisor, Dr David Soto, for plucking me from the crowd and offering me my first clinical research project, and for all the time and help he gave me during the early years of my research.

Thanks also goes to Prof Etienne Burdet and Dr Michael Mace, without whom the development of a product at the conclusion of this thesis would not have been possible, and to all the members of the Human Robotics Group at Imperial College who welcomed me so warmly into their midst.

Special thanks go to all the staff at the Charing Cross Hospital Stroke Unit and those from the Clinical Imagining Department. They made me feel part of the team and were always on hand to offer help in the clinical setting, especially in helping me recruit patients for this study. Very special thanks also go to the patients themselves, who invariably spoke of their willingness to participate in the study, not for their own benefit, but to potentially help future stroke survivors. It is safe to say that none of the research in this thesis would have been possible without their involvement, and I hope that the results of this study may eventually repay some of their generosity.

I would also like to thank all those colleagues who have been members of the Imperial Stroke Research Group during my studies and for making that time so enjoyable, and to my closest family and friends for keeping me going throughout.

And finally, I would like to thank my parents, Paul and Katarzyna Rinne, for the unwavering support and love given to me, not just over the past four years, but throughout my entire life. I hope they can be proud and share in my achievements.
3.4.6 Limitations and Methodological Considerations ............................................. 101
3.5 Conclusion ........................................................................................................ 103
3.5.1 Triple dissociation of attention networks ..................................................... 103
3.5.2 Clinical Importance ...................................................................................... 103

CHAPTER FOUR: ASSESSING ATTENTION DEFICITS AND MOTOR PERFORMANCE RELATIONSHIPS:
DEVELOPMENT OF A NOVEL TASK ................................................................. 105
4.1 Introduction ....................................................................................................... 106
4.2 Methods ........................................................................................................... 109
4.2.1 Subjects ..................................................................................................... 109
4.2.2 Novel Visuomotor Tracking Task ................................................................. 109
4.2.3 Attention-Control and Grip Force Analysis ................................................ 112
4.2.4 Precision-grip and Non-motor Control Tasks ................................................ 112
4.2.5 Voxel-Lesion Symptom Mapping ................................................................. 113
4.2.6 Functional Connectivity Analysis ............................................................... 114
4.2.7 Functional Connectivity Visuomotor Task .................................................... 114
4.3 Results ............................................................................................................. 116
4.3.1 Test Population ......................................................................................... 116
4.3.2 Undistracted performance ......................................................................... 119
4.3.3 Effect of Distractors ................................................................................ 122
4.3.4 Non-motor test of attention-control ............................................................ 128
4.3.5 Lesion Mapping: locations associated with motor and attentional control deficits ........................................................................................................... 129
4.3.6 Functional Network Correlation Analysis ................................................. 133
4.4 Discussion ....................................................................................................... 135
4.4.1 Behavioural Validation ........................................................................... 135
4.4.2 Imaging Validation .................................................................................. 137
4.5 Conclusions .................................................................................................... 140
4.5.1 Visuomotor-Attention-Control Task ......................................................... 140
4.5.2 Clinical Importance .................................................................................. 140

CHAPTER FIVE: POST-LEARNING FUNCTIONAL NETWORK MODULATIONS IN MOTOR STROKE .................................................. 142
5.1 Introduction ..................................................................................................... 143
5.2 Methods ........................................................................................................ 146
5.2.2 Visuomotor Tracking Task ........................................................................ 146
5.2.3 MRI Scanning Protocol ............................................................................ 148
5.2.4 Functional Connectivity Analysis ............................................................... 150
6.3 Results: ........................................................................................................................................... 152
   6.3.1 Test Population ........................................................................................................................ 152
   6.3.2 Task Performance ..................................................................................................................... 152
   6.3.3 Task Motor-Learning ................................................................................................................ 154
   6.3.4 Post Task Functional Network Connectivity ......................................................................... 155
   6.3.5 Correlations of Motor-Learning and Post Task Functional Network Connectivity ............. 158
5.4 Discussion: ...................................................................................................................................... 160
   5.4.1 Post-Task Changes in Functional Network Connectivity ....................................................... 160
   5.4.2 Motor-Learning and Functional Network Connectivity .......................................................... 161
   5.4.3 Conclusions .............................................................................................................................. 162

CHAPTER SIX: IMPROVING ACCESSIBILITY OF ATTENTION-MOTOR ASSESSMENT & TRAINING:
DEVELOPMENT OF A NOVEL DEVICE .............................................................................................. 164
6.1 Introduction ....................................................................................................................................... 165
6.2 Methods – Technology Development ............................................................................................. 169
   6.2.1 Novel Hand-Grip Design and Development ........................................................................... 169
   6.2.2 Visuomotor Task Gaming App Design and Development ....................................................... 169
6.3 Methods - Usability and Feasibility Study ....................................................................................... 171
   6.3.1 Subjects ..................................................................................................................................... 171
   6.3.2 Tablet Control Methods ......................................................................................................... 171
   6.3.3 Primary Outcome Measure .................................................................................................. 172
   6.3.4 Baseline Motor Clinical Data: ................................................................................................ 172
   6.3.5 Qualitative Analysis ............................................................................................................. 173
   6.3.6 Quantitative Analysis .......................................................................................................... 174
6.4 Results - Technology Development ............................................................................................... 175
   6.4.1 Novel Hand-Grip ................................................................................................................ 175
   6.4.2 Visuomotor Task Gaming App ............................................................................................ 177
6.5 Results - Usability and Feasibility Study ......................................................................................... 178
   6.5.1 Test Population .................................................................................................................. 178
   6.5.2 Conventional Device Comparison ......................................................................................... 180
   6.5.3 Conventional vs Novel Hand-Grip Comparison ................................................................. 182
   6.5.4 Accuracy of Hand-grip Control vs Baseline Hand Function .................................................. 183
6.6 Discussion ......................................................................................................................................... 185
   6.6.1 Development of a Novel Hand-grip and Mobile Gaming App ................................................. 185
   6.6.2 Accessibility of Mobile Technologies ..................................................................................... 188
   6.6.3 Accessibility of the Novel Hand-grip ....................................................................................... 188
   6.6.4 Mobile Technologies for Rehabilitation ............................................................................... 189
6.5 Conclusions

CHAPTER SEVEN: GENERAL DISCUSSION

7.1 General Discussion:

7.2 ‘Attention’ Deserves Further Attention

7.3 Development of Novel Rehabilitation Technologies

7.4 Future Directions for Research into Attention-Motor Control

7.5 Final Remarks

REFERENCES

APPENDIX
LIST OF FIGURES

Figure 1: The Motor System .............................................................. 20
Figure 2 The Visual Attention System ............................................ 22
Figure 3 Clinical MRI Scans ................................................................. 52
Figure 4 'Lesion-Find' Lesion Delineation Software ......................... 54
Figure 5 Robust Resting-State Networks ........................................... 61
Figure 6 Generated Resting-State Networks ...................................... 64
Figure 7 Generated Resting-State Networks Overlapped With Beckmann 8 ......................................................................................... 65
Figure 8 Schematic of Attention Network Test .................................... 74
Figure 9 Lesion histogram depicted spatially on normalized MNI template brain ................................................................. 80
Figure 10 Performance of the ANT in the three subject groups: healthy controls, neurological controls, and focal brain lesions ........................................... 81
Figure 11 Lesion sites that enhance conflict costs .................................. 85
Figure 12 Lesion sites that reduce orienting ........................................ 87
Figure 13 Lesion sites that reduce alerting ........................................... 89
Figure 14 Plots of Conflict Size Against Cue Type ................................ 94
Figure 15 Tracking task ................................................................. 111
Figure 16 Tracking task with addition of distractors ....................... 111
Figure 17 Non-motor task ............................................................. 113
Figure 18 Performance of Tracking and Precision Task .................. 119
Figure 19 Undistracted performance correlations .............................. 121
Figure 20 Effect of Distractors on Performance .................................. 124
Figure 21 Distractored performance correlations .................................. 125
Figure 22 Non-motor tracking correlations with conflict .................. 128
Figure 23 Patient performance correlated with corticospinal tracts ...... 129
Figure 24 Performance correlated to lesion overlap volume .............. 130
Figure 25 Performance correlated to frontal-thalamic-striatal tract lesion volumes ................................................................. 131
Figure 26 Lesion overlay map ......................................................... 132
Figure 27 Tracking performance compared with functional networks ................................................................. 134
Figure 28 Tracking task and Scanning Environment ............................ 147
Figure 29 Scanning Protocol ............................................................. 150
Figure 30 Robust Resting State Neworks ........................................... 151
Figure 31 Performance of the tracking task ...................................... 153
Figure 32 Learning effect over task session ....................................... 154
Figure 33 Resting-State Connectivity Time Profiles ............................. 156
Figure 34 Correlations Between Learning and Decreased Connectivity ................................................................. 159
Figure 35 Conventional Mobile Technology Control Methods .......... 172
Figure 36 Graphical Representation of Movement Scale and Score 0-3 ......................................................................................... 173
Figure 37 Design evolution of hand-grip prototypes ........................... 176
Figure 38 Novel Hand-grip Control – ‘gripAble’ .................................. 176
Figure 39 Visuomotor Game App Levels .............................................. 177
Figure 40 Patient Screening and Recruitment Flow Diagram ............. 178
Figure 41 Categorisation of patient strengths .................................... 179
Figure 42 Patient Movement Success by Strength and Device Using the Affected Hand ................................................................. 181
Figure 43 Patient Movement Success for Strength and Device using the Unaffected Hand ................................................................. 181
Figure 44 Accessibility of the Hand-grip Compared with Swipe across Patient Baseline Strength ................................................................. 183
Figure 45 Accuracy of Control Using Hand-grip Compared to Baseline Hand Function ................................................................. 184
LIST OF TABLES

Table 1 Commercially Available Upper Limb Rehabilitation Technologies ........................................ 47
Table 2 Characteristics of subject groups ........................................................................................... 79
Table 3 Subject Diagnoses .................................................................................................. 80
Table 4 Results of mixed-effect ANOVA Cue x Flanker x Group ......................................................... 82
Table 5 Regions showing interaction or main effect of lesion with attentional manipulation (RT data) ........................................................................................................................................... 91
Table 6 Regions showing interaction of lesion with attentional manipulation (Accuracy data) ........ 92
Table 7 Subject characteristics for separate sub-experiments .............................................................. 116
Table 8 Undistracted performance .................................................................................................... 120
Table 9 Effect of Distractors ............................................................................................................. 126
Table 10 Correlations of Significant RSNs Connectivity with Accuracy ........................................... 133
Table 11 Subject characteristics ....................................................................................................... 152
Table 12 Group Connectivity Differences Between RS1 and RS3 .................................................... 157
Table 13 Group Connectivity Differences Between RS2 and RS3 .................................................... 157
Table 14 Correlations Between Learning and Connectivity Changes in 20 RSNs ............................... 158
Table 15 Patient Demographics and Clinical Characteristics .......................................................... 179
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>ADC</td>
<td>apparent diffusion coefficient</td>
</tr>
<tr>
<td>ADLs</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>ANT</td>
<td>attention network test</td>
</tr>
<tr>
<td>BET</td>
<td>brain extraction tool</td>
</tr>
<tr>
<td>BOLD</td>
<td>blood-oxygen-level-dependant</td>
</tr>
<tr>
<td>CAD</td>
<td>computer-aided design</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CST</td>
<td>corticospinal tract</td>
</tr>
<tr>
<td>CT</td>
<td>computer tomography</td>
</tr>
<tr>
<td>DCM</td>
<td>dynamic causal modelling</td>
</tr>
<tr>
<td>DLPF</td>
<td>dorsolateral prefrontal</td>
</tr>
<tr>
<td>dPM</td>
<td>dorsal premotor area</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted MR imaging</td>
</tr>
<tr>
<td>EPSRC</td>
<td>Engineering and Physical Sciences Research Council</td>
</tr>
<tr>
<td>ESD</td>
<td>early supported discharge</td>
</tr>
<tr>
<td>FA</td>
<td>flip angle</td>
</tr>
<tr>
<td>FL</td>
<td>focal brain lesions</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FoV</td>
<td>field of view</td>
</tr>
<tr>
<td>FSL</td>
<td>FMRIB software library</td>
</tr>
<tr>
<td>FTS</td>
<td>fronto-thalamic-striatal</td>
</tr>
<tr>
<td>FWHM</td>
<td>full width at half maximum</td>
</tr>
<tr>
<td>GUI</td>
<td>graphical user interface</td>
</tr>
<tr>
<td>HASU</td>
<td>Hyper Acute Stroke Unit</td>
</tr>
<tr>
<td>HC</td>
<td>healthy controls</td>
</tr>
<tr>
<td>HRG</td>
<td>human robotics group</td>
</tr>
<tr>
<td>ICA</td>
<td>independent component analysis</td>
</tr>
<tr>
<td>IPS</td>
<td>intraparietal sulcus</td>
</tr>
<tr>
<td>ITR</td>
<td>information transfer rate</td>
</tr>
<tr>
<td>L1</td>
<td>right middle corona radiata cluster</td>
</tr>
</tbody>
</table>
LTD  long-term depression
LTP  long-term potentiation
M1   primary motor cortex
MELODIC  multivariate exploratory linear decomposition into independent components
MME  minimum moving error
MNI  Montreal Neurological Institute
MRI  magnetic resonance imaging
NC   neurological controls
NHS  National Health Service
NICE National Institute for Health and Care Excellence
PBSM parallel blade spring mechanism
PCB  printed circuit board
Pre-SMA pre-supplementary motor area
RMCR right middle corona radiata
RMS  root mean squared
ROIs region of Interest
rs-fMRI resting-state functional magnetic resonance imaging
RS   Resting State
RSNs resting-state networks
RT   reaction time
RTPJ right temporoparietal junction
S1   Primary somatosensory cortex
SFM  short fugl-meyer
SLF  superior longitudinal fasciculus
SMA  supplementary motor area
SWI  susceptibility-weighted imaging
tDCS transcranial direct current stimulation
TMS transcranial magnetic stimulation
TPJ  temporoparietal junction
TR   repetition time
UE   user experience
UI   user interface
UL   upper-limb
VLSM voxel-lesion symptom mapping
WM   working memory
CHAPTER ONE: INTRODUCTION
1.1 Impact of Stroke

‘A stroke epidemic’ – the phrase used to describe the growing global impact of stroke. Characterised by a sudden reduction of blood flow to an area of the brain, resulting in neuronal cell loss, stroke is the second biggest cause of death worldwide (6.7 million people per annum) (World Health Organisation 2014), with the estimated global incidence of first time strokes reaching almost 17 million a year (Feigin et al. 2014). With approximately two-thirds of suffers surviving with varying degrees of disability, stroke is also a leading cause of acquired complex adult disability (Langhorne et al. 2009; Go et al. 2014).

The high and growing percentage of survivors, added to an ever increasing, aging and overindulgent population, has fuelled predictions that the global prevalence of stroke will reach 77 million by 2030 (Carandang et al. 2006; Strong et al. 2007; Feigin et al. 2014), with the associated financial burdens projected to more than double (Ovbiagele et al. 2013). Although viewed predominantly as a disease effecting industrialised nations, it is important to note that over the past four decades stroke incidence has declined by over 40% in such high-income countries, whilst it has doubled in low and middle income countries (Feigin et al. 2009; Ferri et al. 2011). This makes the growing socioeconomic costs of stroke a truly global problem.

The EU has an estimated 8 million stroke survivors living within its countries (Gustavsson et al. 2011), currently costing this economy around £45 billion per year. This accounts for 2-3% of the EU’s entire healthcare expenditure (Andreotti 2012). Narrowing these figures down to the UK alone shows that approximately 152,000 strokes occur each year (Townsend et al. 2012), with around 1.2 million survivors living in the UK (Health and Social Care Information Centre. 2014). The health and social costs of caring for these patients sits at approximately £4.38 billion. Added to this, informal care costs of £2.42 billion, productivity losses (i.e. income lost) of £1.33 billion and benefit payments of £841m, mean that the entire economic costs associate with stroke in the UK totals £9 billion per year (Saka et al. 2009).
CHAPTER ONE: INTRODUCTION

Recognising the growing impact of stroke, national UK organisations have launched initiatives aimed at reducing death rates (National Stroke Strategy Report 2007) and improving the provision of care (National Clinical Guideline for Stroke 2012). However, despite seeing steady improvements in mortality, morbidity and prevalence rates have increased (Lee et al. 2011). With a higher percentage of patients surviving stroke, many of whom have a high burden of disability, much of post-stroke care relies on the delivery of effective and guideline driven rehabilitation services. It is because of the need to provide such services, often requiring the employment of multidisciplinary teams, such as: physicians, physiotherapists, occupational therapists, clinical psychologists and speech and language therapists; that the cost of post-stroke care sores. It is estimated that the average total cost of institutional care (acute & rehabilitation) per individual UK stroke patient is £23,315.141, of which approximately only 10% accounts for acute hospital care, leaving 90% of costs on tailored therapy needs (National Audit Office 2010).

1.2 Reducing Costs by Improving Rehabilitation

The increasing need and cost of therapy has forced advisory organisations to re-assess the implementation of their rehabilitation guidelines, with a focus on efficiency and cost-effectiveness of resources. However, this does not mean a reduction in rehabilitation provision. In a recent report published by the National Institute for Health and Care Excellence (NICE), key recommendations highlighted as generating the biggest savings included increased provision of early, intense and efficient therapy, with an aim of increasing the amount of patients able to return to normal daily living and work (NICE Stroke rehabilitation: costing report 2013). The report also suggested further research should be undertaken into the delivery of rehabilitation in home environments, and a particular focus on the development and supply of rehabilitation based technologies capable of reducing the pressure on human based resources. This final point has been echoed by the Engineering and Physical Sciences Research Council (EPSRC), who state that more resources should be geared towards the development and provision of technologies to support increased dose and effectiveness of rehabilitation (Report of EPSRC Rehabilitation Scoping Workshop 2013).
1.3 Developing and Delivering Effective Rehabilitation

The calls for increased rehabilitation provision have coincided with a paradigm shift in the way that neuroscientists are now approaching theories of recovery and goals of rehabilitation. Advances in the fields of cognitive neuroscience and neuroimagining are providing new insight into how the damaged brain is able to process information and recover, stimulating the development of new recovery models aimed at providing the most effective environment for tailored interventions (Carey 2012). However, it has again been noted that although these advances are starting to show great promise, they must be delivered in a manner that will allow for effective translation of new evidence into clinical practice (Cheeran et al. 2009).

The above recommendations are all aimed at improving rehabilitation therapy, thereby reducing recovery time and increasing recovery rates, thus reducing prolonged care and associated socioeconomic costs. It is the goal of this thesis to follow the path of these recommendations and to further the research into the efficacy and delivery of post-stroke rehabilitation. This will be achieved firstly through studying key psychomotor components (specifically attention capacity) of upper limb disabilities and how these impact recovery and rehabilitation; and secondly, by translating the results of this research to a point of commercialisation by developing a cost-effective rehabilitation product targeting attention and upper limb function, which is capable of having a real world impact.

In the below sections we will look into the main disabilities accompanying stroke, the most prominent of which will be further discussed with regards to their underlying healthy state functions, neurophysiology mechanisms and neuroanatomy, before investigating how recovery and rehabilitation of these functions currently occurs.
1.4 Disability Following Stroke

The majority of people who suffer a stroke survive the initial event, but are left with neurological impairments to one or more common functions. These impairments can persist for days, months or years, and in some cases patients may require assistance for the rest of their lives (Kwakkel et al. 2003; Levin et al. 2009). Strokes cause a greater range of disabilities than any other medical condition, including deficits in; movement, vision, cognition, language, sensation and emotion, which makes stroke the most common cause of complex disability (Adamson et al. 2004). These disabilities have a huge impact on the patient’s life and their ability to take part in activities of daily living (ADLs) (i.e. feeding, dressing and personal hygiene, etc.) (Gresham et al. 1975; Bonita et al. 1997; Carod-Artal et al. 2000; Clarke et al. 2000), with 54% of patients reporting problems with the ability to perform household based tasks unassisted 6-months post stroke (Mayo et al. 2002). With one-third of individuals suffering from persistent and long-term disabilities (Mozaffarian et al. 2015), it is the consequences of these post-stroke conditions that has the greatest effect not only on the patients’ quality of life, but also on that of their family and/ or carers (White et al. 2006).

The type and severity of disabilities caused by strokes is determined by the size, and, most importantly, the location of the lesion (Langhorne et al. 2011). However, stroke is more heterogeneous than this in nature. Factors influencing function may be more complex, involving structural and functional integrity of viable brain networks (Stinear et al. 2007; He et al. 2007), as well as stroke type, time taken to begin therapy, motivation, environment and, most importantly in the context of this thesis, the ability to attend and learn (Kolb et al. 2011). All these factors may influence the severity and period of deficit an individual experiences. The mechanisms underlying recovery, which combine complex processes that are both spontaneous and learning-dependent, will be discussed in greater detail later in this chapter.
1.5 Motor Deficits

By far the most commonly diagnosed deficits following stroke are that of motor functions, with 77% of patients exhibiting upper limb impairments and 72% lower limb (Lawrence et al. 2001). The strongest pronunciation of such deficits occur to the side contralateral to the lesioned hemisphere and can range from complete hemiplegia of both limbs, through varying degrees to hemiparesis, to only subtle deficits in motor control of distal hand and finger portions. The high proportion of patients suffering from upper limb deficits and the importance of this function to patients ADLs, make them a key, although often overlooked, rehabilitation target (Langhorne et al. 2011; NICE Stroke rehabilitation: costing report 2013; National Clinical Guideline for Stroke 2012).

Motor deficits are primarily the result of damage to the brain’s motor system, responsible for the initiation and coordination of movements. This system is well defined and is composed of a number of key structures including; the primary motor cortex (M1), dorsal premotor area (dPM), supplementary motor area (SMA), pre-supplementary motor area (pre-SMA), primary somatosensory cortex (S1), prefrontal cortex, basal ganglia, and cerebellum (Scott 2004), with lesions to any of these areas able to disrupt normal motor function. The connections of this system are organised as a network of cortical and subcortical loops focused around M1, which, in turn, are responsible for the primary output of command signals to the spinal cord via corticospinal tract fibres, influencing musculoskeletal mechanics and generating motor behaviours (Scott 2004; Lemon & Griffiths 2005) (Figure 1).

It is the roles of the SMA, pre-SMA and the premotor area, shown to be activated when subjects plan movement (Hoshi & Tanji 2004), as well as the critical involvement of the parietal cortex, prefrontal cortex (Albert et al. 2009; Meehan et al. 2011) and the cerebellum (Ivry & Baldo 1992; Thach 1998; Spencer et al. 2005; Albert et al. 2009), all known to be integral to cognitive functions linked to motor learning and motor control, that remain relatively unexplored regarding their influence on motor recovery post stroke. Exploring the neuroanatomical and functional links between motor functions and cognitive deficits post stroke will remain the focus of this thesis.
Cognition refers to a set of mental abilities responsible for processing information. Cognition is not a single function, but made up of multiple components predominantly reflected in memory, and attention and executive functions, each playing significant roles in behavioural control and ADL (Oliveira et al. 2014; Gamito et al. 2015). It is thought that between 33-70% of survivors experience some form of sustained cognitive based deficit following a stroke (Nys et al. 2005; Wall et al. 2015). Restoration of cognitive function and the development of new therapies for this rank first in the list of top research priorities for improving quality of life after stroke (Pollock et al. 2014).
Out of these components, the ability of attention appears to be particularly affected post stroke (Hochstenbach et al. 1998; Ballard et al. 2003; Posner & Fan 2013), with reports of up to 92% of subacute patients experiencing transient attention deficits (Stapleton et al. 2001) and up to 51% showing persistent deficits into the chronic stage (Hyndman et al. 2008; Barker-Collo 2010), even in those patients exhibiting good clinical outcomes. The severity of deficits in attention post stroke have been shown to correlate with motor recovery rates (Robertson et al. 1997), the ability of motor control (Houwink et al. 2013), and performance of ADLs (Pohjasvaara et al. 2002; McDowd et al. 2003), suggesting that attentional capacity is a vital component of recovery of common functions, likely impacting upon a patient’s rehabilitation capabilities. Although clearly critical for motor recovery, relatively little is known about how a patient’s attentional capacity influences their motor function, motor-learning and recovery. This relationship may present a target for rehabilitation.

The exact frequency of attention deficits after stroke remains open to debate, with the true complexity of attention and its specific subcomponents and processes yet to be fully appreciated. Although more clinically obvious spatial attention deficits are well diagnose, such as ‘neglect’, characterised by an inability to attend to objects in the opposite side to the lesioned hemisphere despite normal vision and seen in 25-30% of patients (Malhotra et al. 2009; Corbetta & Shulman 2011), more subtle attention functions and deficits often remain undiagnosed and untreated (NICE Stroke rehabilitation: costing report 2013). This lack of appropriate diagnosis can not only prevent appropriate provision of cognitive rehabilitation, but also hinder research into how such attention deficits might impact other important functional recovery.

In the following sections, we will further discuss the functional breakdown of the attention system and the brain regions that have been implicated in such control.

1.7 The Attention System

Attention refers to the ability to effectively select and allocate appropriate resources to process pertinent information stimuli, whilst ignoring unnecessary stimuli, and is a key component of normal cognition and behaviour (Petersen & Posner 2012).
The neural anatomy of a general visual attention systems is believed to be well understood (de Schotten et al. 2011). A dorsal pathway, projecting from the occipital cortex through prefrontal to frontal areas including the intraparietal sulcus (IPS), superior parietal lobes, superior frontal cortex and frontal eye fields being responsible for choice of action related functions, and a right hemisphere lateralised ventral pathway projecting into temporal regions including the temporoparietal junction (TPJ), supramarginal gyrus, and middle and inferior prefrontal cortices being responsible for object recognition (Figure 2). These pathways work in a feed-forward and feed-back manner of information processing, with the dorsal system acting in a higher-order, top-down manner (goal-driven), and, through connecting with regions responsible for coordination of action controls, being critical for such functions as controlled hand movements (Crewther et al. 2012). Thus, it is possible that damage to this frontoparietal network due to stroke may severely impede normal upper limb function. On the other hand, the ventral system is thought to work in a bottom-up manner (driven by and reacting to incoming stimuli) (Corbetta & Shulman 2002). Although portrayed as separable entities, a high level of communication exists between these crudely described systems.

**Figure 2 The Visual Attention System** (Adapted from Central Processing Systems: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@6.17:93/Central-Processing)
The crudeness of the above definition does not do justice to the fact that attention is a complex cognitive structure, with multiple further subcomponents and systems. Indeed, it is important to note that multiple theories regarding the organisation of the frontoparietal network exist, with no current firm consensus on the function of subnetworks and systems within it (Erika-Florence et al. 2014). Although a unifying theory of such subsystems does not exist, for the remainder of this thesis we will focus on one increasingly popular framework developed by Michael Posner and Steven Petersen 1990, proposing three distinct attention functions that were understood to be related to three separable attention networks; 1) alerting network, 2) orienting network, and 3) executive control network (Posner & Petersen 1990).

Alerting refers to the functional ability of producing and maintaining optimal vigilance and performance during tasks, i.e. a state of alertness, and is described as a stimulus-driven bottom-up process. Orienting is focused on the ability to prioritise sensory input by selecting and re-selecting a location of focus, thus biasing sensorimotor processing and operating in a top-down manner. Finally, executive control functions as a decision making system, facilitating an ability to choose between competing responses, again in a top-down manner, in order to select an appropriate action (Posner 2011; Petersen & Posner 2012). Thus, this final component is vital for the initiation and modification of actions, as well as generating and implementing strategies necessary to accomplish complex goal-directed tasks. It is believed to operate via methods of conflict monitoring, adaptive behaviour, and conflict resolution/attention-control (i.e. resistance to distraction), responding to external stimuli whilst also drawing on memory stores of prior knowledge (Fitzpatrick & Baum 2012). Research studies have highlighted that up to 65% of acute stroke patients can suffer from differing forms of executive dysfunction (Zinn et al. 2007; Wolf et al. 2009), but diagnosis within a clinical setting is poor (Wall et al. 2015). Although executive deficits have been found to be correlated to poor functional outcomes, assessment and rehabilitation strategies remain undervalued (Leśniak et al. 2008; Krug & McCormack 2009).

While seeming to refer to quite distinct functions, the three sub networks of the Posner attention model all involve potentiation, or selection of processing streams, and so cannot be assumed a priori
to be mediated by separate neural mechanisms (Posner & Petersen 1990). Their functional and neuroanatomical independence or interdependence are, therefore, still an area of contention.

1.7.1 Attention Networks: Independent or Interdependent

The independence of alerting, orienting and conflict functions was originally suggested from a lack of correlations in performance between any pair of the three functional dimensions, when assessed by the Attention Network Test (ANT) in healthy adults (Fan et al. 2002). The ANT combines a cued reaction time task (Posner 1980) with the Eriksen flanker task (Eriksen & Eriksen 1974), into a single, well-controlled instrument, thereby allowing for independent and efficient measurements of the three attention networks. Furthermore, systematic dissociations between the three ANT components are recognized comparing different groups of subjects, e.g. divided by age (Mahoney et al. 2010), genetic polymorphisms (Fossella et al. 2002), or disease (Wang et al. 2005; Fernández et al. 2011). However, further analysis of behavioural data, especially in large populations, or by using more flexible forms of the ANT, reveals interactions and correlations between the three ANT measures (Callejas et al. 2004; Callejas et al. 2005; Macleod et al. 2010; McConnell & Shore 2011). This suggests that either the three ANT functions share some common neural machinery, or at least, that the three networks are heavily functionally interdependent. In support of a tripartite model of attention is a wealth of focal lesion and functional imaging studies.

1.7.2 Lesion Studies

Common experience tells us that clinical syndromes characterized by deficits corresponding to each of the three 'attention networks', tend to be caused by lesions to very separate structures. Impaired alertness is well-recognized with focal lesions to the ascending reticular activating system (Brazis & Masdeau 2007), while spatial neglect, in which patients fail to orient unilaterally, follows most notably from lesions to right posterior parietal or superior temporal gyrus (Mort et al. 2003; Karnath et al. 2011). Regarding executive function, deficits in conflict-resolution, as part of a more general dysexecutive syndrome, are characteristic of dorsolateral or medial prefrontal cortex damage (Vendrell et al. 1995; Stuss et al. 2001), although such bias in damaged frontal regions triggering
dysexecutive syndrome has been challenged, with suggestions that such impairments are more likely attributed to diffuse lesions throughout an executive network (Stuss & Levine 2002; Pessoa 2008). Supporting these main functional-anatomical pairings of the attentional components are animal lesion studies (Newman & McGaughy 2011), and transcranial magnetic stimulation "virtual lesion" studies in healthy humans (Taylor et al. 2007).

Mounting evidence suggests that these archetypal attentional-anatomical pairings significantly underestimate the neural substrates required for each function. More threateningly to the three-network hypothesis, impairments of each attention subtype have been associated with lesions to regions stereotypically assigned to other subtypes. For example, impaired alertness is recognized with lesions to right frontal (Posner & Petersen 1990); parietal (Malhotra et al. 2009; Bays et al. 2010), and temporal lobes (Samuelsson et al. 1998); spatial neglect is recognized with lesions to midbrain, thalamus (Watson et al. 1974; Watson et al. 1981), frontal regions, basal ganglia (Watson et al. 1973; Damasio et al. 1980), and left parietal lobe (Du et al. 2012); while conflict processing can be influenced by lesions to posterior parietal cortex (Pujol et al. 2001; E. J. Coulthard et al. 2008), basal ganglia (Aron et al. 2003) and cerebellum (Schweizer et al. 2007).

Consequently, distinct attentional functions may in fact depend upon closely intertwined, or even the same, neural networks, distributed over wide brain areas (Corbetta & Shulman 2011). Yet, drawing this conclusion from comparisons between studies, that frequently use different behavioural paradigms in different types of patients, is perhaps premature. In order to appraise the relative contribution made by each candidate region to each type of attention, then ideally, 1) a homogeneous group of patients with multiple lesion locations should be tested with the same paradigm; 2) for each patient, different types of attention need to be assessed, with a tool – such as the ANT – that controls for non-attentional confounds; and 3) associations of lesion location with function should be made at the voxel-level, rather than arbitrarily and grossly dividing the brain along conventional boundaries.
1.7.3 Functional Imaging Studies

The second type of evidence supporting anatomically-separable attention networks, comes from functional imaging. Studies using the ANT, or equivalent paradigms, have asked ‘which anatomical areas are activated differentially, or in common, comparing these three types of attention?’. The results are reassuringly close to the most robust neurological associations described earlier, and mostly support a model of spatially-separate attentional networks: namely, alerting activates bilateral thalamus; orienting activates right parietal; and conflict activates dorsolateral and medial frontal/prefrontal regions (Casey et al. 2000; Coull et al. 2004; Botvinick et al. 2004; Fan et al. 2005). With extensive connections to orbitofrontal, parietal and prefrontal cortices, in addition to motor and limbic structures, the suggested localisation of the executive conflict system within dorsolateral and medial frontal regions fits well with an ability of this attention network to perform numerous roles, such as influencing cognitive control of motor function (Ridderinkhof et al. 2004; Rushworth et al. 2004).

In addition to this though, and in a similar vein to the lesion literature, functional imaging has identified extra regions that are recruited with each attention subtype. For example, right temporo-parietal junction, and left cerebral hemisphere with alerting; left parietal cortex with orienting; and parietal, sensory cortices, and thalamus, with conflict (Coull et al. 2001; Thienel et al. 2009; Kim et al. 2010; Clemens et al. 2011). Such studies have advantages over lesion studies in testing for regional associations over the entire brain for a given task; and, for functional magnetic resonance imagine (fMRI), in enabling a spatially-precise functional fractionation of regions.

However, the inferential power of functional imaging is ultimately limited by the fact that it measures correlations and is prone to false-positives (e.g. due to confounds) and false-negatives (e.g. due to control sensorimotor activations masking activations of interest). For instance, the widely-reported activation of anterior cingulate cortex (ACC) with conflict may in fact reflect ‘time on task’ (Grinband et al. 2011), or an uncertainty estimate (Mansouri et al. 2009); which may explain why there is a lack of corroborative lesion evidence to support this association (Nachev 2011).
1.8 Recovery of Function Following Stroke

The term ‘recovery’ following stroke is used both on a neurophysiological level, when looking at the restoration of damaged brain systems, as well as on a behavioural level, in describing clinical improvements in patient functions (Levin et al. 2009). It is the clinical speciality of rehabilitation, specifically ‘neurorehabilitation’, which aims to draw on advances in the understanding of the mechanisms underlying recovery in order to deliver appropriate therapy able to maximise restoration of function (Selzer et al. 2014). When assessing outcomes after stroke, therapists not only assess the explicit functional disabilities, but also how these relate to limitations in a patient’s performance of core tasks that require these functions, such as grasping, and ultimately to ADL that are required for independent living. These are the true disabilities that the patient and their carers can relate to. Although the links between neural recovery and functional behaviour are well studied and will be discussed throughout this thesis, links between neural and behavioural recovery and ADL remain poor (Baum 2011).

Up to a third of people who survive a stroke show a natural ability of motor recovery (Kwakkel et al. 2002). Although greater initial impairment has been shown to correlate with less subsequent recovery of function (Kwakkel & Kollen 2007; Chen & Weinstein 2009), few factors are able to predict individual recovery rates, with patients of similar baseline impairment able to express very different recovery trajectories (Stinear & Byblow 2012). However, Krakaur and colleagues have suggested that spontaneous biological recovery (SBR) in the majority of patients does in fact follow a proportional recovery rule (Prabhakaran et al. 2008). The proportional recovery rule states that, at 3 months, patients should get approximately 70% of their maximum potential recovery back, and has been validated in a further two clinical trials (Zarahn et al. 2011; Winters et al. 2015). Interestingly, patients presenting with severe weakness fail to show this proportional recovery, i.e. some patients with severe hemiparesis recover proportionally as with others, but some are ‘non-recoverers’. In contrast, patients with mild-to-moderate hemiparesis always recover to nearly the same degree. This rule highlights that current rehabilitation programmes in the first 3 months might have little effect on these mild-to-moderate patients, but also shows that there is something inherently different between
severe patients who do and do not recover (Krakauer & Marshall 2015). These observations imply that an inherent mechanism for neuronal recovery exists, but that the substrates of such recovery differ within individual patients.

The most prominent concept aimed at explaining natural recovery is the phenomenon of neuroplasticity, that is, the brain's natural ability to reorganise its neurons and connections following focal damage (Wieloch & Nikolich 2006; Nudo 2011). The process of recovery is undoubtedly complex, occurring through a combination of spontaneous and learning-dependent processes (Sathian et al. 2011). Understanding the factors influencing such processes remains an important part of clinical recovery research, with potential to eventually manipulate such factors in order to improve efficiency of rehabilitation.

In the following section we will look further into the mechanisms of neuroplasticity and its substrates, specifically focusing on motor recovery and the influence of attention as a leading substrate with influences on the learning-dependent processes.

1.8.1 Learning-Dependent Neuroplasticity

Neuroplasticity is defined as ‘the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganising its structure, function and connections’ (Cramer et al. 2011). The healthy human brain has a lifelong ability for neural plastic change, enhanced through learning and new experiences (Bruel-Jungerman et al. 2007; Nudo 2007; Kolb 2010). The maintenance of this ability post stroke is the driving force behind recovery, although mechanisms between a healthy and damaged brain, and the ability between learning and re-learning skills, may differ (Matthews et al. 2004; Kolb 2010). An original view that an early critical time window for neuroplasticity existed in the post stroke brain (Langhorne et al. 2011) has now been superseded by speculation that this time window can remain open for an undefined period, offering potential for rehabilitation for patients even into the chronic stages of recovery (Carey 2012).
The reorganisation processes fundamental to neuroplasticity occur on both micro and larger scale connectivity levels and are discussed in detail through the remainder of this section. It must be born in mind that changes in the brain’s connectivity during recovery can be adaptive, i.e. result in improved function (Cramer et al. 2011), but in some cases may also be maladaptive, i.e. result in increased injury or further functional loss, or compensatory, i.e. result in recruitment of areas not previously specialised in the function at hand and which are suboptimal for a patient’s recovery (Nudo 2007; Levin et al. 2009). Although ‘suboptimal’, it must be bore in mind that this mechanism of recovery and the level achieved through it might still be the best option available for some patients.

The microscale events taking place after neuronal injury have been studied in vitro and in vivo using animal models. They can be divided into three levels contributing to the phenomenon of plasticity. On a molecular level, post stroke motor plasticity has been shown to be dependent on the availability of specific neuromodulators (Conner et al. 2005; Gu et al. 2010), the up/downregulation of their receptors (Myers et al. 2000; Redecker et al. 2000; Nudo 2007), and the synthesis of specific growth related proteins (Luft et al. 2004; Stowe et al. 2007).

