Victoria University

College of Engineering and Science

Investigation of MRI Brain Changes in Developmental Coordination Disorder and Friedreich's ataxia

Saman Rassaei Kashuk, MD

Submitted in total fulfilment of the
requirements for the degree of
Doctor of Philosophy

Supervisors:

Prof. Graham Thorpe: College of Engineering and Science
Victoria University

Prof. Gary Egan: Director,
Monash Biomedical Imaging (MBI),
Monash University

ABSTRACT

‘To move things is all mankind can do. ... whether whispering a syllable or felling a forest.’ - Charles Sherrington

The human motor system is one of the most complicated systems in the human body. This complex system of interactions and collaborations between different regions of the human nervous system enables humans to interact with their external environment. Several parts of the human central nervous system are required to communicate effectively to send signals to the target muscles to carry out the final voluntary or involuntary movements. At the level of the central nervous system (CNS), motor planning and control form the essential element of any voluntary movements and several models have been suggested to describe these processes. Internal models, and specifically the ‘forward model’ is one of the most recognised theories of human motor control function. In this thesis, I have investigated two different movement disorders in which motor dysfunction is suggested to be involved in motor planning level in one disorder and motor execution in the other. I used several novel MRI methods to elucidate the neuro-mechanisms and brain regions likely to be involved in motor impairment in these two disorders, developmental coordination disorder (DCD) and (Freidreich’s ataxia) FRDA. Integral to this process was an endeavor to investigate human motor control theory and examine its pathological aspects through the window of neuroimaging.

Recent advances in neuroimaging technologies, and particularly MRI methods, have provided researchers with invaluable insights into the structure of the human brain compared with those obtained by conventional T1 and T2 MRI imaging methods. I have used novel structural MRI technologies in this research project, including diffusion tensor imaging (DTI) and magnetisation transfer imaging (MTI). I have also harnessed the power of functional magnetic resonance imaging (fMRI), a method of mapping brain activity based on measuring the hemodynamic response related to neural activity. This method has received considerable attention in neuroscience studies because of its non-invasive nature and it offers the potential to map brain activities in considerably higher spatial resolution compared to older methods such as EEG. I have used these

new functional and structural MRI imaging techniques to investigate the dysfunction in human motor execution and planning circuits in DCD and FRDA.

Developmental Coordination Disorder (DCD) is a movement disorder with an unknown aetiology and a prevalence of 5-10% in children. Individuals with DCD show noticeable impairment in motor skills at both fine and gross levels. DCD is mostly diagnosed in children of school ages and there is up to a 50% chance that these symptoms continue into adulthood. There is some evidence that shows DCD is a motor imagery deficit. We investigated the neural basis of DCD using functional MRI whilst participants performed a mental rotation task. An analysis of pilot results supports the impairment of motor imagery ability in the expected areas in individuals with DCD. Using structural and functional MRI techniques we also investigated motor dysfunction in a second movement disorder, namely Friedreich's ataxia (FRDA). FRDA is a genetic systemic disorder in which muscle weakness, ataxia and sensory loss are common neurological manifestations. To investigate the structural changes in the CNS of FRDA patients, we used the Magnetisation Transfer Imaging (MTI) technique. The results Neuroimaging studies of both DCD and FRDA are scare and as mentioned above, I have used different MRI modalities including microstructural and functional methods to investigate neural correlate and pathways characteristics and pathologies in DCD and FRDA.

The results for individuals with DCD showed reduced cortical neural activation of grey matter during the performance of motor imagery task in the middle frontal gyrus bilaterally, the left superior parietal lobe and lobule VI of the cerebellum in adults with probable Developmental Coordination Disorder compared to control group. The individual with DCD compared with controls also showed a reduction in microstructural white matter in pathways including corticospinal tract, superior longitudinal fasciculus and internal capsule. There was also a tentative compensatory maturational compensation in inferior longitudinal fasciculus. The investigation of demyelination in Friedreich's ataxia showed the presence of myelin bulk reduction in the superior cerebellar peduncle (SCP) region in patients suffering FRDA. The results of research presented in thesis are very promising in elucidating the physiopathology of neural damage and involved brain areas of above-mentioned disorders. In addition, the results emphasise the role of novel imaging technologies, such as MRI in the understanding both the theoretical aspects and practical application in individuals with motor dysfunction, especially in movement disorders such as DCD and FRDA in which

conventional methods such as traditional imaging methods and laboratory biochemistry laboratory tests are of very limited value. This research also suggests that MRI findings could be considered as a potential biomarker for determining the severity of motor disorders, following up the clinical progression and evaluating the effectiveness of therapeutic interventions in movement disorders with neurological causes at CNS level.

DECLARATION

I, Saman Rassaei Kashuk, declare that the PhD Thesis entitled “Investigation of MRI brain changes in Developmental Coordination Disorder and Friedreich’s ataxia” is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

_____ ____31/08/2016_____

Signature Date

PREFACE

This PhD project is the result of collaboration between College of Engineering and Science, Victoria University; College of Sport and Exercise Science, Victoria University; and Monash Biomedical Imaging (MBI), School of Psychological Sciences, Faculty of Medicine, Nursing and Health Sciences - Monash University. Work contributed by others throughout completing my thesis project is accordingly acknowledged here:

• Professor Graham Thorpe contributed in all stages of my research, including giving invaluable feedbacks and precise reviewing of the final draft of this thesis. I want to thank him specially for his commitment and dedication throughout all stages of my PhD project and his emotional support and understanding.

• My committed co-supervisor Prof Gary F. Egan contributed to all stages of experimental design, analysis of data, and preparation of this thesis through providing me with invaluable positive critique and corrections.

• Dr Jaqueline Williams performed the analyses of behavioural data in chapter 4 and helped in writing paragraphs contained in discussion parts of Chapter 4 and 5.

• Professor Peter H Wilson contributed in experimental design of DCD-fMRI study and provided me with invaluable feedback during all stages of DCD study

• Dr Louise Corben co-wrote paragraphs contained in discussion section in chapter 6 and preparing figures 6.4 and 6.5

ACKNOWLEDGEMENTS

I gratefully thank all participants for their contribution to this project. I also thank the staff at Monash Biomedical Imaging, Monash University, Victoria. This project was supported by a Research Development Grant from Victoria University. I thank Victoria University for awarding me a Postgraduate Research Scholarship which helped me to complete this research.

Finally, I would like to express my gratitude to my wonderful parents, my great brothers, Sam and Sina and my kind sister Mana for their unconditional support and love.

LIST OF PUBLICATIONS & PRESENTATIONS

PUBLICATIONS

Kashuk, S. R., Corben, L. A., Akhlaghi, H., Jamadar, S., Delatycki, M. B., Fielding, J., ... & Egan, G. F. (2014). Myelin paucity of the superior cerebellar peduncle in individuals with Freidreich's ataxia: an MRI magnetization transfer imaging study. Journal of the neurological sciences, 343 (1), 138143.

Kashuk S.R., Williams J, Wilson P. Thorpe G., Egan G.F (2015), "Diminished motor imagery capability in adults with motor coordination impairment: an fMRI mental rotation study", Behavioural Brain Research, [under review]

Kashuk S.R., Williams J, Wilson P., Thorpe G., Egan G.F (2015), "White matter alterations in adults with probable Developmental Coordination Disorder: an MRI Diffusion Tensor Imaging (DTI) study", Neuroreport, [under review]

CONFERENCE PRESENTATIONS

S.R. Kashuk, J. Williams, P. Wilson, G. Thorpe, G.F Egan, "Mental rotation of hand as a task to evaluate motor imagery capability: an fMRI study", 19th International Conference on Human Brain Mapping (Seattle, June 2013).

S.R. Kashuk, G. Thorpe, J. Williams, P. Wilson, G.F Egan, "Reduced Motor Imagery Capability in Motor Impaired Adults Performing Mental Rotation: an fMRI Study", 21stInternational Conference on Human Brain Mapping (Honolulu, June 2015).

Corben L, Kashuk S, Akhlaghi H, Jamadar S, Delatycki M, Fielding J, Johnson B, GeorgiouKaristianis N and Egan G (2015). Myelin paucity of the superior cerebellar peduncle in individuals with Freidreich's ataxia: an MRI magnetization transfer imaging

study. Front. Hum. Neurosci. Conference Abstract: XII International Conference on Cognitive Neuroscience (ICONXII).doi: 10.3389/conf.fnhum.2015.217.00147
L.A. Corben, S. Jamadar, B. Johnson, M.B. Delatycki, N. GeorgiouKaristianis,

S. Rassaei Kashuk, H. Akhlaghi, G.F. Egan, J. Fielding, "Antisaccade performance in individuals with Friedreich's ataxia indicates disruption to higher order processes", International Cognitive Neuroscience Conference (Brisbane, July 2014).

ACRONYMS

ADC	Adult Developmental Co-ordination Disorders/Dyspraxia Checklist
ADC	Apparent Diffusion Co-efficient
ADHD	Attention Deficit Hyperactivity Disorder
BOLD	Blood Oxygenation Level Dependence
CBF	Cerebral Blood Flow
CC	Corpus Callosum
CHARMED	Composite Hindered and Restricted Model of Diffusion
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CST	Corticospinal Tract
DCD	Developmental Coordination Disorder
DICOM	Digital Imaging and Communications in Medicine
DLPC	Dorso-Lateral Prefrontal Cortex
DN	Dentate Nucleus
DNA	Deoxyribonucleic acid
DRG	Dorsal Root Ganglion
DSM	Diagnostic and statistical manual
DTI	Diffusion Tensor Imaging
EEG	Electroencephalography
EPI	Echo Planar Imaging
DOF	Degree of Freedom
FARS	Freidreich's Ataxia Rating Scale
FDR	False Discovery Rate
FLIRT	FMRIB's linear image registration too Functional MRI
FRDA	Freidreich's Ataxia
FMRIB	Functional MRI of the Brain
FSL	FMRIB Software Library

GAA	Guanine Adenine Adenine (nucleotide bases of a DNA strand)
ICARS	International Cooperative Ataxia Rating Scale
IPS	Intra Parietal Sulcus
IPL	Inferior Parietal Lobe
ILF	Inferior Longitudinal Fasciculus
FARS	Freidreich's Ataxia Rating Scale
fMRI	Functional Magnetisation Resonance Imaging
FA	Fractional anisotropy
FOV	Field of View
M	Mean
MAND	the McCarron Assessment of Neuromuscular Development
MATLAB	Matrix Laboratory
MBI	Monash Biomedical Imaging
MC	Motion Correction
ME	Motor Execution
MD	Mean Diffusivity
MFG	Middle Frontal Gyrus
MI	Motor Imagery
MNI	Montreal Neurological Institute
MP	Motor Planning
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MT	Magnetisation Transfer
MTI	Magnetisation Transfer Imaging
MTR	Magnetisation Transfer Ratio
NDI	Neuromuscular Developmental Index
OD	Oculomotor Disorder
pDCD	Probable Developmental Coordination Disorder
PM	Pre-Motor
PPC	Posterior Parietal Cortex
R	Range
RF	Radio Frequency
ROI	Region of interest

RT	Response Time
SCP	Superior Cerebellar Peduncle
SD	Standard Deviation
SFG	Superior Frontal Gyrus
SLF	Superior Longitudinal Fasciculus
SMA	Supplementary Motor Area
SPL	Superior Parietal Lobe
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Science
SS	Standard Score
TBSS	Tract-Based spatial statistics
TE	Time of Echo
TR	Time of Repetition
VGPT	Visually Guided Pointing Task
WM	White Matter

LIST OF FIGURES

Figure 2.1. Essential parts involved in the human voluntary movement 24
Figure 2.2. 'Forward' and 'inverse' models of motor control system 26
Figure 2.3. Schematic illustration showing elaboration between main regions involved in human motor control and execution 28
Figure 2.4. An illustration of MRI machine 35
Figure 2.5. An illustration showing polarisation induced by a magnetic field 37
Figure 2.6. The concept of MR-image production 37
Figure 2.7. Time series of detected motion in three directions used in the "MCFLIRT" tool in FSL software 39
Figure 2.8. Design matrix used in "Stats" phase of fMRI data analysis using FSL software 40
Figure 2.9. A sample of activation maps produced in the "Post-stat" stage in FSL software showing active block compared to rest 41
Figure 2.10. A sample of thresholded activation maps produced during the "Post-stat" stage in FSL software. The statistical maps show active areas in regions with a parametric increase in the BOLD signal by increased difficulty of task 42
Figure 2.11. Sagittal view of an image of the human brain using diffusion tensor imaging reconstructed by tractography technique 44
Figure 2.12. T1 images without MTpulse , with MT pulse and MTR image. 46
Figure 2.13. The histogram chart of MTR image produced using T1 protocol. 46
Figure 2.14. T2 images without MTpulse , with MT pulse and MTR image. 47
Figure 2.15. The histogram chart for MTR image produced using T2 protocol 47
Figure 3.1. Three main sub-scales in FARS scoring system. 58
Figure 4.1. Hand rotation stimuli 68
Figure 4.2. Group means for response time and accuracy for hand stimuli 73
Figure 4.3. Group means for response time and accuracy at the varying levels of response difficulty 74