At a synaptic level, plasticity is explained through increases in efficacy of communication from persistent stimulation of the postsynaptic cell by its presynaptic partner. Often summarised with the phrase ‘cells that fire together, wire together’, this theory highlights that strengthening of synaptic connections between neurons occurs due to simultaneous activation of neuron pairs, leading to learning of synaptic activity - termed ‘Hebbian learning’ (Cooper 2005). Spontaneous synaptogenesis and long-lasting alterations of synaptic efficacy, such as long-term potentiation (LTP) or long-term depression (LTD), can be seen following stroke and facilitated by both use-dependent and learning paradigms (differentiated below) (Hess & Donoghue 1994; Monfils & Teskey 2004; Teskey et al. 2007; Xu et al. 2009; Francis & Song 2011). These studies suggest that motor learning and formation of memory are associated with rapid but lasting synaptic reorganization following damage, facilitated via the growing/re-growing and adaptive nature of dendrites spines (Sala et al. 2008).
Finally, on a neuronal level, studies have shown dendritic growth, expansion of motor maps and the development of potential motor engrams in areas directly related to task learning (Nudo, Wise, et al. 1996; Nudo & Milliken 1996; Frost et al. 2003; Conner et al. 2005; Dancause et al. 2006). There is growing evidence from animal and human studies for such neural plastic changes associated with recovery after stroke (Nudo 2011). Experience is an important ingredient in these changes, with post-injury behaviour critical in reassembly of adaptive modules (Nudo 2007). Through animal models, Randolph Nudo and his group pioneered work into deciphering the critical behavioural components of plasticity stimulation. Using tasks capable of separating repetitive performance of an action from more difficult skill acquisition based training, they showed that basic repetition movements did not stimulate changes in movement representations mapped in the brain. In order to stimulate such plasticity, and map expansion, the tasks needed to involve the increased difficulty of skills acquisition. Such skilled training resulted in persistent changes and was capable of showing further growth, correlated to functional improvements with increased dose. The expansion of motor engrams was localised in the primary motor cortex (M1), suggesting a role for this region in higher level motor skill memory retention. Interestingly, these studies also showed an actual shrinking of motor representations of the hand area of the brain of the primates that did not receive any rehabilitation at all (Nudo, Milliken, et al. 1996), suggesting a complete lack of activity may result in a further deterioration of function. This is important in the context of human recovery with many stroke patients shown to suffer from apathy (Caeiro et al. 2012) and where minimal stimulation to perform activities unsupervised either at hospital or at home is provided (Shaughnessy et al. 2006).

This work suggests that the driving force behind neural plasticity is learning-dependent training, involving new skill acquisition, and not simply random use-dependent activity (Plautz et al. 2000; Walker-Batson et al. 2004). Thus, a distinct variation has been made between two different behavioural models capable of triggering plastic brain changes; ‘use/ experience-dependent’ plasticity, refers to evidence of reorganization of motor-cortex regions by frequent exposer to a simple motor task (Nudo, Milliken, et al. 1996; Classen et al. 1998); ‘learning-dependent’ plasticity, on the other hand, involves practice, but with the addition of monitored improvements in a certain skill,
requiring complex task-specific training (Plautz et al. 2000; Carey 2012). As discussed, the ability to complete complex tasks is reliant on attentional executive functions.

The extent to which these two different types of plasticity are capable of rewiring the human brain after damage, and thus their respective efficiency in aiding post-stroke rehabilitation, is still a point of contention. Although seemingly sufficient to stimulate behavioural change in healthy subjects, evidence from visual and sensory trials shows that use-dependent interactions, through exposure to simple stimuli, are insufficient to trigger plastic changes in the unhealthy post-stroke brain (Zihl 1981; Carey et al. 1993; Carey 2012). Thus, it seems that learning-dependent based plasticity, is needed to stimulate efficient re-learning, and strong associations have been observed between motor learning and neural plasticity in human studies (Hallett 2001; Dimyan & Cohen 2011; Dayan & Cohen 2011). Learning-dependent plasticity has also been shown to trigger changes in additional brain areas to the motor cortices in humans, including those implicated in attention-gated learning (Zhang & Kourtzi 2010), again highlighting a strong link between attention and motor functional requirements during the learning process.

The learning-dependent model forms the basis for training led rehabilitation interventions following stroke, some of which show strong evidence of neural plastic stimulation and correlation to improved motor recovery (Hodics et al. 2006; Richards et al. 2008).

1.8.2 Brain Networks and Post-Stroke Reorganisation

When understanding neuroplasticity following stroke, as well as describing molecular and cellular changes, it is most important to discuss the reorganisation and rerouting of intra/interhemispheric cortical connectivity of both the perilesional cortex and larger scale brain networks. The brain’s functional capacity is understood to be mediated by multiple systems of such connected networks, the sum of whose components as a whole are responsible for information processing and control of functionalities (Sporns et al. 2005; Biswal et al. 2010). This brain network model was first put together by Mesulam, who, in happenstance with the topic of this thesis, described distributed large-
scale neurocognitive networks responsible for attention, spatial neglect and memory processes (Mesulam 1981; Mesulam 1990), the complexity of which has been alluded to earlier in this chapter.

The long ranging connectivity of regions into networks explains the phenomenon of diaschisis, whereby loss is seen in functions that are not associated with the region damaged by the stroke (Nomura et al. 2010). This phenomenon is important when considering the impact of strokes as many functions may be impaired by just one lesion. Although in the context of diaschisis such complex and integral connectivity might be viewed as negative, on the other hand, connectivity of networks and the ability to rearrange such connections allows injured brain regions to recruit other areas in order to restore functional capacities. Such reorganisation can occur both within the surrounding perilesional/ipsilesional cortical areas, as well as across and between remote contralesional regions. A network perspective suggests that the physiological and functional effects of stroke would best be assessed not simply at the site of the lesion, but through the inter-regional dependencies across an entire functionally connected network (Honey & Sporns 2008; Van Dijk et al. 2010).

One methodology that can be used to explain the concept of brain network connectivity and the importance of focal lesions caused by stroke is that of ‘graph theory’. Graph theory utilises the idea that the brain can be divided into a number of ‘nodes’ (denoting neural elements varying in size from single neurons to whole brain regions), connected to one another by a series of ‘edges’ (representing physical connections ranging from a synaptic level to long axonal projections) (Bullmore & Sporns 2009). The length of the physical connections between nodes is thought to ultimately correspond to the efficiency of data transfer within a network and can be used to discriminate between inter-hemispheric, intra-hemispheric and ‘small world topology’ networks, each critical for normal function (Sporns et al. 2000). The shorter the length of these connections the more optimised and specialised the network will be for a specific function (Laughlin & Sejnowski 2003). The importance of certain nodes may also be relevant with regards to the level of their ‘centrality’ within a network. The centrality of a node may be determined by how many of the shortest paths between all other node pairs in the network pass through it (Bullmore & Sporns 2009). Nodes with high centrality, termed ‘hubs’, may be critical in terms of efficient connectivity and communication within the network.
(Klyachko & Stevens 2003; Crofts & Higham 2009). Should a highly centralised node be damaged due to a stroke it could have increased consequences with regards to functional output. Thus, the process of effective neural reorganisation following stroke may hinge on the ability to recreate the most efficient/shortest connectivity pathway to reform a functional network.

Changes to network connectivity both after cortical and sub-cortical stroke are starting to be well documented. Animal and human studies, utilising both imaging and electrophysiological connectivity methods, have shown significant changes following stroke to intra- and interhemispheric interactions between cortical motor areas (primary, premotor and supplementary), subcortical areas (basal ganglia, corticospinal system and cerebellum), and components of sensory systems (e.g. primary somatosensory cortex) (Dijkhuizen et al. 2001; Emerick et al. 2003; Dancause 2006; Ward et al. 2006; Calautti et al. 2007; Grefkes et al. 2008; Wang et al. 2010), which are all required for movement execution and motor learning. The ability to track the changes in network connectivity and correlate the importance of specific networks for learning-dependent recovery following stroke may prove significant in the development of future rehabilitation methods, assuming that methodologies can be harnessed in order to help predict learning capacity.

1.8.3 Ipsilesional Network Reorganisation

The recruitment of local perilesional tissue early after stroke is important for early functional recovery, with this area altered in the penumbra of the lesioned sight, but not permanently damaged due to vascular reperfusion (Kleiser et al. 2005). Again, both animal and human studies have shown evidence of, post injury to primary motor areas, recruitment and activation of adjacent portions of motor cortical areas that were previously not active for specific hand functions prior to the injury, and that the sustained activation of these is required for good recovery (Liu & Rouiller 1999; Kleiser et al. 2005). The role of such local ipsilesional transfer has been confirmed as playing a critical role in human functional recovery with further functional imaging results showing that well-recovered stroke patients exhibit increased activation of more dorsal motor locations even at long term follow up (Jaillard et al. 2005; Gerloff et al. 2006). On top of these imaging based studies, other evidence on the reliance of newly recruited areas comes from transcranial magnetic stimulation (TMS) methods used
to disrupt their activity, resulting in impaired ability of the recently recovered limb (Feydy 2002; Fridman et al. 2004).

In keeping with these observations on the importance of the ipsilesional hemisphere in recovery, fMRI performed in the hyper acute phases of stroke (2 days) revealed activity in more remote regions of the ipsilesional hemisphere, postcentral and posterior cingulate gyri, correlated with motor recovery at 3 months (Marshall et al. 2009), and that restoration of hand function at the same time period was associated with highly lateralised and progressive activation of the ipsilesional sensorimotor cortex (Askim et al. 2009). Using a method of structural equation modelling to assess network connectivity, Sharma et al. further showed that ipsilesional connection strength, between nodes of the cortical motor network, correlated with motor outcome (Sharma et al. 2009). This study also reported abnormally enhanced connectivity between prefrontal cortical areas and the premotor cortex, during motor imagery, suggesting that altered organization of connectivity with and between motor and prefrontal areas may reflect the role of the prefrontal cortex in higher order planning of movement (Sharma et al. 2009), providing a link between these attentional control regions and early recovery adaptations.

1.8.4 Corticospinal Tract Integrity

The integrity of corticospinal tract fibres, as determined by diffusion tensor imaging (DTI), in both the ipsilesional and contralesional hemispheres following stroke has been shown to be correlated with both effective reorganisation of network connectivity (Ward et al. 2006; Schaechter et al. 2008; Swayne et al. 2008) and recovery of motor skills (Schaechter et al. 2009). Damage to the track most often occurs within the posterior limb of the internal capsule, correlating with gross atrophy of the cerebral penduncles (Lindenberg et al. 2010), and impacting upon movement-related motor cortex activation (Stinear et al. 2007). Hence the extent of a patient’s outcome is highly dependent on the baseline integrity of these descending motor fibres (Stinear et al. 2007). In short, the extent of the initial damage to the corticospinal tract is correlated to the severity of the motor impairment, with greater damage and severity leading to poorer outcomes.
In a small series of case studies, Newton et al. 2006 found that inferred corticospinal tract disconnections could explain hand-grip performance, as assessed with functional MRI, in the ipsilesional motor system, confirming that selective disruption of motor corticofugal fibres influences functional reorganization and outcome in individual patients (Newton et al. 2006). The interruption to the integrity of the tract can contribute to dysfunction of motor cortical connectivity, specifically damage was negatively correlated with interhemispheric connectivity between the left and right central sulci (Alex R Carter et al. 2012).

The tract has been shown to split into ventral and dorsal portions in the pons, with patients with poor recovery showing damaged to both, while those with intact dorsal projections showing good recovery (Lindenberg et al. 2010). However, recovery also relied on the status of the contralesional tract; with patients needing elevated fractional anisotropy in both hemispheres to achieve better motor skill scores (Schaechter et al. 2009). Thus, assessment of the integrity of the cortical spinal tract presents a potential target for use in recovery prediction, and therapeutic profiling, of patients undergoing rehabilitation (Lindenberg et al. 2012). The findings relating to the significance of the bilateral integrity of the corticospinal tracts fit well with evidence from functional imaging studies highlighting the required action of both hemispheres for favourable recovery.

1.8.5 Interhemispheric Network Reorganisation

It is now well established that large-scale changes between the ipsilesional and contralesional cortex, and subcortical structures, occur following stroke, with better recovery of motor function in patients highly correlated to a progressive restoration of the interhemispheric balance and normal activation of brain networks (Nhan et al. 2004; Askim et al. 2009; Rehme & Grefkes 2013), i.e. reduced contralesional and greater ipsilesional involvement (Calautti & Baron 2003).

In the acute stage, enhanced activity is typically seen in motor related domains in the contralesional hemisphere (Ward et al. 2003; Rehme et al. 2011; Gerloff et al. 2006). Significant increases in the activation of the contralesional motor cortex area have been shown in stroke patients during paretic arm movement (Zemke et al. 2003), and in response to motor skill learning (Schaechter & Perdue 2008). TMS studies again compliment these results, showing early shifts of increased activation to
Chapter One: Introduction

Contralateral hemisphere domains, with subsequent decreased excitability of these contralateral domains correlating to better recovery (Bütefisch et al. 2003; Bütefisch et al. 2006). Originally believed to be part of a vicarious compensatory mechanism, it is now suggested that this initial overactivation of certain contralateral regions may simply be an epiphenomenon due to the disruption of the natural balance of inhibition between interhemispheric regions, and in fact be detrimental to movement control (Murase et al. 2004; Hummel et al. 2009). For example, the degree to which this overactivation occurs correlates with long term motor outcomes of patients (Ward et al. 2003), and decreases in activation occur as patients show recovery over time (Ward et al. 2003; N. S. Ward et al. 2003; Marshall et al. 2009). It has also been observed that an inhibitory influence from the contralateral to the ipsilesional motor cortex correlates with the degree of movement impairment in the affected hand (Grefkes et al. 2008). This same study, using a measure of effective connectivity, also highlighted a significant reduction in the coupling between the ipsilesional supplementary motor area (SMA) and the contralateral primary motor cortex (M1), which underlined hand motor disability (Grefkes et al. 2008).

Whether such changes in intercortical connectivity following stroke are indeed adaptive or maladaptive in the optimisation of networks remains an area of great debate. There is evidence to indicate that these early imbalances in the cortical equilibrium may actually represent an early period of an adaptive recovery mechanism, with early bilateral activation being present in patients showing good recovery of hand function (Bütefisch et al. 2005). Such early bilateral activation patterns, involving premotor cortical areas, are suggested to be similar to those required for relearning of functions, and so may be critical for plastic reorganisation learning processes (Marshall et al. 2009; Bütefisch et al. 2005).

Studies assessing the functional connectivity of the motor networks in post stroke populations, such as those using resting-state fMRI techniques (rs-fMRI), have detected changes in connectivity patterns for specific networks following ischemic damage (Carter et al. 2010; Grefkes & Fink 2011; Westlye et al. 2011; Rehme & Grefkes 2013). A set of studies by van Meer et al. 2010 revealed considerable loss of functional connectivity between interhemispheric sensorimotor cortex regions, which were
correlated to sensorimotor functional deficits, within the first few days following induced stroke in rats (van Meer, van der Marel, Wang, et al. 2010). Interestingly this study showed that intrahemispheric connectivity, even in preserved areas of the ipsilesional hemisphere, was not affected or correlated to functional output (van Meer, van der Marel, Wang, et al. 2010; van Meer, van der Marel, Otte, et al. 2010). This suggests a crucial role for interhemispheric connectivity in functional motor recovery. These results have recently been paralleled in rs-fMRI studies in human stroke in relation to both attention and motor networks, where disruption of interhemispheric, but not intrahemispheric, connectivity was shown to be significantly correlated with upper extremity impairment and visual attention deficits (He et al. 2007; Carter et al. 2010). Importantly, restoration of interhemispheric connectivity was correlated to improved functional output (Park et al. 2011), suggesting that within the subacute stage it is a better predictor of behaviour than intrahemispheric connectivity. The restoration of interhemispheric connectivity balance within motor networks was particularly seen between the M1 regions. However, reorganisation within the ipsilesional side showed strong excitatory interactions between frontoparietal areas and M1, suggesting increased top-down control over primary motor areas post stroke (Rehme & Grefkes 2013).

These results highlight a functional connection between attention based networks and their increased activity in motor control in the lesioned brain, presumably showing upregulation of learning-dependent processes in recovery. Indeed, in healthy subjects, a few studies have shown changes in frontoparietal connectivity following learning (Coynel et al. 2010; Lin et al. 2013), with data suggesting early phase learning is associated with increased connectivity within frontal regions, which is reduced in later phases once the motor task is learned (Sun et al. 2007). Such increased connectivity of executive control areas was also shown to precede strengthening of connectivity between motor regions (e.g. cerebellum and M1) (Steele & Penhune 2010; Lin et al. 2013).

1.8.6 Attention-Dependent Neuroplasticity

Current evidence clearly indicates that neural plastic reorganisation in both the healthy and damaged brain is a learning-dependent process, requiring repetitive skill use with the addition of complex task-
oriented and task-specific training. In a parallel framework, research into the attention system and its subnetworks/components clearly indicates this function’s requirement in the ability to complete such complex tasks through activation and selection of appropriate actions. It may therefore be assumed that attention functions are a critical component of neuroplasticity and, by association, motor-learning and re-learning post stroke. In fact, one model of motor-learning provides a strong grounding for the importance of attention at the heart of skill acquisition, dividing the process of learning into; an initial cognitive stage, where the individual uses executive function components to attend to and understand the task; an associative stage, where attention is trained and focused on improved motor performance; and an autonomous stage, where the skill is learned and archived in the library of memory (Wulf et al. 2010; Fitzpatrick & Baum 2012).

Although work directly linking attention to motor-learning remains scarce compared to studies looking into the influences of pure motor repetition, associations have been shown through the different levels of the connectivity scale. On a neural level, attention selectively enhances and synchronises single-cell responses during relevant stimuli processing, and suppress them during the presence of distracting stimuli (Burton & Sinclair 2000; Mountcastle et al. 1981; Wannig et al. 2011). On a network scale, fMRI studies have shown activation of areas traditionally associated with working memory (WM), another critical substrate of learning, during attention loaded tasks (Owen et al. 2005), also highlighting anatomical commonality within both the dorsal and ventral attention systems of these separable cognitive functions. It has been argued that WM, responsible for maintaining and processing information, is dependent on the preceding selective actions of attention (Buehner et al. 2005; Crewther et al. 2012). As such, the interplay between WM and attention is considered to be fundamental to the most basic learning and neural plastic processes (Owen et al. 2005).

In terms of connectivity changes, mechanisms of selective attention have been shown to be a potent modulator of cortical plasticity (Kamke et al. 2012), with direct focus of a subject’s attention on their hand being required to stimulate plasticity in associated areas of the motor cortex (Stefan et al. 2004). Within attentional regions, manipulation of network patterns have been shown to differ with regards to the time taken to stimulate change compared with motor and sensory regions. Specifically,
prefrontal attention areas have shown fast, but only temporary (days) changes, with areas more central to the motor system showing larger and more persistent changes over time (Comeau et al. 2010; Kolb 2010). Such functional imaging studies have also correlated changes within attention areas, stimulated via attention-based rehabilitation protocols, to improved motor outcomes (Hodics et al. 2006; Richards et al. 2008; Stinear et al. 2008). Understanding such neurophysiological differences in plasticity in relation to motor and attention functions has important implications when considering the design of post stroke interventions for both, or when looking at the potential influence of attentional impairment on motor recovery. For example, plasticity of prefrontal regions may be targeted early in recovery using attention training in order to then help prime the brain to further neuroplasticity within motor regions.

Finally, with specificity to motor-learning and functional connectivity, it has been shown that task modification of resting-state functional connectivity in healthy subjects is dependent upon whether the preceding task involves attention-dependent learning (Albert et al. 2009; Meehan et al. 2011), suggesting that changes in rs-fMRI activity due to attention-dependent learning may be a signature of neural plasticity.

With regards to brain damaged subjects, damage has been shown to significantly affect attention networks and reduce the process of learning (Kleim & Jones 2008). With attention skill levels being a predictor of outcomes after stroke, attention capacity, with its ability to mediate learning and neural reorganisation, is likely to form a critical part of stroke rehabilitation (Shaughnessy & Resnick 2009). Thus, an individual’s ability to recover motor function may be highly related to their attention capacity, making it a target for rehabilitation and longitudinal assessment to aid the prediction of recovery.

1.9 Rehabilitation

Evidence from the preceding sections has shown a need for adopting a restorative model of rehabilitation in stroke, bringing in the principles of adaptive learning or relearning, with a particular focus on skill based training (Warraich & Kleim 2010). Up until recently, the focus of post stroke
rehabilitation has been on compensatory strategies, such as using the non-affected arm or using supportive equipment, i.e. working around, and not with, the functional losses of the patient. Although such compensatory strategies may increase the independence of a patient in the short term, they are suboptimal for physiological recovery and have the potential to be mal-adaptive in the long term (Carey 2012). The future of rehabilitation lies in helping stroke survivors to relearn lost skills, to improve function and prevent further functional loss, and in doing so increase independence levels. However, the transfer of knowledge gained from neuroscience on the theories of adaptive learning and the factors underlying this have shown little success in translation into clinical rehabilitative practice (Cheeran et al. 2009).

The numerous components of learning-dependent plasticity are all emerging as potential targets for therapies aimed at increasing natural motor recovery after strokes. Although, in this thesis, our focus is on physical rehabilitation therapy, these components are also targets for pharmaceutical interventions (Scheidtmann et al. 2001; Gladstone et al. 2006; Papadopoulos et al. 2009; Chollet et al. 2011), or for more direct electrophysiological approaches such as the use of transcranial magnetic stimulation (TMS) (Dimyan and Cohen 2010; Grefkes et al. 2010), or Transcranial direct current stimulation (tDCS) (Hummel & Cohen 2005; Schlaug & Renga 2008; Polania et al. 2012), which in the future have potential to run as adjunctive therapies to standard rehabilitation.

1.9.1 Learning-Dependent Rehabilitation

In concordance with the theory of learning driven neuroplasticity being the basis of recovery, the most effective current interventions for restoring both motor function and cognitive function after stroke have been shown as repetitive, task-oriented and task-specific exercises (Langhorne et al. 2011; Veerbeek et al. 2014), with a greater amount and intensity of such therapy performed resulting in better outcomes (van der Lee et al. 2001; French et al. 2007; Lohse et al. 2014). The importance of training for motor recovery has now been shown for many years, with practices such as forced use of the affected upper limb, through constraint induced movement therapy with guided practice (Wolf et al. 2006; Boake et al. 2007a), or training within enriched environments, such as action observation training (Celnik et al. 2008) and motor imagery training (Page et al. 2007), showing strong
correlations with return of function. On top of this, rehabilitation practices must also draw on other factors advocated to facilitate recovery, such as patient motivation and attention driven active participation (Cramer et al. 2011). For example, without sufficient cognitive ability and volitional control of both finger and thumb extensions, patients are unable to achieve successful hand shaping and grasping of objects (Lang et al. 2009).

Neurophysiological and neuroimaging research into repetitive learning based training has confirmed the stimulation of underlying neuralplastic adaptations, with general findings showing treatment-associated increase in activation within the ipsilesional primary motor cortex, dorsal premotor cortex, and supplementary motor areas (Wittenberg et al. 2003; Hodics et al. 2006; Sawaki et al. 2008; Mintzopoulos et al. 2008; Boake et al. 2007b), persisting in the initial weeks following training, before decreasing in relation to functional gain. Consistent with these findings, intensive finger tracking training resulted in increased laterality in correlation with clinical improvements in control, reflecting the greater involvement of the ipsilesional hemisphere after training and following the theory of hemispheric equilibrium restoration and recovery (Carey et al. 2002a). Interestingly age does not seem to play a significant role with regards to the effectiveness of intensity therapy, with patients over 65 years of age benefiting as much as younger patients (Batzán et al. 2009), although notably with regard to the final study within this thesis, younger patients are shown to improve their grip strength more (Gosselin et al. 2008).

In specific relation to rehabilitation and motor recovery, a further differentiation must be made between the learning-dependent activity required for permanent motor learning, and the use-dependent activity associated with transient improvements in motor performance. As stated, the successful recovery of motor function after stroke is specifically facilitated by motor learning, and the reorganisation of large scale circuits within the motor system. Even small amounts of practice, 100 repetitions, have shown increases in motor performance correlated to increases in motor cortex representations. However, these observations are thought to be due to changes in synaptic efficiencies and strengthening of existing synapses (Hayashi et al. 2002). Longer term changes in the structural organisation of the nervous system require rehabilitation to be task-specific and intense, as well as
repetitive (the exact number of repetitions required is unknown, suggestions include 300-800 repetitions or up to 40 minutes of additional upper limb therapy per day) (van der Lee et al. 2001; Carey et al. 2002a; Boyd & Winstein 2006; Richards et al. 2008), preferably involving real world relevance and drawing on cognitive influences.

Although new learning/intensity based models are now being more widely adopted in clinical rehabilitation practice (National Clinical Guideline for Stroke 2012), most stroke patients still do not receive anywhere near as much physiotherapy as could be achieved (Bernhardt et al. 2007; NICE Stroke rehabilitation: costing report 2013), meaning their outcome will fall short of what is theoretically attainable.

1.9.2 Clinical Rehabilitation Practice

The goal of this thesis is to use the research undertaken into the influence of attentional control on motor function following stroke and translate it into a digital tool capable of being used for assessment and rehabilitation of function in a clinical practice setting. In order to appreciate how such a tool might be developed and where it may best fit within clinical practice, a general understanding of how rehabilitation is delivered must be provided.

The complex process of rehabilitation following stroke requires the combination of efforts from a multidisciplinary team, from the acute through to the chronic stage (Turner-Stokes 2008). The most effective stroke rehabilitation services are provided when delivered within one unit, allowing for the seamless transition of care between the stages of recovery (Petri 2010). The multidisciplinary team is made up of physicians, stroke specialist nurses, clinical psychologists, speech and language therapists, and, most importantly with relevance to motor and cognitive training, the closely linked work of both physio and occupational therapists. In patients suffering from arm and hand weakness, therapists aid patients in performing and repeating complex and skilled tasks that are needed to accomplish ADLs, combining both cognitive and movement aspects.
Within the UK, guidelines recommend that clinical stroke services be provided in a ‘hub and spoke model’ (National Clinical Guideline for Stroke 2012), where a few hospitals in a region are designated to provide the hyperacute care for all patients, before repatriating patients who require further care to secondary rehabilitation units. These Hyper Acute Stroke Units (HASU) tend to patients for up to 7 days, with rehabilitation units continuing care from 7 days onwards, until the patient reaches a sufficient level of independence to be discharge home. In general it is understood that once a patient is stabilised rehabilitation should begin as soon as possible after stroke, often within the first 24 to 72 hours (National Clinical Guideline for Stroke 2012), with animal studies showing that if intervention is delayed for several weeks, activation of neural plastic mechanisms, adaptive network reorganisation and recovery are severely reduced (Nilsson et al. 2012). However, the optimal time for commencement of rehabilitation remains uncertain in human studies, with recent evidence from the VECTORS (Dromerick et al. 2009) and AVERT (The Avert Trial Collaboration Group 2015) trials suggesting a negative impact on outcome of very early rehabilitation procedures. Although these studies suggest exercising caution with early onset and dose of therapy, each patient is unique and multiple factors should be taken into account by the therapy team when deciding upon commencement of appropriate therapy.

Once discharged, rehabilitation of patients should continue (Langhorne et al. 2011), either in a community or outpatient setting. It has been estimated that between 25-75% of stroke survivors require assistance in completing ADLs once at home (Kalra et al. 2004). A model of Early Supported Discharge (ESD), whereby specialist rehabilitation is provided by community therapist within the patient’s home (Langhorne et al. 2007), has shown success for select patients, resulting in significantly shorter hospital stays, increased patient satisfaction and mental health, and improved motor outcomes (Fisher et al. 2015)

Unfortunately, adherence to the above clinical guidelines for stroke rehabilitation, even within highly developed and established healthcare systems, is generally poor (NICE Stroke rehabilitation: costing report 2013). Within UK hospitals, 55% of stroke patients receive less than half the recommended 45mins of tailored physio-/ occupational therapy per day. A recent review also highlighted that during
inpatient rehabilitation, repetition of arm movements ranged between 23-32 repetitions (Hayward & Brauer 2015), falling well below the amounts required to demonstrate motor learning in humans (van der Lee et al. 2001; Carey et al. 2002a; Boyd & Winstein 2006), and below the average amount of repetitions shown to be possible by chronic stroke patients during intense training (322 repetitions) (Birkenmeier et al. 2010). Once discharged this trend continues, with only 55% of hospitals having community rehabilitation services, effecting predominantly rural and remote areas (Cadilhac et al. 2012). This suggests that patients are not receiving the specialised care that would maximise their recovery potential, making increased availability of care a priority for healthcare providers. Innovative digital technology based solutions aimed at complimenting traditional clinical therapy and compensating for the lack of provision have now become a key part of future planning in stroke rehabilitation.

1.9.3 Technologies for Rehabilitation

As discussed throughout this chapter, the major barrier for the implementation of rehabilitation services is a limitation of resources, specifically the low availability and high costs of trained therapists (Bernhardt et al. 2007). This has led to new guidelines encouraging the development and implementation of technology based interventions in rehabilitation care (National Clinical Guideline Centre 2013; Report of EPSRC Rehabilitation Scoping Workshop 2013). Technologies that allow for self-administration of exercises – provided they are accessible, affordable and motivating - promise to increase rehabilitation time; optimise patients’ functional recovery; and lead to cost-savings by reducing care costs (Turner-Stokes 2005). Ideally, when developing a tool suitable for rehabilitation, the ability for it to deliver its function across the whole spectrum of clinical rehabilitation stages, i.e. acute, subacute, chronic-community, is highly desirable and should be taken into design considerations. Such devices can allow for the seamless transition of training from a specialised hospital environment directly into the patient’s home.

Although a number of different types of technology-based solutions have been proposed and tested in the last decade, none have yet achieved the correct balance between functional effectiveness and feasibility of use, thereby preventing their wide adoption (Brochard et al. 2010). For example, robot-
assisted therapy is known to be safe with an ability to provide intense, highly repeatable, precise and quantifiable treatments (Fasoli et al. 2004; Takahashi et al. 2008; Staubli et al. 2009), and has shown itself to be at least as effective in improving outcomes in stroke patients as conventional intensity matched therapy (Lo et al. 2010). However, the high cost of commercially available rehabilitation robotics (~£10,000-£100,000+) and their complex nature, often needing further therapist and engineering supervision, make them inaccessible even in hospital environments, and certainly not suitable for autonomous or decentralised home use. Added to this, few robotic systems for upper limb training have focused on hand and finger grip functions due to the high degrees of freedom needed to initiate complex movements (Takahashi et al. 2008). This may be one reason why there is still a lack of evidence to show that gains from robotic upper limb training translate into any improvements in ADLs (Mehrholz et al. 2008). Added to this, studies assessing the efficacy of robotic rehabilitation are often poorly designed, not comparing robotic interventions directly to ‘standard’ care and resulting in small effect sizes (e.g. FM < 2) (Poli et al. 2013).

Whereas robotic-assisted devices are actuated systems, providing movement assistance in a similar manner as therapists, a second type of technology, passive sensor-based devices, have also been developed for rehabilitation purposes. These devices do not provide movement assistance, but are instead aimed at tracking movement and allowing for assessment and feedback of function to both the patient and the therapist. Such devices tend to be wearable in nature, but also include motion capture systems often taken from main stream commercial gaming systems. Sensor-based systems have yet to show conclusive proof about their effectiveness in comparison to conventional therapy (Saposnik & Levin 2011; Choi et al. 2014; Thomson et al. 2014), and although cheaper in nature than robotic systems, commercially available options still remain too expensive (~£800-£50,000). In a recent costing report a threshold of £683 per patient per year was set as a cost-effective cap on new therapy intervention methods within the NHS, setting a target for technology adoption.

One common feature between robotic-assisted and sensor-based systems is their use of ‘serious games’, provided by virtual reality gaming interfaces. Such games are used to increase both the quality and quantity of therapy by motivating patients through stimulating environments, and have
shown promising correlations between increased motivation and improvements in motor outcome measures (Turolla et al. 2007; Saposnik & Levin 2011; Turolla et al. 2013; Putrino 2014; Popović et al. 2014). The software behind the games can also be used to remotely assess performance and track therapy progress (telerehabilitation). Other than their use in increasing repetition of movements, the factors underlying such games and their ability to manipulate and increase learning-dependent plasticity remains relatively unexplored. Online adaptation of difficulty is one method used to keep a patient in an optimal state of motivation and learning, known as the ‘challenge point’. However, these methods have yet to take into account a patient’s cognitive state, e.g. a patient’s attention capacity. The use of serious games may allow for a bridge between the assessment of cognitive and motor tracking, which should be exploited in rehabilitation and is a key focus of this thesis, especially as technology-based cognitive assessment and rehabilitation post stroke remain severely underdeveloped (Wall et al. 2015).

Table 1 provides an overview of some of the most prominent commercially available upper limb technology-based rehabilitation products and how each compares with regards to key features needed for decentralised adoption and use, e.g. portable, bedside use, autonomous use, affordability etc. This general overview shows that as yet no single device encompasses all of these necessary features. When considering the translational nature of this thesis, inclusion of these features will remain the driving force behind the design of a clinically relevant product. In pursuit of this, there remains an ability to exploit new technologies, such as mobile technologies, leveraging the highly portable, intuitive and low cost features that such devices already possess.
Table 1: Commercially Available Upper Limb Rehabilitation Technologies

Examples of commercially available upper limb rehabilitation devices, comparing desirable features; Portable, Hospital Bedside, Home Use, Autonomous Rehab, and Cost threshold. The table highlights that no device currently fits all these criteria, suggesting the need for new design consideration to create a ‘Desirable Device’.

<table>
<thead>
<tr>
<th>Example Devices</th>
<th>Company Name</th>
<th>Devices Type</th>
<th>Portable</th>
<th>Hospital Bedside</th>
<th>Home Use</th>
<th>Autonomous Rehab</th>
<th>Below £683</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirable Device</td>
<td>AMES Device</td>
<td>AMES</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>E-LINK for Hand Therapy</td>
<td>Biometrics Ltd</td>
<td>Sensory</td>
<td>Red</td>
<td>Green</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>H200 Wireless Hand Rehabilitation System</td>
<td>Bioness</td>
<td>Robotic + Functional Electrical Stimulation (FES)</td>
<td>Red</td>
<td>Green</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Music Glove</td>
<td>Flint Rehabilitation</td>
<td>Sensory</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Gloreha Lite</td>
<td>Gloreha</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Armeo/ Manovo Spring</td>
<td>Hocoma</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Motion Capture Device</td>
<td>Rehab@Home</td>
<td>Sensory</td>
<td>Red</td>
<td>Green</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>RoboTherapist2D</td>
<td>Instead Technologies</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>InMotionHAND</td>
<td>Interactive Motion Technologies</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>I-TRAVLE</td>
<td>I-TRAVLE</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>BiMeo HOME Training</td>
<td>Kinestica</td>
<td>Sensory</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Hand Mentor</td>
<td>Kinetic Muscles</td>
<td>Robotic</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>Neuro Capture Software</td>
<td>NeuroAtHome</td>
<td>Sensory</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>SaeboReJoyce</td>
<td>Saebo</td>
<td>Assistive Hand Rehab</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td></td>
<td>PABLO® AND TYMO®</td>
<td>Tyromotion</td>
<td>Digital Hand/Arm control</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>
1.10 Hypothesis and Aims of Remaining Thesis Chapters

The growing global impact of stroke has necessitated a shift in strategy for the delivery of effective rehabilitation. This shift has included both an active drive to increase rehabilitation dose as well as a change in how motor rehabilitation is performed, basing new therapy models on learning-dependent techniques derived from neuroscience. It is evident that one of the critical components of learning and re-learning following stroke is attention. Although motor impairment and attention deficits are common in stroke, little is known about how a patient’s attentional capacity influences their motor function, motor-learning and recovery. This relationship may present a target for rehabilitation.

The hypothesis underlying this thesis is that attention-control (resistance to distraction) capacity is significantly effected following a stroke and that deficits in attention-control impact upon and correlate with a stroke patient’s motor deficits and motor-control function. Such deficits can and should be assessed in future clinical practice. The work will explore both the neuroanatomical and behavioural correlates of attention and motor control in acute stroke patients, resulting in the development of a novel behavioural assessment method and production of a digital device able to implement such assessments and autonomous training at the patient’s bedside.

In order to achieve this, each of the experiments presented in this thesis relies on the recruitment of groups of acute stroke patients with both diagnosed and undiagnosed upper limb motor deficits, but with no clinical diagnosis of cognitive impairments. Chapter two describes the main imaging methods employed for both structural and functional neuroanatomical analysis, discussing the benefits and limitations of lesion mapping and functional connectivity imaging approaches used throughout subsequent chapters.

In chapter three, the prevalence and types of attention deficits in an acute stroke population are surveyed using a single digital task (Attention Network Test) that controls for non-attentional confounds, with performance related to lesion anatomy on MRI using a voxel-lesion mapping approach.
In chapter four, the relationship between attention-control deficits and motor performance is investigated using a motor task manipulated via attentional load (a visuomotor tracking task controlled via a hand-grip interface), correlating performance to lesion location and disruption in attention versus motor functional connectivity networks.

In chapter five, we question whether network-specific changes in brain connectivity seen immediately after learning in healthy humans are also observed following exercise in motor stroke. Resting-state functional MRI was used to assess connectivity before, during and after performance of the visuomotor tracking task, comparing the changes in attentional and motor networks between healthy and post stroke subjects.

In chapter six, results from the previous experimental chapters are used to develop and test a practical device that allows for measurement and rehabilitation of stroke-related attention and motor deficits in combination. The feasibility of the device is tested in a clinical environment, assessing its accessibility compared with currently available mobile technology based rehabilitation tools.

Chapter 7, the Conclusions Chapter, contains a general discussion reviewing the experimental findings and how these fit into the current state of knowledge, including arguments concerning the importance of considering attentional dysfunction in motor rehabilitation practice. In addition, the limitations of the current work and possible future lines of investigation are also outlined, with a specific focus on the further development of the novel rehabilitation device.
CHAPTER TWO:
METHODS
2.1 Introduction

In this chapter, the imagining methods used to assess the brain lesion anatomy and functional network connectivity of stroke patients and healthy controls that are referred to in chapters three, four and five are described. There is currently no gold standard method for lesion mapping or assessment of network connectivity following stroke, thus the techniques used, and the limitations of each, need to be carefully considered. This chapter provides a general overview of the techniques used within this thesis, namely voxel-lesion symptom mapping (VLSM) and resting-state functional MRI (rs-fMRI), with further detail of exact scanning parameters and relevant behavioural correlation analysis provided within the following chapters.

The development of modern neuroimaging techniques has allowed the brain to be studied in vivo, with multiple techniques now available to study both structural and function aspects. Such non-invasive methods allow for both retrospective evaluations of lesion anatomy and real-time assessments of brain function, with relation to behavioural performance and/or recovery outcomes. In this thesis, we have used VLSM and rs-fMRI to advance our understanding of the healthy and lesioned brain characteristics associated with performance of attention-control visuomotor tasks, which have provided important insights into functionally dependent areas from a network perspective.

2.2 Lesion Imaging Analysis

2.2.1 Structural Imaging Classifications

Computer tomography (CT) and Magnetic Resonance Imaging (MRI) scanning have transformed the historical autopsy-based processes of correlating neurological deficits with brain lesions. With CT scans routinely used in acute stroke care, and MRI scans often performed in order to confirm a diagnosis of stroke, the majority of stroke patients are now having structural scans completed of their brain (National Clinical Guideline for Stroke 2012), generating large amounts of imaging data for analysis. Use of MRI sequences has become popular for lesion-deficit correlation studies, with T2-
weighted scans providing high resolution structural images (Figure 3 A), and with diffusion-weighted MR imaging (DWI) allowing for early differentiation between lesioned and healthy tissue (Figure 3 B) (Tong et al. 2014).