Figure 4.4. Mean activation map showing parametric increases of activation with the angle of rotation in control group 76
Figure 4.5. Mean activation map showing parametric increases of activation with the angle of rotation in the pDCD group. 77
Figure 4.6. Mean activation map showing activation in easy and hard rotation angles for the controls and pDCD group 78
Figure 4.7. Mean activation map showing parametric increases of activation with the angle of rotation in controls and pDCD group..... 79
Figure 4.8. Regions where parametric increases of activation with the angle of rotation were significantly higher in the control group compared with the pDCD group 79
Figure 4.9. Mean task-induced change in the %BOLD signal during active blocks (easy, medium, hard) in controls and pDCD group. 81
Figure 4.10. Average % BOLD signal change during task activation in ROI for three conditions for the control and pDCD groups. 81
Figure 4.11. Time course of task-induced %BOLD signal change in control group..... 82
Figure 4.12.Time course of task-induced %BOLD signal change in pDCD group. 82
Figure 4.13. Mean BOLD % change in controls and pDCD group 83
Figure 4.14. Parametric increases of activation with the angle of rotation in controls, pDCD and common area of activation..... 83
Figure 4.15. Correlation matrix between BOLD signal time series in ROIs in control group. 84
Figure 4.16. Correlation matrix between BOLD signal time series in ROIs in pDCDgroup..... 84
Figure 5.1. Areas with significant differences between groups in diffusion parameters comparisons..... 100
Figure 5.2. Correlations between WM integrity and movement MAND score..... 101
Figure 6.1. One slice from a multislice data set MTR images 111
Figure 6.2. ROIs used to measure MTR value 112
Figure 6.3. Comparison of mean MTR results between patients and control groups in superior cerebellar peduncle (SCP) and corpus callosum (CC)..... 114
Figure 6.4. Scatter plot indicating the relationship between ΔMTR in the SCP and GAA2 repeat length..... 115
Figure 6.5. Scatter plot indicating the relationship between the MTR in the SCP and GAA2 repeat size 115

LIST OF TABLES

Table 3.1. Group Demographic Data for the Control and pDCD Groups. 54
Table 3.2. Two sets of diagnostic criteria for FRDA 56
Table 3.3. Demographic information and screening measures in individuals with FRDA and Controls. 58
Table 4.1. Descriptive Data and MAN scores for the Controls and pDCD Group 66
Table 4.2 The rotation angle included in each category (easy, medium, hard) for mental rotation of hand task 69
Table 5.1. Demographic information, and diffusion parameters 98
Table 6.1. Mean, standard deviation and range of group characteristics and screening measures for participants with FRDA and Controls. 109

TABLE OF CONTENTS

ABSTRACT **2**

DECLARATION **5**

PREFACE **6**

LIST OF PUBLICATIONS & PRESENTATIONS **8**

PUBLICATIONS **8**

CONFERENCE PRESENTATIONS **8**

ACRONYMS **10**

LIST OF FIGURES **13**

LIST OF TABLES **15**

TABLE OF CONTENTS **16**

Chapter 1 ..... **20**

Thesis Overview **20**

Chapter 2 ..... **23**

Introduction and Literature Review **23**

Human motor system **23**

Human movement control **24**

Forward models vs inverse model **24**

Significance of the forward model in movement planning **25**

Motor imagery **27**

Developmental coordination disorder **29**

Presentation of DCD **29**

DCD in adults **30**

Motor skill impairment in DCD **31**

Visuospatial processing in children with DCD **31**

Motor imagery in DCD 31
Friedreich ataxia 33
Motor system dysfunction in Friedreich's ataxia 34
Brain imaging 34
Principles of magnetic resonance imaging 34
Functional magnetic resonance imaging 37
Diffusion magnetic resonance imaging 42
Magnetic Transfer Imaging (MTI) 44
Neuroimaging studies in DCD 48
Neuroimaging studies in Friedreich's ataxia 49
Aims of the project 50

Chapter 3 52
Methodology 52

Chapter 4 61
Functional MRI study of individuals suffering probable developmental coordination disorder 61
Introduction 62
Material and Methods 65
Participants 65
Procedure 68
Imaging data acquisition 69
Data Analysis 70
Behavioural Data 70
fMRI data analysis 70
Analysis of Percentage of change in BOLD signal 71
Functional connectivity analysis 72
Results 72
Behavioural data 72
fMRI Results 74
Analysis of statistical activation maps 74
Discussion 85
Neuroimaging findings 86
Limitations 90

Conclusions 90

Chapter 5 92

White matter alterations in adults with probable Developmental Coordination Disorder 92

Introduction 92

Aims and hypothesis 93

Methods 94

Participants 94

Motor skill Measures 94

Imaging data acquisition 95

Data Analysis 95

MRI data analysis 95

TBSS Analysis 96

Results 97

Discussion 101

Conclusion 104

Chapter 6 105

Hypo-myelination of the superior cerebellar peduncle in individuals with Friedreich ataxia: an MRI magnetization transfer imaging study 105

Abstract 106

Introduction 106

Methods 108

Participants 108

Imaging data acquisition 110

MR Image Analysis 110

Results 113

MTR 113

Correlations between MTR and clinical parameters 114

Discussion 116

Conclusions 119

Acknowledgements 119

Chapter 7 120

Discussion 120

DCD study **120**
Neuroimaging findings and brain regions involved in motor imagery **120**
Fronto-parietal network **121**
Cerebellum **122**
Occipital cortex **122**
Decreased cortical activation in the adults with pDCD **123**
FRDA study **125**

Chapter 8 ..... **128**
Conclusion **128**
DCD study **128**
FRDA study **128**
Final conclusion **129**
Limitations and future work **129**
DCD study **129**
FRDA study **131**

REFERENCES **132**

APPENDICES **145**
Appendix A. DCD study Scanning full MRI protocol **145**
Appendix B. Adult DCD Checklist (ADC) **166**
Appendix C. The Adult DCD/Dyspraxia Checklist (ADC) Instructions for use **170**
Appendix D. Adult ADHD Self Report checklist (ASR-V1.1) **176**
Appendix E. Adult Participant Explanatory Statement and Consent form for DCD study **179**
Appendix F. Noticeboard flyer for DCD study recruitment **189**
Appendix G. MRI Pre-scanning screening questionnaire **191**
Appendix H. MBI MRI Safety form **194**
Appendix I. MRI sequence parameters in for MTR pilot study **196**
Appendix J. International Cooperative Ataxia Rating Scale (ICARS) for Friedreich's Ataxia **197**
Appendix K. FRDA MRI Protocol **198**
Appendix L. Adult Participant Explanatory Statement and Consent form for FRDA study **199**

Chapter 1

Thesis Overview

The motor system is one of the most complicated systems in the human body. It is essential for our interaction with the external environment, and it plays a vital role in the survival of the human species. Evolutionary processes have moulded the human motor system into a well organised and precise system to which even the slightest disruption can dramatically affect not only the quality of life, but it can result in fatal consequences.

In this thesis, different modalities of magnetic resonance imaging (MRI) including functional MRI (fMRI), diffusion tensor imaging (DTI) and magnetisation transfer imaging (MTI) have been utilised to investigate anatomical, functional and micro-structural changes movement disorders including in individuals with Developmental Coordination Disorder and Friedreich's ataxia (FRDA). In parallel to elucidating the physiopathology and neural basis of these movement disorders, we have taken a broader look at the issues through the window of computational movement modelling theories known as "internal models". The aim of internal model theory is to conceptualise the processes of planning and execution of voluntary movement in the human central nervous system (CNS). We investigated the neuromechnism of movement disorder in DCD which current evidence suggests the motor system is mainly disturbed in the planning stage. We also evaluated the integrity of the myelin membrane in motor related networks in FRDA. In this neuro-degenerative disorder, the motor system seems to be affected in the areas involved in the motor execution, which mainly consist of lower order motor control regions in the CNS and Peripheral Nervous System (PNS). However, recent imaging research suggests that the neural impairment involves higher

motor regions such as subcortical and cortical regions, including brain stem or even cortical and cerebello-cerebral in motor related networks and particularly superior cerebellar peduncles. We have shown that both in DCD and FRDA, several parts of the sensori-motor network involved, including those in motor planning and execution, are disrupted. We also verified the computational models of the motor system and its pathology. We finally concluded that different MRI modalities and their results can be used as a potential clinical biomarker to objectively assess the severity and progression of motor skill impairment in DCD and FRDA. Additionally, it was concluded that the MRI modalities can potentially be used in planning and assessment of the therapeutic interventions in movement disorders when there is no objective measure or laboratory test available.

Thesis outline

This thesis includes an overview of the work (chapter 1), an introduction and literature review (chapter 2), the methodology we adopted (chapter 3) and the threads of our work are drawn together and discussed (chapter7), along with our conclusions (chapter 8). Chapters 4-6 include three major MRI studies; two studies are conducted on individuals with DCD and the third study in on individuals suffering from FRDA.

Chapter 2 provides a review of the human motor system in planning and execution. Then the background literature on certain movement disorders, DCD and FRDA are reviewed in more detail. This section is followed by describing the pathophysiology and clinical manifestation of each disorder. Additionally, the main diagnostic criteria for DCD and FRDA are provided along with the common scoring systems that are currently used to evaluate disease severity and progression in FRDA have been reviewed. An overview of the principles of MRI as an in-vivo non-invasive imaging technology to investigate human brain structure and function has been discussed followed by an overview of main MRI techniques used in this research including functional MRI (fMRI), Diffusion Tensor Imaging (DTI) and Magnetisation Transfer Imaging (MTI) and other relevant literature is reviewed, including previous neuroimaging studies in DCD and FRDA. Eventually, the motivation and aims of the thesis are stated.

In Chapter 3, the material and methods used in this research are reported. These range from the methods of participants' recruitment to the screening process to the imaging acquisition and analysis techniques that have been used.

Chapter 4 describes the brain function during the performance of a motor imagery task and potential re-organisation of brain sensori-motor pathways in individuals suffering from DCD. The comparison analysis is performed in both in behavioural and imaging levels. During the performance of the motor imagery task of mental rotation of the hand, fMRI results show contrasting patterns of brain activity in adults with probable DCD (pDCD) compared to a control group. In addition, the functional connectivity between motor related regions during task performance has been investigated in both pDCD group and controls. This method evaluates the temporal correlation between the pattern of neural activation in different brain regions whilst performing the task.

Chapter 5 examines global and regional white matter (WM) diffusivity measures to examine overall differences in WM micro-structural integrity between individuals with pDCD and controls. The correlation between WM alterations and movement assessment scores in both groups are investigated.

Chapter 6 explores the dysfunction of gray matter neurons in affected motor regions in adults with probable DCD using functional MRI (fMRI). Whilst performing a motor imagery task individual with DCD exhibit different patterns of brain activity in the fronto-parietal and front-occipital and cerebellar regions.

Chapters 7 and 8 summarise the main findings of the thesis followed by their implications in terms of the pathophysiology and treatment interventions in individuals suffering from DCD and FRDA. Finally, the limitations of this research in both the DCD and FRDA studies are discussed, and further neuroimaging studies are proposed to shed light on the pathophysiology of human motor system disorders in general and DCD and FRDA in particular.