![Figure 3 Clinical MRI Scans](A - T2) ![Figure 3 Clinical MRI Scans](B - DWI)

**Figure 3 Clinical MRI Scans**

A – High resolution structural T2 scan  
B – Diffusion Weight Image highlighting the clear visibility of an acute stroke (white)

All patient structural scans used within the experiments conducted throughout this research were done using MRI sequencing. The majority of these were obtained from routinely performed clinical investigations, carried out using a Siemens 1.5T scanner within one week of stroke, with a small proportion of patients having higher resolutions MRI scans carried out on a 3T scanner and performed specifically for research purposes during functional imaging acquisition. These higher resolution scans are preferable to clinical MR sequences (Mort et al. 2003) and were used in the analysis of lesions for chapters four and five. Variation in the quality of images can complicate the process of analysing combined data. Although in practice these differences are often ignored (Kimberg et al. 2007), each of the experiments in this thesis used data gathered from a single scanner.
2.2.2 Lesion Delineation

Acute ischemic lesions were identified on the B1000 DWI and cross examined by an experienced neuroradiologist. DWI measures the random Brownian motion of water molecules within a single voxel of tissue, with cellular tissue exhibiting swelling showing lower diffusion coefficients, and clearly highlighting cerebral ischemia. Thus, DWI has become an integral part of the stroke diagnosis procedure, allowing for accurate acute lesion identification (Rordorf et al. 1998), and has been used previously for lesion plotting in stroke (Karnath et al. 2004). Prior to VLSM analysis, lesions were first classified and normalised across patients, bringing all lesions to a standard space and superimposing them onto a high resolution structural template. This is required in order to further superimpose voxels of interest onto anatomical and tractographic atlases (Behrens et al. 2003; Zhang et al. 2010).

Delineation of acute lesions was performed by a semi-automated, intensity-based technique using MATLAB (v7.10.0) (http://uk.mathworks.com/products/matlab/), producing lesion and lesion masked images. Identified lesions were first ‘seeded’, following which an algorithm (‘Lesion-Find’ - developed in-house by the Imperial College Cerebrovascular Research Unit) identified all adjacent voxels in 3D whose intensity lay above a set threshold. This intensity threshold could then be adjusted allowing for optimum capture of the lesion extent (Figure 4). In certain circumstances, for example where lesions involved areas of haemorrhage transformation or overran into areas of artefactual hyper-intensity, a manual delineation tool-set allowed for drawing or erasing of lesion parts. The manual tool also served to delineate acute lesions on T2 or fluid-attenuated inversion recovery (FLAIR) images for those patients that did not have DWI sequencing, or where these sequences were judged to indicate the lesion most accurately. The resultant lesion image was checked for good fit relative to the original image, by superimposing the lesion image within MRIcron (http://www.mccauslandcenter.sc.edu/micro/) by a separate neurologist.
2.2.3 Lesion Normalisation

Lesions were subsequently normalised to a canonical T2 template in Montreal Neurological Institute (MNI) space (voxel size 2 x 2 x 2mm) using SPM8 software (Wellcome Centre for Neuroimaging at UCL; http://www.fil.ion.ucl.ac.uk/spm; MATLAB (v 7.10.0)). The purpose of inter-subject spatial normalisation to a common template is to align the brains such that voxels match the same coordinates between subjects’. Prior to normalisation, the lesion, lesion mask and the source image (i.e. DWI) were co-registered to a high resolution reference image (corresponding patient T2). Manual reorientation of the patient’s reference T2, and all corresponding co-registered images, was then performed in order to improve matching to the T2 template. Finally, the patient’s T2 scan was normalised to the T2 template, while applying cost-function masking with a lesion mask (Brett et al. 2001). The resultant transformation parameters were applied to the co-registered lesion image, DWI.
and T2. The match between each patient’s normalised scans and the T2 template was carefully evaluated through visual inspection, with the quality of normalisation found to be satisfactory for each case.

2.2.4 Lesion-based Analysis

During typical lesion-based analysis patients are either grouped by lesion location or behavioural deficit. Lesion data is used to provide high-quality causal evidence that observed differences in behaviour are due to a specific damage to brain regions. This is in contrast to the correlative nature of functional imagine studies (Stinear & Ward 2013), discussed in detail later in this chapter.

Although traditional lesion methods have been important in isolating particular regions of interest (ROIs) the value of associating just one key anatomical locus with a complex neurological syndrome, such as attention deficits, is suboptimal from a network perspective. Information can be lost if lesioned ROIs contain multiple sub-regions, or by overlooking addition areas outside the ROI that may be crucial to the behaviour under investigation. On the other hand, even if damage to a certain area is correlated to a decrease in performance, it cannot always be assumed that this exact location is responsible for this function. For example, the lesioned region in question may be adjacent to functionally unrelated areas, but naturally confound their function, or may cause remote impairment within the functional network through diaschisis (Kimberg et al. 2007; Kimberg 2009). Thus, it is clear that although areas of deficits may be attributed to areas of common lesion overlap, traditional lesion based studies fail to capture a whole network perspective. Such limitations of lesion-deficit correlation approaches may be overcome by the development of heavy data-driven lesion mapping techniques, which use similar voxel based statistic approaches seen in functional imaging analysis. Such approaches allow for larger group comparison, the benefits of which are discussed in the following section.
2.2.5 Voxel-Lesion Symptom Mapping

VLSM is the lesion-mapping method used in this thesis, providing a voxel-by-voxel analysis of the relationship between lesion and behavioural data. VLSM does not require patients to be grouped by either lesion site or behavioural cut-off, but instead makes continuous use of both categories (Bates et al. 2003). Thus, VLSM is a power-intensive method (Kimberg 2007), requiring a large pool of patients for optimal analysis. The strengths of VLSM include: 1) the ability to select a relatively homogeneous patient population; 2) the ability to test patients with a relatively small lesion volume, so enhancing the spatial precision of results; 3) delineating all lesions with MRI, before spatially normalising across the group. Most importantly, unlike basic fMRI analysis, VLSM is not simply correlative to behavioural data, but acts as a causative analytical measure.

VLSM allows for the production of 3D lesion maps for each patient, calculating a statistic for each voxel that measures the strength of association between lesioned voxels (lesion+) and undamaged voxels (lesion-) and the behavioural measure being studied (Bates et al. 2003). In this thesis, VLSM provides coordinates of critical lesion sites correlated to specific functional deficits that can then be directly compared to associated regions obtained in both previous functional imaging studies (Molenberghs et al. 2008) and those run in parallel within chapters four and five.

VLSM was carried out by performing a variety of statistical measures at each voxel where at least 2 patients had a lesion (Bates et al. 2003; Rorden et al. 2007). Group comparisons analysis in these cases referred to lesion+ versus lesion- subjects, where lesion+ clearly refers to patients with lesions in the interrogate voxel, but lesion- can refer to both healthy controls (with no lesions) as well as patients with focal lesions affecting other voxels. The VLSM analysis was run iteratively within MATLAB (Statistical Toolbox v7.10); and statistical parameters for each voxel were depicted as a 3D map in MNI space. Correction for multiple comparisons was made using a false-discovery rate procedure, with corrected threshold set at $p<0.05$ (Benjamini & Hochberg 1995a). Without correcting for multiple comparisons, the probability of making a Type I error goes up with increased amounts of statistical tests, which in VLSM becomes a major concern where comparisons are made between tens of thousands of voxels (Kimberg et al. 2007). If the corrected value within a voxel sat below the
chosen p<0.05 threshold, that voxel was automatically registered and highlighted within the 3D map. ROIs could then be defined as clusters of contiguously highlighted voxels. Furthermore, multiple regression analysis was performed in order to correct for confounding effects of age and lesion size on performance of task, in any voxels showing an effect. This analysis confirmed that associations of lesion locations with functional impairments within our test populations were not confounded by lesion size or age.

Once completed and the thresholded 3D maps generated, anatomical localisation of statistically-significant voxels were superimposed upon a variety of reference atlases, e.g. for Brodmann’s areas, cortical and subcortical structures, white matter tracts, thalamic nuclei etc. (Behrens et al. 2003; Desikan et al. 2006; Zhang et al. 2010), normalised to the equivalent space. The volume of each thresholded statistical map that overlay each of the atlas-defined regions and the proportion of each region occupied by significant voxels were determined by matrix multiplication: i.e. thresholded results (as binary row vector) x atlas (as binary column vectors).

2.2.6 Limitations and Interpretations of Voxel-Lesion Symptom Mapping

Studying lesioned populations brings its disadvantages, for which VLSM cannot completely compensate. Firstly, strokes tend to follow non-random distributions sparing certain brain regions, and so the sample space, even using large numbers, cannot be as complete as with fMRI (Kimberg 2009). In addition to this, the ‘mass-univariate’ approach used throughout this thesis assumes that the structure-deficit localisation is not distorted by coincidental damage to other ‘non-critical’ regions within each individual patient – i.e. damage to one voxel is independent of damage to any other spatially separated voxel. Although such voxels may be functionally irrelevant, it cannot be assumed that there is no association between the critical voxels and these, especially when dealing with pathological processes. Any association of this nature would lead to distortions of the inferred critical locus. Recently it has been argued that high-dimensional multivariate approaches, capable of capturing how the presence or absence of damage at every voxel is related to damage in all other voxels (Mah et al. 2014), may be more appropriate when employing VLSM in order to investigate any ‘hidden’ biases. The mass-univariate VLSM used here relies on studies to be high powered in order to
reduce this distribution limitation. However, recruiting a large numbers of acute stroke patients remained no trivial task, and still this may only exacerbate the errors that could be generated using the VLSM approach.

Furthermore, the majority of small strokes tend to involve subcortical regions; whereas strokes that involve cerebral cortex are often large, resulting in disabilities too great, especially in the acute stroke period, to allow for acute behavioural testing (Bentley et al. 2014). Large lesions also complicate VLSM analysis itself, making it difficult to accurately segment images and lesions into grey and white matter (Mehta et al. 2003; Rorden et al. 2007), whilst also effecting the accuracy of spatial normalisation algorithms (Brett et al. 2001). Superimposition of lesions of different subjects also introduces noise to the data set that normalisation to standard templates can only go so far as to alleviate (Tournier et al. 2012). This should be contrasted with functional imaging studies in which the primary source of activation is a metabolically active cerebral cortex. In order to relate the two sets of studies it is advantageous to superimpose significant voxels with brain atlases (Behrens et al. 2003; Zhang et al. 2010; Molenberghs et al. 2008).

2.3 Network Connectivity Imaging Analysis

In parallel to lesion based analysis, chapters four and five also employ functional MRI (fMRI) methodologies in order to study brain network functionality within both patient and healthy control subjects. fMRI methods track changes in blood-oxygen-level-dependent (BOLD) contrasts, detecting differences in the magnetisation of oxygen-bound and oxygen-unbound red blood cells (Ogawa et al. 1990). As such, fMRI allows for the visualisation of brain activity patterns during performance of both motor and cognitive task through mapping increases in the hemodynamic response (Tournier et al. 2012). It must be noted from the outset that tracking the BOLD responses only allows for inference of brain activity, as neural activity is not directly recorded.

With regards to whole brain networks, a variety of neuroimaging techniques have been successfully employed in order to delineate functional networks, each showing high levels of reproducibility and between study robustness (Grefkes & Fink 2011). These techniques can be crudely divided into
methods focused on analysing either functional or effective connectivity (Friston 2011a). Effective connectivity methods, such as dynamic causal modelling (DCM), focus on the influence that one specific brain area exerts on another (Friston 2011b). On the other hand, functional connectivity does not look at direct causal influences, but is instead defined on a temporal basis, analysing activation time courses of structurally separate nodes throughout the brain. The assumption here is that remote areas that share a statistically similar activation time frame are functionally connected (Friston 2011a).

This thesis focuses on the use of resting-state functional MRI (rs-fMRI), one of the most advanced tools used to assess functional connectivity, and its ability to detect changes in brain network functional connectivity directly after acute ischemic damage and early after visuomotor/attention task performance. It is believed that in addition to providing insight into neurobiological activity and mechanisms responsible for neural plastic recovery, tracking changes through rs-fMRI may provide vital information regarding an individual patient’s susceptibility to neural plastic reorganisation (Carter et al. 2010; Cramer et al. 2011; Alex R. Carter et al. 2012). A measure of such reorganisational ability could eventually be used as a biomarker of recovery, allowing for prediction of response to rehabilitation and stratification of patients for treatment. As such, using rs-fMRI to assess viable networks after stroke, and how these relate to and respond to activity compared with healthy subjects, is an important avenue for understanding how attention deficits might impact upon motor control and learning in patients.

2.3.1 Resting-State Functional Magnetic Resonance Imaging

Rs-fMRI assesses functional connectivity by virtue of low frequency (<0.1Hz) BOLD activity correlated between cerebral regions (Biswal et al. 1995; He & Liu 2012). As with many connectivity techniques, rs-fMRI is carried out when the subject is at complete rest. This contrasts with the traditional methods of task-based fMRI, where completion of an active task in the scanner is directly related to high frequency BOLD activity. Even when at ‘rest’ spontaneous low frequency physiological fluctuations are observed throughout the brain and can be recorded using fMRI. The fluctuations between spatially remote regions can then be temporally correlated to one another by
statistically mapping the time series of peak BOLD signals, creating a series of resting state networks (RSNs) (Biswal et al. 1995).

Rs-fMRI has become one of the most prominent and powerful imaging techniques used to assess functional connectivity (Fox & Raichle 2007). Certain temporally coherent RSNs have been reliably found using rs-fMRI including those consisting of regions known to be involved in vision processing, auditory processing, a default mode network, and, most importantly in the context of this PhD, networks mapping sensory-motor function and attention/executive control functions (Fig 5) (Beckmann et al. 2005; Damoiseaux et al. 2006; Fox et al. 2006). These RSNs are robust across subjects, although recently gender differences have been shown to exist (Filippi et al. 2012), and show a strong overlap with the topography of brain regions previously identified by lesion, fMRI task-based, and structural connectivity studies (De Luca et al. 2005; Fox & Raichle 2007; Honey et al. 2009).

A major advantage, and the main justification for employing rs-fMRI in assessment of an acute stroke population, as is done in this thesis, is that the use of standard task-based fMRI in any clinical populations is highly problematic. This is both because patients often have difficulty performing tasks within a MRI scanner, and because differences in performance can confound interpretation of brain activations, especially in motor regions (Alex R. Carter et al. 2012). Rs-fMRI allows scanning of whole brain networks at rest giving a pan-brain reading of functionally active areas that can then be correlated to functional outcome measures gathered outside of the scanner.

Studies into the use of rs-fMRI in post stroke populations have shown it to be sensitive enough to detect changes in functional connectivity for specific networks following ischemic damage (Carter et al. 2010; Grefkes & Fink 2011; Westlye et al. 2011). Importantly, restoration of interhemispheric connectivity was correlated to improved functional output, validating the use of rs-fMRI as a prognostic tool sensitive enough to detect early recovery from stroke (Alex R. Carter et al. 2012) and highlighting its potential as a biomarker to predict response to motor training.
2.3.2 Image Acquisition and Pre-processing

Rs-fMRI data collection was performed using a Siemens Verio 3T scanner. Each rs-fMRI scan sequence lasted 6 minutes and 30 seconds (192 frames, repetition time (TR) 2 s) shown to be an ample time frame for resting-state data collection (Van Dijk et al. 2010; Cole et al. 2010), with a longer time frame risking restlessness and discomfort of the acute stroke patients. Prior to each rs-fMRI sequence a period of rest of 4 minutes and 30 seconds was provided (filled by the completion of a different scan sequence e.g. T1 structural scan, see individual experiment for unique scan protocol details), to allow patients to become accustomed to the scanner environment and to let the brain reach...
a hemodynamic baseline before recording of BOLD activity (Cole et al. 2010; Tung et al. 2013).

During the resting-state scan, subjects were instructed to keep their eyes open and maintain fixation on a central cross displayed on a LCD TV screen at the head of the magnet bore, viewed via a mirror attached to the head coil. Following rs-fMRI scanning, DWI and Fluid-attenuated inversion recovery (FLAIR) structural images were also acquired to aid in lesion based analysis.

Prior to analysis, scan data underwent a well-established set of pre-processing stages aimed at increasing the signal to noise (subject head movement, scanner artefact, heterogeneity of subject cardiac/respiratory cycles, etc.) ratio. These steps form part of a semi-automated analysis process as implemented in Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC), Version 3.10, run through FMRIB Software Library (FSL) and manipulated via a graphical user interface (GUI) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC#Melodic_GUI).

Firstly, for each scan, removal of non-brain tissue was performed using the Brain Extraction Tool (BET). Secondly, the first six scan volumes were removed (12 seconds of data), due to this initial period often being affected by MR artefact. Next, a ‘Pre-Stat’ section allowed for the setting of motion correction parameters (automatically applied through MCFLIRT function - in this case registering all scans to the middle scan volume), spatial smoothing (kernel of 5mm of full width at half maximum (FWHM)) and selection of temporal high pass (100s) and low pass filters (to reduce the influence of temporal drift from the scanner; and physiological cycles). Finally, before multi-session and multi-subject analysis could be performed, co-registration between scans and normalisation to a standard space had to be completed. This function is run automatically within MELODIC, using FEAT functionality, and follows similar principals as the normalisation stages described with lesion analysis, i.e. co-registering each individual’s rs-fMRI scan to their corresponding high resolution (T1) image, followed by normalising the images to a standard space T1 template. Once the rs-fMRI data completed pre-processing, statistical analysis was run using multi-session temporal concatenation in MELODIC, the details of which are described in the following section.

2.3.3 Resting-State Network Identification
A standard method used to analyse resting state data is through a seed-voxel-based approach. This method requires the priori identification of an ROI and subsequent correlation of all other voxels that share its peak BOLD time course (Biswal et al. 1995). Although this ROI based approach is efficient, the requirement of prior knowledge of the functional network under investigation means that it is highly dependent and remains extremely subjective to previous activation-based research. The development of multivariate statistical methods, such as probabilistic independent component analysis (ICA), has allowed researchers to approach rs-fMRI data from a more exploratory angle, without the need of a fundamental hypothesis (Beckmann et al. 2005; Calhoun et al. 2005). Using ICA each component (voxel/group of voxels) expressing a low frequency BOLD signal is correlated to every other component expressing signals of similar intensity and time course throughout the whole brain.

The major advantage of ICA over standard ROI based analysis is the ability to map spatial and/or temporal characteristics of components without needing to first specify the RSN being studied. Another advantage of ICA is the ability to distinguish between RSNs that may overlap spatially/anatomically, as long as they have sufficiently distinct time courses (Beckmann et al. 2005).

These features underlying ICA are vital in cases where the networks of interest cannot be accurately predicted and allow the analysis of multiple RSNs from a single fMRI experiment.

In this thesis, in order to analyse within subject correlation strength changes in a set of RSNs, analysis of healthy control resting-state data was first performed using the multivariate ICA technique to generate a set of RSN, which were then correlated to the 8 well defined RSNs originally shown by Beckmann et al. 2005 (Beckmann et al. 2005), and used as templates to define within single subject ROIs. ICA was performed using multi-session temporal concatenation ICA as implemented in MELODIC Version 3.10 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC#Melodic_GUI).

The reason for performing this initial analysis was to test the reliability of the single 3T scanner used throughout the experiments. Scanners can show high variability in data output both between scanners and over time. Thus, data from a cohort of 54 healthy subjects using the same scanner was collected and run through ICA analysis. This data set generated 51 components, of which 31 clearly related to residual movement artefact, variation in head size, or vascular blood flow. Of the remaining 20, 8
components appeared to correspond with the original Beckmann RSNs, with the addition of a prominent cerebellar component (Figure 6). Indeed, correlation analysis between these components and the 8 Beckmann templates showed strong correlations (Figure 7). These results show that the RSNs generated within the single scanner were both reliably found between subjects and were stable over time in healthy controls. Therefore, should analysis of patient data show significant differences in connectivity or changes in connectivity within these RSNs after task performance, these changes could be directly attributed to ischemic damage.

Figure 6 Generated Resting-State Networks
Figure 7 Generated Resting-State Networks Overlapped With Beckmann 8

8 RSNs identified from group control data (highlighted with yellow). Overlaid with the 8 most common RSNs identified by Beckmann et al. 2005 (highlighted with blue).
CHAPTER TWO: METHODS

2.3.4 Within Single Subject Resting-State Network Analysis

The 9 generated components from the healthy cohort were used as templates to mask ROIs for single subject patient analysis. Rs-fMRI scan data for each individual patient underwent separate pre-processing steps to create an individual ‘filtered functional data’ set normalised to standard space. For each subject, connectivity within each of the 9 functional components was then assessed by extracting the BOLD activation time series for the top 0.1% of peak voxels and producing a between voxel cross correlation coefficient matrix of activity, giving an $R^2$ value for each possible 2-voxel pairing.

2.3.5 Limitations and Interpretations of RSFMRI

The major limitation of rs-fMRI, as with all functional imagining methods, is that the measurements being taken are of activation-related haemodynamics rather than direct readings of neural activity (Attwell & Iadecola 2002). As such the technique can only correlate metabolic activity to functional connectivity. The question that arises with rs-fMRI is whether the BOLD fluctuations being recorded are all indeed functionally significant to RSNs, or are simply a consequence of background noise from physiological confounds such as the cardiac and respiratory cycles. The initial resolution to such confounds is the multivariate and high temporal sampling approach of ICA, which is able to clearly separate simple physiological noise components from low frequency resting fluctuations (Beckmann et al. 2005). Methods for controlling for physiological confounds do exist, including chest belts (measuring breathing rate), and respirometers (recording levels of end tidal CO2), which aim to identify any BOLD activity correlated from these confounds and remove it from data analysis (Birn et al. 2008; Chang & Glover 2009; Murphy et al. 2011). Such methods have been trialled in stroke populations (Geranmayeh et al. 2015), however they remain expensive to run and difficult to utilise on acute clinical populations and within a clinical MRI unit.

Although electrophysiological techniques (e.g. EEG/MEG) are capable of measuring neuronal activity more directly and have a better temporal resolution, they have a much lower spatial resolution in comparison (centimetres compared to millimetres) (Cole et al. 2010). To support the justifying of the use of fMRI data, results from animal studies have indicated that the components of rs-fMRI are in fact tightly coupled with underlying neural activity even after induced stroke (Weber et al. 2008;
Schöölvinck et al. 2010). Nevertheless, caution must be drawn when interpreting any fMRI data with data being gathered in a noisy and uncomfortable environment, where subjects may not be at a normal functional baseline regardless of disease state. Added to this, more basic limitations of prolonged resting scans in patient and elderly populations include the tendency for patients to fall asleep during RS scans or to fatigue across serial acquisitions. These limitation are minimised throughout this thesis by making subjects focus on fixation points during scanning, with instructions to keep their eyes open, and by assessing physical strength (fatigue) immediately before and immediately after scanning.
CHAPTER THREE: DETERMINING LESION LOCATIONS RELATED TO ATTENTION NETWORK DEFICITS
3.1 Introduction

The ability to allocate information-processing resources flexibly, and appropriate to needs - i.e. to attend - is critical for both normal cognition and behaviour. Attentional capacity has also been suggested to be a vital component of recovery following stroke, with deficits in attention specifically influencing and correlating to motor recovery rates (Robertson et al. 1997; Hyndman et al. 2008; Nijboer et al. 2014) and resulting in reduced motor control due to an increased impact of attentional loads (Houwink et al. 2013). However, although it is known that deficits of attention frequently accompany stroke (Stapleton et al. 2001; Barker-Collo 2010), the neurobiological basis of the attention system remains poorly defined (Raz 2006). Before exploring further the impacts of attention deficits on the recovery of other functions, it is important to first understand the prevalence attention deficits have within a stroke population and to define the systems neuroanatomical correlates.

One influential, and unifying, framework of the attention system suggests that attention can be resolved into three fundamental and separable attention networks: 1) alerting - i.e. bottom-up, stimulus-driven activation; 2) orienting - i.e. top-down, biasing of sensori-motor processing; and 3) conflict-resolution (executive control), over competing potential responses (Petersen & Posner 2012; Posner & Petersen 1990); that can be operationally quantified within a single, integrated computer based task - the Attention Network Test (ANT) (Fan et al. 2002). The independence of these networks is first suggested by a lack of correlations between the three ANT measures in healthy adults (Fan et al. 2002), and behavioural dissociations when compared in different subject groups (Mahoney et al. 2010; Fernández et al. 2011; Wang et al. 2005). Further evidence supporting three anatomically-separable networks comes from functional neuroimaging studies recording distinct structural signatures, broadly; alerting with thalamus and ventral aspects of right hemisphere; orienting with parietal cortices; and conflict within the frontal regions of the dorsolateral prefrontal and anterior cingulate cortices (Fan et al. 2005; Botvinick et al. 2004; Casey et al. 2000; Coull et al. 2004).

The attention network model has important predictions and implications for clinical practice. Firstly, given the wide number of regions associated with each of the attention networks - not only within
right hemisphere, but also left hemisphere, striatum, thalamus and brainstem (Clemens et al. 2011; Coull et al. 2001; Kim et al. 2010; Thienel et al. 2009) - it would be expected that a large proportion of patients with focal brain lesions might be characterised into one of three network profiles of attention impairment, depending upon which network each lesion lies principally within.

Secondly, with rehabilitation of cognitive function starting to be considered a critical component of post brain injury care (De Luca et al. 2014), and with specific attention based training post brain injury shown to improve these attentional functions (Sohlberg et al. 2000), which can also be generalised to related cognitive functions (Klingberg 2011), the ability to localise and predict particular attention deficits in stroke patients may then allow for direct retraining of attention functions using other computer based tasks (Posner & Fan 2013; De Luca et al. 2014). As stated, with reduced attention capacity being suggested to impact upon recovery rates of other functions, targeting attention through such training may further influence other functional rehabilitation.

Finally, although out of the scope of this thesis, evidence for a distinct neuropharmacology of each of the three attention network types (Brunyé et al. 2010; Drueke et al. 2009; Wignall & de Wit 2011; Petersen & Posner 2012) points to the possibility of personalized neurotherapeutics for treating specific attention deficits, if focal lesions are indeed resolvable into the three postulated networks, suggesting a potential for combinatorial drug and physical rehabilitation therapies depending on lesion location.

While a long line of clinical neuropsychology studies indicate that impairments in different attention types are associated with different lesion locations (Stuss et al. 2001; Vendrell et al. 1995; Brazis & Masdeau 2007; Verdon et al. 2010; Karnath et al. 2011), there have been no studies to date that directly compare the profile of alerting, orienting and conflict-resolution, over a large number of lesion locations. In fact, given mounting evidence for certain brain regions e.g. right temporoparietal, being implicated in more than one type of attention (E. J. Coulthard et al. 2008; Pujol et al. 2001; Malhotra et al. 2009), and for a strong interdependency between the three attention network...
components (Callejas et al. 2005; Macleod et al. 2010; McConnell & Shore 2011; Corbetta & Shulman 2011), there is a need to assess systematically the degree to which different lesion locations engender specific, versus multiple, attentional impairments. Moreover, studies that select and group patients by prespecified regions of interest may be insensitive to critical anatomical–functional associations, and are unable to ascertain how often focal lesions fall within attention-determining areas. An important prediction of the triple attention model is that behavioural dissociations between these three functions will occur in a significant proportion of patients with brain lesions, depending upon distinct focal lesion location.

**Aims of the Study**

In the following study, the impact of attention deficits on a typical acute stroke population will be assessed and lesion locations that cause these deficits analysed. The aims of the study are to:

- Establish the proportion of acute stroke patients affected by attention deficits.
- Assess the strongest anatomical associations with each attention type using a voxel-lesion method of analysis across a broad range of locations.
- Explore whether certain lesion locations show behavioural dissociations or interactions between attention networks.
- Evaluate how specific lesion locations affecting each attention type relate to cardinal motor associated regions and function.
3. 2 Methods

3.2.1 Subjects

268 consecutive patients admitted with acute stroke were screened at a single-site, Imperial College NHS Healthcare Trust Hyper Acute Stroke Unit, Charing Cross Hospital. Inclusion criteria included: 1) right-handed (similarly for controls); 2) new focal neurological deficit; 3) MRI demonstration of focal brain lesion, judged clinically to be the cause of the acute deficit; 4) able to be tested within ten days of presentation; 5) able to comprehend, memorise and perform ANT task instructions; sit up, discriminate task stimuli on laptop, and press keys reliably. Exclusion criteria were: 1) pre-existing organic brain disease (e.g. clinically assessed dementia); 2) MRI evidence of old focal brain lesion (>10mm), or moderate-severe cerebral small-vessel disease (>1 on Age-Related White Matter Change score 29).

Age matched controls were also screened for testing. Controls comprised of two groups: 1) neurological controls: these were patients who presented to the same unit with acute focal neurological disturbance, but who were subsequently found to have normal MRI brain, and were judged by a neurologist not to be a stroke; and 2) healthy adults with no history of organic brain disease. All recruited participants gave written and signed informed consent. Ethical approval was granted by the Charing Cross Hospital Research Ethics Committee.

3.2.2 Behavioural test

The Attention Network Test (ANT - Figure 8) measures the three components of attention - alerting, orienting and conflict - within one session by manipulating stimulus properties, for a constant set of instructions. Subjects are requested to indicate the direction (right or left) of a visually-presented target arrow (black arrow against a grey background). To introduce a conflict resolution component, the target arrow is flanked by two further stimuli on either side. These flankers may either be arrows pointing in the same direction as the target arrow (congruent), in the opposite direction as the target arrow (incongruent), or could be plain lines with no arrow heads (neutral). To introduce an orienting
component, the target arrow is presented either 1cm above or below a centrally located fixation cross. To stimulate an alerting component, targets may, or may not, be preceded by 1 of 4 visual cue conditions; 1) no-cue, 2) centre-cue - in which the cue appeared on the central fixation point, 3) double-cue – in which cues were presented at both possible target locations (above and below the fixation point) or 4) spatial-cue – in which the cue was presented at a single location that always predicted the location of the subsequent target.

The task was constructed and run in MATLAB (v7.0.1), using Cogent 2000 graphics toolbox (www.vislab.ucl.ac.uk), matching the original task parameters designed by Fan et al. 2002 (Fan et al. 2002). The task was presented to participants using an Intel-Centrino hp-laptop running Windows XP, on a 15” colour monitor. Patients were asked to sit up-right in their beds while the laptop was placed on an adjustable non-tilt over-bed table and positioned directly in front of them. Controls performed the task in an identical manner whilst sitting up-right in a chair. All participants viewed the screen from a distance of approximately 60cm. The entire visual stimulus display subtended a 3.1° horizontal and 2.1° vertical visual angle.

Practice and test sessions were performed on the same sitting. Participants were instructed to focus on the centrally-located fixation cross, and respond as quickly, and as accurately as possible by pressing the corresponding left, or right, arrow key on the laptop keyboard with their right hand; unless this was paralysed, in which case they used their non-paretic hand. Subjects performed 3 x 15-trial practice blocks, with auditory feedback indicating correct or incorrect responses. Only subjects who achieved more than two-thirds correct in the latter half of this session, proceeded to the test session.

Test sessions consisted of two blocks of 96 trials (4 cue conditions x 2 target locations x 2 target directions x 3 flanker conditions x 2 repetitions). The presentation of stimuli was pseudo-randomised, with 40 congruent, 40 incongruent and 16 neutral trials per block. A third block, although present in the original Fan et al. task, was discarded owing to a high rate of patient dropout, or poor performance.
**Procedure:** The time period for each trail was divided into five events, each differing with the variable conditions. First, there was a fixation period for a random/varying duration ranging between 400-1600msec. This was followed by the presentation of a warning cue for 100msec. A further fixation period of 400msec followed the warning cue before the target and flankers appeared simultaneously. The target and flankers remained presented to the participant until a response was recorded, but for no longer than 1700msec. After the target and flankers had disappeared a final post-target fixation period was given again with a variable duration dependant on the duration of the initial fixation period (3500msec minus the original duration period), meaning that each trail lasted exactly 4000msec. The aim of the variable duration of the first fixation period was to provide additional uncertainty as to cue appearance.
3.2.3 Attention Component Analysis

The difference between mean RT, recorded across the different experimental conditions, and accuracy data, were used as a measure to derive alerting, orienting, and conflict components (see below). Results were normalised into percentage differences between mean RT of each condition compared with each participant’s standard Baseline Reaction Time (BLRT = mean Neutral Condition Trials RT). Error trials (incorrect, or RT > 1800ms) were excluded from the RT analysis. Subjects had to respond to >60% trials, and achieve >80% accuracy on response trials to be included in the final analysis.

Alerting Component

Alerting effect was calculated by subtracting the mean RTs of the double cue conditions from the mean RTs of the no cue conditions OR by subtracting the accuracy to the double cue conditions from the mean RTs to the no cue conditions:

\[
\text{Alerting} = \begin{cases} 
\text{meanRT (No Cue) - meanRT (Double Cue)} \\
\text{Accuracy (Double Cue) - Accuracy (No Cue)}
\end{cases}
\]

Orienting Component

Orienting effect was calculated by subtracting the mean RTs of the spatial cue conditions from the mean RTs of the centre cue conditions OR by subtracting the accuracy to the spatial cue conditions from the accuracy to the centre cue conditions:

\[
\text{Orienting} = \begin{cases} 
\text{meanRT (Central Cue) - meanRT (Spatial Cue)} \\
\text{Accuracy (Single Cue) - Accuracy (Central Cue)}
\end{cases}
\]
Conflict Component

Conflict effect was calculated by subtracting the mean RTs of the congruent conditions from the mean RTs of the incongruent conditions OR by subtracting the accuracy to the incongruent conditions from the accuracy to the congruent conditions:

\[
\text{Conflict} = \frac{\text{meanRT (Incongruent)} - \text{meanRT (Congruent)}}{\text{Accuracy (Congruent)} - \text{Accuracy (Incongruent)}}
\]

Although participants were presented with a third condition, the neutral condition, neutral performance was not included in our measure of conflict as previous studies have shown only small difference to exist between the neutral and congruent flanker conditions (Fan et al. 2002).

3.2.4 MRI Image Acquisition, Lesion Delineation and Normalisation

All patients underwent MRI 2-7 days post-stroke. MR imaging was carried out using a Siemens 1.5T scanner, providing T2, Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion-Weighted (DWI), Apparent Diffusion Coefficient (ADC) and Susceptibility-Weighted (SWI) acquisitions (except in 5 patients in whom DWI/ADC and SWI were not performed, due to lack of scanning time tolerance). DWI dimensions were 192 x 192 x 19. Acute lesions were identified on DWI and delineated using a semi-automated method producing lesion and lesion mask images. Lesions were subsequently normalised to a canonical T2 template in Montreal Neurological Institute (MNI) space (voxel size 2 x 2 x 2mm) (For detailed methodology on lesion delineation and image pre-processing see chapter 2, Methods).

3.2.5 Statistics and Voxel Lesion Symptom Mapping

Differences between the focal brain lesion group, and two control groups, in terms of subject characteristics were performed by one-way analysis of variance (ANOVA)s, in SPSS (v 19.0), assumptions having been met. The effect of subject group on ANT performance was assessed by a 3-
way mixed-effect ANOVA, with factors: group (3 levels: stroke lesions, neurological controls, healthy controls), flanker condition (3 levels: congruent, neutral, incongruent), and cue condition (4 levels: none, double, central, selective); for both RT and accuracy data. Since there were no significant main effects, or cue or flanker interactions with group (p>0.05), comparing the neurological and healthy groups, we merged the two control groups for subsequent analyses.

The effects of lesion location on ANT performance was similarly assessed using a mixed-effect ANOVA (group X flanker (or/and) X cue), but now performed using the VLSM method (Bates et al. 2003) (see chapter 2, Methods). Correction for multiple comparisons was made using a false-discovery rate procedure, with corrected threshold set at p<0.05 (Benjamini & Hochberg 1995b). For clarity, we initially performed ANOVAs to assess group x flanker, and group x cue interactions, separately, before performing group x cue x flanker ANOVAs on the peak coordinates already showing 2-way interactions.

Where significant interactions occurred, the nature of these were determined by performing post hoc t-tests (p < 0.001) that tested for each of the three attentional contrasts of interest (thresholded at p < 0.05, corrected for the respective ANOVA search volume; and for exploratory purposes, at p <0.001, uncorrected). Regions showing such effects were subsequently probed for group effects in the remaining attention contrasts down to a threshold of p < 0.05, uncorrected). In order to correct for confounding effects of age and lesion size on ANT performance, the t-tests performed for Lesion+ versus Lesion- reflected the regression coefficient (relative to 0) of the lesion-presence term in the following multiple regression analysis: attentional contrast size = B0 + (B1 x lesion presence or absence at tested voxel) + (B2 x age) + (B3 x overall lesion size). Tests of data normality (Kolmogorov-Smirnov) and homogeneity of variance (Levene) were performed at each significant cluster to confirm that the parametric assumptions of ANOVA were met. Furthermore, Mauchley’s test of sphericity was applied at each reported region, and if significant, Greenhouse-Geisser corrected statistics were reported instead.
The above analyses resulted in the demarcation of three sets of regions, grouped according to whether the greatest group effect was apparent for conflict, orienting or alerting. To test for attentional specificity of lesion locations, and also to identify confounding by RT-accuracy trade-offs, we recalculated for each of the three attentional contrasts an efficiency metric, defined as accuracy / RT (e.g. orienting = accuracy /RT (for selective cues) – accuracy / RT (for central cues)); and then performed group x attention-type ANOVAs on these metrics at each peak identified for the group x flanker, or group x cue interaction (Townsend & Ashby 1978). For these analyses we used conflict-resolution (i.e. the negative of conflict), rather than conflict, so that lesion locations associated with generalised attentional impairments would theoretically result in decreases across all three measures. In order to ascertain dissociations in attention between regions showing predominantly conflict, orienting or alerting effects, we performed lesion-location x attention-type ANOVAs that compared the size of the three attentional contrasts for each pairwise combination of regions taken from separate categories (e.g. lesions in region A1 showing raised conflict, versus lesions in regions B1 showing reduced orienting). Threshold 3D maps showing statistically-significant voxels were superimposed upon reference atlases for analysis.
3.3 Results

3.3.1 Test Population

Of the 268 patients screened, 110 patients with acute unifocal lesions were recruited. A further 22 patients were enrolled, but their results were discarded as performance was established as too poor to be included (threshold of >50% accuracy set). There was no over-representation of any particular lesion location amongst this discarded group. 62 aged matched controls were recruited.

3.3.2 Group Characteristics

Patients and controls were matched for age and sex. The characteristics and diagnoses of patients with acute stroke focal brain lesions (FL), neurological controls (NC) and healthy controls (HC) are displayed in Table 2 & 3. Lesions were distributed among right hemisphere, left hemisphere, and brainstem-cerebellum in the ratio 41:47:22 (Figure 9).

Table 2 Characteristics of subject groups

<table>
<thead>
<tr>
<th></th>
<th>Focal Brain Lesions (n=110)</th>
<th>Neurological Controls (n=30)</th>
<th>Healthy Controls (n=32)</th>
<th>Group Comparison p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.8 (15.6)</td>
<td>61.9 (14.4)</td>
<td>62.5 (13.9)</td>
<td>.97</td>
</tr>
<tr>
<td>% Males</td>
<td>58.2%</td>
<td>53.3%</td>
<td>56.3%</td>
<td>.98</td>
</tr>
<tr>
<td>Diabetes or Hypertension</td>
<td>51.8%</td>
<td>34.5%</td>
<td>32.0%</td>
<td>.10</td>
</tr>
<tr>
<td>Clinical deficit (NIHSS)</td>
<td>2.85 (1.98)</td>
<td>1.53 (1.33)</td>
<td>n/a</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Clinical neglect or extinction (n)</td>
<td>5</td>
<td>0</td>
<td>n/a</td>
<td>.59**</td>
</tr>
<tr>
<td>MMSE*</td>
<td>28.7 (1.3)</td>
<td>28.4 (1.7)</td>
<td>29.1 (1.1)</td>
<td>.46</td>
</tr>
<tr>
<td>Time to MRI from presentation (days)</td>
<td>3.56 (1.6)</td>
<td>3.35 (1.9)</td>
<td>n/a</td>
<td>.66</td>
</tr>
<tr>
<td>Time to ANT from presentation (days)</td>
<td>5.72 (3.14)</td>
<td>5.04 (3.22)</td>
<td>n/a</td>
<td>.35</td>
</tr>
</tbody>
</table>

Mean (Standard deviation). * Excludes patients with lesion-associated aphasia. ** Fisher’s Exact Test
Table 3 Subject Diagnoses

<table>
<thead>
<tr>
<th>Focal Brain Lesions*</th>
<th>n</th>
<th>Neurological Controls</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemic stroke</td>
<td>108</td>
<td>Migraine</td>
<td>13</td>
</tr>
<tr>
<td>Acute hemorrhagic stroke</td>
<td>2</td>
<td>Functional or non-organic disorder</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral nervous or spinal disorder</td>
<td>8</td>
</tr>
</tbody>
</table>

*Median lesion volume was 4.08cc (IQR: 1.14-15.3)
2 ischemic stroke cases were due to vasculitis

Figure 9 Lesion histogram depicted spatially on normalized MNI template brain

3.3.3 Group Comparisons

The effects of the Attention Network Test (ANT) manipulations on performance, and differences in these between the three groups, was assessed with a mixed-effects ANOVA for factors cue (none, double, central, selective); flanker (congruent, neutral, incongruent) and group (FL, NC, HC). Reaction time and accuracy differed between the groups (p <0.01), with FL being slower and less accurate than all controls across the entire ANT (p≤0.001); but neurological controls not differing significantly from healthy controls (p>0.1) (Figure 4 A). Both RT and accuracy were influenced by cue (p<0.001) and flanker stimuli (p<0.001), but there were no overall group x cue, group x flanker, or group x cue x flanker interactions (p>0.05). These effects can be appreciated by plotting the size of the pre-specified attentional contrasts, as a percentage of subjects' average performance, separately for each group (Figure 4 B). A cue x flanker interaction for RTs (p<0.05) is explored further in the final results section (Lesion x cue x flanker interactions). Correlation analyses between each of the ANT measures and lesion size, or age (across FL only or all subjects), were not significant (|r|<0.19; p>0.05).
Figure 10 Performance of the ANT in the three subject groups: healthy controls, neurological controls, and focal brain lesions

A. Plots of RT and accuracy data averaged over all trials show inferior overall performance in lesion patients. B. Plots of each ANT measure (as a % of average RT or accuracy) show no differential modulation by group.
Table 4: Results of mixed-effect ANOVA Cue x Flanker x Group; A - Reaction Time Data; B – Accuracy Data

Results of mixed-effect ANOVA with factors Cue (no cue; double cue; central cue; and selective cue), Flanker (congruent, neutral and incongruent) and Group (Brain Lesions, Neurological Controls, Healthy Controls) are as follows:

A. RT Data

Table 4 Results of mixed-effect ANOVA Cue x Flanker x Group

<table>
<thead>
<tr>
<th>Effect</th>
<th>d.f.</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cue</td>
<td>2.8, 479</td>
<td>108.5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Flanker</td>
<td>1.8, 305</td>
<td>276.4</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Group</td>
<td>2, 169</td>
<td>6.7</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Cue x Flanker</td>
<td>5.6, 948</td>
<td>2.4</td>
<td>P=0.05</td>
</tr>
<tr>
<td>Cue x Group</td>
<td>5.7, 479</td>
<td>2.1</td>
<td>P=0.056</td>
</tr>
<tr>
<td>Flanker x Group</td>
<td>3.6, 305</td>
<td>0.4</td>
<td>ns</td>
</tr>
<tr>
<td>Cue x Flanker x Group</td>
<td>11.2, 948</td>
<td>0.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

ns: non-significant

Planned Contrasts:

<table>
<thead>
<tr>
<th>Contrast</th>
<th>d.f.</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double – No Cue</td>
<td>1, 169</td>
<td>67.4</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Central – Double Cue</td>
<td>1, 169</td>
<td>0.7</td>
<td>ns</td>
</tr>
<tr>
<td>Selective – Central Cue</td>
<td>1, 169</td>
<td>95.5</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

| Flanker:                      |       |       |       |
| Incongruent – Congruent       | 1, 169 | 373.6 | P<0.001 |
| Incongruent – Neutral         | 1, 169 | 345.6 | P<0.001 |

| Group:                        |       |       |       |
| Brain Lesions – All Controls  | 1, 170 | 11.6  | P=0.001 |

| Cue x Flanker:                |       |       |       |
| (Incongruent – Congruent) X (Double - No Cue) | 1, 169 | 6.8   | P=0.01  |
| (Incongruent – Congruent) X (Double - Central Cue) | 1, 169 | 3.4   | P=0.068 |
| (Incongruent – Congruent) X (Double - Selective Cue) | 1, 169 | 6.9   | P<0.01  |
**B. Accuracy Data:**

<table>
<thead>
<tr>
<th>Effect</th>
<th>d.f.</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cue</td>
<td>3,</td>
<td>507</td>
<td>6.9</td>
</tr>
<tr>
<td>Flanker</td>
<td>1.4,</td>
<td>233</td>
<td>28.8</td>
</tr>
<tr>
<td>Group</td>
<td>2,</td>
<td>169</td>
<td>8.3</td>
</tr>
<tr>
<td>Cue x Flanker</td>
<td>6,</td>
<td>1014</td>
<td>1.6</td>
</tr>
<tr>
<td>Cue x Group</td>
<td>6,</td>
<td>507</td>
<td>0.1</td>
</tr>
<tr>
<td>Flanker x Group</td>
<td>2.8,</td>
<td>233</td>
<td>1.6</td>
</tr>
<tr>
<td>Cue x Flanker x Group</td>
<td>12,</td>
<td>1014</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*ns: non-significant*

**Planned Contrasts:**

<table>
<thead>
<tr>
<th>Contrast</th>
<th>d.f.</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cue:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double – No Cue</td>
<td>1,</td>
<td>169</td>
<td>14.6</td>
</tr>
<tr>
<td>Central – Double Cue</td>
<td>1,</td>
<td>169</td>
<td>0.7</td>
</tr>
<tr>
<td>Selective – Central Cue</td>
<td>1,</td>
<td>169</td>
<td>0.4</td>
</tr>
</tbody>
</table>

| Flanker:                |      |     |       |
| Incongruent – Congruent | 1,   | 169 | 32.5  | P<0.001 |
| Incongruent – Neutral   | 1,   | 169 | 32.0  | P<0.001 |

| Group:                  |      |     |       |
| Brain Lesions – All Controls | 1, | 170 | 13.6 | P<0.001 |
3.3.4 VLSM: locations associated with heightened conflict

Lesion locations that influenced conflict-processing were determined by testing for group x flanker interactions at each sampled voxel, where the group comparison was between lesion presence in the test voxel (Lesion+) and either 1) Controls (HC and NC combined); or 2) lesion elsewhere (Lesion-). This analysis identified multiple regions (F≥8.3; p <0.05, corrected), predominantly in bilateral frontal white matter, where Lesion+ increased performance difference between incongruent and congruent flankers (increased conflict), relative to both Controls and Lesion-, for both RTs and accuracy (T≥3.4; p<0.001) (Table 5A; Figure 11A, B). The largest cluster to show this effect was in the right middle corona radiata (RMCR), anterior to corticospinal tract, and in white matter connecting prefrontal with premotor cortices subjacent to premotor cortex (i.e. BA 6; see Appendix Supplementary Data 1 for detailed characterisation). The size and spatial extent of this effect was greater for RT than accuracy data; and stronger for comparisons of Lesion+ versus Controls than versus Lesion-. Smaller clusters were also found in right anterior corona radiata, inferior prefrontal white matter and anterior insula; as well as left superior frontal cortex. There was no difference in the effect size comparing lesions to RMCR alone versus right prefrontal regions ±RMCR overlap and no differences in stroke severity or lesion size between patients with lesions in the main RMCR cluster vs lesions elsewhere (p<0.01). Simple effects revealed that lesions to all these regions impaired performance specifically during incongruent trials, relative to Controls or Lesion- (T≥2.2; p<0.05, except left superior frontal).

Lesions to these frontal regions increased conflict, but did not modify other attention effects, except in two areas that additionally showed reduced orienting, albeit at the more liberal threshold of p<0.01, uncorrected (Table 5A). This specificity for attention type was more formally assessed through the interaction term of a group (Lesions vs. Controls) x attention-type ANOVA, using an efficiency measure that incorporated both accuracy and RT. This demonstrated significant group x attention-type interactions in all the reported peaks (F≥3.6; p<0.05; Figure 11C). There were no differences in response hand, or limb weakness severity (using NIHSS subscale), between patients with lesions in the main RMCR cluster versus lesions elsewhere (p>0.1).
A. Results of a Group x Flanker ANOVA (p<0.05, corrected) were masked by a T-test comparing Lesion+ versus Controls for conflict (i.e. Incongruent - Congruent Flanker), thresholded at p<0.001, uncorrected. These are shown separately for RT (first pane) and accuracy (second pane). The third pane shows cortical and white-matter anatomical landmarks relevant to the results, derived from co-registered standard atlases. B. Plots of RT and accuracy for the three flanker conditions in Lesion+, Lesion- and Control groups, where Lesion+ refers to lesions affecting the right middle corona radiata cluster (L1). C. Plot of efficiency (i.e. RT/accuracy) for each ANT measure at the same region as in B, showing selective conflict-heightening without impact on other functions.

Figure 11 Lesion sites that enhance conflict
3.3.5 VLSM: locations associated with reduced orienting

Lesion locations that influenced spatial orienting were those showing group x cue interactions (p<0.05, corrected), qualified with masking for the between-group t-contrast of spatial-cue versus central-cue (p<0.001). For RT, lesions to right pulvinar, right lateral temporal and adjacent posterior parietal cortex (temporoparietal junction (RTPJ)), posterior insula and intervening white matter, all reduced orienting (Table 5B; Figure 12 A,B; Appendix Supplementary Data 1). This effect was accountable by both Controls and Lesion- groups showing speeding to spatial-cues relative to central-cues (p<0.001), whereas Lesion+ did not show any effect (p>0.1). For accuracy, a smaller subset of RTPJ regions also demonstrated less orienting due to reduced accuracy to spatial cues (explored in the Lesion x cue x flanker interactions section below). For accuracy, the effect was driven by Lesion+ reducing accuracy to selective-cues relative to central-cues (F=11.3; p<0.05), while Controls and Lesion- did not show any effect (F≤1.0; p>0.1) (Table 6B).

The reduction in orienting due to lesions in right pulvinar and RTPJ was specific, as suggested by non-significant effects of lesions here on conflict, and alerting, for both RT and accuracy data (p>0.05). A small cluster where lesions reduced orienting in RMCR and anterior insula (for RTs only; p<0.001), did however, also show lesion-associated heightened conflict (T=2.5; p<0.05); and was located just inferiorly to the main conflict-increasing RMCR cluster identified earlier. For right pulvinar and RTPJ regions, a differential effect of lesion on attention was further suggested by significant group x attention-type interactions, using efficiency scores (F≥3.8; p<0.05). In the former region this was contributed to by lesions resulting in reduced efficiency for selective relative to central cues (p<0.05) – i.e. a reversal of the normal advantage conferred by selective cues (Figure 12 C).
A. Results of a Group x Cue ANOVA (p<0.05, corrected) were masked by a T-test comparing Lesion+ versus Controls for orienting (i.e. Central - Spatial Cue), thresholded at p<0.001, uncorrected. These are shown separately for RT (first pane) and accuracy (second pane). The third pane shows cortical and white-matter anatomical landmarks relevant to the results. B. Plots of RT and accuracy for the four cue conditions in Lesion+, Lesion- and Control groups, where Lesion+ refers to lesions affecting the right pulvinar (L2), or right angular gyrus (L3). C. Plot of efficiency for each ANT measure in right angular gyrus, showing both orienting reduction (p<0.001) and conflict reduction (p<0.01).
3.3.6 VLSM: locations associated with reduced alerting

Lesion locations associated with reduced alerting were identified as those showing both a group x cue interaction, and a significant between-group difference for the contrast of double-cue versus no-cue (p<0.001). For RT, this analysis demonstrated that lesions to bilateral anteromedial thalamus and upper, centro-dorsal, brainstem resulted in reduced alerting relative to Controls (F≥11.0; p<0.05, corrected; T≥3.31; p≤0.001); or relative to lesions elsewhere (F≥6.8; p<0.001, uncorrected; T≥2.59; p≤0.05) (Table 3C; Figure 13A,B). For accuracy, reduced alerting was also manifest with lesions to right thalamus, with smaller clusters seen in right cerebral peduncle, and several other small regions within the right hemispheric (versus Controls: F≥11.6; p<0.05, corrected; T≥3.39; p≤0.001; versus Lesion-: F≥5.5; p<0.001, uncorrected; T≥2.37; p≤0.05) (Table 4C; Figure 13A,B). Overlaying these results onto standard atlases indicated that the greatest volume of significant thalamic voxels overlay those nuclei projecting to prefrontal regions (Appendix Supplementary Data 1). Sub-group analyses revealed that these interactions were driven by Controls and Lesion- showing speedier (F≥54.4; p<0.001), and more accurate (F≥14.1; p<0.001), responses to double-cue versus no-cue; while Lesion+ showed neither (F≤1.8; p>0.1), for the same comparison.

The bi-thalamic and brainstem peaks where lesions reduced alerting did not show effects of lesions on other attention types; whereas two of the right frontoparietal regions (including frontal operculum, close to anterior insula), that showed reduced alerting (with accuracy data) also heightened conflict at lower statistical threshold (p<0.05). Furthermore, a significant group x attention-type interaction using efficiency scores was apparent for thalamic lesions (p<0.01; Figure 13C); but not at other locations associated with reduced alerting.
A. Results of a Group x Cue ANOVA (p<0.05, corrected) were masked by a T-test comparing Lesion+ versus Controls for orienting (i.e. Double - No Cue), thresholded at p<0.001, uncorrected. These are shown separately for RT (first and second pane) and accuracy (third pane). The second pane shows these effects within upper brainstem at an exploratory threshold of p<0.01. B. Plots of RT and accuracy for the four cue conditions in Lesion+, Lesion- and Control groups, where Lesion+ refers to the right and left anteromedial thalamus (L2), or right medial thalamus (L4). Note that the apparent numerical reversal of alerting effects in Lesion+ (i.e. negative alerting) is not significantly different to 0. C. Plot of efficiency for each ANT measure in right and left anteromedial thalamus, showing selective alerting reduction (p<0.001).

Figure 13 Lesion sites that reduce alerting
3.3.7 VLSM: dissociations

In order to verify that the stereotypical attentional profiles in each of the regions described above differed between regions - i.e. double dissociations - we performed pairwise location x attention-type ANOVAs that tested for differences in the relative modulation of conflict, orienting and alerting between lesion sites (final column Tables 5, 6). Significant interactions (p<0.05) occurred contrasting peaks from each of the three attention-network categories pairwise with peaks from either of the other two categories, e.g. comparing RMCR (raising conflict) versus right pulvinar (reducing orienting); or right pulvinar versus anteromedial thalamus (lowering alerting).
Table 5 Regions showing interaction or main effect of lesion with attentional manipulation (RT data)

Regions showing both group x flanker (or group x cue) interaction (F value reported), and a group effect for at least one of the three attention types (i.e. simple effect t-test thresholded at p<0.001, performed on pre-specified contrast, e.g. Conflict = incongruent – congruent flanker). T-tests for each of the three cardinal contrasts were performed at each F maxima. T values reported for Lesion+ vs. Lesion- reflect regression coefficient for lesion presence in a multivariable regression equation including age and lesion size as covariates. Final column lists regions compared with which dissociations occurred.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coords.</th>
<th>Lesion+ vs Controls</th>
<th>Lesion+ vs Lesion- (other lesion sites)</th>
<th>N of lesions</th>
<th>Dissociations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x   y   z</td>
<td>F Conflict</td>
<td>T Orient</td>
<td>T Alert</td>
<td>F Conflict</td>
</tr>
<tr>
<td>A: Group x Flanker Interaction: Conflict-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R middle corona radiata</td>
<td>36, 6, 22</td>
<td>26.3</td>
<td>6.61</td>
<td>17.9</td>
<td>5.68</td>
</tr>
<tr>
<td></td>
<td>32, 6, 38</td>
<td>28.9</td>
<td>6.75</td>
<td>16.6</td>
<td>5.39</td>
</tr>
<tr>
<td></td>
<td>28, 12, -16</td>
<td>12.7</td>
<td>5.21</td>
<td>11.0</td>
<td>4.73</td>
</tr>
<tr>
<td>2. R anterior corona radiata</td>
<td>26, 24, 18</td>
<td>17.7</td>
<td>5.77</td>
<td>11.9</td>
<td>4.66</td>
</tr>
<tr>
<td>3. R anterior insula</td>
<td>36, 12, -10</td>
<td>24.2</td>
<td>6.64</td>
<td>15.1</td>
<td>5.48</td>
</tr>
<tr>
<td></td>
<td>24, 20, -10</td>
<td>15.1</td>
<td>4.84</td>
<td>16.6</td>
<td>5.39</td>
</tr>
<tr>
<td>5. R superior frontal gyrus</td>
<td>30, 20, 46</td>
<td>8.7</td>
<td>3.87</td>
<td>4.6</td>
<td>2.75</td>
</tr>
<tr>
<td>6. L superior frontal gyrus</td>
<td>-20, -4, 62</td>
<td>14.6</td>
<td>4.71</td>
<td>2.72</td>
<td>5</td>
</tr>
<tr>
<td>B: Group x Cue Interaction: Orienting-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R pulvinar</td>
<td>16, -26, -4</td>
<td>19.5</td>
<td>4.42</td>
<td>14.8</td>
<td>4.00</td>
</tr>
<tr>
<td>2. R posterior insula white matter</td>
<td>36, -28, 10</td>
<td>20.3</td>
<td>4.50</td>
<td>14.5</td>
<td>3.19</td>
</tr>
<tr>
<td>3. R superior, middle temporal gyri</td>
<td>64, -26, 16</td>
<td>14.0</td>
<td>3.75</td>
<td>9.0</td>
<td>2.05</td>
</tr>
<tr>
<td>4. R angular, supramarginal gyri</td>
<td>54, -44, 40</td>
<td>13.2</td>
<td>3.62</td>
<td>8.8</td>
<td>2.11</td>
</tr>
<tr>
<td>5. R anterior insula, corona radiata</td>
<td>30, 18, 8</td>
<td>11.6</td>
<td>2.49</td>
<td>3.41</td>
<td>2.21</td>
</tr>
<tr>
<td>C: Group x Cue Interaction: Alerting-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. L anteromedial thalamus</td>
<td>-12, -8, 12</td>
<td>11.9</td>
<td>3.47</td>
<td>7.8</td>
<td>2.82</td>
</tr>
<tr>
<td>2. R anteromedial thalamus</td>
<td>8, -8, 12</td>
<td>15.0</td>
<td>3.88</td>
<td>8.9</td>
<td>2.90</td>
</tr>
<tr>
<td>3. Dorsal midbrain</td>
<td>2, -30, -14</td>
<td>13.0</td>
<td>3.60</td>
<td>7.5</td>
<td>2.71</td>
</tr>
<tr>
<td>4. Upper pons</td>
<td>-2, -26, -28</td>
<td>11.0</td>
<td>3.31</td>
<td>6.8</td>
<td>2.59</td>
</tr>
</tbody>
</table>

All F-values are p<0.05, corrected except ** that signify p<0.001, <0.01, uncorrected. All T-values are p<0.001, except *** , ** that signify p=0.001, <0.01, or <0.05.
Table 6 Regions showing interaction of lesion with attentional manipulation (Accuracy data)

Regions showing both group x flanker (or group x cue) interaction (F value reported), and a group effect for at least one of the three attention types (i.e. simple effect t-test thresholded at p<0.001, performed on pre-specified contrast, e.g. Conflict = incongruent – congruent flanker). T-tests for each of the three cardinal contrasts were performed at each F maxima. T values reported for Lesion+ vs. Lesion- reflect regression coefficient for lesion presence in a multivariable regression equation including age and lesion size as covariates. Final column lists regions compared with which dissociations occurred (location x attention ANOVA).

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coords.</th>
<th>Lesion+ vs Controls</th>
<th>Lesion+ vs Lesion- (other lesion sites)</th>
<th>N of lesions</th>
<th>Dissocn. P &lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x y z local maxima</td>
<td>F T Conflict T Orient T Alert</td>
<td>F T Conflict T Orient T Alert</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Group x Flanker Interaction: Conflict-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R middle corona radiata</td>
<td>28, 12, 14</td>
<td>21.6 5.28</td>
<td>11.1 3.68</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>2. R anterior corona radiata</td>
<td>26, 26, 16</td>
<td>13.5 4.23</td>
<td>6.6** 2.52*</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>3. R anterior insula</td>
<td>32, 6, -18</td>
<td>11.5 3.96</td>
<td>5.6** 2.62*</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4. R inferior prefrontal white matter</td>
<td>30, 36, -2</td>
<td>20.0 5.34</td>
<td>10.2 3.79</td>
<td>2</td>
<td>C1 (B1: p=0.088)</td>
</tr>
<tr>
<td>5. L lateral precentral gyrus</td>
<td>-54, 0, 32</td>
<td>14.9 4.50</td>
<td>7.0** 2.98**</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>6. L superior frontal gyrus</td>
<td>-18, -4, 72</td>
<td>17.1 4.13</td>
<td>9.4 2.85*</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>7. R posterior corona radiata</td>
<td>30, -34, 36</td>
<td>12.5 4.27</td>
<td>5.3** 2.54*</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>8. R occipital cortex</td>
<td>18, -60, 50</td>
<td>8.5 3.43</td>
<td>ns ns</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>B: Group x Cue Interaction: Orienting-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R temporoparietal junction</td>
<td>54, -50, 32</td>
<td>12.9 3.59</td>
<td>8.58*** 3.22**</td>
<td>4</td>
<td>(A4: p=0.088)</td>
</tr>
<tr>
<td>2. L temporal pole</td>
<td>68, -24, -10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: Group x Cue Interaction: Alerting-predominant effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R anteromedial thalamus</td>
<td>6, -12, 8</td>
<td>42.9</td>
<td>6.55</td>
<td>22.0</td>
<td>4.73</td>
</tr>
<tr>
<td>2. R lateral occipital - middle temporal gyrus</td>
<td>48, -62, 0</td>
<td>21.7</td>
<td>4.70</td>
<td>9.9</td>
<td>3.19**</td>
</tr>
<tr>
<td>3. R supramarginal gyrus (anterior)</td>
<td>54, -28, 30</td>
<td>15.1</td>
<td>3.88</td>
<td>6.5**</td>
<td>2.69*</td>
</tr>
<tr>
<td>4. R postcentral gyrus</td>
<td>32, -34, 60</td>
<td>11.9 3.25**</td>
<td>3.47 5.5**</td>
<td>2.37*</td>
<td>3</td>
</tr>
<tr>
<td>5. R middle corona radiata</td>
<td>28, 4, 12</td>
<td>11.6 2.22*</td>
<td>3.39 5.6**</td>
<td>2.37*</td>
<td>5</td>
</tr>
<tr>
<td>6. R frontal operculum</td>
<td>48, 14, -2</td>
<td>12.1</td>
<td>3.47 5.8*</td>
<td>2.41*</td>
<td>4</td>
</tr>
<tr>
<td>7. R midbrain - cerebral peduncle</td>
<td>16, -16, -14</td>
<td>14.6</td>
<td>3.83 6.5**</td>
<td>2.58*</td>
<td>4</td>
</tr>
</tbody>
</table>

All F-values are p<0.05, corrected, except ***, that signify p<0.001, <0.01, uncorrected. All T-values are p<0.001, except *, that signify p<0.01, or
3.3.8 VLSM: lesion x cue x flanker interactions

In controls, an interaction was shown between cue and flanker (F(3,183)=4.3; p<0.01), that could be broken down into an increase in conflict with alerting (F(1,61)=6.5; p=0.01), but a decrease in conflict with orienting (most apparent for selective-cue versus double-cue; F(1,61)=12.9; p<0.001) (Figure 14 - dashed line). In order to establish whether certain lesion locations changed this control profile, we performed a group x cue x flanker ANOVA in each region also showing group x flanker, or group x cue, interactions (Appendix Supplementary Data 2).

For RT data, RMCR and inferior prefrontal white matter, that had shown greater lesion-associated conflict, also showed group x flanker x cue interactions (for RTs; F≥4.1; p<0.001; Figure 14A). These could be accounted for by two effects: firstly, alerting decreased conflict in Lesion+ (p<0.05); secondly, orienting increased conflict in Lesion+ (p<0.01); thus reversing the profile seen in controls. An alternative way of interpreting the interaction is that Lesion+ heightened conflict in all conditions except central-cue, given that, in addition to the above two effects, there was higher conflict with double-cue relative to central-cue (p<0.05).

For accuracy data, right RTPJ lesions resulted in a similar group x cue x flanker interaction profile (p<0.001; Figure 14B) as described above for RMCR – i.e. less conflict for alerting (p<0.01) but increased conflict with orienting (p<0.05). One interpretation of increased conflict with orienting - and more generally, of decreased accuracy with orienting, noted earlier – is that peripheral, but not central, cues misdirected attention towards flanker, rather than target, locations (Làdavas et al. 1994a). This is supported by the observation that, with RTPJ lesions, but not Controls, or lesions elsewhere, orienting worsened accuracy similarly for both neutral and incongruent targets, relative to congruent targets, (p<0.001; compare lower panes of Figures 14A and 14B). Since errors to neutral targets in the RTPJ lesion group were more likely to be due to omissions (as opposed to incorrect responses), rather than errors with incongruent targets (93% vs 61%; p<0.05), then this is consistent with patients’ responses to peripheral cues reflecting flanker, rather than, target visual properties.
Interactions of group x flanker (or cue) x target location x target direction, in each of the regions presented as influencing conflict, orienting and alerting, are described in Appendix Supplementary Data 3.

![Figure 14 Plots of Conflict Size Against Cue Type](image)

Conflict size (Incongruent - Congruent Flanker, expressed as % of mean) against Cue type, for each subject group, demonstrating significant Group x Cue x Flanker interactions (p<0.001) in A: right middle corona radiata (for RTs) and B: right temporoparietal junction (for accuracy). For RTs, Controls (dashed line) showed a significant Cue x Flanker interaction due to greater conflict with alerting, but less conflict with orienting - both of which patterns were reversed in these lesion groups. The lower figures for each of A and B indicate the raw values of RT and accuracy, for each cue type, and for each flanker. Note that for right temporoparietal lesions, spatial cues resulted in poorer accuracy for both neutral and incongruent targets (arrowed), a pattern not seen elsewhere, and possibly indicating that such subjects were misdirected by spatial cues towards flanker locations.
3.4 Discussion

In this chapter we explored the impact of attention deficits in an acute stroke population and examined the relationship between lesion location and the attention type impaired. We have identified three distinct sets of lesion locations that result in selective impairments to one of either conflict-resolution, orienting, or alerting functions (Fan et al. 2002). The strongest associations found are: conflict-resolution with bilateral prefrontal (including premotor) areas; orienting with right pulvinar and right temporoparietal regions; and alerting with anteromedial bithalamic nuclei and upper brainstem. The fact that these anatomical pairings are largely non-overlapping, and that relative performance on the three measures differs significantly between the three sets of regions, provides strong support for the Posner independent attention network model (Petersen & Posner 2012). Further to these neuroanatomical findings, our results hold implications from a clinical perspective with more than half of our unselected sample of stroke patients contributing to 1 of the 3 principal anatomical networks and showed associated attentional dysfunction while a far smaller proportion actually had neglect or inattention clinically diagnosed and recorded.

3.4.1 Attention Network Dissociations

Whereas previous evidence for network independence has come from directly comparing attentional functions with the ANT, using solely behavioural (Fan et al. 2002; Callejas et al. 2004), functional imaging (Fan et al. 2005; Thienel et al. 2009), or structural imaging methodologies (Westlye et al. 2011; Yin et al. 2011), our results provide causal neuroanatomical evidence by demonstrating behavioural dissociations between the ANT components, in patients with different lesion locations.

Our results are also important in assessing the extent to which functional dependency is proportionate between anatomical sites. In particular, it provides a reconciliation between the facts that: 1) clinical neurology clearly recognizes distinct attentional syndromes secondary to lesions in different brain regions; and that 2) more detailed probing of certain nodes - especially within right frontoparietal cortices - indicates a critical role for them in more than one type of attention (Nachev & Husain 2006; Corbetta & Shulman 2011). To the extent that we found the three ANT measures were dependent
upon spatially separate regions, we can conclude that most parts of the putative attentional networks
do not share equally in their participation with these three functions. Only a small volume of regions
showed associations with more than one type of attention, e.g. inferior right middle corona radiata
(RMCR) lesions impaired both conflict-resolution and orienting; and anterior insula lesions degraded
all three types of attention. Our additional finding that lesions to right frontoparietal areas altered the
interaction between ANT components, indicates that these regions account for interdependency
between networks. The following sections will discuss these findings in further detail.

3.4.2 Conflict-resolution

The most significant region where lesions impaired conflict-resolution were found in premotor areas
(RMCR), and those involving predominantly prefrontal-to-precentral gyrus association fibres. As
such, this area is more posterior, or downstream within the frontal processing hierarchy than the usual
spatial loci attributed to conflict processing, i.e. the dorsal anterior cingulate cortex (ACC)
(MacDonald et al. 2000; Botvinick et al. 2004; Westlye et al. 2011; Yin et al. 2011) and dorsolateral
prefrontal (DLPF) (MacDonald et al. 2000) or inferior prefrontal (Egner 2011) cortices. Voxel-based
morphometry (Westlye et al. 2011) and tractography (Yin et al. 2011) studies in healthy adults,
performing the ANT, have also shown correlations between conflict and structural measures of
cingulate and prefrontal cortices, as well as of anterior - rather than middle - corona radiata. While
some of our results are consistent with these findings - in that damage to (right) anterior corona
radiata and inferior prefrontal cortex resulted in impaired conflict resolution – the fact that the greatest
effect on conflict was localized to premotor regions deserves explanation.

One reason for this discrepancy may be on account of lesion-sampling bias. Both medial and anterior
prefrontal regions were not adequately assessed by our study owing to the rarity of strokes that affect
these locations (Nachev 2011), and so are poorly represented in our sample (Figure 3). Conversely,
right RMCR, as one of the most populous sites for stroke, would have had greater statistical power to
manifest a significant result than more anterior, prefrontal regions. Nevertheless, both the effect size
and significance level were greater for lesions to RMCR, than more anterior lesions. Moreover, the
fact that there was no difference in conflict between lesions affecting RMCR alone, compared to those in overlapping right prefrontal regions, implies that RMCR lesions are sufficient to impair conflict processing, and not that this effect is due to a tendency for some RMCR lesions to extend anteriorly.

Does other evidence support our finding that conflict-resolution depends upon integrity of premotor cortex, and its associated white matter inputs, in addition to more anterior structures? Recently, the dogma that the ACC and DLPF cortex serve as conflict-monitoring and action-control modules, respectively, has been challenged (Grinband et al. 2011). According to an alternative “hierarchical” model of motor control, based partly upon single-unit recordings from monkeys, that both premotor (including supplementary motor complex) and prefrontal regions are involved in rule-based, action decisions, with more anterior units becoming engaged as the number and complexity of stimulus inputs required to weigh up decisions increase (Nachev et al. 2008; Badre & D’Esposito 2009). In other words, the position along an anteroposterior frontal axis at which units become activated depends upon the number and complexity of rule inputs. By this account, premotor lesions might be sufficient to impede conflict processing, when the stimulus components that generate conflict are relatively low order, as is the case for the ANT (Fan et al. 2009). Consistent with this, both functional imaging (Hanakawa et al. 2002; Badre & D’Esposito 2009) and lesion studies (Badre et al. 2009), show that competition between responses, guided by stimulus features that vary along only one or two dimensions, activates, or depends upon premotor cortices.

Moreover, our finding that conflict processing was impaired most strongly with lesions to prefrontal–premotor white matter projections, supports functional imaging findings of prefrontal–premotor coactivation during conflict, where competition occurs at the level of response (Egner et al. 2007; Melcher & Gruber 2009) or stimulus (Kim et al. 2010). Since conflict-specific premotor modulations often co-occur with anterior cingulate - DLPFC activations, and given anatomical evidence for hierarchical control between these regions (Badre & D’Esposito 2009), then premotor cortex may represent the most downstream end of a conflict-resolution network. This would account for our finding that processing of incongruent, but not congruent, stimuli are impaired with lesions to white
matter projections from prefrontal to premotor cortices. One mechanism by which such a hierarchy could operate is through premotor cortex suppressing prepotent responses (Picton et al. 2007; O’Shea et al. 2007), or itself being suppressed by higher control centres. However, while such a model predicts that premotor cortex lesions would result in poorer accuracy on incongruent trials – as we found; this model would also predict disinhibition on the same trial type – when in fact we found slower, rather than faster, responding. The latter finding implies that premotor cortex may be (at least) one site where competing responses are resolved (see also Soto et al, 2009 for a similar conclusion drawn from TMS applied to motor cortex (Soto et al. 2009).

Given the large number of white matter tracts that course through, or close to, the RMCR conflict-heightening cluster, we cannot exclude the possibility that structures other than premotor regions are critical to the deficit observed. Thus, disruption of anterior right superior longitudinal fasciculus (SLF), and thalamo-prefrontal projections may also have contributed to the deficit observed. The right SLF, in particular, is likely to be a critical link within a fronto-parietal attentional network, and its integrity has been shown to correlate with executive function (Makris et al. 2008; Seiler et al. 2011); possibly by potentiating signal gain in anterior areas (Roberts et al. 2010). Our additional finding that anterior insula lesions increase conflict is in line with other lesion (E. J. Coulthard et al. 2008) and functional imaging studies (Coxon et al. 2009); that indicate an inferior frontal - anterior insula 'cognitive control' network (Tops & Boksem 2011).

3.4.3 Orienting

In contrast to the anatomical pairings we found for conflict, the associations found for orienting matched more closely those reported from functional imaging of the ANT, and from lesion studies testing these functions in isolation. Lesions to both right posterior parietal and superior temporal regions classically show the strongest associations with spatial hemineglect (Verdon et al. 2010; Ptak & Schnider 2011), that is characterized by a lateralized orientation deficit. This impairment is sensitive to cue competition, indicating a problem with attentional disengagement (Posner et al.
1984). By contrast, lesions to pulvinar are not as sensitive to cues, implying a purer orientation, or engagement, deficit (Posner & Petersen 1990).

We found that slowing to selective cues was most significant for lesions to right pulvinar and right temporoparietal junction (RTPJ); although the orientation deficit secondary to parietal lesions could be interpreted within the above framework as a failure to disengage from central fixation. We also note that in our study, patients with lesions to both of these areas showed a deficit in vertical orienting, with both upwards and downwards orienting impaired, supporting a model of right posterior parietal cortex as processing spatial orienting in general, and not just lateralized orienting (Nachev & Husain 2006). Vertical orienting deficits have previously been described with RTPJ lesions (Rapcsak et al. 1988; Shelton et al. 1990; Pitzalis et al. 1997). However, with cueing having been shown to be most impaired in either lower, or upper, sensory fields, depending upon lesions occurring in predominantly parietal or temporal regions (Mennemeier et al. 1992), it is possible that our RTPJ lesion set straddled both these upper and lower hemifield representations. Additionally, orienting dysfunction was greater for left than right-pointing targets, indicating that the overall effect manifest itself due to a double challenge of vertical cueing, plus leftwards (sensory, motor or object-based) neglect.

3.4.4 Alerting

Although less well defined by previous research, as with orienting our anatomical correlations for alerting pair well with suggested alerting network architectures. Firstly, ascending norepinephrinergic fibres, between locus coeruleus, reticular thalamic nuclei and cerebral hemispheres, are important in mediating intensity aspects of cognition activation systems (Coull et al. 1997), with lesions here resulting in reduced arousal or consciousness (Schmahmann 2003; Gompf et al. 2010). Our results strongly support this model, with the distribution of lesions that reduced speeding to alerting cues – in paramedian, dorsal upper pons and midbrain (upper brainstem) – fitting well with the locus coeruleus and its proximate projections. Similarly, lesions to bilateral anteromedial bithalamic nuclei also impaired alerting, and it is through these regions that norepinephrinergic fibres are known to be
concentrated before fanning out to diffuse frontal and then parietal regions (Posner & Petersen 1990). The second proposed alerting system is located in ventral regions of right hemisphere, including temporoparietal junction and inferior prefrontal cortices (Thiel & Fink 2007; Corbetta & Shulman 2011), although some functional overlap may occur with the more dorsally-placed nodes of an orienting network (Malhotra et al. 2009; Bays et al. 2010). This might account for our additional finding that several small areas across right>left cerebral hemisphere – including posterior temporal cortex – reduced any accuracy advantage of double cues versus no cues (a similar non-significant trend can also be seen for right angular gyrus).

3.4.5 Attention Network Interactions

While in principle we have confirmed separable anatomical networks for the 3 attention types, our results are also important in assessing the extent to which functional dependency is commensurate between certain anatomical sites. In addition to our primary results, we found evidence for inter-network interactions and, to a lesser extent, overlap (e.g. in anterior insula), indicating a critical role for such areas in more than one type of attention (Nachev & Husain 2006; Corbetta & Shulman 2011). Lesion locations in pivotal regions of right hemisphere that had shown strong conflict- or orienting-specific deficits, showed a reversal of the normal profile by which alerting and orienting influence conflict (Callejas et al. 2005).

The first finding - that with right inferior frontal, RMCR and RTPJ lesions, alerting ameliorates conflict processing - supports studies showing that alerting may enhance other attention types when they are suboptimal (e.g. due to disease), whilst being counterproductive when attention is optimal (Chica et al. 2011; Robertson et al. 1998). This interaction implies that RTPJ, in addition to frontal regions, contributes to conflict processing; possibly via its role in registering unexpected/ uncued events (Corbetta & Shulman 2011; Bonnelle et al. 2012), that is a prerequisite for subsequent conflict-resolution.
The second finding - that with RMCR-prefrontal and RTPJ lesions, orienting worsens conflict processing - may be because right hemisphere lesions result in impaired processing at the same locations as preceding spatial cues, (i.e. ‘attentional blink’) (Husain et al. 1997; Correani & Humphreys 2011). Alternatively, lesions here may have engendered inappropriately vectored orientation (Ladavas et al. 1994b), or motor plans (Nachev et al. 2008), with spatial rather than central cues. Finally, the fact that lesions to RTPJ and anteromedial thalamus impaired performance across all conditions underlines the importance of these regions in mediating general responsiveness or sustained attention (Malhotra et al. 2009; Clemens et al. 2011) as well as orienting and phasic alerting, respectively. By contrast, lesions to RMCR engendered a deficit specifically under high-conflict conditions, matching results of previous studies of frontal lesions (Alexander et al. 2007).

3.4.6 Limitations and Methodological Considerations

A practical issue with the use of acute brain injury patients is that being at the maximum of their disability, they are often intolerant of prolonged testing. This explains why we were forced to use a shorter version of the original ANT. Although patients could have been retested on the ANT at repeated time points, so as to verify intra-subject reliability (Macleod et al. 2010), we expected that differences over retesting would have been likely, given that performance variation is highest in the first few weeks. Rather, the reliability of our findings is expressed through inter-subject concordance across anatomically-related networks. Thus for each of the principle anatomical associations with the ANT components that we report, there are at least ten patients that contribute to these effects, either as single clusters (e.g. RMCR for conflict-resolution), or across homologous (e.g. right and left anteromedial thalamus for alerting), or anatomically-connected regions (e.g. right pulvinar and superior parietal regions for orienting; prefrontal and premotor regions for conflict). Furthermore, the fact that many regions showed similar attention-specific effects for orthogonal measures of RT and accuracy provides further verification.