Chapter 2

Introduction and Literature Review

Human motor system

'To move things is all mankind can do... whether whispering a syllable or felling a forest.' This is a lyrical description of the significance of the human motor system by Charles Sherrington one of the most brilliant neuroscientists of late 19th and early 20th century. This wonderful quote highlights the magnificence of the human motor system and persuades us to take a new look at how well our nervous system is structured to properly plan the motor tasks essential for our daily interactions with the surrounding world. The human motor system consists of central and peripheral neurons. Several parts of the central nervous system (CNS) communicate and collaborate to receive sensory signals, plan desired actions, and send the final signals to peripheral nerves (Figure 2.1 and 2.3). The key essential regions that are recognised to contribute to this system are the frontal and parietal cortex, basal ganglia, thalamus and cerebellum. Each region has its explicit role in this process and any dysfunction or disruption of the connection between them could lead to a range of movement disorders from coordination problems to different types of ataxia. To elucidate the physiopathology of these movement disorders we need first to describe the basis of the human motor control system.

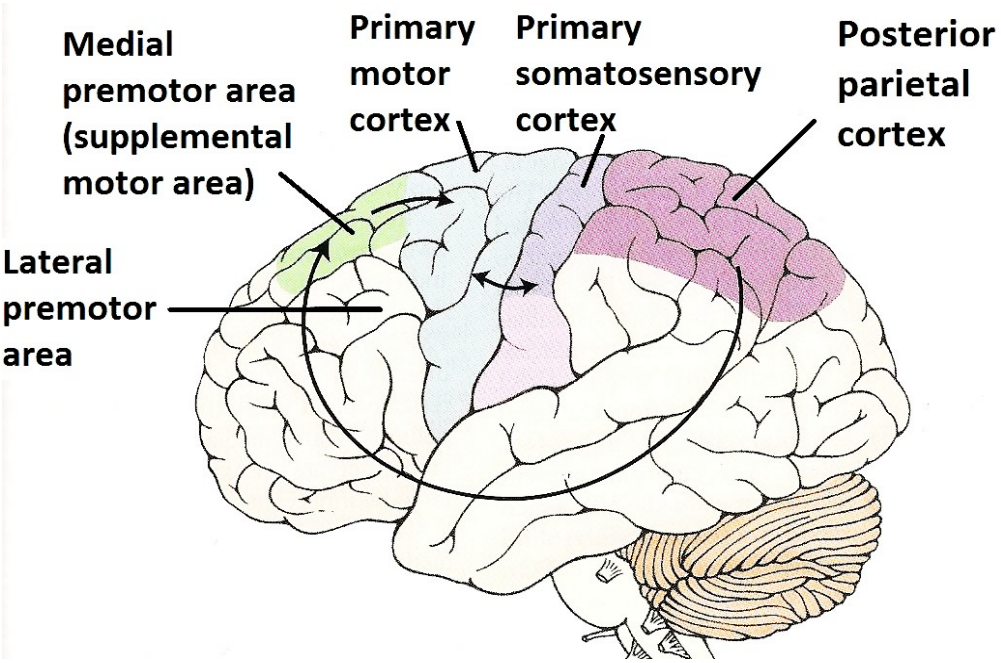


Figure 2. 1. Essential parts involved in the human voluntary movement. Figure Reproduced from (Siegel & Sapru, 2006).

Human movement control

Performing voluntary movements at the CNS level mainly involves two essential procedures: motor planning (MP) and motor execution (ME). Prediction of the desired action at MP level is the essential element of motor activities such as postural adjustment, planning an arm trajectory and following moving objects by eye and it is suggested that the parietal cortex and cerebellum play the essential role in sensorimotor prediction (Blakemore & Sirigu, 2003). Blakemore & Sirigu, (2003) and Wolpert & Ghahramani, (1995), proposed that the CNS uses internal models for movement prediction. As mentioned above presenting internal models seems to be an essential part of motor planning. There are two types of internal models: 'inverse models' and 'forward models'.

Forward models vs inverse model

Our understanding of motor control processes has evolved substantially with the recent innovations in neuroimaging techniques and computational modelling. For example, computational modelling of motor control views the human brain as a processing machine and investigates the connection between the inputs to the brain as sensory

signals and outputs from the brain to target muscles as motor commands (D M Wolpert & Ghahramani, 2000; Daniel M Wolpert & Ghahramani, 1995; Daniel M. Wolpert, Ghahramani, & Flanagan, 2001). This computational approach has led to theories of internal models, both inverse and forward models. (D. M. Wolpert & Kawato, 1998; D. Wolpert, 1997). The terminology of "forward" models comes from the fact that in this approach the causal relationship between actions (motor commands) and their consequences (expected sensory signals) is modelled (D M Wolpert & Ghahramani, 2000). Forward models anticipate the behaviour of the motor system and its sensory consequences (Desmurget & Grafton, 2000; Daniel M Wolpert & Ghahramani, 1995; Daniel M. Wolpert et al., 2001). When planning a movement, a sensorimotor copy of the motor command, in combination with egocentric data such as the orientation of limbs is used to make a prediction of the sensory outcome of the movement (Daniel M Wolpert & Ghahramani, 1995). These are of particular interest in respect to our study of Developmental Coordination Disorder (DCD as will be explained later.

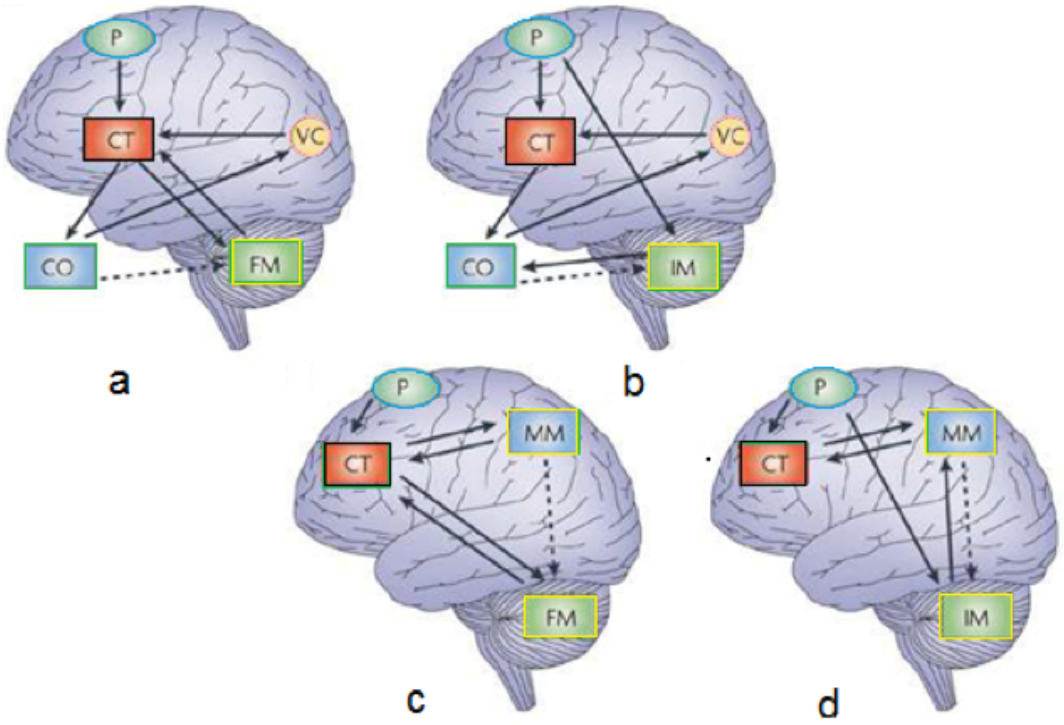
On the other hand, in inverse models, the flow of sensory information is in the opposite direction, from the consequence to the action, meaning there is no sensorimotor prediction for the outcome of the motor command. Although both are important to motor control and learning, this review will focus on forward models and the role of forward motor impairment in DCD.

Significance of the forward model in movement planning

Forward models provide stability, speed, and smoothness to the human motor system by predicting the desired state of each stage of motion whilst performing a complex movement. Based on the forward model theory, whenever a motor command is created, a copy of the command, the 'efference copy' is also issued without wasting time for slow sensori-motor feedback to be delivered (D. Wolpert, 1997). This efference copy is then used to form a predicted state. This is the expected state of the motor system once the current motor commands are executed. This predicted state would be compared to the desired state, without the need for sensory feedback and therefore spontaneous corrections to the movement can be made if the internal model deviates significantly from the intended goal. This online correction is crucial in performing quick motions, without compromising accuracy or smoothness of the movement (Frith, Blakemore, & Wolpert, 2000). As the time delays between efferent motor commands and sensory

feedback of those commands can be rather large, the state of the system may have already changed when the sensory feedback arrives and consequently could lead to errors between the perceived and actual outcomes (Frith et al., 2000). The schematic illustration of internal models incorporated to sensori-motor circuits in human brain is presented in Figure 2.2

Figure 2.2. 'Forward' (a) and 'inverse' (b) model of motor control systems for movement and mental activities. The instructor (P) in the premotor cortex, the supplementary cortex or the anterior cingulate gyrus, the controller (CT) in the motor cortex sends



command signals to the controlled object (CO; a body part or a lower motor center). The visual cortex (VC) mediates feedback from the body part to the motor cortex. The dashed arrow forward model (FM) or an inverse model (IM). In the forward model control system, control of the CO by the CT can be precisely performed by referring to the internal feedback from the forward model. In the inverse model control system, feedback control by the CT is replaced by the inverse model itself. (c) & (d). Forward and inverse model control systems for mental activities: in response to an instructor located in brain tissues that include the anterior cingulate gyrus, the controller in the prefrontal cortex initially controls a mental model (MM) that is expressed in the temporo–parietal cortex. The dashed arrow shows that the mental model is copied to a forward model or an inverse model in the cerebellum. Reproduced from Ito, M (2008).

Motor imagery

Motor imagery (MI) is the ability to internally present the movement in the absence of overt action. Traditionally, the parietal cortex has been known to be associated with somatosensory perception and MP and the frontal cortex and cerebellum have been linked to ME. However, recent studies have indicated that MI and ME overlap in many anatomical regions; especially the posterior supplementary motor area (SMA) and the premotor cortex (known as Brodmann area number 4 or BA 4) (Lotze & Halsband, 2006). However, (Stephan et al., 1995) demonstrated that MI activates different areas within the SMA from the ME. Some studies showed that MI also activates dorsal parts of the primary motor cortex (PMC) (Gerardin et al., 2000; Stephan et al., 1995). Although these parts also become activated during ME, more ventral parts are involved in MI (Gerardin et al., 2000). In addition to the frontal and parietal cortex, the cerebellum has been identified as a crucial component in movement coordination and adjustment. The cerebellum neurons are traditionally known to be associated with movement execution and coordination in a lower level in comparison to highly developed cerebral cortex neurons. However, recent studies suggest a more significant role for the cerebellum in motor prediction and imagery (Lotze & Halsband, 2006). It is shown that the cerebellum is activated during imagery of simple hand movements (Ryding et al., 1993). Despite the traditional view of associating distinct roles individually for the parietal lobe and cerebellum in motor prediction, it seems that these two regions work as a functional loop to estimate the current status of the motor system throughout movement execution (Blakemore & Sirigu, 2003).