To minimize confounds of stress and neurological disability, we included control patients who presented with focal disability but who had normal brain scans. Their performance was not
significantly different from healthy aged-matched controls. Furthermore, we confirmed that associations of lesion locations with functional impairments were not confounded by lesion size or age. While having an acute focal lesion per se, regardless of location, detrimentally affected overall performance, this did not cause significant changes in the relative strength of attentional effects. Nor were there correlations between lesion size and ANT scores. These facts argue against any attention type, being dependent upon a 'mass action' feature of brain function, e.g. of alerting being due to pan-cerebral release of norepinephrine or acetylcholine (Descarries et al. 1997).

Finally, although the VLSM approach used here allows for more robust, population-level inferences about lesion-deficit relationships to be made through the aggregation of data from many patients, the ‘mass univariate’ approach used may result in errors due to its inability to describe the influence of one damaged voxel onto another. Thus, future work may explore the use of more recently developed ‘multivariate’ approaches capable of capturing how the presence or absence of damage at every voxel is related to damage in all other voxels (Mah et al. 2014). Use of such analytical techniques has shown that hidden bias does exist in standard VLSM approaches, suggesting that such high-dimensional techniques warrant further investigation when employing voxel-lesion analyses.
3.5 Conclusion

3.5.1 Triple dissociation of attention networks

Employing and merging the use of a VLSM technique and a one-off ANT task in a 110 patients of anatomically-unselected focal lesions, allowed us to combine the advantage of a pan-brain, data-driven approach of functional imaging, with the superior inferential value of lesion studies, to assess for anatomical correlates of the three cardinal types of attention. Our findings provide strong evidence for the triple dissociation of the attention functions, subserved by three anatomically-segregated, albeit interdependent, networks (Posner 2011). While the regional associations we found for orienting and alerting concord well with classical models of attention, our association of premotor regions with conflict support a hierarchical organization of executive function across frontal regions (Badre & D’Esposito 2009). This association with higher order motor regions has important implications for linking the role of attention-control with motor impairment and recovery following stroke, with activation of these regions along the frontal-parietal axis shown to be vital for motor-learning (Albert et al. 2009; Meehan et al. 2011), thus critical for effective rehabilitation of motor function.

3.5.2 Clinical Importance

As well as consolidating the influential neurobiological theory of a tripartite attention system, our results also have important clinical resonance. More than half of our unselected sample of stroke patients contributed to 1 of the 3 principle anatomical networks showing specific associations with 1 of the 3 attention network functions; while a far smaller proportion actually had any clinically-obvious attentional deficit or neglect. These results support observations showing that clinically relevant attentional deficits may be missed by crude bedside examination, but detectable by computer based tests (Westlye et al. 2011; Posner & Fan 2013), and indicate those lesion locations most at risk of attentional deficits, for which more thorough assessment might be worthwhile. The ability to detect subtle attention deficits and the potential to use lesion location as a marker of specific attention function is interesting, not only because attention deficits can impact upon motor impairments (Robertson et al. 1997; Leśniak et al. 2008); but because each of the three attention networks can be
influenced by separate pharmacologic (Petersen & Posner 2012), electrical (Schiff et al. 2011), or computer based cognitivebehavioral therapies (Posner & Fan 2013; Posner et al. 2015), thereby suggesting our results might help in the stratification of patients for rehabilitation. Finally, apart from stroke, normal aging, dementia, and many psychopathologies of adults and children alike, involve specific problems of the 3 attentional networks (Rothbart & Posner 2006), and so may also benefit from training via such computer based attention games as the ANT.
CHAPTER FOUR: ASSESSING ATTENTION DEFICITS AND MOTOR PERFORMANCE RELATIONSHIPS: DEVELOPMENT OF A NOVEL TASK
4.1 Introduction

Attention, and specifically the subcomponent of executive function, is known to play a fundamental role in the learning-dependent processes of neuroplasticity (Kamke et al. 2012). Motor related neural plastic reorganisation in both the healthy and damaged brain requires repetitive skill-use with the addition of complex task-oriented and task-specific training (Walker-Batson et al. 2004; Nudo 2011). It is the ability to complete such complex tasks for which executive functions are critical, allowing for the effective selection of pertinent information stimuli, whilst ignoring unnecessary stimuli, in order to choose an appropriate action (Petersen & Posner 2012). It may therefore be assumed that executive functions are a critical component of motor-learning, and, importantly, re-learning post stroke. Unfortunately, studies investigating the effect of attention deficits on motor performance in stroke survivors remain scarce. With motor-learning forming such an important part of the majority of stroke patients’ recovery (Langhorne et al. 2011), the effects of distracting stimuli within a rehabilitation environment (e.g. noise, pain, other patients and staff, etc.) on a patient’s motor performance warrant further investigation.

Motor-learning requires the effective integration of perceptual information with the controlled and corresponding output of motor actions. This integration of visually led attention to external stimuli and action generation is termed visuomotor control (Sanes & Donoghue 2000). It is the process of visuomotor learning that is responsible for acquiring the knowledge behind a novel pattern of muscle activations in a temporal and spatial manner that matches the requirement of the complex task at hand (Sanes & Donoghue 2000). Thus, visuomotor control is integral to normal daily living, and, in the case of post stroke rehabilitation, the recovery of motor functions. Studies utilising simple visuomotor tracking tasks have shown that repetitive practice is capable of stimulating learning associated increases in fronto-parietal network connectivity (Vidoni et al. 2010; Meehan et al. 2011). Visuomotor learning-dependent models now form the basis for training led rehabilitation interventions following stroke, showing strong evidence of neural plastic stimulation and correlation to improved motor recovery (Hodics et al. 2006; Richards et al. 2008).
Executive control functions as a decision making system for visuomotor control. It is not only responsible for the initiation and modification of actions (McDowd et al. 2003; Fitzpatrick & Baum 2012), but also for generating and implementing strategies, drawing on working memory (WM) stores, in order to allow completion of complex movements (Anguera et al. 2010). Although a number of separate mechanisms of executive control have been described; e.g. conflict monitoring, error detection, motor inhibition (Raz 2006; Petersen & Posner 2012), the focus of this chapter remains on the mechanism of conflict-resolution, i.e. the ability to process multiple stimuli and resist those that are not pertinent to task objectives (i.e. distractors), here on in termed attention-control.

The mechanisms and neuroanatomical associations underlying conflict-resolution have been extensively explored in both healthy subjects (Nee et al. 2007), and stroke patients (Vendrell et al. 1995; Stuss et al. 2001; Coulthard et al. 2008; Posner & Fan 2013; and in Chapter Three of this thesis), through a variety of conflict interference behavioural tasks (i.e. Stroop, flanker, go/no-go, stimulus–response compatibility, Simon, and stop signal tasks). However, such tasks focus on the subject performing one-off actions after selecting an appropriate response (serial reaction time tasks (SRTT)), which does not translate into the complex nature of visuomotor learning that is required for functional movement re-training following stroke. No paradigm effectively stimulates both attention-control and visuomotor control, and allows for qualitative and quantitative measures of the different components.

In this chapter we develop a novel task capable of exploring the relationship between impairments in attentional-control and visuomotor control in an acute stroke population. Previous studies may not have attempted this due to the difficulty in dissociating attention associated motor deficits from pure motor deficits. Thus, in order to validate the novel task, motor performance in relation to distractors will be assessed bilaterally in order to gain an understanding of any global attention-motor deficits that a patient suffering from unilateral motor impairment may be experiencing. Behavioural results will be further validated using measures of neuroanatomical analysis, in an attempt to differentiate attention-control and motor deficits through association of the well characterised brain regions and networks of each function. We hypothesis that the degree to which a patient suffers from attention-
control deficits will correlate to their motor control performance and that any such relationship between deficits will be related specifically to damage in brain regions and functional networks known to support executive functions.

**Aims of the Study**

- To develop a novel visuomotor-skill task under escalating conflict, measuring how motor accuracy is influenced by attentional control.
- To use this novel task to investigate the relationship between stroke-related attention deficits and motor performance
- To assess how stroke lesion location determines the extent of attention-motor dysfunction
- To relate attention-motor dysfunction with the integrity of attention and motor functional brain networks
4.2 Methods

4.2.1 Subjects

Right-handed patients with unilateral arm paresis, and/or impaired dexterity, due to recent stroke (<4 weeks), confirmed on MRI or CT, were screened at the Imperial College NHS Healthcare Trust Hyper Acute Stroke Unit, Charing Cross Hospital. Exclusion criteria were: 1) severe finger-flexion weakness (MRC power grade <2); 2) pre-existing, or bilateral, arm impairment; 3) history or examination evidence of cognitive impairment, Mini-Mental State Examination <27, or errors on clinical frontal lobe tests (including Trail-Making part B); 4) sensory or motor neglect (assessement of repetitive hand movements in each hand individually and then in both together. A significant decrease in the speed on bilateral movements denoted motor neglect (E. Coulthard et al. 2008)); 5) comprehension difficulty; 6) clinical anxiety or depression (Hospital Anxiety and Depression Scale); 7) severe cerebral white-matter disease or other brain lesions; 8) clinically diagnosed visual impairments. Age-matched controls were either healthy volunteers, or non-stroke patients (e.g. migraine) who had no arm deficit symptoms or signs; no significant brain MRI lesions; but otherwise fitted the above inclusion and exclusion criteria. Subjects were excluded who were unable to perform the Tracking task with either hand with ≥10% accuracy (i.e. chance level).

For the Precision task and Non-motor tasks, we recruited a separate pool of patients, disregarding affected arm ability, to explore whether effects observed with Tracking generalised to more severe paresis. All recruited participants gave written and signed informed consent. Ethical approval was granted by the NRES Committee South East Coast-Kent Committee.

4.2.2 Novel Visuomotor Tracking Task

Design and development of the novel visuomotor tracking task was performed using E-Prime software (V2.0) (http://www.pstnet.com/eprime.cfm) and displayed to subjects on an Intel-Centrino hp-laptop running Windows XP, on a 15" colour monitor. Interaction with the task was facilitated through a commercially available digital hand-grip force sensor – ‘Grip Force’ – developed and supplied by ‘Current Designs’ (http://www.curdes.com/mainforp/response_devices/hhsc-1x1-grfc-
The hand-grip utilised a spring based mechanism with a protruding force bar that moves in when gripped to produce a roughly linear force measurement output based on the pressure applied. The hand-grip had a sensitivity range of <100N. A hand-grip was selected as the manipulandum of choice as the ability to perform hand-grip has been shown to return relatively early compared with more complex fractionated finger movements following stroke (Heller et al. 1987), thus allowing for the inclusion of a larger spectrum of paretic patients. The neural correlates and reorganisation of activity following performance of visual feedback tasks controlled through hand-grip force sensing have also been well documented (Ward & Frackowiak 2003; Ward, M M Brown, et al. 2003; Ward & Frackowiak 2006). Patients and controls were tested for motor dexterity and strength using the visuomotor tracking task and a secondary Force task respectively.

The Tracking task consisted of a green star (1.2°) moving up and down the screen, the temporal profile of which described a polynomial sine-cosine function (Meehan et al. 2011), varying trial-to-trial, but fixed between patients. Subjects tracked the star by varying force on the handgrip, that proportionately moved a crosshair, which when overlying the star turned it pink (Figure 15).

Attention-control was manipulated by varying the number of Distractor stimuli (0,1,3), that moved asynchronously relative to the target, and had overlapping characteristics with the target (e.g. same colour, different shape) (Figure 16). The task also varied Speed (number of target direction changes per trial: slow = 4-6 versus fast = 8-12, during a 16 second time window). The main results of this study are restricted to the performance of the slow trials; fast trials were used only to match baselines between groups and to test whether conflict size was dependent upon tracking speed.

Performance was calculated as percentage time the crosshair overlay the target star, across a 16 s trial, x 16 trials per hand. Subjects rested for 6s between trials. Hand-use alternated twice across a session (RLRL/ LRLR), with the order counterbalanced across subjects. Subjects practiced for 8 trials prior to the test session. The software was calibrated initially so that the greatest vertical crosshair excursion corresponded to 70% of a subject’s maximal grip force, up to 70N.
CHAPTER FOUR: ASSESSING ATTENTION DEFICITS AND MOTOR PERFORMANCE RELATIONSHIPS

Figure 15 Tracking task

Example of the visuomotor tracking task without distractors. Green star (Target)

Figure 16 Tracking task with addition of distractors

Tracking and Precision tasks required subjects to vary grip-force, thereby moving a crosshair (X) onto a target (T) that moved vertically (Tracking), or was stationary (Precision), in presence of 0, 1 or 3 distractors (D).
4.2.3 Attention-Control and Grip Force Analysis

Attention-control was measured in two ways. Firstly, performance accuracy was entered as a dependent variable into an ANOVA with factors: Distractor number, Hand-Use, Speed and Group (between-subject factor). Secondly, we calculated normalised conflict as the difference in performance between 0 and 3 Distractors, divided by baseline (0 Distractor) performance. This then became the dependent variable in an ANOVA with factors Hand-Use, Speed and Group.

The Force task required subjects to grip maximally over a 7s window, whilst recording peak force relative to the device’s maximum range. Visual feedback was provided as a vertical bar proportionate to force. Four trials per hand were performed, split either side of the Tracking task. Performance on this task was related to conflict during the Tracking task.

4.2.4 Precision-grip and Non-motor Control Tasks

Subsequently, we tested variations of the Tracking task: Precision-grip and Non-motor control - to see if results observed with Tracking generalised to tasks without speeded pursuit, and motor, elements of this task respectively. The Precision task was similar to that of Tracking, except the target remained stationary for 8 s, changing position once per trial. Performance assessment excluded the first 2 s of each trial.

The Non-motor task was similar to the slow Tracking task, only now subjects paid attention to the star’s colour (red/green/blue/pink), movement direction (up/down) and whether a crosshair, no longer controlled by the subject, overlay it (yes/no). Characteristics changed every 2 –4 s. Trials varied 4 – 16 s in duration, and subjects were immediately afterwards probed for the star characteristics just before trial termination, via three successive questions (subjects were told that only response accuracy was important; not response time). Accuracy reflected the proportion of trials in which all three characteristics were correctly remembered. Attention-control was manipulated by adding, in half of the trials, 3 distractors, e.g. incomplete stars (Figure 17). The same subjects also performed the Tracking task, the undistracted version of which was related to Non-motor conflict.
Statistical tests were non-parametric throughout all behavioural tasks analysis and performed in MATLAB (2012b) (http://uk.mathworks.com/products/matlab/).

4.2.5 Voxel-Lesion Symptom Mapping

Acute stroke lesions were manually delineated by an experienced stroke scientist on patients’ DWI-MRI images and spatially normalised using SPM8 (For detailed methodology on lesion delineation and image pre-processing see Chapter Two, Methods). To increase power, and given similar performances of right and left hemiparetic patients, left-sided lesions were flipped onto the right-side. Summary lesion-overlay maps of patient numbers with high-versus-low conflict and R-L hand differences (both measured during Tracking task) were projected in MRICroN. For conflict, we used a VLSM analysis (Brunner-Haenstel and Liebermeister tests) to assess all regions showing high versus low conflict. For both conflict and R-L conflict we also tested theoretically-driven hypotheses that: high conflict and high laterality difference would correlate with lesion overlap of a fronto-thalamic-striatal network (FTS) and corticospinal tract-motor cortex (CST) respectively.

Figure 17 Non-motor task

Test:
2. Up/Down? (U,D,DK)
3. Crosshair? (Y,N,DK)
4.2.6 Functional Connectivity Analysis

A separate group of hemiparetic stroke patients and controls underwent a resting-state BOLD FMRI protocol (Siemens Verio 3T scanner). For each subject data from a single resting-state scan lasting 6 min 30 sec (192 frames, repetition time (TR) 2s, echo time (TE) = 25ms, voxel- size 3.4 x 3.4 x 4mm, 32 slices, flip angle (FA) 90°, field of view (FoV) 220mm) was gathered. During the scan, subjects were instructed to keep their eyes open and maintain fixation on a central cross displayed on a LCD TV screen. Analysis of resting-state time-series data proceeded the following pre-processing stages, using FSL software (www.fsl.fmrib.ox.ac.uk/fsl/, v 3.10): removal of non-brain tissue, and the first 6 volumes per scan; temporal highpass and lowpass filtering; motion correction, normalization of the voxelwise variance; spatial smoothing; registration to standard MNI space; and exclusive masking of acute-stroke lesions (from co-registered DWI). Resting-state component generation was performed using group concatenation Probabilistic Independent Component Analysis (Beckmann and Smith, 2004) as implemented in MELODIC Version 3.10, part of FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC#Melodic_GUI).

MELODIC generated a set of anatomical networks; characterised with reference to a healthy-control dataset gathered from the same scanner (n=54), which enabled the 8 most well-characterised and robust RSNs to be distinguished (Beckmann et al. 2005). For each subject, measures of connectivity strength (activity cross correlation coefficient between the top 0.1% of peak voxels) within each network was correlated against accuracy on the subsequent tracking task. (For detailed methodology on image pre-processing and rs-fMRI analysis see Chapter Two, Methods).

4.2.7 Functional Connectivity Visuomotor Task

Immediately after the Rs-fMRI block, subjects performed a variant of the hand-grip visuomotor Tracking task. In this version, only the paretic (or right hand in controls) was tested; and only the slow target, undistracted condition was used. Combining data from subjects using different hands is justified from behavioural results of the main study, showing that, intersubject variation of Tracking accuracy is roughly 6-fold larger than intrasubject between-hand accuracy variation. Active trials
varied in length between 6 – 15s, with rest intervals of 6 – 15s, over a 6.5 minute epoch. Accuracy was calculated as the proportion of time the crosshair overlay the target. Subjects were trained and practiced the task for 2 minutes beforehand.
4.3 Results

4.3.1 Test Population

In total: 92 patients and 49 control subjects were recruited for the Tracking task experiment; 27 patients and 10 controls for the Precision experiment; 25 patients and 11 controls for the Non-motor experiment; and 23 patients and 23 controls for the rs-fMRI experiment. Subject characteristics for each separate sub-experiment are described in Table 7 A, B, C, D. There were no significant differences between R-weak patients, L-weak patients and controls in terms of age, gender, handedness, background cerebral white-matter disease (Wahlund et al. 2001) and anxiety, but patients reported slightly more depression (median difference 1/15 points; \( p<0.002 \)). L-weak patients had larger lesions than R-weak patients (median 8 vs 3 cc; \( p=0.001 \); Tracking and Force experiments only), although function and strength measures of affected arms were matched between the two patient groups.

Table 7 Subject characteristics for separate sub-experiments

**A. Subject characteristics (Tracking and Force experiments)**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>R-hand weak†</th>
<th>L-hand weak†</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>49</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>56 (45 - 70)</td>
<td>57 (45-65)</td>
<td>63 (55-69)</td>
</tr>
<tr>
<td>Males / %</td>
<td>59</td>
<td>62</td>
<td>69</td>
</tr>
<tr>
<td>Handedness (EHI)</td>
<td>90 (89 - 100)</td>
<td>100 (90 - 100)</td>
<td>100 (90 - 100)</td>
</tr>
<tr>
<td>NIHSS – overall /42</td>
<td>0</td>
<td>5 (3 - 6)</td>
<td>4 (3 - 5)*†</td>
</tr>
<tr>
<td>HADS – Depression /15</td>
<td>2 (2 -3)</td>
<td>3 (2 - 4)</td>
<td>3 (2 - 5)*†</td>
</tr>
<tr>
<td>HADS – Anxiety /15</td>
<td>2 (2 - 3)</td>
<td>3 (2 - 4)</td>
<td>3 (2 - 4)</td>
</tr>
<tr>
<td>Age-Related White Matter Score /3</td>
<td>1 (1 - 1)</td>
<td>1 (1 - 1)</td>
<td>1 (1 - 2)</td>
</tr>
<tr>
<td>Lesion volume /cc.</td>
<td>0</td>
<td>3.3 (1.1 – 6.0)</td>
<td>8.1 (3.8 – 20.1)<em>†</em>‡</td>
</tr>
</tbody>
</table>
# Chapter Four: Assessing Attention Deficits and Motor Performance Relationships

## Arm Specific Tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS – arm motor /4</td>
<td>0</td>
<td>1.5*</td>
<td>2*</td>
</tr>
<tr>
<td>(0: normal)</td>
<td></td>
<td>(1 - 2)</td>
<td>(1 - 2)</td>
</tr>
<tr>
<td>Short Fugl Meyer arm function /12</td>
<td>12</td>
<td>9.5*</td>
<td>8.5*</td>
</tr>
<tr>
<td>(12: normal)</td>
<td></td>
<td>(8 - 12)</td>
<td>(7 - 10)</td>
</tr>
<tr>
<td>Grip force /%</td>
<td>100</td>
<td>98*</td>
<td>93*</td>
</tr>
<tr>
<td>(100% ≡ ≥100N)</td>
<td></td>
<td>(92-100)</td>
<td>(70-100)</td>
</tr>
</tbody>
</table>

* Median (interquartile range).
*1 p<0.01, all patients vs controls. *2 p<0.01, L-weak vs R-weak patients. *3 p<0.01, affected-arm vs equivalent arm in other groups (e.g. L arm in L-hand weak group vs. L arm in other groups). All other group comparisons are insignificant (p>0.05), including comparing affected arms of R-weak versus L-weak (Kruskal-Wallis, rank sum or chi2-tests where appropriate).

**B. Subject characteristics (Precision experiment)**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>68 (52 - 74)</td>
<td>58 (50 - 70)</td>
<td>68 (49 - 82)</td>
</tr>
<tr>
<td>Males / %</td>
<td>60</td>
<td>85</td>
<td>57</td>
</tr>
<tr>
<td>Handedness (EHI)</td>
<td>90 (90 - 90)</td>
<td>90 (90 - 100)</td>
<td>90 (80 - 100)</td>
</tr>
<tr>
<td>RH = ≥ +40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS – overall /42</td>
<td>0</td>
<td>4 (3 - 5)</td>
<td>4 (4 - 5)*1</td>
</tr>
<tr>
<td>HADS – Depression /15</td>
<td>2 (1 - 3)</td>
<td>3 (2 - 6)</td>
<td>4 (2 - 5)*1</td>
</tr>
<tr>
<td>HADS – Anxiety /15</td>
<td>3 (2 - 4)</td>
<td>2 (2 - 5)</td>
<td>3 (2 - 4)</td>
</tr>
<tr>
<td>Lesion volume /cc.</td>
<td>n/a</td>
<td>3.0 (1.0 - 3.9)</td>
<td>4.2 (1.0 - 15)*1</td>
</tr>
<tr>
<td>Age-Related White Matter Score /3</td>
<td>1 (1 - 2)</td>
<td>1 (1 - 2)</td>
<td>1 (1 - 2)</td>
</tr>
</tbody>
</table>

**Arm Specific Tests:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS – arm motor /4</td>
<td>0</td>
<td>2*</td>
<td>1.5*</td>
</tr>
<tr>
<td>(0: normal)</td>
<td></td>
<td>(1 - 2)</td>
<td>(1 - 2)</td>
</tr>
<tr>
<td>Short Fugl Meyer arm function /12</td>
<td>12</td>
<td>9*</td>
<td>9*</td>
</tr>
<tr>
<td>(12: normal)</td>
<td></td>
<td>(9 - 11)</td>
<td>(7 - 10)</td>
</tr>
<tr>
<td>Grip force /%</td>
<td>100</td>
<td>87*</td>
<td>92*</td>
</tr>
<tr>
<td>(100% ≡ ≥100N)</td>
<td></td>
<td>(81-99)</td>
<td>(89-96)</td>
</tr>
</tbody>
</table>

* Median (interquartile range). *1 p<0.05, patients vs controls only. *2 p<0.05, affected-arm vs equivalent arm in other groups. All other group comparisons are insignificant (p>0.05), including comparing affected arms of R-weak versus L-weak (Kruskal-Wallis, rank sum or chi2-tests where appropriate).
C. Subject characteristics (Non-motor experiment)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>63 (56 - 68)</td>
<td>58 (50 - 64)</td>
<td>63 (58 - 70)</td>
</tr>
<tr>
<td>Males / %</td>
<td>46</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>Handedness (EHI)</td>
<td>90 (83 - 100)</td>
<td>90 (88 - 100)</td>
<td>90 (80 - 100)</td>
</tr>
<tr>
<td>NIHSS – overall /42</td>
<td>0</td>
<td>5 (4 - 6)</td>
<td>5 (4 - 6) *1</td>
</tr>
<tr>
<td>HADS – Depression /15</td>
<td>2 (1 – 3)</td>
<td>2 (2 - 3)</td>
<td>2 (1 - 3)</td>
</tr>
<tr>
<td>HADS – Anxiety /15</td>
<td>3 (2 - 3)</td>
<td>2 (2 - 3)</td>
<td>3 (1 - 4)</td>
</tr>
<tr>
<td>Lesion volume /cc.</td>
<td>n/a</td>
<td>1.4 (0.4 – 10)</td>
<td>14 (6 - 31)<em>1</em>2</td>
</tr>
<tr>
<td>Age-Related White Matter Score /3</td>
<td>1 (1 - 1)</td>
<td>1 (1 - 1)</td>
<td>1 (1 - 2)</td>
</tr>
</tbody>
</table>

Arm specific tests:

<table>
<thead>
<tr>
<th>Hand use</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS – arm motor /4 (0: normal)</td>
<td>0</td>
<td>0</td>
<td>2*3</td>
<td>0</td>
<td>2*3</td>
<td>(1 - 3)</td>
</tr>
<tr>
<td>Short Fugl Meyer arm function /12 (12: normal)</td>
<td>12</td>
<td>12</td>
<td>9*3</td>
<td>12</td>
<td>8*3</td>
<td>(8 - 11)</td>
</tr>
<tr>
<td>Grip force /% (100% = ≥100N)</td>
<td>99</td>
<td>99</td>
<td>97</td>
<td>99</td>
<td>100</td>
<td>88*3</td>
</tr>
</tbody>
</table>

Median (interquartile range). *1 p<0.05, patients vs controls only. *2 p<0.01, L-weak vs R-weak patients. *3 p<0.05, affected-arm vs equivalent arm in other groups. All other group comparisons are insignificant (p>0.05), including comparing affected arms of R-weak versus L-weak (Kruskal-Wallis, rank sum or chi2-tests where appropriate).

D. Subject characteristics (rs-fMRI experiment)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>56 (50 - 62)</td>
<td>60 (50 - 72)</td>
<td>62 (57 - 67)</td>
</tr>
<tr>
<td>Males / %</td>
<td>56</td>
<td>66</td>
<td>100<em>1</em>2</td>
</tr>
<tr>
<td>Handedness (EHI)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HADS – /42</td>
<td>5 (2 – 6)</td>
<td>5 (2 - 7)</td>
<td>8 (5.5- 10) <em>1</em>2</td>
</tr>
</tbody>
</table>

Arm specific tests:

<table>
<thead>
<tr>
<th>Hand use</th>
<th>Right-Hand</th>
<th>Right-Hand</th>
<th>Left-Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Fugl Meyer arm function /12 (12: normal)</td>
<td>12</td>
<td>9*1  (8-11)</td>
<td>7*1  (5-10)</td>
</tr>
<tr>
<td>Hand Section Fugl Meyer /14 (14: normal)</td>
<td>14</td>
<td>9*1  (8-12)</td>
<td>9*1  (7-12)</td>
</tr>
<tr>
<td>Grip force /% (100% = ≥100N)</td>
<td>99</td>
<td>88*1  (83-98)</td>
<td>83*1  (80-97)</td>
</tr>
</tbody>
</table>

Median (interquartile range). *1 p<0.05, patients vs controls. *2 p<0.01, L-weak vs R-weak patients
All other group comparisons are insignificant (p>0.05)
4.3.2 Undistracted performance

In all three tasks, without distraction, patients’ affected-hand performance was worse than with their unaffected-hand (Figure 18 provides a graphical representation of a typical tracking map for both a control and patient); while controls were worse using left compared to right hand with Tracking only (Table 8). At the same time, affected-hand performance correlated with unaffected-hand performance, or left correlated with right in controls, for all tasks (Figure 19); although the y-intercept and r², progressively decreased between Tracking, Precision and Force, reflecting increasing proportions of subjects showing a wide performance gap between affected and unaffected hands. Comparing groups, patients performed worse than controls, whether measuring affected or unaffected hands, thus revealing ipsilesional deficits in both dexterity and strength.

![Graphs](image-url)

**Figure 18 Performance of Tracking and Precision Task**

Examples of target and crosshair vertical position over a single trial, in control (Tracking) and patient (Tracking, Precision).
Table 8 Undistracted performance

<table>
<thead>
<tr>
<th>Task</th>
<th>Tracking (slow)</th>
<th>Precision</th>
<th>Force</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>R-weak</td>
<td>L-weak</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Age</td>
<td>56</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>Median difference: Controls: R vs L</td>
<td>5.5%, p&lt;0.01</td>
<td>4.3%, p=0.015</td>
<td>11.1%, p&lt;0.001</td>
</tr>
<tr>
<td>Patients: unaffected vs affected</td>
<td>4.3%, p=0.015</td>
<td>11.1%, p&lt;0.001</td>
<td>9.1%, p&lt;0.001</td>
</tr>
<tr>
<td>Correlation (r²)</td>
<td>0.52, p&lt;0.001</td>
<td>0.76, p&lt;0.001</td>
<td>0.71, p&lt;0.001</td>
</tr>
<tr>
<td>R vs L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group differences: controls vs. patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R hand use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L hand use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Restricting analysis to patients with submaximal grip force in either hand (n=31, 29, for R- and L-weak, respectively)

Statistical tests used for median difference: sign test; correlation: Spearman’s rank; group-differences: rank sum.
CHAPTER FOUR: ASSESSING ATTENTION DEFICITS AND MOTOR PERFORMANCE RELATIONSHIPS

Figure 19 Undistracted performance correlations

Scatterplots of accuracy in affected (hemiplegic side) versus unaffected hand, in patients with R-weakness (red diamond), L-weakness (red diamond crossed), and controls (blue), for undistracted trials of Tracking, Precision and Maximum Grip tasks respectively. In all three tasks, datapoints fall generally below the $45^0$ line (indicating worse performance in plegic versus non-plegic side), but there are also correlations for all.
4.3.3 Effect of Distractors

As the number of distractors increased during Tracking, performance became progressively impaired, with the degree of impairment (conflict = difference in performance between 0 and 3 Distractors, divided by baseline (0 Distractor) performance)) greater for patients than controls (Figure 20A, B; Table 9). One explanation for this group difference, is that when patients use their affected arm, less attention is available to resist distraction. However, conflict increases in patients occurred similarly in plegic and nonplegic hands (Group x Hand-use interaction, p=0.26); or was even greater in patients’ nonplegic hands, using unnormalized data, (Group x Distractor x Hand-use; p=0.02). Furthermore, by matching undistracted performance (comparing fast-tracking in controls, with slow-tracking in patients; p>0.1 comparing baselines; circled in Figure 20A), conflict was still greater in patients (p<0.01 for all) – suggesting that poor performance per se did not drive increased distractibility.

A further explanation for heightened conflict in patients during Tracking, is that this reflects a sensitivity to high attentional demands of visual-motion processing, or a continuously moving motor plan, rather than motor control per se. However, similar conflict increases occurred in patients, relative to controls, under both slow and fast Tracking (Group x Distractor x Speed, p=0.30; Figure 20B). Furthermore, a similar increase in conflict size was seen in patients versus controls in the Precision task, in which the target was stationary (conflict size with Tracking and Precision: 21% and 24%, respectively; difference: p=0.89). These findings suggest that a similar degree of attention-control impairment is seen across a range of dexterity tasks.

The association of high-conflict with poor undistracted performance is seen, not only as a group effect, but also as a between-subject correlation (Figure 21; Table 9B). This was found significantly for all three tasks, whether measuring plegic or nonplegic-arms, and persisted after correction for lesion-volume, mood, fatigue or pain scores; and whether taking average or best grip-strength. As for correlations between hands, conflict-performance correlation coefficients decreased progressively between Tracking, Precision and Force, although only Tracking > Force was significant (Z=2.2; p=0.030).
In order to understand the directionality of these associations, we note that poor performance was associated with high or low conflict, whereas good performance was never, or rarely, associated with high conflict. This dissociation is seen as a relative absence of cases in upper-right, relative to lower-left, sections of each Figure 21 graph. More formally, this is demonstrated as less conflict variability comparing upper versus lower tertile performances (p<0.05, for Tracking); or a negative correlation between absolute residuals (from linear conflict-performance models shown in Figure 21) and plegic-arm performance ($r = -0.2 \sim 0.4$; p<0.05, for all tasks: i.e. as performance worsens, the association with conflict weakens). This suggests that normal performance in all three tasks (without distraction) requires intact attention-control, whereas impaired performance may occur due to deficits in attention-control or other factors.

Since correlations between conflict and undistracted performance were similar for plegic and nonplegic hands ($r$ comparison: p>0.1; Table 9B), this suggests a relationship between attention and movement regardless of side (i.e. bilateral component). By contrast, conflict was not, or only weakly, associated with performance difference between nonplegic and plegic sides (i.e. unilateral component), with the conflict-performance correlation being significantly less for unilateral, relative to bilateral, components ($r$ comparison: p<0.01 for all tasks).

Negative correlations between performance and conflict were seen similarly for controls, R- and L-weak patients, across all tasks (group comparisons of correlation coefficients: p>0.05), with one exception. That is, with Tracking, L-weak patients showed less correlation than other groups ($r = -0.09$ versus -0.62; p<0.01). This may be accounted for by the earlier observation that poorer performance is associated with higher conflict variability, given that L-weak patients were worse at Tracking than R-weak patients in their plegic hand (p<0.01; difference: 18%; corrected for lesion volume).
CHAPTER FOUR: ASSESSING ATTENTION DEFICITS AND MOTOR PERFORMANCE RELATIONSHIPS

Figure 20 Effect of Distractors on Performance

A. Graphs of Tracking accuracy as a function of Distractor number, in slow and fast versions, in right and left hands, separately for controls, R-weak and L-weak subjects. Line gradients are steeper in patients in both hands, even when matching groups for baseline accuracy (circled). B. Normalized conflict values for each hand in controls, R-weak, and L-weak subjects, in slow and fast Tracking, and Precision experiments. The conflict increases found in patients relative to controls are similar for both hands, across all three types of dexterity task.
Figure 21 Distractored performance correlations

Scatterplots of affected-hand accuracy versus normalized-conflict measured in unaffected-hand, in controls, R-weak and L-weak subjects, in Tracking, Precision and Grip tasks (for the latter, maximum grip force was compared to conflict values measured during Tracking). Not only do all three tasks show negative correlations, but, for all, the residuals (i.e. average distance from regression line) get progressively smaller the better the affected arm performance. This is also seen as a significantly higher variance of conflict values in lowest accuracy than highest accuracy tertiles (for Tracking).
**Table 9 Effect of Distractors**

<table>
<thead>
<tr>
<th>Task</th>
<th>Tracking</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw-accuracy*</td>
<td>Factors: Distractors, Hand-use, Speed, Group</td>
<td>Factors: Distractors, Hand-use, Group</td>
</tr>
<tr>
<td>- distractors 0,1,3 (tracking)</td>
<td>Distractors: F(2,276) = 427, p&lt;0.001</td>
<td>Distractors: F(2,34) = 46.6, p&lt;0.001</td>
</tr>
<tr>
<td>- distractors 0,3</td>
<td>- linear contrast: F(1,138) = 660, p&lt;0.001</td>
<td>Group x Distractors: F(2,34)=1.0, p=0.38</td>
</tr>
<tr>
<td></td>
<td>Group x Distractors: F(4,276) = 7.5, p&lt;0.001</td>
<td>Group x Distractors x Hand-Use: F(2,34)=2.9, p=0.071, due to Distraction greater for <em>Nonplegic-Hand</em> in R-weak and L-weak patients.</td>
</tr>
<tr>
<td></td>
<td>- linear contrast: F(2,138) =11.5, p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group x Distractors x Hand-Use: F(4,276)=2.70, p=0.024, due to Distraction greater for <em>Nonplegic-Hand</em> in R-weak and L-weak patients.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group x Distractor x Speed, and 4-way interaction non-significant (p&gt;0.05)</td>
<td>Group x Distractor x Speed, and 4-way interaction non-significant (p&gt;0.05)</td>
</tr>
</tbody>
</table>

Normalized interference = \( \frac{(\text{Distractor 0} - 3)}{\text{Distractor 0}} \)

<table>
<thead>
<tr>
<th>Task</th>
<th>Tracking</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized interference</td>
<td>Factors: Hand-use, Speed, Group</td>
<td>Factors: Hand-use, Group</td>
</tr>
<tr>
<td></td>
<td>Group: F(2,138) = 34.6, p&lt;0.001</td>
<td>Group: F(1,35) = 6.6, p=0.013</td>
</tr>
<tr>
<td></td>
<td>but Group x Hand-Use, or x Speed, or 3-way interaction non-significant</td>
<td>but Group x Hand-Use non-significant</td>
</tr>
</tbody>
</table>

Normalized interference: Task comparison

<table>
<thead>
<tr>
<th>Task</th>
<th>Tracking</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task x Group: F(2,172)=0.12, p=0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Also Hand-Use, Group x Hand-Use x Task : all p&gt;0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significance ascertained by non-parametric ANOVA (permutation test). *Only Distractor effects reported.
### 9B: Correlations of interference with undistracted performance: bilateral (1 or 2) or unilateral (3) components

<table>
<thead>
<tr>
<th>Task</th>
<th>Tracking (slow)</th>
<th>Precision</th>
<th>Force†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
<td>p</td>
<td>r²</td>
</tr>
<tr>
<td>(1) Nonplegic-hand interference vs. Plegic-hand performance</td>
<td>0.39</td>
<td>&lt;0.001</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Nonplegic-hand interference vs. Nonplegic-hand performance</td>
<td>0.36</td>
<td>&lt;0.001</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) partialling out lesion volume, mood</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) partialling out lesion volume, mood</td>
<td>0.21</td>
<td>&lt;0.001</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3) Nonplegic -hand interference vs. [Nonplegic - Plegic performance]</td>
<td>0.04**</td>
<td>0.013</td>
<td>0.01*</td>
</tr>
<tr>
<td>partialling out lesion volume, mood</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlations ascertained by Spearman’s rank test.
† Correlations here reflect comparison of interference assessed during Tracking with maximum grip force.
A: average of 4 trials; B: best of 4 trials.
** p<0.001, *<0.01: comparison of r between bilateral ((2), nonplegic) vs. unilateral ((3), nonplegic-plegic) components.
All comparisons of (1) vs. (2) are non-significant (p>0.1).
Fatigue and pain self-rating scores showed no correlations (p>0.1) with conflict or performance in either hand (n=46).
4.3.4 Non-motor test of attention-control

An alternative explanation for correlated conflict and performance, measured in opposite arms, is that unilateral lesions disrupt bilateral motor systems (Noskin et al. 2008). Consequently, increased conflict, measured in the unaffected-arm, may be secondary to performance difficulties in this arm, causing attentional re-allocation, rather than vice versa. Against this, is our earlier observation that patients’ conflict level was as high, or greater, using the nonplegic than the plegic arm. Additionally, we measured conflict during a non-motor, working-memory (WM) task; and compared this to performance on motor Tracking and Force tasks. As before, patients showed greater conflict effects on WM performance, than controls (25% vs 0%; p<0.01); and there were negative correlations between WM conflict and performance on motor Tracking and Force, including after correction for lesion volume and mood (Figure 22B; once again outliers were predominantly normal-interference/low-performance; not high-interference/normal-performance). Since these correlation coefficients are numerically greater than that seen with Tracking conflict, this argues against high conflict in patients being secondary to motor impairment, but suggests that a domain-general processing impairment underlies failures of both distraction suppression and dexterity or strength.

Figure 22 Non-motor tracking correlations with conflict

Scatterplot of normalized conflict on Non-motor task versus Tracking performance with affected hand. The negative correlation was greater than that found for conflict with Tracking versus Tracking accuracy (Figure 2C), even after correction for lesion volume.
4.3.5 Lesion Mapping: locations associated with motor and attentional control deficits

Lesion mapping analysis resulted in significant correlations of differing conflict and motor control behavioural scores between distinct lesion locations. Comparisons were made at each voxel for patients showing high vs low conflict and also for patients showing high vs low Unaffected-Affected (U-A) hand performance difference (with high U-A difference highlighting more unilateral deficit; and low U-A difference highlighting a matching in performance between the unaffected and affected hand, thus a bilateral deficit and ‘global’ attention deficit in patients with high conflict scores in the unaffected hand).

Patients with high U-A scores showed lesions overlapping with corticospinal tracts (CST) (Figure 23), with increases in the difference correlating with increased lesion overlap volume (Figure 24). This suggests that damage to the CST is responsible for unilateral deficits only.

Figure 23 Patient performance correlated with corticospinal tracts
Lesions showing high conflict in the Unaffected hand (p < 0.001, relative to controls), masked with those of low conflict lesion (those areas where > 10% of subjects with low conflict had a lesion), showed correlations of conflict overlapped prefrontal-thalamic-striatal tract regions (Figure 25). The results of the Liebermeister permutation test, comparing groups of high versus low conflict lesions (thresholded at p 0.05 corrected), consolidated these findings, narrowing down the lesion overlay map further to FTS cross-sections (Figure 26). This finding shows that lesions in the FTS pathways are particularly susceptible to conflict, replicating results of conflict lesion analysis from Chapter Three.

Furthermore, decreases in accuracy in the unaffected hand (a reflection of bilateral weakness) correlated with increased lesion overlap of FTS (Figure B1). This suggests that bilateral weakness is due to damage in areas specifically associated with attention-control functions, implicating global deficit in attentional-control as the cause of impaired motor control in these subject.

These results highlight that lesion dependency is specific in that there is a significant correlation of bilateral deficits with frontal regions (but not CST) and a correlation of unilateral deficit with CST (but not frontal).
Figure 25 Performance correlated to frontal-thalamic-striatal tract lesion volumes
Figure 26 Lesion overlay maps correlating with different analysis of conflict
4.3.6 Functional Network Correlation Analysis

In order to relate motor performance with integrity of attention-control and motor functional networks, we compared Tracking performance with connectivity of the 8 Beckmann RSNs. Tracking performance was significantly correlated to three of these RSNs; two attentional networks - Executive and Visuo-Spatial; and the Sensorimotor network (Figure 27; Correlation results provided in Table 10). The difference error values (ie performance) over time are normalised to the baseline performance. The results hold whether we use absolute difference values or normalised values.

Across all these networks a decrease in baseline connectivity correlated with a decrease in individual patient accuracy, highlighting that patients experiencing disruption in these networks are particularly susceptible to reductions in visuomotor tracking and that disruptions in the executive (attention-control related) network are as important as those seen in traditional motor based networks.

Table 10 Correlations of Significant RSNs Connectivity with Accuracy

<table>
<thead>
<tr>
<th>EXECUTIVE RSN</th>
<th>RSN Connectivity vs Accuracy = r²: 0.181, p: 3.46e-03</th>
</tr>
</thead>
<tbody>
<tr>
<td>All:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.149, p: 6.95e-02</td>
</tr>
<tr>
<td>Controls:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.240, p: 1.88e-02</td>
</tr>
<tr>
<td>Patients:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.117, p: 2.17e-02</td>
</tr>
<tr>
<td>** Partialling out Visuospatial network</td>
<td>RSN Connectivity vs Accuracy = r²: 0.095, p: 3.90e-02</td>
</tr>
<tr>
<td>** Partialling out Sensory-Motor network</td>
<td>RSN Connectivity vs Accuracy = r²: 0.166, p: 5.30e-03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VISUO-SPATIAL RSN</th>
<th>RSN Connectivity vs Accuracy = r²: 0.121, p: 1.84e-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>All:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.060, p: 2.61e-01</td>
</tr>
<tr>
<td>Controls:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.071, p: 2.18e-01</td>
</tr>
<tr>
<td>Patients:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.033, p: 4.02e-01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SENSORIMOTOR RSN</th>
<th>RSN Connectivity vs Accuracy = r²: 0.279, p: 1.05e-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>All:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.166, p: 5.30e-03</td>
</tr>
<tr>
<td>Controls:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.033, p: 4.02e-01</td>
</tr>
<tr>
<td>Patients:</td>
<td>RSN Connectivity vs Accuracy = r²: 0.279, p: 1.05e-02</td>
</tr>
</tbody>
</table>

** results of partial correlations - exec RSN connectivity is correlated with performance even after correction for Visuospatial and Sensory-Motor RSNs connectivity.
1. Attention-control RSN

Maps of relative voxel weightings comprising the two attentional and primary sensorimotor resting-state networks listed in Table 10 (obtained from independent-components analysis). Scatterplots of each RSN’s integrity with Tracking accuracy shown alongside.

2. Visuospatial RSN

3. Primary Sensorimotor RSN

Figure 27 Tracking performance compared with functional network correlations
4.4 Discussion

In this chapter we have developed a novel visuomotor task capable of tracking attention-control influences on hand motor control and have used it to differentiate attention dependent motor deficits from pure motor impairment. We recruited 92 hemiparetic stroke patients, with no overt cognitive deficits or neglect, and 49 controls, and tested them separately with the novel visuomotor tracking task and non-motor control variants of the tracking task. Validation of the tasks ability was determined through analysing behavioural relationships between motor-tracking performance, grip-strength and distractibility in patients, and secondly through correlating the dependency of these behavioural measures to distinct lesion locations and to interference with both attention-control and sensorimotor network connectivity.

4.4.1 Behavioural Validation

Motor control was tested using both the unaffected and affected (right and left for controls) hands as a measure of capturing motor deficits causes specifically be attention-control, which would not be side specific if caused by global attention function disruptions. Across all tasks, performance was worse with the affected hand, than the unaffected hand, but there were also strong correlations between hands. Patients were also shown to perform worse than controls regardless of the hand they used, highlighting a common presence of ipsilesional deficits in both motor dexterity and total strength. Motor function deficits in the supposedly ‘unaffected hand’ of stroke patients with hemiplegia are well recognised (Pohl et al. 1997; Debaere et al. 2001; Noskin et al. 2008), although trivialised within a clinical rehabilitation setting owing to the extent of motor disability of the affected hand (Zhang et al. 2014).

Increasing the number of distracts resulted in reduced performance, validating the main principle of the attention-manipulation parameters of the visuomotor task. The degree of attentional impairment was greater in patients than controls, which could been explained due to patients potentially requiring motor attention when having to control impaired limbs, resulting in less attention being available to resist distractors.
(Houwink et al. 2013). However, conflict increases in patients occurred at a similar level across both the affected and unaffected hand, or even more so in the unaffected hand, again suggesting that attention-control was important for bilateral motor impairments. Even when matching for baseline performance, susceptibility to conflict was still greater in the patient population, confirming that poor motor control was not the driving force behind this increased distractibility.

A further explanation for heightened patient conflict with the tracking task, is that this reflects the high attentional demands of visual-motion processing, rather than the attentional demands of the motor control itself. However, analysis comparing performance of slow and fast versions of the tracking task showed that similar conflict increases occurred in patients relative to controls, and that motion speed was not a factor in healthy performance. Results from the non-tracking Precision task were used to corroborate this theory, and showed that increases in conflict were similar between both patients and controls even in this stationary task. These findings argue in favour of attention-control impairment being a cause of poor performance, rather than attention-control impairment being a result of performance impairment, or task-specific effects.

The negative relationship between (unaffected-arm) conflict and motor performance was shown, not only as a group effect, but also as a between-subject correlation, measuring performance in either affected or unaffected hand and found across all three tasks. With size of conflict shown to correlate similarly with undistracted performance in both the affected and unaffected hand, this suggests a relationship between attention and movement regardless of the side.

An alternative explanation for correlated conflict and performance, measured in opposite arms, is that unilateral lesions actually disrupt bilateral motor systems causing ipsilesional motor impairments (Newton et al. 2006; Noskin et al. 2008). Consequently, increased conflict, measured in the unaffected-arm, may be secondary to performance difficulties in the same arm, and causing attentional re-allocation (Houwink et al. 2013), rather than vice versa. Arguing against this is the previously stated observation that patients’ conflict levels were greater using the unaffected than the affected arm, despite relative performance being better in the unaffected arm. However, we also re-
designed the Tracking task so as to obtain a measure of conflict on working-memory (i.e. non-motor) performance and correlated this with subjects’ affected-arm performance on the undistracted Tracking task. Once again, patients showed greater conflict effects on WM performance than controls; and across all subjects, there was a negative correlation between WM conflict and Tracking performance. Since this correlation was greater than that seen with the motor Tracking conflict task, this argues against increased conflict in patients being secondary to motor impairment.

In summary, results from performing the novel visuomotor task highlighted that performance with either arm correlated strongly with attention-control, including after correction for baseline performance, task speed, lesion size, or on using a non-motor task. Additionally, a dissociation occurred in that patients with poor performance showed either impaired or intact attention-control, whereas good performance was never, or rarely, associated with impaired attention-control – suggesting that impaired attention-control causes impaired motor performance, rather than vice versa.

4.4.2 Imaging Validation

On top of behavioural analysis measures, both lesion and functional network imaging analysis was performed to help dissociate attention-control functions for pure motor performance deficits and further validate the effectiveness of the novel task. Results from lesion mapping showed that bilateral motor impairments, those associated with attention-control capacity, correlated with the degree of lesions overlapping fronto-thalamic-striatal tracts; whereas unilateral (contralateral) motor impairment correlated with the degree of disruption to corticospinal tract integrity. This not only shows that lesion locations associated with attentional function and separate from motor associated tracts can be specifically responsible for motor deficits, but again confirms the tasks ability to separate distinct attention driven from motor driven deficits.

The overlap of attention-control with tracts responsible for frontal processes fits well with the general neuroanatomical model of a dorsal fronto-parietal attention network housing executive functions. The frontoparietal functions include initiating and adjusting control of performance on a trial-by-trial basis, responds differentially depending on whether participants perform correctly or incorrectly on
individual trials, indicating the network’s activity is sensitive to online feedback (Dosenbach et al. 2008; Fitzpatrick & Baum 2012). Specifically for executive functions, lesion based studies utilising non-visuomotor tracking conflict control tasks (e.g. Stroop, flanker etc.) have predominately characterising deficits in conflict-resolution with dorsolateral or medial prefrontal cortex damage (Vendrell et al. 1995; Stuss et al. 2001), although executive processing has also been shown to be influenced by lesions to posterior parietal cortex (Pujol et al. 2001; E. J. Coulthard et al. 2008), basal ganglia (Aron et al. 2003), cerebellum (Schweizer et al. 2007), and, as seen in the previous chapter of this thesis, areas with prefrontal and premotor association (Chapter Three). Lesion based analysis has been backed-up by functional neuroimaging studies also associating conflict functions with dorsolateral and medial frontal/ prefrontal regions (Casey et al. 2000; Coull et al. 2004; Botvinick et al. 2004; Fan et al. 2005), but these again are not conclusive with parietal, sensory cortices, and thalamic regions also showing activation (Coull et al. 2001; Thienel et al. 2009; Kim et al. 2010; Clemens et al. 2011).

The suggested involvement of thalamic regions in executive control again fits well with our results implicating fronto-thalamic tracts. The thalamus is understood to form part of the cingulo-opercular attention network (Sadaghiani & D’Esposito 2014), which operates at a slower temporal scale then the frontoparietal and is responsible for maintaining set (the ability to be prepared to respond in a particular way) over a continuous period (Fitzpatrick & Baum 2012), fitting well with the continuous tracking nature of a visuomotor task. Other components of the cingulo-opercular network include the cerebellum, anterior insula and the dorsal anterior cingulate cortex (ACC) (Sadaghiani & D’Esposito 2014). Disruptions in fronto-thalamic tracts may thus be critical for allowing processing along this network, from thalamic regions to frontal areas further up the tradition attentional network hierarchy usually attributed to conflict processing, i.e. ACC (MacDonal et al. 2000; Botvinick et al. 2004; Westlye et al. 2011; Yin et al. 2011). Added to the associations with the ACC, involvement of the anterior insula in the cingulo-opercular network link well the lesion mapping results from this chapter to those in Chapter Three, where the anterior insula was also correlated to conflict resolution.
Regardless of an exact cortical processing location of attention-control, our results show the significance of damage to white matter fronto-subcortical tracts in attentional-control, and fit well with results from Chapter Three, where impairment in conflict resolution was correlated with lesions at the middle corona radiate (connecting prefrontal and premotor cortices).

Lesion mapping results were complimented by functional imagining analysis showing correlation of bilateral motor impairments with the degree of disruption in connectivity not only in primary sensorimotor RSNs, but in a well characterised executive control network (Beckmann et al. 2005). Discrepancies in pinpointing cortical regions to exact cognitive functions make it vital to look at attentional-control functions as a property of spatially distributed functional networks (Markett et al. 2014). A network perspective suggests that the physiological and functional effects of stroke would best be assessed not simply at the site of the lesion, but through the inter-regional dependencies across an entire functionally connected network (Honey & Sporns 2008; Van Dijk et al. 2010). Indeed, it has been suggested that frontal cortex sub-regions are not functionally unique in their sensitivities to attention-control functionalities, with no specific modules existing within the frontal lobes (Erika-Florence et al. 2014). This theory highlights that deficits in attention-control should instead be analysed as components of spatially distributed functional networks, allowing for the effects across entire networks to be taken into consideration.

In light of the above, the significant correlation of connectivity disruption in both motor and attention networks with performance of the visuomotor task warrants further investigation in relation to differences in connectivity of viable networks following stroke, especially as intensive training and learning of simple finger tracking tasks has not only been shown to result in improvements in grasp and release functions, but that these improvements were accompanied by brain reorganisation (Carey et al. 2002b). Thus, modulations in functional RSN correlations post performance of the visuomotor task should be explored in greater depth.
4.5 Conclusions

4.5.1 Visuomotor-Attention-Control Task

By employing and testing motor tasks with low-cognitive demands – visuomotor tracking, precision grip and grip force – we have successfully developed and validated a novel visuomotor-attention-control task capable of assessing attention-control influences on hand motor control and have used it to differentiate attention dependent motor deficits from pure motor impairment. We distinguished unilateral from bilateral impairments in patients with unilateral motor lesions, and tested how both relate to a behavioural measure of attention-control (resistance to distraction), as well as lesion-overlap and functional disconnection of attention-control versus motor networks. Performance with either arm correlated strongly with attention-control and a dissociation was observed between patients exhibiting high motor control deficits - showing either impaired or intact attention-control, compared with those exhibiting good motor control - never, or rarely, showing impaired attention-control. This suggests that impaired attention-control causes impaired motor performance, rather than vice versa.

Finally, we have shown that bilateral motor impairments correlated with the degree of disruption to an anterior FTS network; whereas contralateral motor impairment correlated with the degree of disruption to CSTs. The ability of the visuomotor tracking task to correlate impaired attention control with relevant attention and motor functional brain networks may form an important step in understanding attentional impacts on large scale network reorganisation and learning-dependent neuroplasticity following stroke (Cramer et al. 2011), and will be the focus of further detailed investigations in the following chapter (Chapter Five).

4.5.2 Clinical Importance

Our results suggest that hemiplegia after stroke is not only a disorder of motor pathways, but can also be associated with disorders of attention-control. Good performance was strictly associated with intact attention-control, whereas poor performance co-existed with impaired or intact attention-control - suggesting that impaired attention-control causes impaired motor performance rather than vice versa,
and thus can be dissociated from pure motor control impairment. Once again, we show that a high proportion of our tested patients are affected by attention-control impairments and so assessment of such deficits should be taken into serious consideration within post-stroke rehabilitation where attention is known to be critical for learning-dependent training and where attention deficits are known to effect motor recovery outcomes. Susceptibility to distractors may be particularly relevant in hospital rehabilitation environments considering the high and un-controlled levels of exposure to distractors a patient may experience whilst performing both controlled rehabilitation tasks as well as common ADLs, e.g. noise, pain, other patients and staff etc. We show that the relative contribution of either pure motor or attention-control impairments can each be assessed by bilateral behavioural testing and lesion anatomy, and is likely to be important for therapy considerations. Such assessments could allow for stratification of patients relative to their attention impairments and for provision of increased or tailored attention-motor based therapy. Finally, through this study, we have shown that integration of attention-control testing may be feasible through simple, but highly sensitive, interactive computer based tasks, similar to the one we have developed in this chapter, suggesting the potential for deployment of such devices directly into the clinical rehabilitation environment.
CHAPTER FIVE: POST-LEARNING FUNCTIONAL NETWORK MODULATIONS IN MOTOR STROKE
5.1 Introduction

Resting-state functional MRI (rs-fMRI) analysis methodologies have emerged as leading tools for assessing and detecting resting connectivity changes in functional brain networks, defined as Resting-State Networks (RSNs). With regards to motor-learning, the changes observed in RSNs in healthy subjects are believed to be neural biomarkers (i.e. measurable alterations relating to outcomes) of the larger scale network reorganisations representing neuroplasticity (Albert et al. 2009; Vahdat 2011). Functional motor recovery from stroke is likely to involve neural plastic reorganisation mechanisms that may be similar to those of normal motor skill-learning, suggesting that there may be functional imaging signatures common to both. These neural signatures may help to characterise the poorly defined learning-dependent mechanisms underlying effective plasticity, and thus help to further the understanding of the natural recovery processes following damage (Cramer et al. 2011). Here we question whether network-specific changes in brain connectivity seen immediately after learning in healthy subjects are also observed following learning in motor stroke patients, and whether such changes are seen not just in defined motor RSNs, but also in attention associated RSNs, as is the underlying theory of this thesis.

The experiments described in this chapter were performed as a continuation into the exploration of the functional neural correlates utilised in the performance of the attention based visuomotor tracking task developed in Chapter Four. The results generated as part of Chapter Four highlighted a correlation between decreased visuomotor tracking performance (not learning) and decreased baseline connectivity of both attention and motor associated networks. Further assessment of the effects of the task on these RSN neural associations following learning will not only help validate the visuomotor paradigm as a potential attention-motor deficit assessment tool, but also highlight its possible use, in conjunction with rs-fMRI, as a tool to assess the neural plastic capacity of individual patients (Cramer et al. 2011; Alex R. Carter et al. 2012). As of yet, no significant biomarkers capable of predcating individual post stroke recovery rates have been characterised, meaning there is no way of identifying a patient’s potential for recovery (Kwakkel & Kollen 2007; Langhorne et al. 2011). Careful analysis of the impact of lesions on brain networks, as well as knowledge of how viable brain networks...
respond to motor learning tasks, has the potential to guide clinicians to individualise stroke rehabilitation programs (Stinear & Byblow 2012).

Rs-fMRI techniques have been successfully employed in studies detecting changes in connectivity of both attentional and motor networks following motor stroke (Carter et al. 2010), highlighting correlations between disruptions in these networks with relevant attention and motor functional abilities (Rehme & Grefkes 2013). Results from RSN connectivity studies in stroke suggest a crucial role for interhemispheric connectivity in functional motor recovery, highlighting that the integrity of interhemispheric, but not intrahemispheric, network connectivity correlates significantly with upper extremity impairment and visual attention deficits (Carter et al. 2010; Park et al. 2011; Rehme et al. 2012). Resting-state connectivity data, analysed through a method of structural equation modelling, has also been used to show changes in RSN connectivity after prolonged and intensive physiotherapy (i.e. increased influence of the affected hemisphere premotor cortex upon the unaffected hemisphere premotor cortex). These studies validating the use of rs-fMRI as a sensitive connectivity assessment tool in the lesioned brain (Alex R. Carter et al. 2012; Rehme & Grefkes 2013).

Specifically in relation to motor-learning and functional connectivity, it has been shown that motor learning tasks, but not simple motor performance tasks, can modulate subsequent connectivity within particular RSNs in healthy subjects. Studies reveal a potential link between learning generated neuroplasticity and changes in fronto-parietal (Albert et al. 2009; Vahdat 2011), frontal motor (primary motor (M1) and supplementary motor (SMA)) (Vahdat 2011), inferior frontal (Sami & Miall 2013), and numerous cerebellar RSNs (Albert et al. 2009; Vahdat 2011; Sami & Miall 2013). A general pattern of alterations in frontal-parietal-cerebellar connectivity, as is suggested by these studies, is consistent with the idea that a distributed pattern of sensory and motor plasticity accompanies motor learning (Vahdat 2011).

Implicit motor learning is known to be preserved in stroke and is fundamental to the learning-dependent neural plastic process driving recovery (Krakauer 2006). However, although activity based fMRI has been used to investigate how the brain compensates for damage following stroke to
facilitate learning, showing decreased activity in the left dorsolateral prefrontal cortex versus increased activity in left dorsal premotor cortex in healthy subjects (highlighting the potential importance of a prefrontal-based attentional network for implicit motor learning after stroke) (Meehan et al. 2011), the patterns of functional connectivity changes following learning within an acute stroke population have yet to be appreciated.

The ability to track changes in network connectivity in an acute stroke population and correlate the importance of specific networks associated with learning-dependent activity may prove significant in the understanding of neural recovery mechanisms and development of future rehabilitation methods. We expect post-learning connectivity changes to effect sensorimotor, attentional and cerebellar RSNs, as seen in healthy subjects, but with specific profiles to stroke, and that these profiles relate to the performance level of the patient.

**Aims of the Study**

- To assess connectivity strength profiles within a set of RSNs before and after performance of a visuomotor tracking task.
- To assess whether the visuomotor tracking task developed in Chapter Four can stimulate a learning effect and influence RSN connectivity across a short session of activity.
- To relate any learning effects in performance of the visuomotor task to connectivity changes between before task and after task rs-fMRI scans
5.2 Methods

5.2.1 Subjects

Right-handed patients with unilateral arm paresis, and/or impaired dexterity, due to recent stroke (<4 weeks), confirmed on MRI or CT, were screened at the Imperial College NHS Healthcare Trust Hyper Acute Stroke Unit, Charing Cross Hospital. Exclusion criteria were: 1) previous stroke; 2) pre-existing arm impairment; 3) history or examination evidence of cognitive impairment, Mini-Mental State Examination <27, or errors on clinical frontal lobe tests (including Trail-Making part B); 4) sensory or motor neglect; 5) comprehension difficulty; 6) clinical anxiety or depression (Hospital Anxiety and Depression Scale); 7) severe cerebral white-matter disease or other brain lesions; 8) clinically diagnosed visual impairments or, due to incompatibility with the MR scanner, those patients unable to discriminate task stimuli without glasses (assessed via a bedside target recognition test). Age-matched controls were either healthy volunteers, or non-stroke patients (e.g. migraine) who had no arm deficit symptoms or signs; no significant brain MRI lesions; but otherwise fitted the above inclusion and exclusion criteria.

5.2.2 Visuomotor Tracking Task

The visuomotor tracking task was a variant of the task developed and described in the previous chapter (Chapter Four), designed using E-Prime software (V2.0) (http://www.pstnet.com/eprime.cfm). Interaction with the task was facilitated through a commercially available, MRI compatible, isokinetic hand-grip force sensor – ‘Grip Force’ – supplied by ‘Current Designs’ (http://www.curdes.com
/mainforp/response devices/hhsc-1x1-grfc-v2.html). The hand-grip utilised a spring based mechanism with a protruding force bar that moves in when gripped to produce a roughly linear force measurement output based on the pressure applied. The hand-grip had a sensitivity range of <100N. A hand-grip device was selected as the manipulandum of choice as the ability to perform hand-grip has been shown to return relatively early compared with more complex fractionated finger movements following stroke (Heller et al. 1987), thus allowing for the inclusion of a larger spectrum of paretic patients. The neural correlates and reorganisation of activity following performance of visual feedback tasks controlled through hand-grip force sensing have also been well documented (Ward &
The task consisted of a green star (1.2°) moving up and down the screen, the temporal profile of which described a polynomial sine-cosine function (Meehan et al. 2011), varying trial-to-trial, but fixed between patients (allowing for implicit learning). Subjects tracked the star by varying force on the hand-grip, that proportionately moved a crosshair, which when overlying the star turned it pink (Figure 28 A). The target star trajectory was set at a consistent speed, with direction of movement changing between 4-6 times per trial over a 16 second window. No additional distractors were incorporated into these trials (as seen with the Tracking task in Chapter Four). Subjects performed the task inside an MRI scanner whilst undergoing an fMRI scan, with the task presented to them on a LCD TV screen at the head of the magnet bore, viewed via a mirror attached to the head coil. The hand-grip was placed within the subjects hand at the beginning of the scanning protocol and subjects were asked to maintain the hand position holding the grip flat across their midriff (Figure 28B).

Figure 28 Tracking task and Scanning Environment

A – The visuomotor tracking task. Green Star (Target) B – Subject were asked to lay in the scanner holding the handgrip flat on their midriff
The task was divided into active and rest periods, varying in length between 6 – 15secs, over a 6.5 minute epoch. Rest periods were denoted by the target star turning black, upon which subjects had been instructed to relax their grip. In order to ensure task comprehension, subjects performed one minute of supervised training on screening (minimum 3 hours before scanning), and a further minute whilst in the scanner directly prior to the commencement of the main task trial and fMRI scan. Prolonged pre-training was not performed so as not to allow for any learning effects to occur prior to the first resting-state scan.

Task performance was calculated through both accuracy (the proportion of time the crosshair overlay the target during the active period) and absolute error analysis (difference between the target position and crosshair, i.e. target – crosshair position). An analysis of a motor learning effect was run by dividing the active portions of the task session into 5 time bins, calculating error for each. We deleted the first 2 sec of each active trial and smoothed the error data across sessions within MATLAB (2012b) (http://uk.mathworks.com/products/matlab/). Error changes of epoch 1 – epoch 5 (i.e. learning effect) were subsequently correlated with the connectivity differences in RSNs before and after task completion, to test whether connectivity changes between before task and after task were related to performance improvement changes (learning) over the session.

Patients used their paretic hand to perform the task, with subjects always using their right hand. The task was calibrated so that motor effort was matched between groups. Combining data from subjects using different hands is justified from results obtained when validating the visuomotor task in Chapter Four, which showed that intersubject variation of tracking accuracy was roughly 6-fold larger than intrasubject between-hand accuracy variation.

5.2.3 MRI Scanning Protocol

Rs-fMRI and fMRI data collection was performed using a Siemens Verio 3T scanner. Each subject underwent a single scan session, with the scanning protocol for this session divided into a series of separable scan sequences. The functional sequence portions of the scan were set in an A-B-A-A block design, where A denotes rs-fMRI block (RS) and B denotes an active fMRI block (Active). Thus,
within one session each subject had a total of three rs-fMRI scans performed; RS1, RS2 and RS3. RS1 allowed for assessment of baseline functional network connectivity, following which the visuomotor task was performed during the Active block. After the task was performed network connectivity was reassessed in RS2 and RS3. This protocol allowed for connectivity assessment before, during and after task performance.

Each functional scan sequence lasted 6 minutes and 30 seconds (192 frames, repetition time (TR) 2sec, echo time (TE) = 25msec, voxel-size 3.4 x 3.4 x 4mm, 32 slices, flip angle (FA) 90°, field of view (FoV) 220mm), shown to be an ample time frame for resting-state data collection (Van Dijk et al. 2010; Cole et al. 2010). Longer scan times risk patients becoming uncomfortable and restless, especially in the acute stroke state, increasing the risk of both movement and changes in the subject’s mood, shown to result in changes in baseline brain state and connectivity (Harrison et al. 2008). During the resting-state scan, subjects were instructed to keep their eyes open and maintain fixation on a central cross displayed on the TV screen.

Prior to each rs-fMRI sequence a period of rest lasting 4 minutes and 30 seconds was provided to allow patients to become accustomed to the scanner and to let the brain reach a hemodynamic baseline before recording of BOLD activity (Cole et al. 2010; Tung et al. 2013). Prior to RS1, this rest period was filled by the completion of a T1 structural scan (used for normalisation during analysis), with RS2 being preceded by an arterial spin labelling (ASL) perfusion scan sequence (data to be utilised in future analysis) of equal length to the T1 scan, allowing subjects to again reach a hemodynamic baseline following task performance. Finally, RS3 was followed by structural DWI and FLAIR scans, which were acquired to aid in lesion identification for lesion masking pre-processing (Figure 29).
5.2.4 Functional Connectivity Analysis

Comparison between the connectivity of RSNs in each of the RS blocks was used to generate a profile of connectivity changes across time for each subject. The connectivity strength of 20 networks, extracted from a set of 51 anatomical components (characterised with reference to a healthy-control dataset gathered from the same scanner (n=54)); 8 of which correlated to a well-characterised and robust set of RSNs (Beckmann et al. 2005) (Figure 30), was interrogated by extracting the BOLD time series for voxels within each separable network and measuring the activity correlation (cross correlation coefficient matrix) between the top 0.1% of peak voxels. The connectivity strengths of each respective network were subsequently compared between RS1, RS2 and RS3 for each subject.
Analysis of resting-state time-series data proceeded the following pre-processing stages, using FSL software (www.fsl.fmrib.ox.ac.uk/fsl/, v 3.10): removal of non-brain tissue, and the first 6 volumes per scan; temporal highpass and lowpass filtering; motion correction, normalisation of the voxelwise variance; spatial smoothing; registration to standard MNI space; and exclusive masking of acute-stroke lesions (from co-registered DWI). Resting-state component generation was performed using group concatenation Probabilistic Independent Component Analysis (ICA) (Beckmann and Smith, 2004) as implemented in MELODIC Version 3.10, part of FSL (http://fsl.fmrib.ox.ac.uk/fslwiki/MELODIC#Melodic_GUI) (see Chapter Two for detailed pre-processing and ICA methods).
5.3 Results:

5.3.1 Test Population

In total 23 patients and 23 controls were recruited. There were no significant differences between R-weak patients, L-weak patients and controls in terms of age or handedness. There was a significantly higher number of males in the L-hand weak patient group, who also reported slightly more depression. Function and strength measures of affected arms were matched between the both R-hand and L-hand weak patients. Subject characteristics are described in Table 11.

Table 11 Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>R-hand weak</th>
<th>L-hand weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>56 (50 - 62)</td>
<td>60 (50 - 72)</td>
<td>62 (57 - 67)</td>
</tr>
<tr>
<td>Males / %</td>
<td>56</td>
<td>66</td>
<td>100<em>1</em>2</td>
</tr>
<tr>
<td>Handedness (EHI)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HADS – /42</td>
<td>5 (2 – 6)</td>
<td>5 (2 - 7)</td>
<td>8 (5.5 - 10) <em>1</em>2</td>
</tr>
</tbody>
</table>

Arm specific tests:

<table>
<thead>
<tr>
<th></th>
<th>Right-Hand</th>
<th>Right-Hand</th>
<th>Left-Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Fugl Meyer arm function /12 (12: normal)</td>
<td>12</td>
<td>9 *1</td>
<td>7 *1</td>
</tr>
<tr>
<td>Hand portion Fugl Meyer /14 (14: normal)</td>
<td>14</td>
<td>9 *1</td>
<td>9 *1</td>
</tr>
<tr>
<td>Grip force /% (100% ≡ ≥100N)</td>
<td>99</td>
<td>88*1</td>
<td>83*1</td>
</tr>
</tbody>
</table>

Median (interquartile range). *1 p<0.05, patients vs controls. *2 p<0.01, L-weak vs R-weak patients
All other group comparisons are insignificant (p>0.05)

5.3.2 Task Performance

Throughout the 6.5min visuomotor tracking task patients were shown to be less accurate (higher error; p = 0.0032) overall compared to controls, but difference in force between patients and controls did not differ (p = 0.12) (Figure 31). This highlights that patients exerted similar levels of relative force as controls, showing that they were able to engage with and play the task to an appropriate level (validating calibration across motor strengths) (Figure 31).
Figure 31 Performance of the tracking task
5.3.3 Task Motor-Learning

A net effect of learning was shown over both controls and patients when comparing error in epochs 5 to 1 across the visuomotor tracking session (i.e. a reduction in error) (Figure 32 A). Calculations of absolute error showed higher error overall in patients compared with controls (as expected). However, both groups showed significant reductions in error over the task (control: p 1.561e-03; patients p 1.731e-03). Once normalised for baseline performance the reduction in error remained significant and was similar between both groups (control: Diff: 0.192; patients 0.149) (Figure 32 B). No correlation was seen between learning and baseline performance (time bin 1) (controls: r: -0.014, p: 0.951; patients: r: 0.236, p: 0.279), indicating no relationship between learning and baseline performance (.

![Figure 32 Learning effect over task session](image)

A – Change in absolute error over the 5 session time bins, seen in each subject (thin lines) and with control and patient group averages (bold line). B - Change in normalised error over the 5 session time bins, seen in each subject (thin lines) and with control and patient group averages (bold line). Wilcoxon signed-rank test used for all comparisons.
5.3.4 Post Task Functional Network Connectivity

Changes in activity correlations, representing connectivity strengths, analysed for each of the 20 isolated networks across all four functional scanning blocks (RS1, Active, RS2, RS3), resulted in varying change profiles across time. Specific interest was paid to 7 RSNs from Beckmann et al. 2005 (lateral dorsal attention networks combined) and an additional cerebellar network (showing significant connectivity changes). Changes in network connectivity of controls were used as a marker of ‘normal’ post task activation patterns, allowing for patient comparison. Connectivity profiles of these 8 networks are represented in Figure 33.

The results of between block comparisons (RS1 versus RS3; and RS2 versus RS3) (Tables 12 and 13 respectively) showed that sensorimotor network connectivity across all epochs was closely matched between patients and controls, consistent with similar motor effort, showing no significant difference (p = 0.759) in the profile of connectivity manipulation within this primary motor network. By contrast, visuospatial and cerebellar networks showed significant differences between stroke patients and controls, albeit with differing profiles. No other significant differences were observed with the remaining 15 networks, thus confirming high relevance of the changes seen in the visuospatial and cerebellar networks.

Within the visuospatial network, controls showed progressively increasing connectivity post-task (p = 0.025), the profile of which was reversed in patients who showed progressively decreasing connectivity (p = 0.036) post-task. This led to a significant difference in visuospatial network profiles between the groups (p = 0.01). Conversely, within the interrogated cerebellar network, patients showed a significant progressive increase in connectivity both during and post-task (p = 0.021), compared with controls who showed progressive decreases in connectivity in the cerebellar network during both task and post-task (p = 0.005). Thus, post visuomotor exercise functional connectivity changes are seen most strongly in the cerebellum RSN, although the changes seen show significantly different profiles of activity manipulation across RS1 to RS3 between the healthy and post-motor stroke groups (p = 0.0016).
Figure 33 Resting-State Connectivity Time Profiles
### Table 12 Group Connectivity Differences Between RS1 and RS3

<table>
<thead>
<tr>
<th>Resting-state network</th>
<th>Controls d</th>
<th>Controls p</th>
<th>Patients d</th>
<th>Patients p</th>
<th>Difference d</th>
<th>Difference p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SensoriMotor</td>
<td>-0.001</td>
<td>0.978</td>
<td>+0.0115</td>
<td>0.586</td>
<td>+0.0123</td>
<td>0.759</td>
</tr>
<tr>
<td>Visuospatial attention</td>
<td>-0.0095</td>
<td>0.503</td>
<td>-0.083</td>
<td>0.0302</td>
<td>-0.0788</td>
<td>0.0744</td>
</tr>
<tr>
<td>Executive attention</td>
<td>-0.0064</td>
<td>0.725</td>
<td>+0.0290</td>
<td>0.171</td>
<td>+0.0355</td>
<td>0.234</td>
</tr>
<tr>
<td>L Dorsal attention</td>
<td>-0.0183</td>
<td>0.361</td>
<td>-0.0305</td>
<td>0.138</td>
<td>-0.0122</td>
<td>0.687</td>
</tr>
<tr>
<td>Medial visual</td>
<td>+0.0479</td>
<td>0.053</td>
<td>+0.0508</td>
<td>0.0795</td>
<td>+0.0026</td>
<td>0.948</td>
</tr>
<tr>
<td>Lateral visual</td>
<td>-0.0145</td>
<td>0.530</td>
<td>-0.0360</td>
<td>0.257</td>
<td>-0.0215</td>
<td>0.600</td>
</tr>
<tr>
<td>Auditory</td>
<td>+0.0141</td>
<td>0.395</td>
<td>-0.0087</td>
<td>0.622</td>
<td>-0.0228</td>
<td>0.379</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>-0.127</td>
<td><strong>0.0029</strong></td>
<td>+0.105</td>
<td><strong>0.0362</strong></td>
<td><strong>+0.232</strong></td>
<td><strong>0.0016</strong></td>
</tr>
</tbody>
</table>

$d = \text{Difference in connectivity (R}^2\text{) between RS1 versus RS3. Only cerebellar RSN showed a time effect; and this differed between groups (p<0.05)}$

### Table 13 Group Connectivity Differences Between RS2 and RS3

<table>
<thead>
<tr>
<th>Resting-state network</th>
<th>Controls d</th>
<th>Controls p</th>
<th>Patients d</th>
<th>Patients p</th>
<th>Difference d</th>
<th>Difference p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SensoriMotor</td>
<td>-0.0291</td>
<td>0.142</td>
<td>+0.0163</td>
<td>0.528</td>
<td>-0.0128</td>
<td>0.710</td>
</tr>
<tr>
<td>Visuospatial attention</td>
<td><strong>+0.0258</strong></td>
<td><strong>0.0249</strong></td>
<td>-0.0746</td>
<td><strong>0.0364</strong></td>
<td><strong>-0.1004</strong></td>
<td><strong>0.0106</strong></td>
</tr>
<tr>
<td>Executive attention</td>
<td>-0.0102</td>
<td>0.574</td>
<td>+0.0132</td>
<td>0.556</td>
<td>+0.0030</td>
<td>0.920</td>
</tr>
<tr>
<td>L Dorsal attention</td>
<td>+0.0276</td>
<td>0.132</td>
<td>-0.0126</td>
<td>0.378</td>
<td>-0.0401</td>
<td>0.115</td>
</tr>
<tr>
<td>Medial visual</td>
<td>+0.0376</td>
<td>0.0411</td>
<td>+0.0234</td>
<td>0.452</td>
<td>-0.0141</td>
<td>0.716</td>
</tr>
<tr>
<td>Lateral visual</td>
<td>+0.0374</td>
<td>0.0330</td>
<td>+0.0011</td>
<td>0.979</td>
<td>+0.0268</td>
<td>0.576</td>
</tr>
<tr>
<td>Auditory</td>
<td>+0.0030</td>
<td>0.825</td>
<td>+0.0180</td>
<td>0.283</td>
<td>+0.0150</td>
<td>0.521</td>
</tr>
<tr>
<td>Cerebellar</td>
<td><strong>-0.118</strong></td>
<td><strong>0.0054</strong></td>
<td><strong>+0.0924</strong></td>
<td><strong>0.0215</strong></td>
<td><strong>+0.132</strong></td>
<td><strong>0.0218</strong></td>
</tr>
</tbody>
</table>

$d = \text{Difference in connectivity (R}^2\text{) between RS2 versus RS3. Late normalisation of visuospatial RSN connectivity; reversed in patients, group difference (p<0.05).}$
5.3.5 Correlations of Motor-Learning and Post Task Functional Network Connectivity

Correlation analysis between the changes in connectivity seen from RS1 to RS3, across all 20 networks, and differences in performance of the visuomotor task, showed a significant correlation between improvements in motor-learning and connectivity changes in visuospatial, sensorimotor and cerebellar RSNs post task (p = 0.006, p = 0.001 respectively) in patients. These RSNs did not show significant correlations in controls, who only showed a correlation in a biparietal-dorsal RSN (Table 14). These results indicate that the greater the learning effect shown by a patient during task performance the greater the subsequent decrease in connectivity of both attention and motor based networks (Figure 34). Thus, the level of activity and disruption in connectivity in viable attention and motor networks, stimulated by motor-learning, may be a strong biomarker of a patient’s neural plastic capacity.