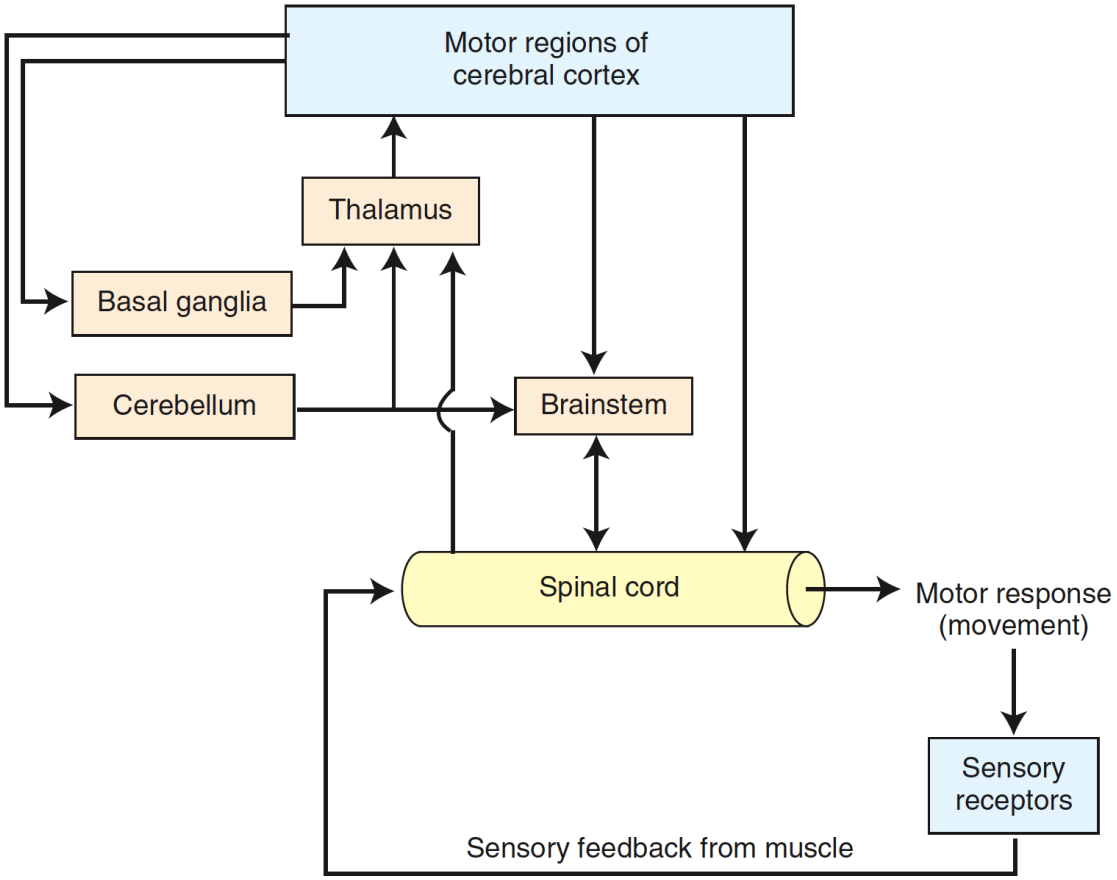


Figure 2. 3. Schematic illustration showing elaboration between main regions involved in human motor control and execution of main circuits involved in human motor control and execution elaboration between several regions involve in producing motor signals and sensory feedback. Internal models both "inverse" and "forward" models are copied into the cerebellum and sent to upper motor regions (motor cortex) and lower regions (brainstem) for creating the final motor signal. Taken from (Siegel & Sapru, 2006 p.322).

Since several parts of the CNS are involved in the processes of the motor at planning and motor execution, any abnormality in these regions could potentially lead to human motor dysfunction. Based on the mechanism of disorders and involved CNS regions, we can divide the movement disorders to ME and MP categories. However, as mentioned above, there are some overlaps in planning and execution areas of the CNS which sometimes makes it difficult to assign a specific movement disorders to one of these categories, especially when the exact mechanism of a movement disorder is unknown. We are specifically interested in 'internal models' theory of motor control. We investigated the impact of dysfunction of specific CNS regions in movement control and

execution loops. We nominated two separate movement disorders to investigate impairment in human motor planning and execution. We selected DCD, a neurodevelopmental movement disorder in which the motor dysfunction is believed to be at planning level and FRDA in which motor skill impairment is believed to be mainly at the execution level. In both DCD and FRDA the neuroimaging studies are scarce. We used several MRI modalities to investigate the underlying mechanism of these disorders. Utilising novel imaging techniques led to improvement in our understanding of the nature of motor dysfunction in each disorder. We interpreted the outcomes of our work in a wider context by studying practical aspects of human movement control theory, particularly inverse model in normal and pathological conditions.

Developmental coordination disorder

Developmental Coordination Disorder (DCD) is a moderately common chronic movement disorder in children which is identified by motor coordination impairment at both gross and fine levels. In recent years some theories concerning the underlying aetiology of DCD have been proposed (Kirby, Edwards, Sugden, & Rosenblum, 2010). However, since the precise neuromechanism of motor skill impairment and underlying brain regions observed in DCD are not yet clearly identified, the exact aetiology still remains controversial. The diagnostic criteria for DCD by the American Psychiatric Association includes (American Psychiatric Association, 2013)

i. Motor coordination during daily activities should be substantially below that expected for age and intelligence.
ii. Resulting motor difficulties interfere with academic achievement or activities of daily living.

The coordination problems are not due to a general medical condition (e.g., cerebral palsy or muscular dystrophy) or a pervasive developmental disorder. If mental retardation is present, the motor difficulties are in excess of those usually associated with such a condition.

Presentation of DCD

The clinical manifestation of DCD varies greatly between children (S. E. Henderson & Sugden, 1992). The differences may occur in the type of impairment displayed, with some children impaired only in fine motor activities, some in gross motor activities only, and others across all types of motor skills. In addition to differences in the type of impairment, there is variation in the strength of the impairment, and also in the way the impairment progresses and transforms over the time. In some children, motor skill impairment may be obvious from infancy whilst in others there is no evidence of motor deficit until school age. As Smyth, (1992) suggests, a child's motor skill impairment would be noticed in school because of the increased demand on physical skills in the school where children are inevitably compared to their peers. Consequently, it is not surprising that many children with motor skill deficits remain undiagnosed until school age.

DCD in adults

There is increasing evidence that not all the children with DCD will eventually grow out of the symptoms and it is found that DCD symptoms can persist into adulthood. (Cousins & Smyth, 2003); (Hellgren, Gillberg, & Gillberg, 1994); (Losse et al., 1991) Lack of standardised screening tools for assessing functional motor deficits in adolescents and adults make it difficult to accurately predict the prevalence of DCD in this group. Studies of DCD in adults have generally adapted the measurements obtained from assessment batteries used to diagnose children. Furthermore, the criteria used for diagnosing adults as DCD are inconsistent and they vary between different studies. As a result, the prevalence of DCD in adulthood has been estimated to be in the range 30% to 87% (Kirby et al., 2010); Cantell, Smyth, & Ahonen, 2003; Geuze & Borger, 1993; Knuckey & Gubbay, 1983; Losse et al., 1991).

Despite the conflicting evidence for the prevalence of DCD in adulthood, there is an increasing trend toward acknowledging DCD as a lifetime disorder that is not necessarily limited to childhood. This new perspective has led to changes being made in the new version of diagnostic criteria for DCD published by American Psychiatric Association (APA). In DSM V (The Diagnostic and Statistical Manual of Mental Disorders, Version 5) (American Psychiatric Association, 2013), the term 'child' has been replaced by the word 'individual'. Our knowledge of the course of the disorder and presentation of motor coordination symptoms in adults with DCD are still ambiguous.

In addition, there is insufficient evidence for the level of impact of DCD on individuals' daily lives (Cousins & Smyth, 2003); Kirby, Sugden, Beveridge, & Edwards, 2008). However, there is increasing evidence that suggests young adults with DCD have problem in performing tasks that require use of motor control (de Oliveira R et al 2010)

Motor skill impairment in DCD

It is shown that children with DCD show impairment in motor imagery (the ability to imagine the movements at the neural level before doing the real task) (J. Williams, Thomas, Maruff, Butson, & Wilson, 2006; Jacqueline Williams, Thomas, Maruff, & Wilson, 2008; P H Wilson et al., 2004; Peter H. Wilson, Maruff, Ives, & Currie, 2001) hence it would be helpful to evaluate the motor imagery capacity in children with DCD using fMRI to determine the mechanisms of movement disorders in DCD. It is expected that children with DCD present some atypical activation in their parietal brain lobe because they manifest similar patterns in performing movement tasks to those patients with posterior parietal brain injures (Sirigu et al., 1996).

Visuospatial processing in children with DCD

Wilson and colleagues have suggested the Internal Modelling Deficit (IMD) hypothesis in DCD (Wilson & Maruff, 1999; P. H. Wilson et al., 2004; P. H. Wilson et al., 2001; P. H. Wilson, Maruff, & McKenzie, 1997). The IMD hypothesis suggests that the main reason for motor skill impairment observed in individuals with DCD is the inability to utilise internal models properly for motor control. Given the crucial role that internal models play in motor control and learning in children with DCD, this might be one of the main candidates for the underlying causes of DCD.

Motor imagery in DCD

There is some inconsistency in motor imagery deficit in the DCD literature and the level of deficits in the observed patterns between groups varies among different studies. There is consequentially a greater level of variation in terms of task complexity is

accompanying the results. Furthermore, different analysis techniques within motor imagery assessment have been utilised. Strong support for motor imagery deficits arises from the studies using the visually guided pointing task paradigm (VGPT)(Katschmarsky et al., 2001; Lewis et al., 2008; Maruff et al., 1999; Williams et al., 2013; Wilson et al., 2001) and imagined reaching tasks (Cac¸ola et al., 2014). Moderate support is provided in the hand laterality judgment literature (Katschmarsky et al., 2001; Lewis et al., 2008; Lust et al., 2006; Noten et al., 2014; Williams et al., 2011, 2013, 2006, 2008; Wilson et al., 2004) and studies that utilize the whole body rotation for assessment of motor imagery capability in individuals affected by DCD (Williams et al., 2006, 2008) paradigms. Whilst in most cases differences in the response patterns between groups are observed, a large variations in results may be attributed to the differences in the level of complexity of the tasks, with more complex tasks more likely to identify differences. Inconsistent results have been reported in the studies using Praxis Imagery Questionnaires (Sinani et al., 2011; Wilson et al., 2001), This difference in the results might be due to using different questionnaires in addition to observing he potential ceiling in the results of Sinani et al., (2011) and; Wilson et al., 2001) studies. Also, using hand laterality in a mental rotation task, Williams et al., (2006; 2008) showed that in addition to differences observed in response patterns in children with DCD, the level of motor imagery deficits was related to the severity of motor difficulties. Additionally, DCD groups revealed less benefit from explicit motor imagery instructions compared to their peer controls. When no imagery instructions were provided for a hand laterality task, no difference in accuracy was observed between the groups. However, control groups were significantly more accurate when provided with explicit motor imagery instructions (Williams et al., 2006) suggesting that individuals suffering from DCD with less profound motor skill impairment, are able to benefit from motor imagery instructions. Consistent with this, a positive relationship was reported between movement performance score, measured by using Movement Assessment Battery for Children-2 (Henderson, Sugden, & Barnett, 2007), and motor imagery proficiency score, measured by using an imagined reach task in a group of children with and without movement difficulties compared to controls (Gabbard, Cacola, & Bobbio, 2012).

Although the level of motor imagery deficit and response pattern is slightly different in the DCD literature, there is sufficient evidence to acknowledge that there is at least a mild impairment in motor imagery performance in children and adults suffering from

DCD (Reynolds et al., 2015). Although not specifically exploring the role of regions involved in motor imagery, neuroimaging evidence indicates differences in brain activation patterns in frontal, and cerebellar and temporal networks between individuals with and without DCD (Reynolds et al., 2015). This preliminary evidence provides support for the motor imagery hypothesis, thus further neuroimaging research is required to extend existing knowledge regarding motor control theories. Particularly neuroimagiung research in the field of motor imitation and imagery seems to be a promising research direction toward elucidating aetiology of movement disorders such as DCD there is no biomarker available and the neuromechanism of disorder remains ambiguous.

Friedreich ataxia

Friedreich ataxia is the most common form of hereditary ataxias with early onset among the Caucasian population. (Pandolfo M. 2009 Mar;256 Suppl1:3-8). The genetic disorder results from a mutation of a gene locus on chromosome 9 (Campuzano et al., 1996).

As a part of the research program reported in this thesis we carried out a study of movement disorders, and we used novel MRI methods to elucidate neurological characteristics associated with Friedrich's ataxia. The disease is named after Professor Nicholaus Friedreich, a physician and pathologist who first described the disease in Heidelberg, Germany in 1863. He described the disease as a hereditary clinical syndrome mainly characterised by "ataxia" that affects descendants of unaffected parents (Friedreich, 1863). He reported the disease in nine patients during 1863-1877 (Delatycki MB, Williamson R, Forrest SM. 2000) and suggested the physiopathology of the disease as "degenerative atrophy of the posterior columns of the spinal cord". FRDA usually starts in the first and second decade of the life (Delatycki et al 2000) FRDA in s multisystemic disorder. The neurological manifestations of FRDA include progressive ataxia, dysarthria, absent lower limb reflexes, extensor plantar reflexes, spasticity and impaired or loss of vibration sense and proprioception. Other non-neurological symptoms include scoliosis and foot deformity. Other vital organs involved are the heart and pancreas the involvement of which could lead to diabetes and cardiomyopathy ((Santos R, Lefevre S, Sliwa D, 2010 Sep). Hypertrophic cardiomyopathy is the most

common manifestation of heart involvement and the most common cause of death in individuals with FRDA [(Said G, Marion MH, Neurology. 1986), (Albano LM, Nishioka SA, 2002). The hallmark symptoms are generalised clumsiness and gait problems (Pandolfo, 2009); however, in rare cases cardiac manifestations may precede neurological signs (Quercia et al., 2010). The course of the disease is with very progressive and disabling with such a poor prognosis that most of the patients will lose their ability to independently walk, stand or sit within 10 to 15 years of the onset of the disease (Pandolfo & Pastore, 2009) and usually become wheelchair bound by the third decade of the life (Harding, 1981; Pandolfo, 2009).To date, there is no effective drug or treatment that prevents the eventual outcome.