Table 14 Correlations Between Learning and Connectivity Changes in 20 RSNs

<table>
<thead>
<tr>
<th>RS Component</th>
<th>Anatomical Network</th>
<th>Learning Correlations</th>
<th>Control</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSN1</td>
<td>R Dorsal Visual Stream</td>
<td>r: 0.297, p: 0.168</td>
<td>r: 0.176, p: 0.422</td>
<td></td>
</tr>
<tr>
<td>RSN2</td>
<td>Dorsal Visuospatial</td>
<td>r: 0.276, p: 0.202</td>
<td>r: 0.496, p: 0.016*</td>
<td></td>
</tr>
<tr>
<td>RSN3</td>
<td>R Brainstem</td>
<td>r: -0.365, p: 0.088</td>
<td>r: 0.210, p: 0.336</td>
<td></td>
</tr>
<tr>
<td>RSN4</td>
<td>Cerebellar</td>
<td>r: -0.005, p: 0.984</td>
<td>r: 0.419, p: 0.047*</td>
<td></td>
</tr>
<tr>
<td>RSN5</td>
<td>Upper brainstem</td>
<td>r: -0.058, p: 0.792</td>
<td>r: 0.132, p: 0.547</td>
<td></td>
</tr>
<tr>
<td>RSN6</td>
<td>Cerebellar 2</td>
<td>r: 0.301, p: 0.162</td>
<td>r: -0.065, p: 0.769</td>
<td></td>
</tr>
<tr>
<td>RSN7</td>
<td>Visuo-Spatial (BiParietal)</td>
<td>r: 0.145, p: 0.507</td>
<td>r: 0.552, p: 0.006*</td>
<td></td>
</tr>
<tr>
<td>RSN8</td>
<td>SensoriMotor</td>
<td>r: 0.364, p: 0.089</td>
<td>r: 0.627, p: 0.001**</td>
<td></td>
</tr>
<tr>
<td>RSN9</td>
<td>SensoriMotor (Lateral)</td>
<td>r: 0.387, p: 0.069</td>
<td>r: 0.189, p: 0.387</td>
<td></td>
</tr>
<tr>
<td>RSN10</td>
<td>Medial Visual</td>
<td>r: 0.224, p: 0.302</td>
<td>r: 0.389, p: 0.067</td>
<td></td>
</tr>
<tr>
<td>RSN11</td>
<td>Executive 1</td>
<td>r: 0.115, p: 0.601</td>
<td>r: 0.210, p: 0.337</td>
<td></td>
</tr>
<tr>
<td>RSN12</td>
<td>Executive 2</td>
<td>r: 0.062, p: 0.778</td>
<td>r: 0.345, p: 0.107</td>
<td></td>
</tr>
<tr>
<td>RSN13</td>
<td>Medial Frontal</td>
<td>r: 0.271, p: 0.211</td>
<td>r: 0.396, p: 0.061</td>
<td></td>
</tr>
<tr>
<td>RSN14</td>
<td>Medial Visual 2</td>
<td>r: 0.225, p: 0.133</td>
<td>r: 0.477, p: 0.021</td>
<td></td>
</tr>
<tr>
<td>RSN15</td>
<td>BiParietal-Dorsal visual</td>
<td>r: 0.556, p: 0.007*</td>
<td>r: 0.361, p: 0.091</td>
<td></td>
</tr>
<tr>
<td>RSN16</td>
<td>L Dorsal Visual Stream</td>
<td>r: 0.375, p: 0.079</td>
<td>r: 0.327, p: 0.128</td>
<td></td>
</tr>
<tr>
<td>RSN17</td>
<td>Auditory-BiInsular</td>
<td>r: 0.426, p: 0.044</td>
<td>r: 0.148, p: 0.500</td>
<td></td>
</tr>
<tr>
<td>RSN18</td>
<td>Auditory-BiInsular 2</td>
<td>r: 0.274, p: 0.206</td>
<td>r: -0.191, p: 0.383</td>
<td></td>
</tr>
<tr>
<td>RSN19</td>
<td>Brainstem</td>
<td>r: -0.183, p: 0.402</td>
<td>r: 0.055, p: 0.802</td>
<td></td>
</tr>
<tr>
<td>RSN20</td>
<td>R Temporal</td>
<td>r: 0.418, p: 0.048</td>
<td>r: -0.177, p: 0.418</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001
Correlation of normalised learning improvement against RSN 1–RSN3, hence positive changes mean connectivity decreases over time.
5.4 Discussion:

Resting networks are believed to actively and selectively process previous activity based experiences (McGregor & Gribble 2015) suggesting a key role in learning-dependent neuronal plasticity and presenting a potential assessment biomarker of patient recovery potentials. In healthy subjects it has been shown that motor learning tasks can modulate a specific set of RSNs (Albert et al. 2009; Vahdat 2011; Sami & Miall 2013). In this study we have shown that the attention and motor associated RSN changes seen in healthy subjects are only replicated in part during learning in motor stroke patients, and that differences in learning in stroke patients are associated with differences in connectivity modulation profiles.

Primary analysis of changing RSN connectivity profiles seen before and after visuomotor task performance showed a close relationship between controls and patients in the majority of RSNs, including within the sensorimotor RSN. However, significant differences in response were observed in visuospatial and cerebellar RSNs, with post exercise changes seen most strongly in the cerebellum. Secondary analysis indicated that patients showing greater learning, shown to be induced across the task session, also experienced a subsequent greater decrease in connectivity within attention and motor control associated networks.

5.4.1 Post-Task Changes in Functional Network Connectivity

The different connectivity response profiles between patients and controls, seen in visuospatial and cerebellar RSNs, showed that where controls experienced a progressive increase in connectivity in the visuospatial system, patients showed a significant decrease. This profile was reversed in the cerebellar RSN, which showed the most significant changes and differences in connectivity, where controls showed a decrease in connectivity compared with a significant increase in synchronised activity seen in patients. The strong modulation of the cerebellum is consistent with this regions role in the control of complex motor tasks (Hardwick et al. 2013), with a suggested involvement in the timing of movements and relevant attentional functions (Allen et al. 1997; Schmahmann & Caplan 2006; Ohyama & Mauk 2007). Despite a great deal of research, the exact function of the cerebellum in
motor function remains unclear. Neuroimaging studies have demonstrated the involvement of the cerebello-cortical loops during motor learning (Doyon & Benali 2005), with a critical role in early activation during the transfer of motor skill acquisition from a novel to a learnt state (Seidler & Noll 2008). It has thus been proposed that the activity of the cerebellum during motor learning, and differences between individuals, may explain individual differences in learning. This could potentially relate to a patient’s ability to benefit from rehabilitation (Nilsson et al. 2012). The differing profiles in cerebellar connectivity changes between the patient and control group in our results suggest the existence of one motor-learning network response for healthy individuals and a variable compensatory network response for individuals with acute stroke. However, conclusion cannot be drawn on the adaptive or maladaptive nature of these differences from the group data without considering the relationship between these changes and the levels of motor learning taking place by each individual subject.

5.4.2 Motor-Learning and Functional Network Connectivity

Increased learning of the visuomotor tracking task was correlated to subsequent decreases in connectivity in visuospatial, sensorimotor and the cerebellar RSNs. Although contradicting the original work of Albert et al. 2009, who showed that motor learning resulted in the increased RSN connectivity in fronto-parietal and cerebellar network in healthy subjects (Albert et al. 2009), these results are in line with more recent studies where efficient motor-learning was also characterised by decreases in the connectivity of networks involving temporoparietal, frontal motor (M1 and SMA) and cerebellar components (Vahdat 2011; McGregor & Gribble 2015).

Decreases in the identified RSN may reflect a decoupling of within network activity as the processes of learning disrupt established neuronal connections and the consolidation of new learned functions between networks occurs. Indeed, short term memories of recent motor experiences are known to be consolidated over a period of time after activity (Krakauer & Shadmehr 2006; Diekelmann & Born 2007; Robertson 2009), with processing demands needing to be met by a combination of activity between ‘resting’ attentional, memory and motor based networks (Miall & Robertson 2006). Alternatively, it could be suggested that the decreases in the RSNs we show are merely a result of
continued suppression of RSNs by active networks in individuals still ruminating about the visuomotor tracking task. However, any suppressing effects on activity in the post task resting brain are likely to still from part of the continued ‘off-line’ processing of information gained from learning and so form part of the natural memory processes needed for consolidation of long term learning (Albert et al. 2009). The heightened level of disruption in connectivity in patients showing good learning may, therefore, reflect an adaptive increased learning state of the brain following damage where upregulation of certain recovery mechanisms, e.g. neurotrophic factors, may lead to increased sensitivity to reorganisation in order to mend damage and restore a natural connectivity balance (Cramer et al. 2011). Indeed, when considering that the average group data showed an increase in post task connectivity in the cerebellar network in patients, compared with a decrease in controls, but that individual patients exhibiting good learning showed a decrease in cerebellar connectivity, suggesting that overall patient group increases may have been caused by large increases in a select number patients. Considering normal activity (controls) and good learning correlated to decreases in connectivity, the increases in connectivity seen in these patients may have been due to maladaptive process, e.g. overactivation due to increased attentional and motor demands, but a lack of effective cross functional network reorganisation and consolidation strategies.

5.4.3 Conclusions

By employing the visuomotor tracking task developed in Chapter Four in combination with a rs-fMRI scanning protocol, capable of tracking functional connectivity changes within a single scanning session, we were able to successfully assess functional connectivity strength changes in a set of RSNs directly following the performance of a visuomotor task in stroke patients. The task was shown to stimulate motor-learning in both controls and stroke patients, which allowed for the correlation of motor learning to individual patient connectivity profiles.

Our results show that a set of attention and motor related RSNs, namely: visuospatial, sensorimotor and cerebellar, express variable profiles of connectivity change both between patients and controls and in relation to the level of motor-learning achieved by individuals. Significantly, the changes following learning were associated with decreases in connectivity in these networks. Thus, the level
of activity and disruption in connectivity in viable attention and motor networks, stimulated by motor-learning, may be a strong biomarker of a patient’s neural plastic capacity. It must be noted that the analysis of the learning effect was scaled by the baseline task scores, meaning an assumption that the learning effect should scale with this baseline was made. This data should be revisited in future work in order to allow for analysis of individual differences to support this assumption, especially as currently the imaging analysis does not seek to differentiate effects due to scaled learning from baseline or non-scaled learning.

Although better motor-learning has been shown to correlate to the integrity of baseline network connectivities in stroke patients (Bonzano et al. 2015), we show that an assessment of post task correlations is essential in order to help understand the processes occurring during learning in the damaged brain. The ability to track changes in network connectivity following motor stroke and correlate these to learning may prove significant in helping to understand learning-driven neuroplasticity, and thus shape future rehabilitation strategies. However, in order to fully appreciate the significance of any motor-learning based functional network reorganisation patterns, well controlled longitudinal studies need to be performed to correlate early neural plastic abilities to actual motor recovery outcomes.

In terms of the progression in the development of a hand-grip visuomotor task, which forms the spine of this thesis, the ability to achieve the results reported in this chapter indicates that recent and short performance of this task is capable of stimulating rapid changes in connectivity that can be detected and compared in an acute stroke setting. The results help consolidate the findings from Chapter Four and further validate the potential of developing and using a simple hand-grip controlled visuomotor tracking system for the assessment of different markers for attention-weighted motor deficits and also to stimulate learning driven neuroplasticity of hand motor control. Thus, the final ‘experimental’ chapter of this thesis (Chapter Six) will be dedicated to translating the visuomotor tracking task, controlled via a hand-grip, into a device capable of being used as an assessment tool in a real world clinical rehabilitation environment.
CHAPTER SIX: IMPROVING ACCESSIBILITY OF ATTENTION-MOTOR ASSESSMENT & TRAINING: DEVELOPMENT OF A NOVEL DEVICE
6.1 Introduction

In chapters four and five, a novel attentional-control motor task capable of assessing the effects of attentional dysfunction upon fine-motor performance was developed, tested and validated using a commercially available MRI compatible hand-grip control. It is the ultimate goal of this thesis to translate this work into a real world environment, using the novel task as a basis to develop a new ‘hand and attention’ assessment and rehabilitative system, with potential for direct use in stroke patient care.

The only interventions shown to improve motor function after stroke are repetitive, task-oriented and task-specific exercises (Veerbeek et al. 2014), with increased amount of exercise suggested to lead to both faster and increased recovery (Lohse et al. 2014). However, implementation of such interventions is currently limited by resources, specifically the availability and cost of trained therapists (Bernhardt et al. 2007). Within the UK, 55% of stroke patients receive less than half the recommended physiotherapy time of 45 minutes per day whilst in hospital (NICE Stroke rehabilitation: costing report 2013). Even in specialised stroke units with dedicated therapy teams, therapy session may only last an average of 23 minutes, with only 4–11 minutes of upper-limb (UL) training (Bernhardt et al. 2007), and with almost no focus on direct cognitive training (Krug & McCormack 2009). Thus, development of effective neuro-rehabilitation technologies capable of supplementing standard UL therapy is of high significance in stroke research (Reinkensmeyer & Boninger 2012). The potential benefits of technologies include the ability to allow for independent ‘self-administration’ of functional training and to increase patient adherence to repetition of movements via motivational gamification (e.g. virtual reality gaming) (Turolla et al. 2007; Saposnik & Levin 2011; Rand et al. 2014; Laver et al. 2012). It is believed that these factors will increase the amount of time patients perform independent therapy, thereby improving cost-benefit ratios.

The effectiveness of current therapies targeting subtle or ‘hidden’ attention deficits post stroke is still disputed (Krug & McCormack 2009; Hoffmann et al. 2010). However, rehabilitation of hand function is known to be critical for a stroke patient’s ability to reengage with and complete activities of daily
living (Oujamaa et al. 2009), as well as being an important predictive marker of whole arm recovery (Nijland et al. 2010; Stinear 2010). Development of new therapies for these two common deficits rank 1st and 4th respectively as the top research priorities for improving quality of life after stroke (Pollock et al. 2014), with recovery of hand use being most important to patients with movement disabilities in general (Anderson 2004). The use of new technologies in rehabilitation may allow for both efficient assessment and rehabilitation of attention and hand deficits in combination.

Although there is an ever growing body of research into technologies for rehabilitation (Poli et al. 2013; Thomson et al. 2014), successful translation along a pipeline i.e. from the laboratory through to clinically available products at the bedside, has been very poor. This has led to limited clinical adoption of new technologies, resulting in a failure to improve rehabilitation provision for people after stroke (Cheeran et al. 2009). This failure may be attributed to the fact that most commercially available technologies to date are either (a) efficacious (e.g. rehabilitation robots designed to train therapeutically relevant tasks (Lo et al. 2010; Lum et al. 2012; Poli et al. 2013)) but too expensive; or (b) are systems that are affordable (e.g. commercial gaming consoles - Nintendo-Wii, PlayStation 2 and Microsoft Kinect interfaces), but are ad-hoc solutions that lack proper neuro-rehabilitation context, with inconclusive proof about their effectiveness compared with conventional therapy (Saposnik & Levin 2011; Choi et al. 2014; Thomson et al. 2014). Although Laver et al. 2015 have recently reported evidence that use of motion tracking gaming systems, when used in conjunction with standard care, may be beneficial for improving both upper limb function and completions of ADL, they find insufficient evidence on benefits for regaining such abilities as hand grip function (Laver et al. 2012; Laver et al. 2015). These results highlight that commercial gaming systems still lack the ability for hand grip-force sensing and control tracking. Digital ‘smart object’ rehabilitation systems, such as Tyromotion’s Pablo handle (~£4.5k) (Tyromotion 2015), or research focused digital hand-grips, such as Biometrics’s E-Link (~£3k) (Biometrics 2015), are able to provide hand-grip force sensing, but suffer from limited range of motion, resolution and feedback capabilities.

All of the above technologies suffer from not being portable and are often too time consuming or complex to set up even by therapists (Putrino 2014; Thomson et al. 2014; Thomson 2015). This
makes current technologies unfeasible for patient bedside use whilst in hospital. Many devices can also be inaccessible to the most severely impaired (but therapy-dependent) patients, due to requirement of high levels of baseline function to operate them correctly, needing therapist supervision during use (Thomson et al. 2014). This prevents the possibility of increased independent therapy during the first few months following stroke, when potential for recovery is greatest (Wade et al. 1983; Kwakkel 2004).

The recent release of the MusicGlove (~£900) has shown a new trend towards the development of simple, affordable and portable systems for hand therapy (Friedman et al. 2014; Flint Rehabilitation 2015). Results showed subjects (n=12) improved hand function on the Box and Block test, relating to grasping of small objects, more after MusicGlove compared to conventional training. However, this product again only seems suited for patients with relatively high baseline arm function (FMUL 34 – 62) and hand dexterity, owing to the high levels of coordination and cognitive ability needed to interact with the music based game (Friedman et al. 2014). Although much lower in cost compared with robotic based therapies, it seems that devices such as the MusicGlove are still too expensive for public healthcare providers to purchase and incorporate into standard care (National Clinical Guideline Centre 2013).

The problems of high cost and inaccessibility may soon be overcome by the availability of mobile technologies (tablets & smartphones). In recent years there has been a vast public uptake in mobile technology use, with 63% of the UK population owning a smartphone and 44% having a tablet in their household (Ofcom 2014). These devices are highly portable and allow for feedback gaming to be delivered directly to the patient via ‘apps’. To date, most apps marketed for stroke therapy have focused on speech deficits (Lingraphica 2015; NeuroHero 2015), with a handful beginning to target cognitive training (Constant Therapy 2015; Cambridge Cognition 2015) and motor control (The mindMender Project 2015; Dexteria 2015). Highly addictive cognitive ‘brain-training’ apps requiring fine-motor control have seen unprecedented use amongst healthy individuals (Lumosity n.d.; Memorado n.d.; Fit Brains n.d.; Elevate n.d.; Brain + n.d.), but as of yet very little evidence exists accessing the use of mobile technologies in a population suffering from upper limb impairment. This
may be due to limitations in the conventional control methods required to interact with apps, which need a high level of baseline function and do not involve training functionally relevant movements, instead relying on touch screen finger pressing, swiping and device tilting.

The ready availability of tablet technologies presents the perfect opportunity to deliver the hand-grip attention-control motor task developed in this thesis to a large number of post stroke patients via an app. In order to achieve maximum benefits, a novel hand-grip controller, designed in-line with the low-cost portable nature of mobile technology, must also be developed. To assess the novel devices accessibility, its use must be compared with existing conventional motor control methods supported by mobile technologies.

Aims of the Study

The aim of the following study was to make progress towards developing a simple system allowing for independent bedside hand and attention rehabilitation by:

- Developing a wireless, portable, hand-grip force sensor able to interact with a visuomotor tracking task via a tablet screen.
- Running a usability and feasibility study of conventional mobile technology control methods in a large population of stroke patients presenting with UL impairment, and comparing the accessibility of the novel hand-grip device to these.
- Assessing the success of use of the novel hand-grip device across a wide spectrum of upper limb impairment in this population.
6.2 Methods – Technology Development

6.2.1 Novel Hand-Grip Design and Development

Design and development of the novel hand-grip controller was performed in collaboration with engineers from the Human Robotics Group (HRG), Department of Bioengineering, Imperial College London. The following key design goals for the device were provided to the engineers, the device should:

- Measure flexion and extension forces
- Allow for independent bedside use
- Be lightweight
- Use embedded power
- Connect wirelessly to a mobile tablet to control a visual tracking, one degree of freedom, task
- Remain comfortable while held in the hand
- Be accessible to a wide demographic of stroke patients (baseline grip strength and hand size)
- Provide haptic feedback
- Cost no more than £100 in production materials

A fast-prototyping and an iterative methodology was used to design the device, incorporating both patient and therapists gathered feedback. Computer-aided design (CAD), 3D printing (Makerbot 3D printer), and an Arduino development printed circuit boards (PCB) enabled rapid building of prototypes for testing.

6.2.2 Visuomotor Task Gaming App Design and Development

Design and development of the game was based on the attention-control visuomotor tracking task developed in Chapter four. The engineers at the HRG were asked to take the key features of this task, controlling a crosshair to track a vertically moving star and convert it into a gaming app capable of
being displayed and controlled on a tablet screen of any size. To take full advantage of tablet
technology and motivational gaming, the following design goals were also provided:

- Patient and therapist friendly user interface (UI) and user experience (UX)
- Visual reward feedback (e.g. points collection and ‘level-up’ features)
- Audio reward feedback
- Haptic reward feedback

Unity, a flexible and powerful development platform for creating multiplatform 3D and 2D games and
interactive experiences ([https://unity3d.com/](https://unity3d.com/)) was used to develop the app for tablets running Android
systems.
6.3 Methods - Usability and Feasibility Study

6.3.1 Subjects

All patients presenting with arm weakness on admission, secondary to acute stroke, were screened over a 6-month period at the Imperial College NHS Healthcare Trust Hyper Acute Stroke Unit, Charing Cross Hospital. Exclusion criteria were: 1) clinical cognitive impairment (Mini-Mental State Examination <27), 2) pre-existing weakness, 3) an inability to comprehend the task e.g. due to aphasia, 4) severe co-morbidities, 5) non-stroke, 6) language barrier. Participants were assessed for clinically-apparent sensory or motor neglect (including >25% errors with star-cancellation, or inattention) and for depression or anxiety (Hospital Anxiety and Depression Scale). Handedness was assessed using the Edinburgh Handedness Inventory. All recruited participants gave written and signed informed consent. Ethical approval was granted by the NRES Committee South East Coast-Kent Committee.

6.3.2 Tablet Control Methods

To assess accessibility of the different control methods conventionally used with mobile technologies, available game apps with similar motor control tasks were selected, each corresponding to a specific movement control method. The conventional control methods tested were: Touch screen button press (Tablet - 9.7-inch); Touch screen finger swipe (Tablet – 9.7-inch); Joystick (Atari Arcade Duo Powered Joystick & Tablet); Tilt (Smartphone – 3.5inch) (Figure 35). These were then compared to a novel force-sensing hand-grip controller, connected to a tablet.
6.3.3 Primary Outcome Measure

For each control method, subjects were asked to move a cursor, presented to them on the mobile device screen, along the vertical plane of the device screen. Success of control was qualitatively analysed for each control method using a movement scale of 0-3 (Figure 36), with 0 being no success of moving the cursor and 3 showing full control.

6.3.4 Baseline Motor Clinical Data:

Baseline arm and hand motor function/strength was recorded using: Short Fugl-Meyer (S-FM) (Hsieh et al. 2007); hand and wrist sub-section of the FMUL (FM-Hand); and grip force strength (kg of force), measured by a hand dynamometer (http://www.bleng.com/ptv-65.aspx). General admission impairment level was recorded using the NIH Stroke Scale.
6.3.5 Qualitative Analysis

A Generalised Linear Model (Generalised Estimating Equation, SPSS V.22) was used to assess interactions of (baseline arm) strength vs. device, on movement success. Patients were categorised into 3 strength groups depending on baseline motor outcome results; Severe Weakness, Moderate Weakness and Mild Weakness. First, we compared accessibility of the 4 conventional types of mobile device control - button-press, swipe, joystick, tilt. With movement ability scored on a scale 0,1,2,3 (the model used was an ordinal logistic regression). Patients attempted to use each device with both affected and unaffected hands, and so hand-used was tested as a third factor.

Accessibility of the hand-grip was compared with finger-swipe (the latter selected from the conventional control methods due to its high information transfer rate (ITR) and commonly used in touch-screen based motor control rehabilitation apps (The mindMender Project 2015; Dexteria 2015). Finger-swipe success was defined as either score 2+ (i.e. at least able to move up/down across the
entire range) or 3 (i.e. able to move up/down to specified position). Hand-grip success is defined as 3 (ability to move cursor up/down to a specified position).

6.3.6 Quantitative Analysis

For the hand-grip device, quantitative analysis of control was performed using data recorded during the task and analysed in MATLAB (statistical toolbox v2012). For this, the position of the cursor was assessed in relation to the position of the target, with error calculated as the distance between the two. The root mean squared (RMS) error was calculated within consecutive (and overlapping) 15 second windows (control periods). Therefore, an RMS value was calculated at each time point based on +/- 7.5 seconds of data. The window showing the lowest RMS error highlighted the period of best continuous control in a 15 second window and enabled any data artifacts recorded during the trial to be ignored. This measure has been named the minimum moving error (MME). Correlation between the MME and motor outcome measures was performed across patients using linear regression.
6.4 Results - Technology Development

6.4.1 Novel Hand-Grip

Using the parameters provided, collaboration with the HRG resulted in the development of a low-cost, wireless and portable hand-grip device (UK Patent - No. 1500840.2). This included the design of a novel force sensing mechanism, using a parallel blade spring mechanism (PBSM), and an ergonomically designed plastic shell to house the PBSM, a vibration motor and other necessary electronic equipment.

The PBSM technology allows for variable stiffness force-sensing, enabling the coupling of force and movement. It has been designed in such a way so as to be free from friction and backlash while supporting bidirectional movements (Liardon 2014). This makes the device highly sensitive, with a maximum sensitivity of < 1.5N. If completely compressed, the hand-grip will measure grip force up to a maximum force of 50N. Grip force information is transmitted wirelessly, via Bluetooth, to a mobile device screen (Mace et al. 2015).

Before arriving at the final design, multiple iterations of the housing shell occurred, requiring close coordination between the HRG engineers and therapy teams from the Charing Cross Hospital Stroke Unit. Each iteration contained ergonomic design improvements to increase the comfort of the handle, whilst reducing the size and weight. The handle was designed to fit within the power grasp of a human hand, with the rear shell located against the thenar eminence and the front shell in contact with the phalanges (Liardon 2014). The CAD evolution of the hand-grip prototypes is shown in Figure 37, with the final prototype design, ‘gripAble’, presented in Figure 38.

An internal study by the HRG compared the comfort and usability of a rigid hand-grip force sensing device against that of the novel hand-grip, which allows for flexion and extension range of motion. It was found that on average 62% of the subjects preferred using the flexible device and felt that they performed better, exerting more control whilst interacting with it. Quantitatively, it was found that there was a decrease in the overall tracking error when using the flexible device (Mace et al. 2015).
Figure 37 Design evolution of hand-grip prototypes

Design 1: Rod shaped for grasped hand, with cone shaped head; Design 2: Adapted to allow for change in extension and hand size; Design 3: First working prototype with embedded electronics.

Figure 38 Novel Hand-grip Control – ‘gripAble’

Exterior CAD view of the final fully working prototype. The final system has variable compliance, can measure tension and compression grip forces, generates haptic feedback and can connect to an Android tablet device via Bluetooth. The grasp diameter is adaptable.
6.4.2 Visuomotor Task Gaming App

A Beta version of an Android app was designed to interact with the wireless hand-grip device. The app was presented on a Toshiba AT300SE tablet. Importantly, the UI and UX design allowed for users to easily connect to the hand-grip, navigate to the visuomotor game, and play. The visuomotor game was successfully implemented, with the hand-grip controlling a centrally located crosshair on the tablet screen, allowing tracking of a vertically moving star following a fixed sinusoid trajectory. In addition, a set of levels was created, introducing different motivational features (visual reward, auditory, haptic) and attentional distractors (additional star stimuli) as seen in the design of the attention-control visuomotor tracking task in Chapter Four (Figure 39).

Figure 39 Visuomotor Game App Levels

A - Level 1: A pink start was presented on a blue screen, turning gold when the crosshair was successfully directed over it (Figure 4). B - Level 2: an additional coin stack was placed at each side of the screen, providing a means of points collection during successful tracking (1 coin = crosshair dwell time of 2 seconds over the star). Each coin collected was coupled with an auditory bell sound from the tablet speakers and vibration in the hand-grip. C - Level 3, addition of similar stars acted as distractors, allowing for attention-control testing.
6.5 Results - Usability and Feasibility Study

6.5.1 Test Population

342 patients with arm-weakness were screened, of which 89 were recruited and 84 completed the protocols (Figure 40). Patient demographics, baseline clinical characteristics are presented in Table 15. Figure 41 shows the number of patients categorised into the 3 different strength groups: Severe Weakness, Moderate Weakness and Mild Weakness (using the S-FM).

Patients screened - presenting with arm weakness

(n= 342)

Ineligible (n=229)

1. Cognitive impairment/Co-morbidities (n=130)
2. Communication difficulties (n=36)
3. Resolved weakness (n=34)
4. Pre-existing arm weakness (n=24)
5. Non-stroke (n=5)

• Refused consent (n=24)

Patients recruited to study

(n=89)

• Withdrew consent (n=3)
• Unilateral spatial neglect (n=2)

Patients completing protocols

(n=84)

Figure 40 Patient Screening and Recruitment Flow Diagram

342 patients presenting with arm weakness were screened, of which 229 were ineligible due to not meeting exclusion criteria and 24 refused consent. 89 patients were recruited into the study of which 3 withdrew consent after commencing the protocol and 2 were diagnosed with clinically significant unilateral spatial neglect. In total, 84 patients completed the study protocol.
Table 15 Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Recruited</th>
<th>Not Recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>89</td>
<td>253</td>
</tr>
<tr>
<td>Age / yrs</td>
<td>65 (55 - 75)</td>
<td>72 (64 - 85)</td>
</tr>
<tr>
<td>Males / %</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>NIHSS – overall /42</td>
<td>5 (2 - 6)</td>
<td>9 (4 - 14) *1</td>
</tr>
<tr>
<td>HADS – /42</td>
<td>3 (1 – 3)</td>
<td></td>
</tr>
</tbody>
</table>

Arm Specific Tests:

<table>
<thead>
<tr>
<th></th>
<th>Weak Hand</th>
<th>Not Performed if Not Recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Fugl Meyer arm function /12 (12: normal)</td>
<td>8 (6-11)</td>
<td></td>
</tr>
<tr>
<td>Hand Section Fugl Meyer /14 (14: normal)</td>
<td>8 (2-13)</td>
<td></td>
</tr>
<tr>
<td>Grip force /Kg</td>
<td>13 (2-22)</td>
<td></td>
</tr>
</tbody>
</table>

Median (interquartile range). *1 p<0.05, Recruited vs Not Recruited
All other group comparisons are insignificant (p>0.05)

Figure 41 Categorisation of patient strengths

Patients were categorised into 3 groups of strength depending on their baseline S-FM score. These groups were; Severe Weakness, 0-4 S-FM (n=14); Moderate Weakness, 5-8 S-FM (n=16); Mild Weakness, 9-12 S-FM (n=54).
6.5.2 Conventional Device Comparison

Here we assessed control success of the 4 conventional control methods, comparing these with the patients’ baseline strength. Movement scores were worse for patients with more severe baseline strength, and while using their affected (Figure 42) versus unaffected hand (Figure 43) (main effects chi2(1)=23.3, 40.5, respectively; p<0.001 for both); with the difference between unaffected and affected hands greater for patients with more severe weakness (Hand-use x Severity interaction: chi2(1)=10.9; p<0.001). Hence, on average, patients with severe weakness (median score: 0) were unable to effect any control; with moderate weakness (median score: 2.5) were able to make vertical movements, but below reasonable accuracy; and with mild weakness (median score: 3) were able to make accurate vertical movements. There were no significant differences between the four conventional control types on movement score, either as a main effect (chi2(3)=4.89; p=0.180), or as an interaction with hand-use (chi2(3)=2.73; p=0.435), baseline strength (chi2(3)=0.66; p=0.883), or as an interaction between all three factors (chi2(4)=9.21; p=0.056). In total, using their weak hand, 50% of patients were able to control with swipe, 59.3% with button and tilt, and 61.5% with joystick.
Severe patients show a mean movement scores (mms) of 0.2 for swipe and joystick and 0 for button press and title; Moderate patients show 2.3mms for swipe, 2.3mms for button, 1.7mms for tilt and 2.5mms for joystick; and Mild patients show 3mms for swipe, 2.75mms for button, 2.8mms for tilt and 2.8mms for joystick.

Severe patients show a mean movement scores (mms) of 2.8mms for swipe, 1.8mms for button, 2.2mms for tilt and 3mms for joystick; Moderate patients show 3mms for swipe, 2.8mms for button, 2.6mms for tilt and 3mms for joystick; and Mild patients show 3mms for swipe, 2.75mms for button, 2.8mms for tilt and 2.8mms for joystick (identical to weak hand).
6.5.3 Conventional vs Novel Hand-Grip Comparison

Here we assessed control success of the novel hand-grip device across patient baseline strength, comparing it to success using the conventional swipe control. Hand-grip resulted in greater control success than swipe (main effects of Device: chi²(1)=15.1, p<0.001; OR=1.48), even when using a liberal criterion of movement success for swipe assessment (movement score 2). Furthermore, as expected, patients with mild baseline arm deficit used either control with more success (main effect of strength: chi²(1)=37.6, p<0.001; OR=1.93 for high vs mid-lower baseline function). There was also a Device x Strength interaction (chi²(1)=4.76, p=0.029) reflecting a superiority of hand-grip, versus swipe, in severe (OR=Inf) but not moderate (OR=1.44), or mild (OR=1.12) deficit groups. 88.9% of severe patients were able to exert control using the hand-grip, versus 0% for swipe (Figure 44). Using a more stringent measure of success for swipe control (full range and control i.e. movement score 3), revealed an effect of Device, as before, but no Device x Strength interaction. This was because the hand-grip was now superior across low, mid- and high-functioning groups (chi²(1)=7.06, 4.40, 5.07; p=0.003, 0.036, 0.024; OR=Inf, 2.02, 1.41, respectively). In total, using their weak hand, 93.8% of patients showed success using the hand-grip, versus 50% using swipe.
Hand-grip success was shown by 88.9% of severe patients, 77.8% moderate and 100% mild; Swipe success, using movement score of 2, was shown by 0% of severe, 53.8% moderate and 89.5% mild; and, using a more stringent movement score of 3 0% of severe, 38.5% moderate and 71.1% mild.

6.5.4 Accuracy of Hand-grip Control vs Baseline Hand Function:

Quantitative analysis using the MME as a measure of accurate control was examined for the hand-grip device. Game data was collected from the final twelve patients. Figure 45 A shows individual MME plotted against baseline S-FM, while Figure 45 B shows individual MME plotted against baseline FM-Hand. Results show that there was no significant difference in MME across baseline strength (S-FM) (p = 0.3792, R2 = 0.0868, R2adj = -0.0147), even when taking into consideration an outlier patient showing high MME (p = 0.1841, R2 = 0.1691, R2adj = 0.0868). Patients with a FH-Hand score of >2 exhibited low error with no significant difference in their MME score (p = 0.2131, R2 = 0.1663, R2adj = 0.0737). These results confirm previous qualitative analysis, i.e. that control using the hand-grip is accurate and similar across a wide range of motor severities.
Figure 45 Accuracy of Control Using Hand-grip Compared to Baseline Hand Function

MME scores plotted against patient baseline S-FM (Solid line: $p = 0.3792$, $R^2 = 0.0868$, $R^2_{adj} = -0.0147$; Dashed line: $p = 0.1841$, $R^2 = 0.1691$, $R^2_{adj} = 0.0868$). Far right - Box plot visualisation of the MME scores across the 12 patients, showing mean/median, +/-1std or inter-quartile range and outliers (red cross).
6.6 Discussion

In this chapter we continue from the work undertaken in chapters four and five, translating the visuomotor tracking task controlled via a research oriented hand-grip, into a product with real world clinical potential. The work was divided into 3 stages; 1) development of a novel portable hand-grip device and creation of an app capable of presenting the visuomotor task on mobile technologies; 2) assessing the general accessibility of standard mobile technology control methods as a potential means of allowing for independent patient assessment and rehabilitation; 3) comparing accessibility of the newly developed hand-grip device to the standard mobile technology controls.

We screened 342 patients presenting with arm weakness on admission of which 84 patients were included and completed the study. Results show that the newly developed hand-grip device can be used by 94% of eligible patients to engage with a task on a tablet compared with 56-62% using standard mobile technology controls, with 89% of severely impaired patients being able to use the hand-grip, versus 0% when using a traditional swipe control.

6.6.1 Development of a Novel Hand-grip and Mobile Gaming App

Collaboration with the HRG resulted in the successfully development of a first working prototype of a novel digital hand-grip device. The hand-grip is light-weight (0.25 kg) and wireless (connecting via Bluetooth), making it extremely portable. The force sensing mechanism (PSBM) is highly sensitive and free from friction and backlash, allowing for a wide range of grip forces to be recorded (<1.5-50N). The ability to accurately sense forces of <1.5N allows for recordings from patients with only minimal flicker finger movements, often preserved in patients with severe hemiparesis (Collin & Wade 1990), making the hand-grip accessible to even the most impaired patients. The device records force during both grasp flexion and extension movements, permitting for quantitative assessment of both functions, and can be calibrated to each patient to accommodate all levels of impairment. This is beneficial for future applications of the device as both a rehabilitative and assessment tool for hand function, with training of grasp vital for patient rehabilitation (Oujamaa et al. 2009), and with grip
strength and finger extension shown to be strong predictors of recovery of dextrous hand function (Fritz et al. 2005; Smania et al. 2007; Au-Yeung & Hui-Chan 2009).

Bluetooth connectivity allows the hand-grip to interact with mobile technologies, specifically to control the visuomotor tracking task, which was converted into an app and run on an Android tablet. In addition to the original task, a number of motivational features including reward, visual, auditory and haptic (vibration through hand-grip) feedback were introduced. The ability to provide these motivational aspects is highly desirable in order to maximise the impact of the new mobile system.

Around 38% of acute stroke patients are affected by apathy, a general lack of motivation, with potential effects on self-efficiency of rehabilitation (Caeiro et al. 2012). It is known that inpatients show poor participation during therapy, resulting in less improvement in function independence measures and increases in their length of hospitalisation (Lenze et al. 2004). Once discharged, only 31% of patients actually perform therapist recommended exercises (Shaughnessy et al. 2006), with minimal reported use of the upper extremity even during non-therapy daily activities (Donoso Brown et al. 2015).

In healthy subjects, reward feedback through gamification has been shown to increase motivation and engagement in task participation (Richter et al. 2015), with positive reward having important positive influences on motor learning and retention of motor memory formation that persist over time (Wickens et al. 2003; Abe et al. 2011; Bavelier et al. 2012; Galea et al. 2015). Combinations of reward and sensory feedback have been shown to accelerate motor learning (Nikooyan et al. 2015).

This has led to feedback based gamification mechanisms being employed in rehabilitation focused games, in an attempt to increase training time and motor learning (Burke et al. 2009; Delbressine 2012; Richter et al. 2015). Incorporation of further sensory feedback has also shown positive results in stroke, with auditory feedback showing decreases in game error and increases in patient effort (Secoli et al. 2011); and combinations of visual and haptic feedback yielded positive findings for enhanced manual dexterity and accomplishment of activities of daily living (Broeren et al. 2008; Broeren et al. 2009). Ability to apply sensory feedback through the hand-grip device is particularly important as it has been well established that such feedback is critical for object manipulation (Bilodeau & Bilodeau
1961) and control of grasp force (Johansson & Westling 1984; Johansson & Westling 1987) as well as specifically beneficial for attention training following brain damage (Dvorkin et al. 2013).

In addition to incorporating aspects of the above feedback mechanisms, the new app task was also divided into ‘levels’, with each level corresponding to the introducing of additional attentional distractor stimuli, as seen in the original motor-attention task. These levels in themselves are designed to act as a motivational tool for patients, with points and levels known to facilitate increased engagement in self-management in patients with chronic conditions (Miller et al. 2014).

Although progress has been made in developing technologies and serious games for patient self-therapy, adoption by patients has still seen little success. An example of this can be seen in a study by Standen et al. 2014, who provided patients with a virtual glove and serious game on a desk top computer to perform home-based therapy for 8 weeks (Standen et al. 2014). Although motivating, daily use of the technology varied widely between patients and fell far short of the therapist recommended dose. Patients reported a lack of familiarity with the technology and inconvenience as barriers to use. These results highlight the importance of making patient-centric design and accessibility of devices a priority for future technologies.

Development of the portable digital hand grip and app mobile system will allow for data collection and training using the visuomotor task developed as part of this thesis on a much larger scale. A major limitation of the equipment used for gaining results in chapters four and five was its cumbersome and costly nature. This equipment could not be easily set up and it was not possible to leave it with patients. The new system will not only allow for easy assessment of motor and attention deficits, but also holds future potential to be used repeatedly by patients as a form of low-cost mobile rehabilitation. In order to justify such future developments accessibility of the hand-grip was compared to conventional mobile technology control methods.
6.6.2 Accessibility of Mobile Technologies

As expected, we have shown that control of mobile technologies using conventionally available methods is worse for patients with more severe baseline strength, and when using their affected compared with their unaffected hand. When using the affected hand, results showed that conventional methods enabled cursor control between 50-61.5% of patients, with no significant differences between the four conventional control types on movement score. However, although patients with mild weakness were able to exert full and accurate control, and those with moderate weakness were able to show full vertical movement, albeit below reasonable accuracy, none of the severely impaired patients attained any level of control. These results highlight that while conventional mobile controls can be used by a majority of stroke patients presenting with moderate-mild arm weakness, enabling access to mobile gaming technology, mobile technologies remain inaccessible for assessment and training of the affected hand in patients suffering from severe motor impairment.

When using the unaffected hand, patients were able to exert reasonable to accurate control with all conventional methods, regardless of the severity of impairment of their affected hand. This suggests there is potential for all suitable patients to use their unaffected hand to interact with tablet technology to assess ipsilateral motor function (Noskin et al. 2008; Zhang et al. 2014), or to engage with tablet-based speech and cognitive assessment apps (Des Roches et al. 2015; MoCa Online 2015). However, a support for the tablet would have to be taken into consideration for those unable to hold the tablet with their weak hand.

6.6.3 Accessibility of the Novel Hand-grip

Examining the accessibility of the novel hand-grip device versus the conventional mobile control methods showed that 94% of patients were able to achieve an accurate level of control using the hand-grip compared with only 50% using swipe. Again, as expected, patients with mild baseline arm deficit were able to exert greater levels of control with either method compared with weaker patients. However, the most significant difference between the two methods was observed in severely impaired patients, of whom 89% were able to exert accurate control using the hand-grip, but none of whom could use standard swipe input. These results highlight the relative inaccessibility of standard mobile
technologies for those with severe motor impairment, and show a vast superiority of the novel hand-grip in being able to provide access to mobile gaming to this subset of patients that, arguably, would benefit most from a higher amount of training and feedback.

The difference in accessibility between the two control methods may be due in part to the movements required to exert control; the tablet alone requires movement at the elbow and/or wrist, along with a high level of finger dexterity (extension and flexion) to enable touch screen control. The hand-grip requires only low active levels of finger flexion and extension, preserved in a majority of patients (Collin & Wade 1990), to allow for interaction and control. Further quantitative analysis, using accuracy control data from the tracking task, confirmed that patients were able to exercise similar control using the hand-grip regardless of their baseline strength. This result highlights the ability of compatible devices, such as the hand-grip, to be calibrated to each patient, accommodating for all levels of impairment.

6.6.4 Mobile Technologies for Rehabilitation

Technology based approaches for motor therapy are becoming more widely utilised as benefits begin to emerge and implementations become more refined (Reinkensmeyer & Boninger 2012; Poli et al. 2013; Shapi’i et al. 2014; Rand et al. 2014; Laver et al. 2012). However, there still remain numerous barriers for wider adoption relating to inaccessibility to both patients and therapists, and for use in hospital and/or at home (Connor 2012; Standen et al. 2014; Putrino 2014; Thomson 2015; Dolce et al. 2015; Tatla et al. 2015). Such barriers are preventing rehabilitation technologies from having the impact they have been touted to achieve, meaning that future developments must take greater care in considering the accessibility needs for both patients and therapist to improve adoption into standard care.

Mobile technologies have emerged as a candidate capable of overcoming previous accessibility limitations. They are low-cost and already widely adopted within the population, reducing the need for further cost of purchase; are highly portable; allow for a degree of familiarity due to previous use; and, via apps, permit for delivery of motivational gaming regardless of the patients location (e.g.
therapy gym, bedside, home, on holiday). Incorporating mobile technologies into stroke rehabilitation has already been shown to be feasible and accepted by patients (White et al. 2014; Des Roches et al. 2015). With rehabilitation of cognitive function starting to be considered a critical component of post brain injury medical care (De Luca et al. 2014), and computer based games showing promise in assessment and training of cognitive impairments (Tang & Posner 2009; Rinne et al. 2013; Posner & Fan 2013; Shapi’i et al. 2014; De Luca et al. 2014), mobile apps for cognitive assessment and training are already being developed for both research (Oliveira et al. 2014; McNab & Dolan 2014) and commercial purposes (Constant Therapy 2015; Cambridge Cognition 2015). However, the transfer effects of training using current commercially available ‘brain-trainer’ apps, at least in healthy populations, is still disputed (Owen et al. 2010).

More recently, apps for motor assessment and rehabilitation have also emerged, including ad-hoc untested examples such as mindMender (The mindMender Project 2015), ReHaptix (ReHaptix 2015) and Dexteria (Dexteria 2015), entering directly into a commercial setting, and research led iHome being taken through feasibility testing (Saposnik et al. 2014). Although these motor control based apps highlight the ability of mobile technologies to capture fine motor movements using conventional touch screens methods, the accessibility of this method of control within a motor impaired population has not yet been analysed. We show here that although mobile apps targeted for motor rehabilitation can be controlled via conventional methods by a majority of minimally impaired patients, patient-centric control devices should be considered as an adjunct to provide access to the broadest range of impairments. It is important that any such devices maintain the same principles of mobile technologies, remaining low-cost and portable, whilst allowing for assessment and independent training of functionally relevant movements.
6.5 Conclusions

Translation of the visuomotor task was successfully completed and resulted in the development of a novel portable hand-grip, gripAble, capable of facilitating stroke patient interactions with mobile technology devices. Results from the feasibility study show that standard mobile gaming technology can be used by a majority of stroke patients with mild arm weakness, and may enable adjunctive and economical self-therapy. Novel control devices adapted for patients, of the kind developed and trialled here, can broaden access to patients with more severe impairments, improving accessibility of mobile gaming technologies for self-rehabilitation of UL function in stroke.

On top of this, devices such as gripAble will allow for training of functionally relevant movements, e.g. grip, which standard mobile technology controls do not permit. These interactions can eventually be used not only for functional movement training, but also to stimulate attention (or other cognitive task) training in suitable patients via gamification. This will strengthen the case for the deployment of mobile technologies into clinical rehabilitation practice, providing therapists with a feasible technology based option for increasing motor and cognitive therapy doses. The pairing of mobile technologies with portable, low-cost interactive devices may help overcome many of the barriers currently associated with rehabilitation technologies, and allow for deployment and use of such technology from acute hospital to chronic home-based settings.
CHAPTER SEVEN: GENERAL DISCUSSION
7.1 General Discussion:

This thesis set out with the aim of addressing the hypothesis that attention deficits are not only common in a post stroke population, but that they have a large and underappreciated impact upon motor deficits, thus potentially effecting rehabilitation and recovery of motor functions. If found to be true, it was believed that new methods of assessing and training such attention-motor control deficits could be translated directly into a clinical setting through the development of novel digital technologies, which have the potential to alleviate the strain on stretched rehabilitation resources, but are currently underprovided to patients due to cost, usability and feasibility barriers.

In this final chapter we present a summary of the work undertaken and discuss key findings, the development of a novel attention-control behavioural assessment method and production of a corresponding digital assessment device, and recommendations for future directions of research into the implications of attention-motor deficits in stroke recovery, as well as into improving the design and implementation of future technologies for motor rehabilitation.

The introductory chapter provided an overview of the impact of motor deficits in stroke and of the current state of clinical motor rehabilitation, including the relatively recent adoption of learning based rehabilitation programmes. Such programmes have been created due to the understanding that motor-learning dependent neuroplasticity is responsible for recovery following stroke and so can be targeted in order to improve patient outcomes. The ability to increase the efficiency of rehabilitation was highlighted as a priority in stroke care, suggesting the need for further work into the understanding of the mechanisms underlying neuroplasticity and how these can be positively manipulated during rehabilitation to improve recovery. With a strongly suggested role in motor-learning and neuroplasticity, along with deficits within its functionalities correlating to poor motor recovery outcomes following stroke, ‘attention’ was highlighted as a key factor that could play a critical role in post-stroke motor re-learning, warranting research into the impact of specific attention deficits upon motor control. Finally, the concluding portion of this introductory chapter highlighted current trends in the development and attempted implementation of technologies in clinical rehabilitation.
Principally, these technologies aim to increase dose of rehabilitation whilst reducing the strains on human resources, and often rely on the use of virtual reality gaming in order to increase patient adherence. The use of such ‘serious games’ may be influenced by a patient’s attentional-control ability, but may also present an opportunity to deliver attention–control assessments and rehabilitation through suitably designed and accessible technologies.

In Chapter Two, the imaging methods employed throughout this thesis to evaluate the neuroanatomical and behavioural correlates of attention and motor control were explained and the justification for their employment presented. A combination of structural lesion mapping and resting-state functional techniques successfully provided evidence to allow for strong conclusions to be drawn from the relationships of post stroke attention and motor functions.

In order to establish the prevalence of attention deficits in a post stroke population and correlate specific subcomponents of attention to motor related functions, a pan-brain data-driven lesion analysis approach was combined with a highly sensitive attention test (ANT) and is discussed and developed in Chapter Three. It is understood that attention can be resolved into three fundamental subtypes - alerting, orienting and conflict-resolution that are mediated by three anatomically-distinct but broadly-spaced brain networks. An important prediction of this model is that behavioural dissociations between these three functions will occur in a significant proportion of patients with focal brain lesions, depending upon lesion location. The ability to resolve these components was important in order to extract anatomical regions specifically related to the conflict resolution subcomponent, the function of which is known to be critical for good motor control and complex task learning. 110 consecutive acute stroke patients with anatomically-unselected unifocal lesions and 62 age-matched controls were recruited. Results localised specific attention deficits to distinct anatomical locations, with conflict resolution, showing associations with bilateral frontal regions, and especially white matter tracts between prefrontal and premotor cortices. This association with higher order motor regions provided an important link for the role of attention-control with motor impairment.

Having established neuroanatomical associations between attention-control and motor regions, Chapter Four focused on the development of a more complex visuomotor task capable of tracking
attention-control influences on hand motor control and utilised it to differentiate attention dependent motor deficits from pure motor impairment. The novel task required subjects to apply varying grip strength through a commercially available force transducer, so as to make a visual cursor track a moving target. Attention-control was then manipulated by adjusting the number of visual distracters. 92 hemiparetic stroke patients, with no overt cognitive deficits or neglect, and 49 controls, were recruited, with bilateral hand functions tested using the novel visuomotor tracking task. Unilateral motor impairments were distinguished from bilateral motor impairments with performance correlated strongly with attention-control. A dissociation was seen in that patients with poor motor performance showed either impaired or intact attention-control, whereas good performance was never, or rarely, associated with impaired attention-control – which suggested that impaired attention-control causes impaired motor performance, rather than vice versa. Bilateral motor impairments, caused by global attention deficits, were then shown to correlated with the degree of disruption to an anterior frontal attention associated network (via both lesion mapping and functional connectivity imaging), consolidating findings that motor impairments in these patients occurred as a result of disruption in attention. The results of this chapter confirmed the critical role of attention-control in good motor performance and also validated the task as a novel method of tracking attention-control motor deficits in stroke.

With the aim of understanding in greater detail the relationships seen between performance of the visuomotor task and correlations in attention and motor functional connectivity networks, in Chapter Five we employed a resting-state functional MRI protocol to track connectivity changes following task performance in 23 patients and 23 control subjects. Results showed that a set of attention and motor related functional networks, namely: visuospatial, sensorimotor and cerebellar, expressed different levels of modulation between patients and controls. Importantly, short term performance of the task was shown to stimulate motor-learning, allowing for correlations to be made between individual patient abilities of motor learning and differences in network connectivity changes. Greater motor-learning was associated with greater decreases within connectivity of networks, suggesting that between network, compared to within network, reorganisation and disruption of attention and motor resting state networks in the damaged brain may be associated with better learning, and be a potential
biomarker of learning-dependent neuroplasticity. The ability of the visuomotor task to stimulate motor-learning and allow for the evaluation of rapid changes of network connectivity in an acute stroke setting further validated the potential of this task to be used as an attention-motor control assessment and rehabilitation aid.

In light of the results generated from the chapters investigating the impact of attention deficit on motor impairments (i.e. attention deficits are common in stroke, share neuroanatomical markers with motor performance and significantly contribute to motor control deficits), and showing that the visuomotor task controlled through a hand-grip device was capable of not only assessing attention-motor control deficits, but was also able to stimulate a learning effect and allow for assessments of related changes in neuroplasticity driven functional network reorganisations, it was the desire of this thesis to further translate the use of the novel visuomotor task into a real world rehabilitation environment. A review of currently available rehabilitation technologies highlighted a number of significant barriers to their wide-spread adoption in both highly dynamic clinical and isolated home based settings. Thus, the development of a novel hand-grip device, capable of allowing for autonomous practice of the visuomotor task, followed a set of design principles to ensure that it was highly portable, low-cost and designed in a patient and therapist-centric format. The successful development of such a device, ‘gripAble’, was achieved in Chapter Six, and allowed for the performance of a variant of the visuomotor task on mobile tablet devices. Mobile technologies, such as tablets, follow the same portable and low-cost features highlighted as desirable for technology adoption, suggesting that these alone could be used for rehabilitation purposes. However, the accessibility of such devices within a motor stroke population had not yet been tested.

In order to test the use of the novel hand-grip against standard mobile technologies, a usability and feasibility study was performed comparing different mobile technology control methods against the control provided by gripAble. 342 patients with arm weakness secondary to acute stroke were screened over a 6-month period in a single centre, with 89 subjects tested with the different types of hand-control interfaces. Conventional mobile interfaces enabled cursor control in 50-62% of patients, compared with 94% of patients being able to successfully use the novel hand-grip controller. The
improvement in interface accessibility of the novel, relative to conventional, controller was specific to patients within the lowest tertile of baseline arm-function, where 89% of the most severely impaired patients were able to use gripAble, compared with 0% being able to interact with mobile technologies alone. Although these results highlighted that standard mobile gaming technology can be used by a majority of stroke patients with mild arm weakness, and may enable adjunctive and economical self-therapy, use of the novel patient-centric hand-grip control significantly broadened access to patients with more severe impairments. Taken together, the results from Chapter Six form the first steps in the translation of the attention-motor control task, developed in this thesis, for use in a clinical setting.

7.2 ‘Attention’ Deserves Further Attention

First and foremost, the results observed in this thesis suggest that hemiplegia after stroke is not only a disorder of motor pathways, but also often reflects a disorder of attention-control. Thus, strokes can result in a number of different impairments, both pure motor and cognitive, each of which can impact upon motor recovery. Our results implicate attention as being a critical component of good motor control in patients, with deficits likely to impact upon motor-learning and, thus, motor recovery potentials. Therefore, we suggest that highly sensitive assessments of attention deficits should be routinely performed on stroke patients, the vast majority of whom exhibit motor impairments. Current clinical attention assessment methods are often crude, not allowing for the detection of subtle deficits that may not be apparent upon standard bedside examination. Indeed, results from Chapter Three indicated that more than half of our unselected sample of stroke patients had impaired attentional capacity; while a far smaller proportion were reported as having any clinically-obvious attentional deficit or neglect. Advanced cognitive testing, in general, is known to be underdeveloped and underused in post stroke settings. However, the use of computer-based assessments in research is well documented. Thus, the translation of sensitive computer-based and research proven attention tests into clinical use, such as the ANT, should be taken into serious consideration and may allow for the stratification of patients according to attention deficit type and allow for targeted therapy.
Adding to this, a combination of digital attention and motor assessments, such as the attention-control visuomotor tracking task developed as part of this thesis, can allow for advanced identification of patients specifically suffering from motor deficits due to reduced attentional capacity. Deployment of such an assessment may again allow for further stratification of patients who require additional motor therapy or who may benefit from the performance of initial motor therapy in environments where they are less distracted by continuous external stimuli (e.g. group rehabilitation gyms, etc.). Attention training has been shown to improve attention levels in stroke, suggesting that repetitive performance of digital attention task may improve performance of fine motor skills. However, although we show that our visuomotor task is capable of detecting attention-control deficits and stimulating motor-learning, a connection between improved attention training and recovery has not yet been established.

Although the increased adoption of attention-control behavioural testing and training is highly desirable as a means of assessing a spectrum of attention deficits and potentially stratifying patients for targeted motor therapy, our results also show that stratification of patients may also be achieved through the use of lesion based and functional imagine protocols. We show that patients exhibiting attention-control deficits can be characterised according to specific lesion locations and potentially through the assessments of varying motor-learning dependent resting network connectivity profiles.

With MRI scanning routinely performed following stroke, analysis of lesion data may be a possible route for building attention deficit and recovery profiles of patients. Although less achievable, due to the complex and costly nature of functional scanning, our results also suggest that resting state functional analysis has the potential to be used as a biomarker of differing abilities of motor-learning following stroke, and that differing profiles of both attention and motor networks between patients may be a signature of recovery potential. However, as with pure behavioural testing, conclusions related to recovery cannot be drawn without assessment of longer term patient outcomes.

7.3 Development of Novel Rehabilitation Technologies

Chapter Six of this thesis focused on the how technologies allowing for increased repetition of movements, touted as the future of rehabilitation provision, are seeing high levels of development,
but are not showing a wide adoption across clinical care. The final goal of this thesis was to develop a digital device capable of utilising the work undertaken within it and deliver attention-control assessments and training into a clinical setting. Thus, the design of a suitable device able to overcome the barriers befalling previous technologies was undertaken and resulted in the production of ‘gripAble’, a portable ‘hand-and-brain’ trainer. Although not capable of actively moving the hand of a patient, gripAble is highly portable and low-cost, and we show it allows for high accessibility of interactions with mobile based gaming. We suggest that portable sensor-based devices such as gripAble, which allow for truly autonomous decentralised training, should remain a key focus of the future development of rehabilitation technologies to be used as an adjunct to standard care.

With relation to technologies and their employment of digital training games, we also put forward a cautionary note in that patient performance levels, when using highly motivational and stimulating games, may in fact be susceptible to attention-control deficits, as have been reported in this thesis, and bias recovery outcomes seen after their use. Research into attention-control deficits influencing performance across such stimulating games warrants further investigation.

### 7.4 Future Directions for Research into Attention-Motor Control

Although our results indicate that attention deficits impact upon motor performance and learning, which strongly suggests that the presence of attention deficits in patients are related to a patient’s recovery potential, future research requires the use of well controlled longitudinal follow-up studies in order to relate any acute attention deficits to motor outcome. With regards to purely behavioural studies, the translation of the visuomotor task into a relatively cost effective device, capable of being widely adopted in clinical environments, will allow for its use in larger multi-centre randomised clinical trials, where early attention-control assessments and subsequent repetitive training across a large pool of patients (which would provide significant statistical power), can be eventually correlated to individual attention and motor recovery outcomes. A lack of sufficient statistical power has been a key downfall of studies assessing the quality and efficacy of current rehabilitation technologies. Here we suggest that the gripAble device, due to its accessible nature, can overcome these issues.
Similarly, future work correlating baseline lesion and functional connectivity profiles to long term outcome requires follow up of patients across both early subacute recovery (e.g. 3 months) and long term chronic periods (e.g. 12 months+). Follow-up of patients showing distinct functional connectivity motor-learning profiles should involve both correlation of recovery to baseline scans and early modulations (as was tested in this thesis), but also employ further follow-up scanning protocols to analyse changes in patient connectivity modulation profiles and how these relate to both training and motor outcomes.

7.5 Final Remarks

The work in this thesis has confirmed the hypothesis that attention deficits are both common following stroke and that they impact upon motor control. Such deficits can be detected and potentially targeted with training using novel assessment and rehabilitative technologies. However, the future development of such technologies must take into account design features that allow for their adoption in a true rehabilitation environment. The study has generated new hypotheses to further test how attention deficits may impact upon long term recovery and whether signatures of attention-control deficits can be used as biomarkers of recovery potential.

In conclusion, this thesis provides the scientific community with new methodologies for assessing the impact of attention deficits on motor control; provides recommendations to the clinical stroke community about the need to consider such impacts and assess them directly in rehabilitation practice; and presents a new patient-centric and clinically friendly device that has the potential to facilitate this.


Barker-Collo, 2010. Attention deficits after incident stroke in the acute period: frequency across types of attention and relationships to patient characteristics and functional outcomes.
References


Birkenmeier, R. et al., 2010. Translating animal doses of task-specific training to people with chronic stroke in one hour therapy sessions: a proof-of-concept study., 24(7), pp.620–635.


Burke, J.W. et al., 2009. Serious Games for Upper Limb Rehabilitation Following Stroke. *2009 Conference in Games and Virtual Worlds for Serious Applications*.


REFERENCES


REFERENCES


Fossella, J. et al., 2002. *Assessing the molecular genetics of attention networks*.


REFERENCES


Go, A.S. et al., 2014. *Heart Disease and Stroke Statistics - 2014 Update: A report from the American Heart Association,*


Hochstenbach, J. et al., 1998. *Cognitive decline following stroke: a comprehensive study of cognitive decline following stroke,*


REFERENCES


Kalra, L. et al., 2004. *Training carers of stroke patients: randomised controlled trial*,.


REFERENCES


Mace, M. et al., 2015. Comparison of isokinetic and isometric handgrip control during a feed-forward visual tracking task. *Proc. of the International Conference on Rehabilitation Robotics (ICORR)*.


REFERENCES


Reference:


REFERENCES


Rehme, A.K. et al., 2011. The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. *Cerebral cortex (New York, N.Y. :*
References


REFERENCES


Staubli, P. et al., 2009. Effects of intensive arm training with the rehabilitation robot ARMin II in chronic stroke patients: four single-cases. Journal of neuroengineering and rehabilitation, 6, p.46.


References


Wahlund, L.O. et al., 2001. *A new rating scale for age-related white matter changes applicable to MRI and CT*,


### Supplementary Data 1

Results of t-tests (Lesion+ vs Controls or Lesion-) for each attention-type were thresholded at $p<0.001$ (as reported in Tables 2,3), and overlaid onto reference grey-matter, thalamic, and white-matter atlases. The volume, in cc, of significant voxels is listed, as well as the % of each region occupied by significant voxels (in brackets), are listed; thalamic voxels are further subdivided according to their relative occupancy of subdivisions categorised by their cortical target (italics).

<table>
<thead>
<tr>
<th>Harvard-Oxford Atlases (Desikan et al, 2006; Behrens et al, 2003)</th>
<th>Conflict</th>
<th>Orient</th>
<th>Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT</td>
<td>Accuracy</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>vs Con</td>
<td>vs L-</td>
<td>vs Con</td>
</tr>
<tr>
<td>R PreCentral Gyrus</td>
<td>7.9 (14)</td>
<td>1.8 (3)</td>
<td></td>
</tr>
<tr>
<td>R Inferior Frontal Gyrus</td>
<td>4.3 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle Frontal Gyrus</td>
<td>2.4 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Insular Cortex</td>
<td>1.8 (12)</td>
<td>0.9 (7)</td>
<td></td>
</tr>
<tr>
<td>R Putamen</td>
<td>1.2 (19)</td>
<td>0.6 (9)</td>
<td></td>
</tr>
<tr>
<td>R Frontal Operculum Cortex</td>
<td>0.8 (19)</td>
<td>0.2 (5)</td>
<td></td>
</tr>
<tr>
<td>R Central Opercular Cortex</td>
<td>0.5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Orbitofrontal Cortex</td>
<td>0.4 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Caudate</td>
<td>0.2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Superior Frontal Gyrus</td>
<td>2.8 (7)</td>
<td>0.3 (1)</td>
<td></td>
</tr>
<tr>
<td>L PreCentral Gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Supramarginal Gyrus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Angular Gyrus</td>
<td>1.4 (8)</td>
<td>0.3 (2)</td>
<td>0.3 (2)</td>
</tr>
<tr>
<td>R Superior Temporal Gyrus</td>
<td>2.3 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Middle temporal Gyrus</td>
<td>4.3 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Inferior temporal Gyrus</td>
<td></td>
<td>0.6 (3)</td>
<td>0.6 (3)</td>
</tr>
<tr>
<td>L Lateral Occipital Cortex</td>
<td>2.0 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Thalamus</td>
<td>0.6 (6)</td>
<td>0.2 (2)</td>
<td></td>
</tr>
<tr>
<td>- posterior parietal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- premotor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- prefrontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- somatosensory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Thalamus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- prefrontal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

List restricted to regions with ≥1% significant voxel occupancy.
## Supplementary Data 1- continued

<table>
<thead>
<tr>
<th>Mori Probabilistic Fibre Atlas (Zhang et al, 2010)</th>
<th>Conflict</th>
<th>Orient</th>
<th>Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.B. only covers cerebral fibres</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>Accuracy</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>vs Con</td>
<td>vs L-</td>
<td>vs Con</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Inferior Frontal - PreCentral Gyrus</td>
<td>13 (38)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>R Middle Frontal - PreCentral Gyrus</td>
<td>12 (28)</td>
<td>4 (9)</td>
<td></td>
</tr>
<tr>
<td>R Superior Frontal - PreCentral Gyrus</td>
<td>10 (23)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>R SLF (FrontoTemporal, FrontoParietal)</td>
<td>13 (21)</td>
<td>2 (4)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>R PreCentral - PostCentral Gyrus</td>
<td>10 (13)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>R Superior Frontal - Middle Frontal Gyrus</td>
<td>8 (9)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>R Uncinate</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R IFO</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>L Superior Frontal - Middle Frontal Gyrus</td>
<td>5 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Superior Frontal - PreCentral Gyrus</td>
<td>4 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Middle Frontal - PreCentral Gyrus</td>
<td>2 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L SLF (FrontoTemporal, FrontoParietal)</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>L PreCentral - PostCentral Gyrus</td>
<td>4 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R SLF (ParietoTemporal)</td>
<td></td>
<td>11 (14)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>R Middle - Superior Temporal Gyrus</td>
<td></td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>R Inferior - Middle Temporal Gyrus</td>
<td></td>
<td>5 (12)</td>
<td></td>
</tr>
<tr>
<td>R Superior Temporal – Supramarginal Gy.</td>
<td></td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>R Superior Parietal – Supramarginal Gyrus</td>
<td></td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>R ILF</td>
<td></td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>R Superior Parietal – Angular gyrus</td>
<td></td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>R Supramarginal - PostCentral Gyrus</td>
<td></td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>R Thalamus - Superior Frontal Gyrus</td>
<td>6 (9)</td>
<td>4 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>R Thalamus - Middle Frontal Gyrus</td>
<td>5 (10)</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>R Thalamus - PreCentral Gyrus</td>
<td>4 (12)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>R Thalamus – Precuneus</td>
<td></td>
<td>1 (4)</td>
<td>0.2 (1)</td>
</tr>
<tr>
<td>R Thalamus – PostCentral Gyrus</td>
<td></td>
<td>1 (3)</td>
<td>0.2 (1)</td>
</tr>
<tr>
<td>R Thalamus – Superior Parietal Gyrus</td>
<td></td>
<td>1 (3)</td>
<td>0.1 (.4)</td>
</tr>
<tr>
<td>L Thalamus - Superior Frontal Gyrus</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SLF, ILF: Superior and Inferior Longitudinal Fasciculi, respectively. IFO: Inferior frontal-occipital fasciculus. Note that white matter tracts overlap. List restricted to regions with ≥3% significant voxel occupancy in at least one condition.
Supplementary Data 2

Effects of lesions on cue x flanker interactions were determined by performing a 3-way, mixed-effect ANOVA [Factors: Cue (no cue; central cue; non-selective peripheral cue; and selective peripheral cue), Flanker (congruent, neutral and incongruent) and Group (Lesion + (i.e. at region specified) vs. Controls; or Lesion + vs. Lesion - (i.e. elsewhere)], on raw RT or accuracy data, at regions also showing group x flanker, or group x cue, interactions (from Tables 2, 3). Cue x Flanker x Group interactions (p<0.01) are reported, with planned contrasts - reflecting conflict size under alerting and orienting - limited to regions showing significance at p<0.001. Additional contrasts were performed after inspection of raw data, so as to aid interpretation (see Figure 7).

A. Reaction Time Data

<table>
<thead>
<tr>
<th>Region</th>
<th>x, y, z</th>
<th>F</th>
<th>P</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Conflict-predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R middle corona radiata</td>
<td>36, 6, 22</td>
<td>2.3</td>
<td>ns</td>
<td>1.3</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>32, 6, 38</td>
<td>4.8</td>
<td>P&lt;0.001</td>
<td>2.8</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>28, 12, 16</td>
<td>4.1</td>
<td>P&lt;0.001</td>
<td>2.6</td>
<td>ns</td>
</tr>
<tr>
<td>2. R anterior corona radiata</td>
<td>26, 24, 18</td>
<td>3.2</td>
<td>P&lt;0.01</td>
<td>1.8</td>
<td>ns</td>
</tr>
<tr>
<td>3. R anterior insula</td>
<td>36, 12, -10</td>
<td>3.5</td>
<td>P&lt;0.01</td>
<td>2.1</td>
<td>ns</td>
</tr>
<tr>
<td>4. R inferior prefrontal WM</td>
<td>24, 20, -10</td>
<td>8.0</td>
<td>P&lt;0.001</td>
<td>4.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>5. R superior frontal gyrus</td>
<td>30, 20, 46</td>
<td>1.5</td>
<td>ns</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>6. L superior frontal gyrus</td>
<td>-20, -4, 62</td>
<td>3.4</td>
<td>P&lt;0.01</td>
<td>2.0</td>
<td>ns</td>
</tr>
<tr>
<td>B: Orienting-predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R pulvinar</td>
<td>16, -26, -4</td>
<td>1.2</td>
<td>ns</td>
<td>0.7</td>
<td>ns</td>
</tr>
<tr>
<td>2. R posterior insula WM</td>
<td>36, -28, 10</td>
<td>1.8</td>
<td>ns</td>
<td>1.5</td>
<td>ns</td>
</tr>
<tr>
<td>3. R superior, middle temporal gyri</td>
<td>64, -26, 16</td>
<td>2.4</td>
<td>ns</td>
<td>2.0</td>
<td>ns</td>
</tr>
<tr>
<td>4. R angular, supramarginal gyri</td>
<td>54, -44, 40</td>
<td>2.1</td>
<td>ns</td>
<td>1.7</td>
<td>ns</td>
</tr>
<tr>
<td>5. R insula, corona radiata</td>
<td>30, 18, 8</td>
<td>2.6</td>
<td>ns</td>
<td>1.5</td>
<td>ns</td>
</tr>
<tr>
<td>C: Alerting-predominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. L anteromedial thalamus</td>
<td>-12, 8, 12</td>
<td>1.8</td>
<td>ns</td>
<td>1.2</td>
<td>ns</td>
</tr>
<tr>
<td>2. R anteromedial thalamus</td>
<td>8, -8, 12</td>
<td>1.1</td>
<td>ns</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>3. Dorsal midbrain</td>
<td>2, -30, -14</td>
<td>1.6</td>
<td>ns</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>4. Upper pons</td>
<td>-2, -26, -28</td>
<td>0.8</td>
<td>ns</td>
<td>0.3</td>
<td>ns</td>
</tr>
</tbody>
</table>
**Planned Contrasts:** Conflict (i.e. I-C: Incongruent – Congruent) compared for different levels of Cue

<table>
<thead>
<tr>
<th>Region</th>
<th>No Cue (I–C) – Dble. Cue (I–C)</th>
<th>T</th>
<th>P</th>
<th>Cent. (I–C) – Select. Cue (I–C)</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R mid corona radiata (1)</strong></td>
<td>Lesion + 127 (105)</td>
<td></td>
<td></td>
<td>-290 (205)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - -20 (12)</td>
<td>1.7</td>
<td>ns</td>
<td>-8 (13)</td>
<td>2.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Controls -34 (14)</td>
<td>2.0</td>
<td>&lt;0.05</td>
<td>22 (13)</td>
<td>4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>R mid corona radiata (2)</strong></td>
<td>Lesion + 78 (67)</td>
<td></td>
<td></td>
<td>-198 (104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - -22 (12)</td>
<td>1.8</td>
<td>ns</td>
<td>-4 (13)</td>
<td>3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Controls -34 (14)</td>
<td>2.1</td>
<td>&lt;0.05</td>
<td>22 (13)</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>R inferior prefrontal WM</strong></td>
<td>Lesion + 167 (73)</td>
<td></td>
<td></td>
<td>-327 (124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lesion</strong></td>
<td>Lesion - -23 (12)</td>
<td>2.7</td>
<td>&lt;0.01</td>
<td>-4 (12)</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Controls -34 (14)</td>
<td>3.0</td>
<td>&lt;0.01</td>
<td>22 (13)</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Units: ms (SEM)

**Additional Contrast:** Conflict (i.e. I-C: Incongruent – Congruent) compared for Double - Central Cue

<table>
<thead>
<tr>
<th>Region</th>
<th>Dbl. Cue (I–C) – Cent. Cue (I–C)</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R mid corona radiata (1)</strong></td>
<td>Lesion + 101 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - 26 (13)</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Controls 19 (16)</td>
<td>0.9</td>
<td>ns</td>
</tr>
<tr>
<td><strong>R mid corona radiata (2)</strong></td>
<td>Lesion + 152 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - 21 (13)</td>
<td>2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Controls 19 (16)</td>
<td>2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>R inferior prefrontal WM</strong></td>
<td>Lesion + 154 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - 23 (13)</td>
<td>1.7</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Controls 19 (16)</td>
<td>1.8</td>
<td>ns</td>
</tr>
</tbody>
</table>
**APPENDIX**

### B. Accuracy Data

<table>
<thead>
<tr>
<th>Cue x Flanker x Group Interaction</th>
<th>Region</th>
<th>Lesion + versus Controls</th>
<th>Lesion + versus Lesion – (other lesion sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td><strong>A: Conflict-predominant</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. R middle corona radiata</td>
<td>28, 12, 14</td>
<td>2.7</td>
<td>ns</td>
</tr>
<tr>
<td>2. R anterior corona radiata</td>
<td>26, 26, 16</td>
<td>3.3</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>3. R anterior insula</td>
<td>32, 6, -18</td>
<td>1.0</td>
<td>ns</td>
</tr>
<tr>
<td>4. R inferior prefrontal WM</td>
<td>30, 36, -2</td>
<td>0.2</td>
<td>ns</td>
</tr>
<tr>
<td>5. L lateral precentral gyrus</td>
<td>-54, 0, 32</td>
<td>1.6</td>
<td>ns</td>
</tr>
<tr>
<td>6. L superior frontal gyrus</td>
<td>-18, -4, 72</td>
<td>0.8</td>
<td>ns</td>
</tr>
<tr>
<td>7. R posterior corona radiata</td>
<td>30, -34, 36</td>
<td>0.7</td>
<td>ns</td>
</tr>
<tr>
<td>8. R occipital cortex</td>
<td>18, -60, 50</td>
<td>2.5</td>
<td>ns</td>
</tr>
</tbody>
</table>

| **B: Orienting-predominant**      |        |   |   |   |   |
| 1. R temporoparietal junction     | 54, -50, 32 |  4.6 | P<0.001 |  4.1 | P<0.001 |

| **C: Alerting-predominant**       |        |   |   |   |   |
| 1. R anteromedial thalamus        | 6, -12, 8 |  2.0 | ns |  1.7 | ns |
| 2. R supramarginal gyrus          | 54, -28, 30 |  3.1 | P<0.01 |  1.8 | ns |
| 3. R postcentral gyrus            | 32, -34, 60 |  1.5 | ns |  0.7 | ns |
| 4. R middle corona radiata        | 28, -4, 12 |  2.8 | P=0.01 |  1.7 | ns |
| 5. R frontal operculum            | 48, 14, -2 |  2.0 | ns |  1.1 | ns |
| 6. R midbrain - cerebral peduncle | 16, -16, -14 |  3.4 | P<0.01 |  1.8 | ns |

**Planned Contrasts:** Conflict (i.e. I-C: Incongruent – Congruent) compared for different levels of Cue

<table>
<thead>
<tr>
<th>Region</th>
<th>No Cue (I–C) – Dble. Cue (I–C)</th>
<th>T</th>
<th>P</th>
<th>Cent. (I–C) – Select. Cue (I–C)</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R temporoparietal junction</td>
<td>Lesion + 22 (16)</td>
<td>2.7</td>
<td>&lt;0.01</td>
<td>-19 (23)</td>
<td>2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Lesion - -2 (2)</td>
<td>2.7</td>
<td>&lt;0.01</td>
<td>1 (2)</td>
<td>2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Controls 1 (2)</td>
<td>2.6</td>
<td>&lt;0.01</td>
<td>1 (2)</td>
<td>2.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Units: % (SEM)

**Additional Contrast:** N-C: (Neutral– Congruent) compared for different levels of Cue

<table>
<thead>
<tr>
<th>Region</th>
<th>No Cue (N–C) – Dble. Cue (N–C)</th>
<th>T</th>
<th>P</th>
<th>Cent. (N–C) – Select. Cue (N–C)</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>R temporoparietal junction</td>
<td>Lesion + -6 (11)</td>
<td></td>
<td></td>
<td>25 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lesion - 4 (2)</td>
<td>1.1</td>
<td>ns</td>
<td>0 (2)</td>
<td>2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Controls 4 (2)</td>
<td>1.3</td>
<td>ns</td>
<td>0 (1)</td>
<td>3.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Supplementary Data 3

Here we summarise the results of group (Lesion+/Controls) x flanker (or cue) x target location (up/down) x target direction (R/L) for each of the principle clusters identified in the main paper.

Conflict

ANOVAs of group x flanker x target location x target direction in RMCR revealed, for RTs only, that lesions heightened conflict more for left-, than right-pointing, targets (group x flanker x RL: F(2,136)=4.1; p<0.05; conflict for Lesion+: 40% versus 24% for left- and right-pointing; compared with 14% and 14% for Controls); and more for up- than down-located targets (group x flanker x location: F(2,136)=3.7; p<0.05; conflict for Lesion+: 37% versus 27% for up and down locations; compared with 14% and 14% for Controls); but no group x flanker x target location x target direction interaction. The equivalent analyses for the left prefrontal cluster were insignificant.

Orienting

ANOVAs of group x cue x target location x target direction in the right temporoparietal cortex cluster showed that lesions here reduced speed (group x RL: F(1,69)=5.60; p<0.05), and worsened accuracy (F(1,65)=8.10; p<0.01) to left-, versus right-, pointing targets. For accuracy, this R-L difference was manifest predominantly in trials with peripheral cues, relative to other cues (group x cue x RL: F(3,192)=7.0; p<0.001; R-L accuracy being 23%, 25%, 3%, 3% respectively for selective-, double-, central- and no-cue, for Lesion+; and <2% for all cue types in Controls). There were no interactions of target location with group (with or without additional interactions with cue and/or RL); and no equivalent interactions were found in right pulvinar.

Alerting

ANOVAs of group x cue x target location x target direction in right anteromedial thalamus, but not left thalamus nor brainstem, also showed a significantly greater decrement of alerting relative to Controls for down (-22%), relative to up (-5%), target locations (group x cue x target location ANOVA for accuracy: F(3,192)=6.8; p<0.01), but there were no interactions for any of these regions with target direction.