Motor system dysfunction in Friedreich's ataxia

A mentioned above, FRDA is a neurodegenerative disorder. Neurological manifestations mainly include muscle weakness, clumsiness and gait disturbance (ataxia). Several regions of the human nervous system, from peripheral sensory neurons to the spinal cord and cerebellum have been shown to be involved in movement impairment in FRDA (Alper & Narayanan, 2003) and the symptoms are mostly attributed to the peripheral nerve and cerebellum (Simon et al., 2004) but recent neuroimaging studies (Akhlaghi et al., 2012; Corben, Akhlaghi, et al., 2011; Della Nave et al., 2008; Georgiou-Karistianis et al., 2012; Mantovan et al., 2006; Zalesky et al., 2013) have paid more attention to connection between higher areas (cerebral corex) and cerebellum in FRDA. Since the exact neuromechanism of motor dysfunction remains unclear, new MRI techniques studies can be helpful in determining the aetiology and better understanding of FRDA neurologic manifestations.

Brain imaging

Principles of magnetic resonance imaging

In the late 1940's, physical chemists initially developed NMR spectroscopy for investigating properties of atoms nuclei. However, it was not until the early 70's that

NMR was used as an imaging method to determine the molecular structure of organic compounds inside the human body (Lauterbur, 1973). (See Figure 2.4)

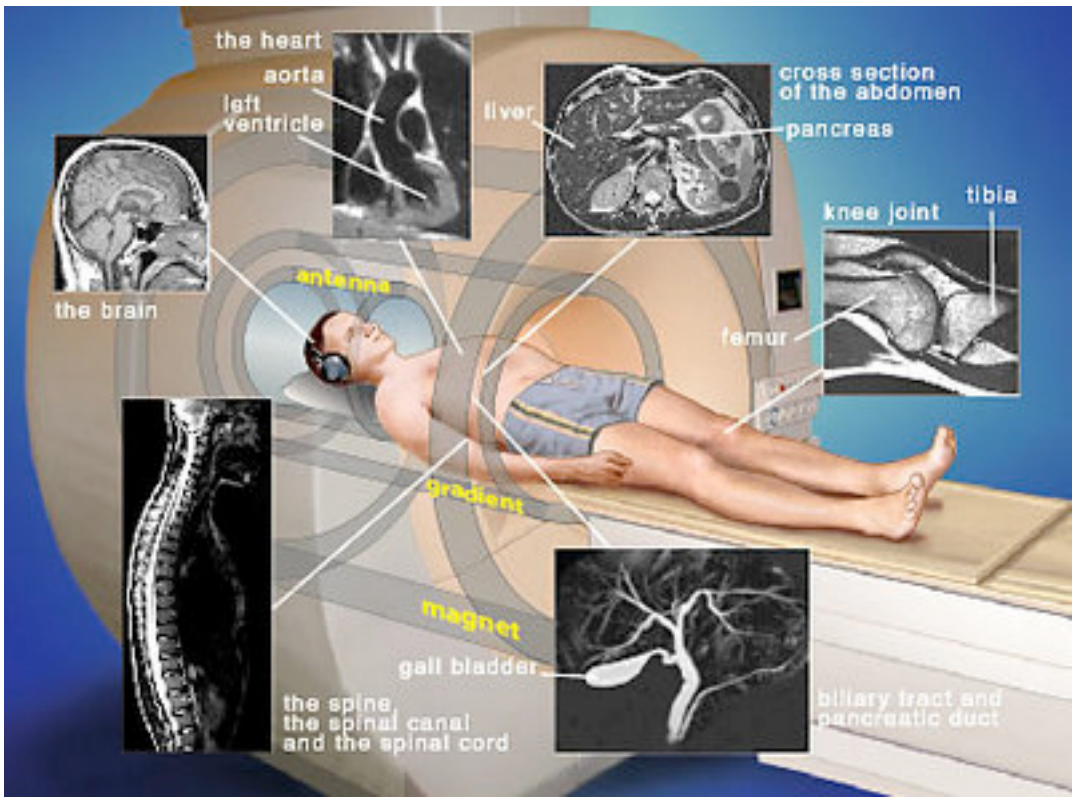
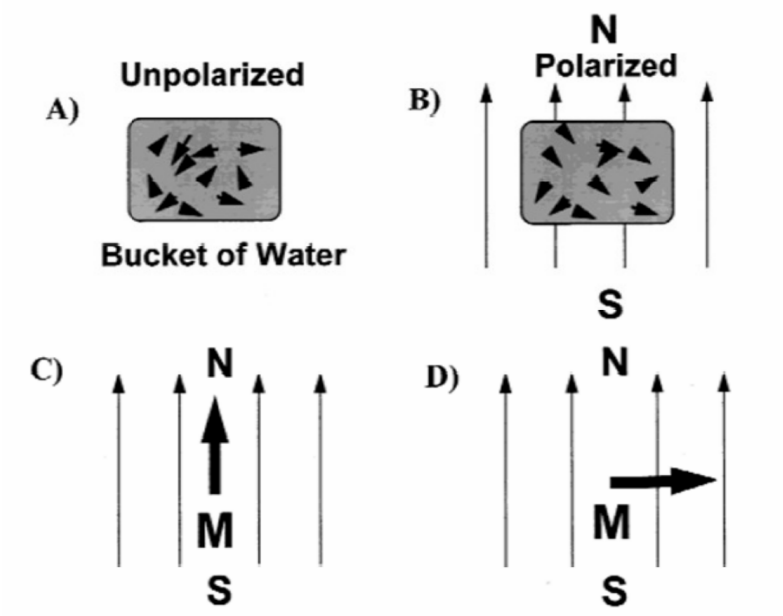


Figure 2.4. An illustration of MRI machine showing sample of MRI images acquired from different parts of human body. Figure was taken from http://c3e308.medialib.glogster.com/media/23/23015be408a96d0b5155e8be01b0f534181b66db04c6e1cdca398873cb412b1b/400px-mrifig2.jpg accessed 4/1/2016)

The utility of NMR arises from the angular momenta of atomic nuclei. Just as electrons have a +1/2, -1/2 spins, certain nuclei also manifest charged spins. These charged spins can create a magnetic field called the' magnetic moment' (Yurkanis Bruice, 1998)[p. 527, P.Y. Bruice, Organic Chemistry (4^{th} ed.)], which allows imaging scientists to study the structure of organic compounds using NMR. When there is no applied magnetic field, the nuclear spins orient randomly; however, when there is an applied magnetic field, all nuclear spins become oriented into opposite direction, parallel to the applied magnetic field. This leads to excitation of the protons (H^+) and makes the all nuclear spins become oriented in one direction opposite to the applied magnetic field and they display homogeneity. When these excited nuclei restore to their original state, the nuclear spins return to their heterogeneous state, and the energy absorbed during

excitation is emitted as electromagnetic energy. This energy, detected by an MRI machine, is known as NMR (Nuclear Magnetic Resonance). The NMR signal intensity is dependent on the strength of applied magnetic field and the concentration of protons (mainly as HO^2 per hydroxyl radicals) in the scanned material. The higher the concentration of water and the higher strength of applied magnetic field in a specific part of body tissue, the stronger is the NMR signal. Based on the concentration of water in a specific tissue the NMR signal is stronger. Hence, the ultimate constructed NMR image of a specific human body part or organ is essentially the concentration map of water molecules in that specific tissue. These maps are constructed based on the time it takes for the spin to get back to the relaxation state. Based to these relaxation times, generally two types of images are reconstructed: T1 weighted and T2 weighted. T1 images are more sensitive to fat while T2 images are more sensitive to water. Since water is the principal element in most human organs and tissues, this map can represent an accurate structural map. This 3D map has sufficient resolution to identify structures within tissues, and the resolution is dependent on the strength of magnetic fields, the duration of scanning process and number of slices of scanned tissue that is acquired (Lauterbur, 1973).



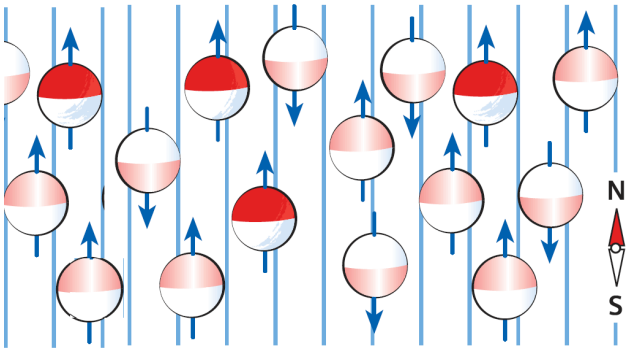


Figure 2. 5. An illustration showing polarisation induced by a magnetic field in an unpolarised compound, the proton spins are randomly pointing in every direction. (A) The compound is placed inside a magnetic field. Now the protons are oriented parallel with the magnetic field (B) The polarization direction is shown as a vector **M** (C). The vector **M** is tilted vertically by applying an RF pulse to the diagonal plane, producing an RF signal from the compound (D) [Figure reproduced from (Mulkern & Chung, 2000)].

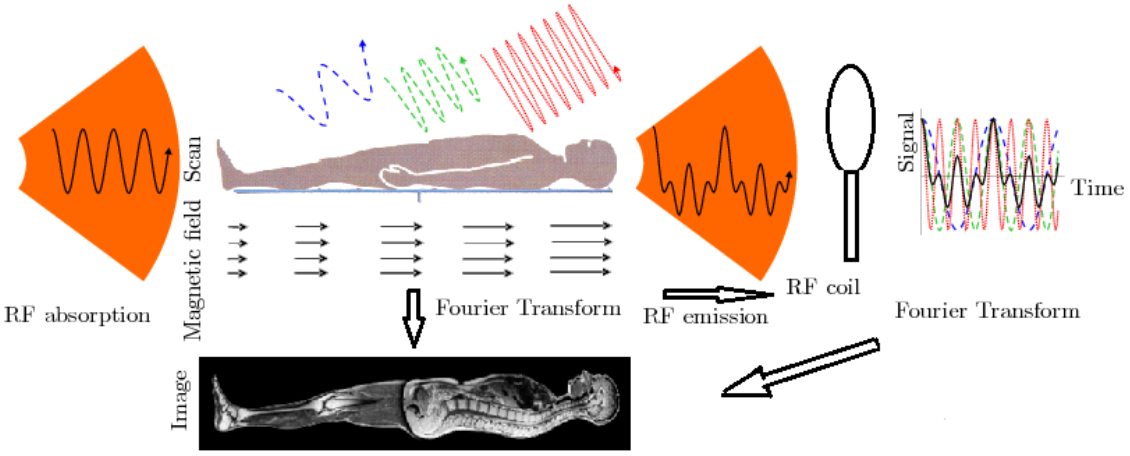


Figure 2. 6. The concept of MR-image production. After excitation of the subject, by applying a magnetic gradient field an RF signal will be emitted by the subject. This RF signal consists of several waves with different frequencies and that are converted by a Fourier transform into an image. [Figure reproduced from (http://fieremans.diffusion-mri.com/phd/PhDch2.html#x10-21004r5 accessed 18/1/2016]

Functional magnetic resonance imaging

Before the invention of brain imaging techniques, observations of the changes made in patients with brain lesions were the sole source of information regarding human nervous

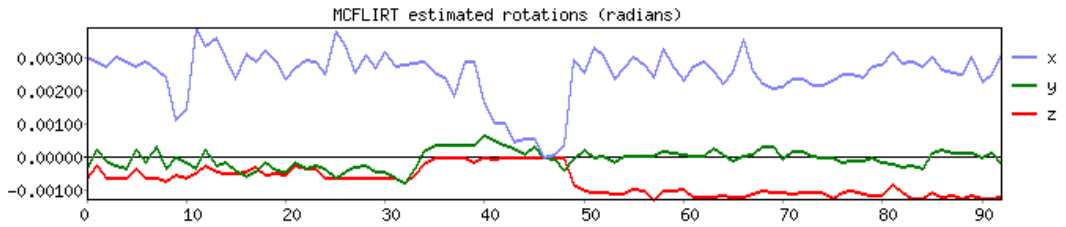
system functionality. The roles of specific brain regions were mainly determined by distinguishing the changes observed in these patients after pathological changes occurred in these regions. This information was very restricted by the nature of the human brain disorders and this 'post brain injury observation' approach was obviously limited to underlying affected regions. It did not have the potential to give a comprehensive overview of brain functionality and was unable to give scientists means of accurately mapping the functionality of the human brain. To understand the roles of different brain regions and their connectivity neuroscientists needed techniques that enable them to observe the change in human brain activity *in vivo* whilst performing a motor, sensory or cognitive tasks.

Several imaging methods are sensitive to the cerebral oxygenation level of blood. Among these methods fMRI has gained significant attention by neuroscientists in recent years Blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI), has sparked significant interest in the properties and role of oxygen delivery and consumption in the brain, particularly during changes in brain function. Two main methods of developing research designs for fMRI include the block design paradigm and event-related paradigm. In the block design paradigm, a series of stimuli in one condition is presented during a specific time period called blocks. During each time block, the NMR signal climbs to a steady plateau and declines when the block finishes. The collected BOLD signal from one block is then compared against other blocks which could include different task conditions. The effect of the BOLD signal difference between the tasks then processed to ensure that the results are statistically meaning. Block design has several advantages which include its significant experimental flexibility (including parametric or multi-factorial designs) and removing noise by the averaging of NMR signals which lead to a higher statistical reliability. (Amaro & Barker, 2006). In the event- related designs, the BOLD signal associated with each individual trial is measured instead of a temporally integrated signal. Another widely used fMRI analysing paradigm, "event related", allows representation of temporal changes of the BOLD signal by detecting temporary variations in hemodynamic responses induced by a task (Amaro & Barker, 2006). This design requires fast and frequent sampling of the fMRI signal so it is less sensitive to excessive head motion. Also, the event-related design is more appropriate when the task is complex and it is difficult to emulate by block design. (Amaro & Barker, 2006)

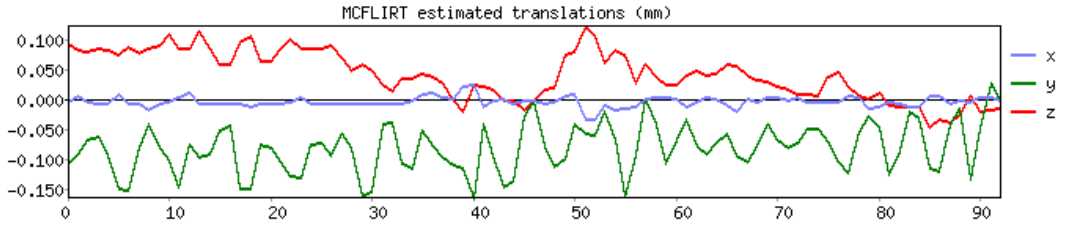
Two principle items of software are used for fMRI analysis include FSL as independent software packages and the SPM (Statistical Parametric Mapping) package design for using in a MATLAB environment.

fMRI analysis using FSL software includes three main stages: “Pre-stats”, “Stats” and “Post-stats”. A sample of each stage of fMRI analysis with FSL software is shown in Figures 2.7-2.10.

(a)



(b)



(c)

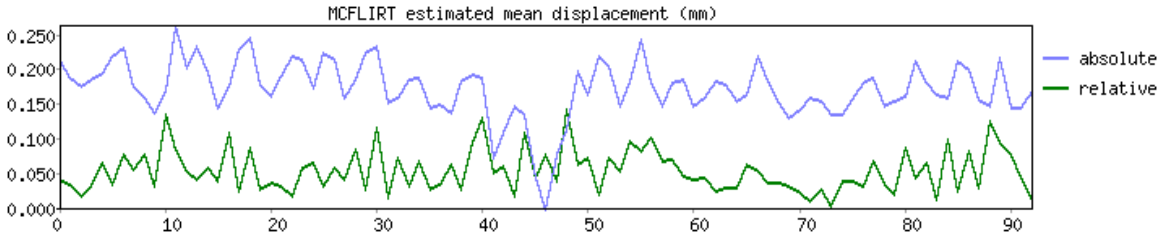
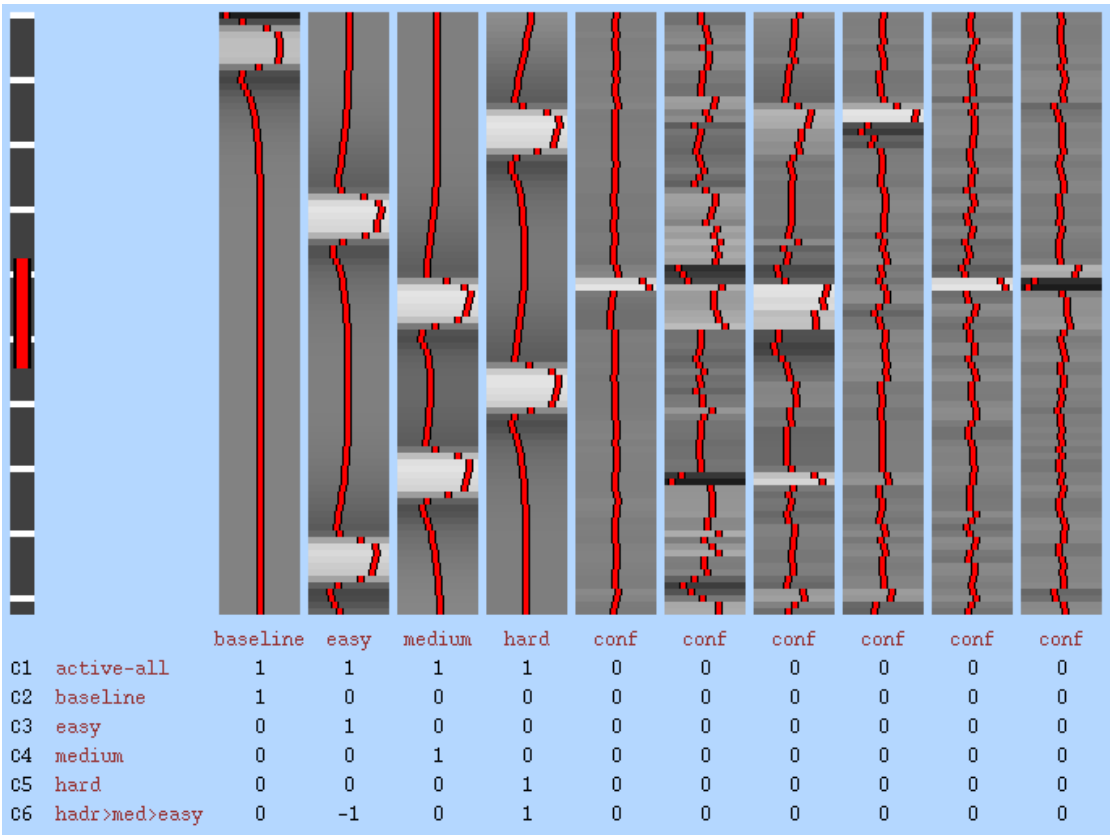


Figure 2.7. Time series of detected motion in three directions used in the “MCFLIRT” tool in FSL software.MCFLIRT is utilised for “Motion Correction” to remove extraneous motions of the head. This process is performed as part of “Prestat” phase in FSL package. MCFLIRT includes estimation and correction of rotation (a), translation (b) and total displacement (c). The fMRI data is collected from a participant from control group.



		baseline	easy	medium	hard	conf	conf	conf	conf	conf	conf
C1	active-all	1	1	1	1	0	0	0	0	0	0
C2	baseline	1	0	0	0	0	0	0	0	0	0
C3	easy	0	1	0	0	0	0	0	0	0	0
C4	medium	0	0	1	0	0	0	0	0	0	0
C5	hard	0	0	0	1	0	0	0	0	0	0
C6	hadr>med>easy	0	-1	0	1	0	0	0	0	0	0

Figure 2. 8. Design matrix used in “Stats” phase of fMRI data analysis in FSL software in a participant from control group.

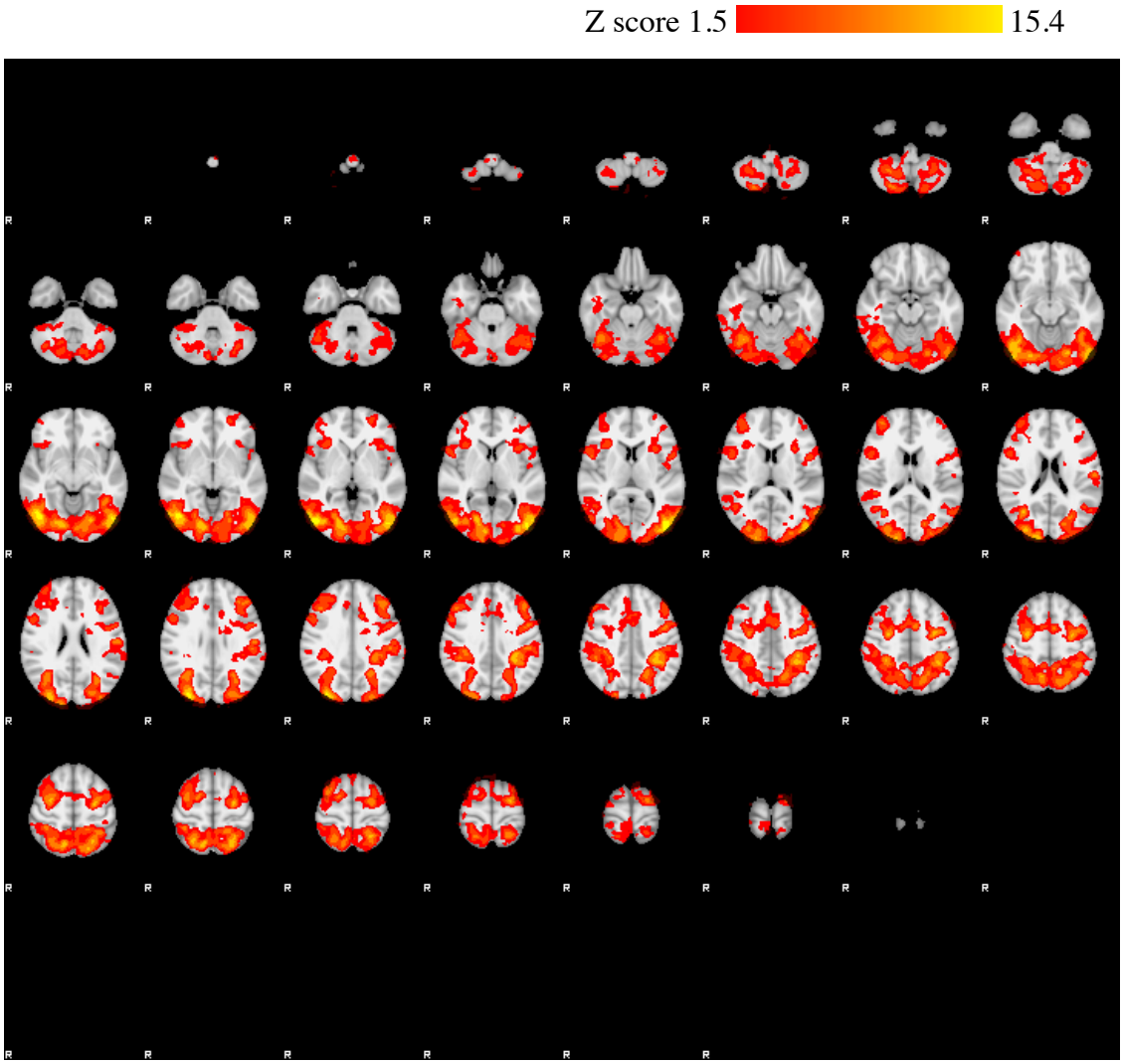


Figure 2. 9. A sample of thresholded activation maps produced during the “Post-stat” stage in FSL software. The statistical maps show active areas during the task compared to rest phase in a participant from control group.

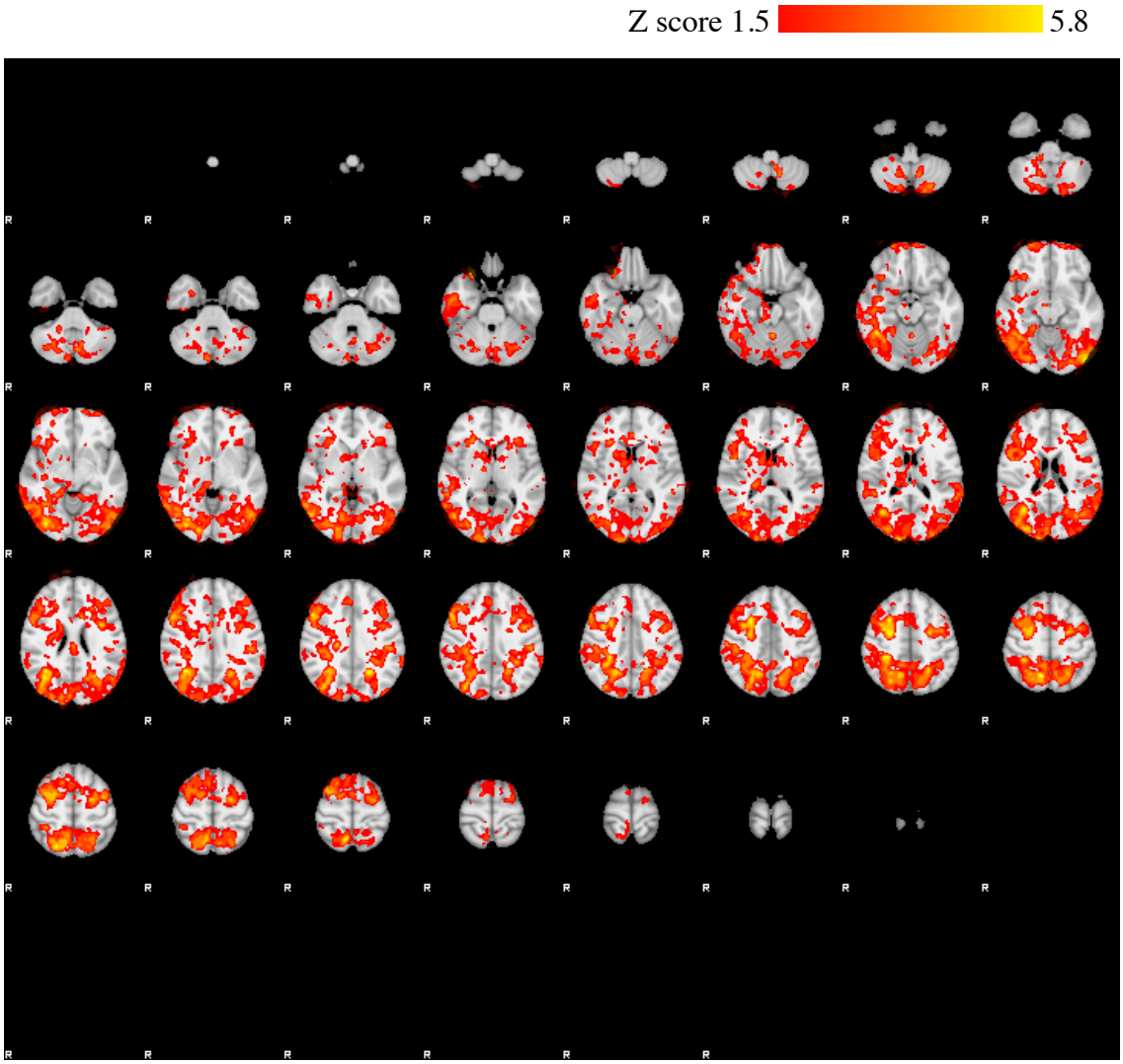


Figure 2. 10. A sample of thresholded activation maps produced during the "Post-stat" stage in FSL software. The statistical maps show active areas in regions with a parametric increase in the BOLD signal by increased difficulty of task in a participant from control group.

Diffusion magnetic resonance imaging

Diffusion magnetic resonance imaging is one of the most rapidly evolving techniques in the MRI field. The random diffusional motion of water molecules is the basis of producing images using DTI method. Construction and visualization of 3D images are based on applying a magnetic field gradient to the subject and measuring the signal attenuation caused by the random thermal motion of water molecules in different directions. The boundaries made by the cellular membrane forms a physical Barrie that constrains the free motion of water molecules in specific directions. The degree of

anisotropy due to this limitation is calculated in three directions which are represented by three diagonal vertices, called eigenvalues and displayed as λ1, λ2 and λ3 (Mori & Barker, 1999). Diffusion-weighted images are eventually produced by calculating λ1, λ2 and λ3 for each voxel which provides visualisation of the location, orientation and anisotropy of a specific tissue(Mori & Barker, 1999). The signal attenuation along a specific axis can be altered by manipulating the direction and magnitude of radiofrequency (RF) pulse field gradient. This adjustment of signal loss in a specific direction is applied to provide optimum parameters required for determining main eigenvalues and producing high-quality images (Luypaert, Boujraf, Sourbron, & Osteaux, 2001).

In situations in which water molecules can randomly move in different directions without any barrier gives rise to no diffusion anisotropy and the apparent diffusion coefficient (ADC) is not dependent on the axis of applied gradient. However, in a living organism, water cellule diffusion is constrained in specific directions defined by cellular membrane boundaries. Consequently, diffusion tensors can be used to define characteristics of diffusion anisotropy and produce 3D structures, which are known as diffusion ellipsoids (Luypaert et al., 2001). The more asymmetrical and ellipsoid the shape of a cellule, the stronger is the ADC. Unique properties of brain white matter which are mainly made of a collection of long shaped axons render it ideal tissue~~s~~ for producing DTI images in the human body. In brain imagery by the DTI method at least six directions are required for each voxel to establish the diffusion ellipsoid and create the final 3D structure of axonal pathways and
distinguish them from grey matter (Mukherjee, Chung, Berman, Hess, & Henry, 2008)
Diffusion tensor imaging (DTI) has been mainly used for in-vivo evaluation of alterations in the white matter (WM). These changes include axonal degeneration and demyelination in the human nervous system (Mori & Barker, 1999).

There are several methods for estimating and reconstructing white matter structure, including deterministic tractography, probabilistic tractography and Tract-Based Spatial Statistics (TBSS) (Behrens et al., 2003; Mukherjee et al., 2008; Smith et al., 2006) (Figure 2.11).

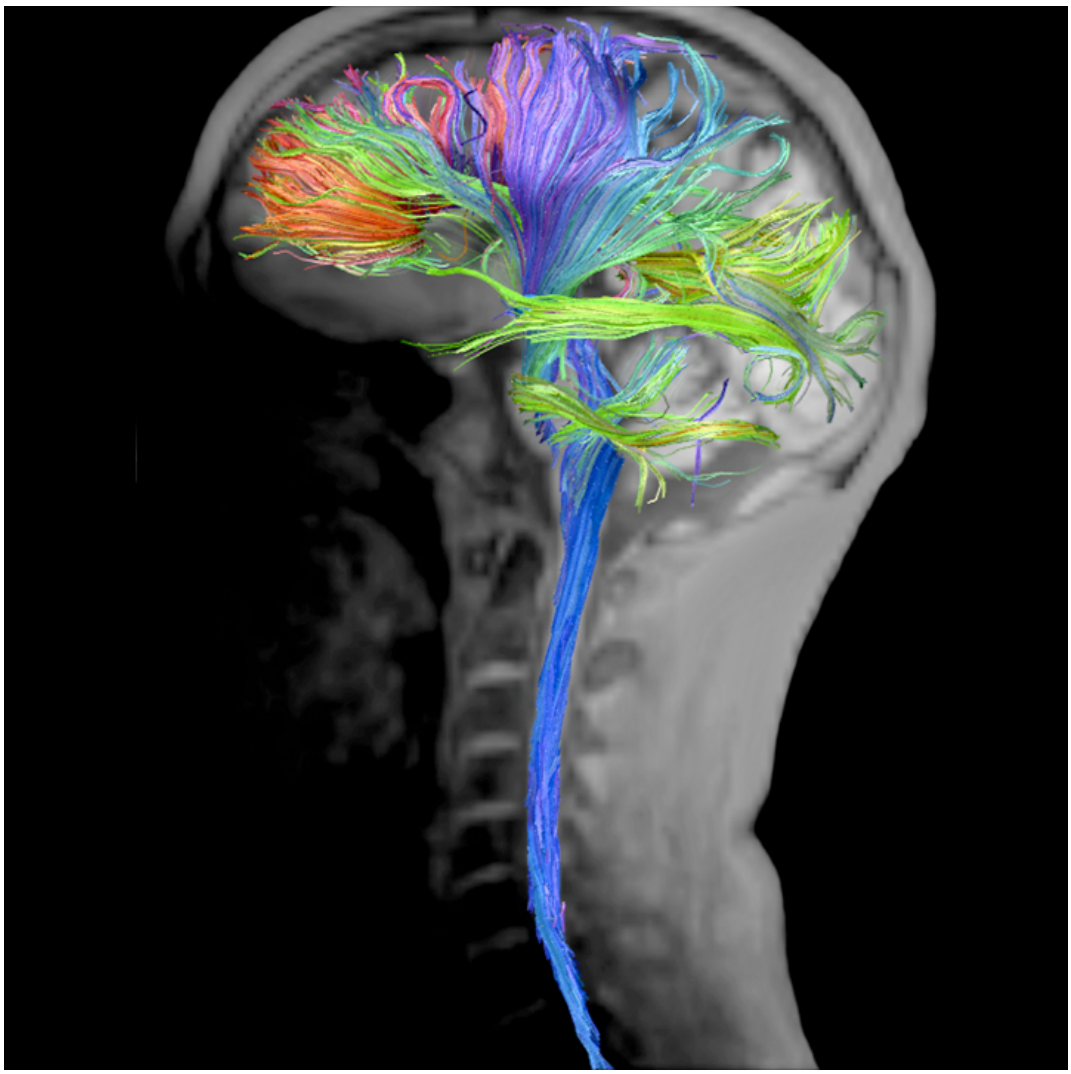


Figure 2 11. Sagittal view of an image of the human brain using diffusion tensor imaging reconstructed by tractography technique [Figure adapted from (https://www.healthcare.siemens.com/siemens_hwem-hwem_ssxa_websites-context-root/wcm/idc/groups/public/@global/@imaging/@mri/documents/image/mdaw/mjew/~edisp/mri-syngo-resolve-dti-tractography-00200930/~renditions/mri-syngo-resolve-dti-tractography-00200930~8.jpg
accessed 28/6/2016].

Magnetic Transfer Imaging (MTI)

Magnetization transfer imaging (MTI) is a relatively recent magnetic resonance imaging (MRI) technique which uses an off-resonance magnetization pulse to measure the variation in the exchange of protons between free water and macromolecules including protein and lipid molecules (Wolff & Balaban, 1994). The pathological processes lead to a reduction of macromolecular bound protons and induce a decrease in

the magnetisation transfer ratio (MTR) value. The reduction of MTI values in the brain is expressed by a decrease in the MTR value, and it is reflective of a quantitative measure of the amount of change myelination in axonal fibers. It is believed that MTI is more specific in determining the myelination status of axons compared to DTI techniques (Stanisz, Kecojevic, Bronskill, & Henkelman, 1999). Most of the published studies examining MTR values in the human brain have examined myelination in people with multiple sclerosis (MS). These studies have indicated that MTR Images are more sensitive than DTI in the detection of demyelination and they aver that MTI is valuable for detection of new MS plaques and following up the demyelination process and recurrence of lesions in patients suffering MS (Dousset et al., 1992; Harrison et al., 2013).

The MT images are created by calculating the MTR for each voxel using the following formula: $MTR = 100*(MT_0-MT)/MT_0$. MT_0 is the intensity value of a voxel without induction of MT pulse, whereas MT is the value when MT pulse in induced (Wolff & Balaban, 1994).

MTI studies have used T1 weighted or T2 weighted images for creating MTI images. However, the preference of each sequence in not mentioned (Dousset et al., 1992; Harrison et al., 2013; Stanisz et al., 1999).

To achieve the best protocol for the MRI scanner used in our study, two different MTI scan sequences were tested using different parameters. The first scan was acquired using T1 weighted protocol and the second one was performed using T2 weighted sequences. The MTR (Magnetic Transfer Ratio) was calculated for each voxel based on above mentioned equation for creating MTR images. The images histograms showed that T1 based scans have higher peak MTR values for T2 weighted images (52%) compared to T1 weighted images (26%). The images acquired using each protocol and the histogram chart (Figures 2.12-2.15)

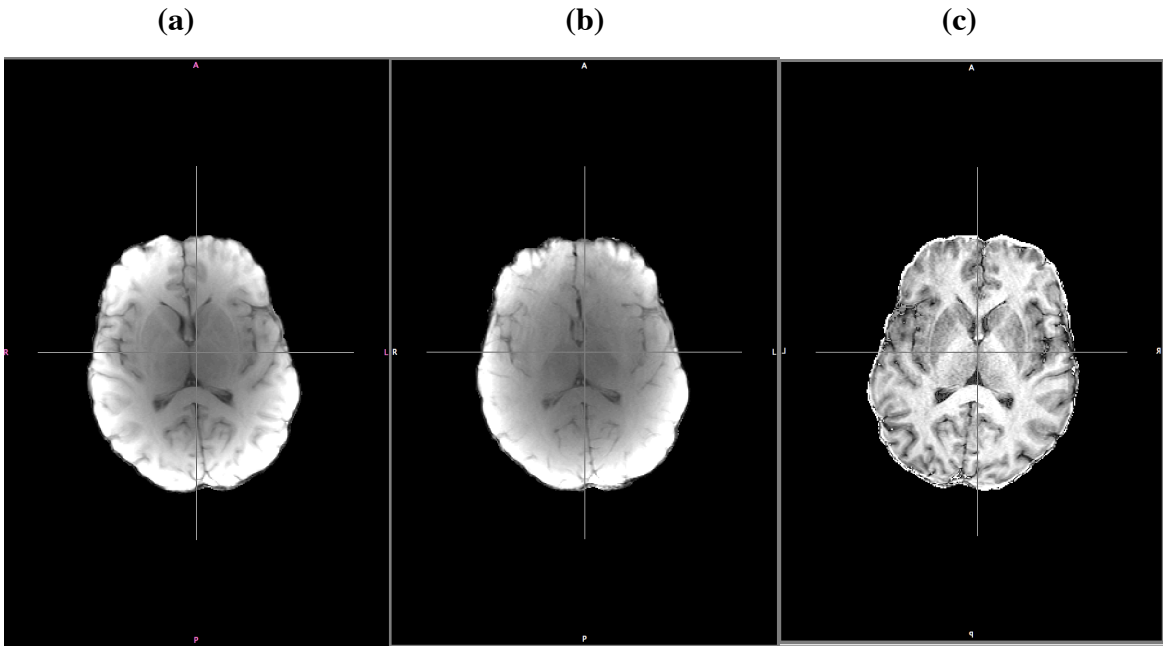


Figure 2. 12. T1 image without MT pulse (a), T1 image with MT pulse (b), MTR image

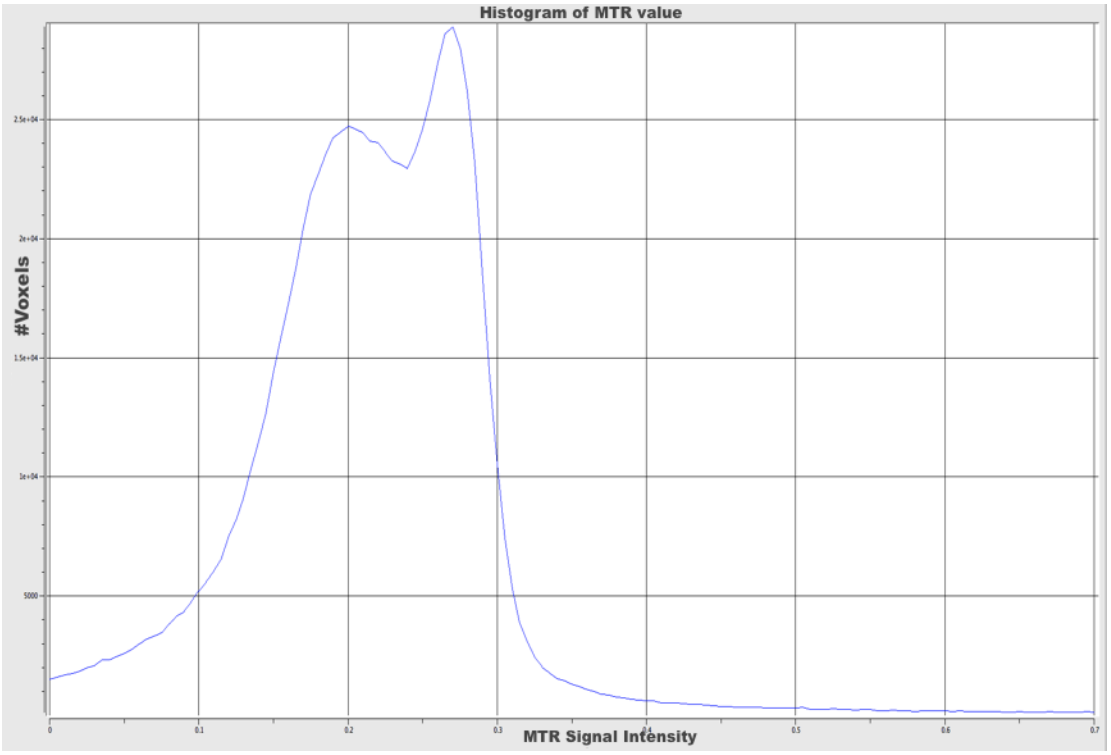


Figure 2.13. The histogram chart of MTR image produced using T1 protocol shows Peak MTR at 26%.

(a) **(b)** **(c)**

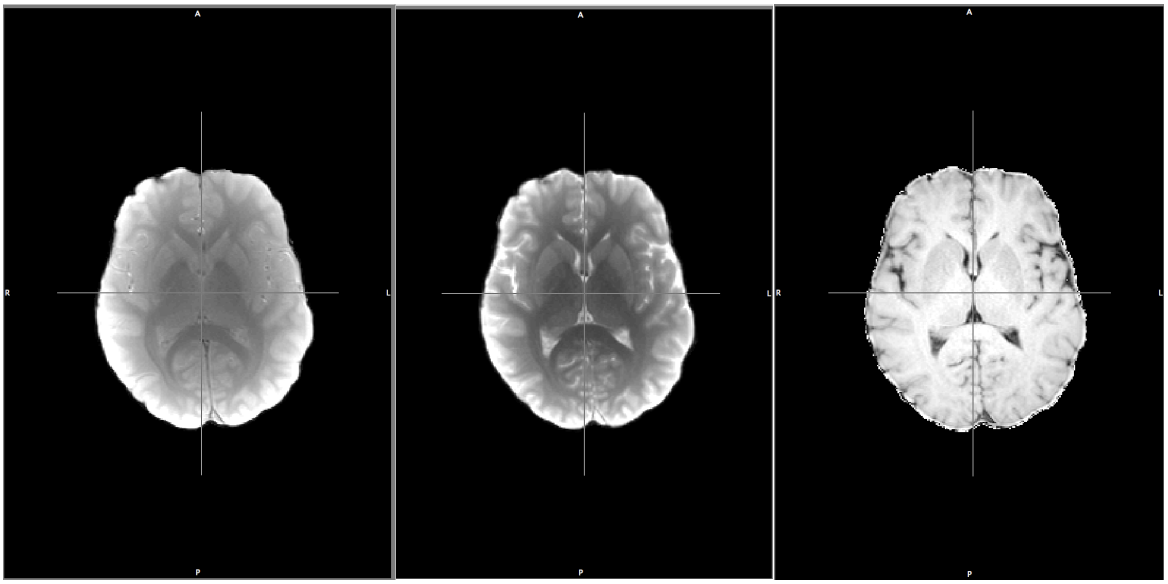


Figure 2.14. T2 image without MT pulse (a),MT T2 image with MT pulse (b) and MTR image(c).

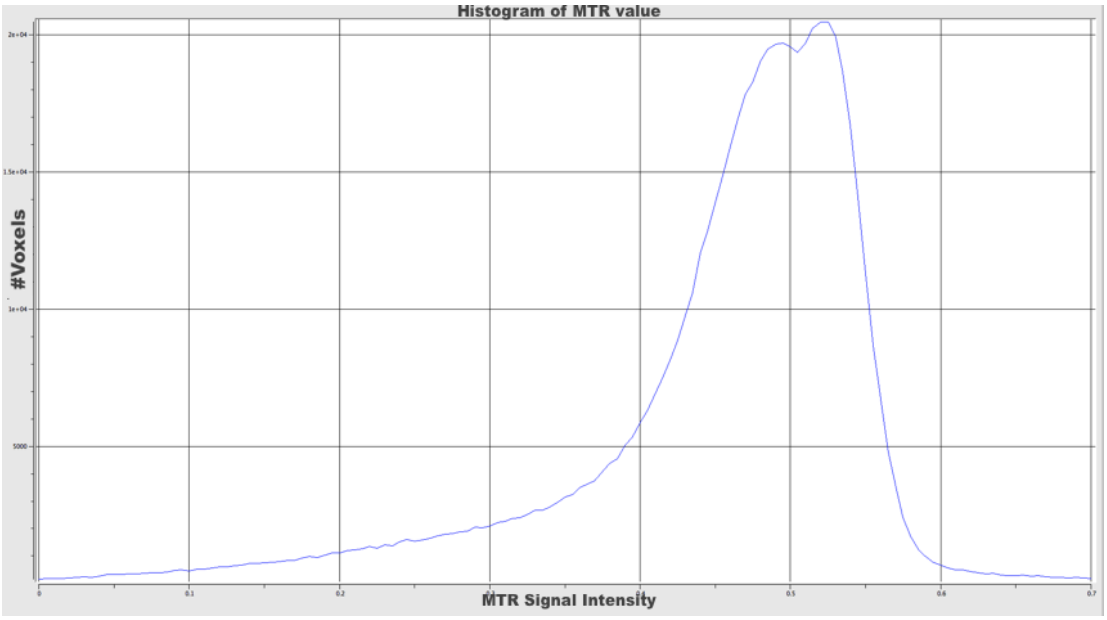


Figure 2.15. The histogram chart for MTR image produced using T2 protocol shows Peak MTR at 52%.

Neuroimaging studies in DCD

Recent research highlights similarities between the patterns of motor performance by individuals diagnosed as DCD across a range of tasks (motor imagery, double-step saccades and covert orienting) with those observed in patients with posterior parietal damage [e.g. (Sirigu et al., 1996)]. This finding supports the hypothesis that suggests the parietal lobe might be one of the main regions affected in individuals with DCD. One of the few fMRI studies of DCD which was conducted by Kashiwagi et al., (2009 #18). has shown a decrease in neural activation in the parietal cortex during performance of a motor sequencing task Atypical activation in the parietal lobe, along with the frontal and temporal lobes, was also recently reported in a further DCD study, though on this trail-tracing task, the DCD group showed a significantly increased BOLD signal in these regions compared to controls (Jill G. Zwicker, Missiuna, Harris, & Boyd, 2011). It has also been suggested that the cerebellum plays a role in forward internal modelling of movement (Kawato, 1999; Daniel M. Wolpert, Miall, & Kawato, 1998). In a recent fMRI study utilising a predictive motor timing task, Debrabant et al., (2013) compared neural activation in DCD subjects and a control group. They reported that while the control group, like adults, showed increased activation in the dorsolateral prefrontal cortex (DLPC), left posterior cerebellum and the right temporo-parietal junction when responding to a variable inter-stimulus interval compared to a constant, predictable interval, the DCD group did not, resulting in significant group differences. In addition, Zwicker et al., (2011) observed a reduction in neural activation in the cerebellar–parietal and cerebellar–prefrontal networks in children with DCD during a motor learning activity. Taken together, the findings suggest that DCD may stem from dysfunction across more than one brain region (Peters et al.., 2013) and that poor coupling between parietal and cerebellar networks may underlie the deficits in internal movement simulation, and thereby motor skill development, in DCD.

A number of studies of adults have used variants of the hand rotation task to investigate motor imagery ability (de Lange, Hagoort, & Toni, 2005; de Lange, Helmich, & Toni, 2006; Kosslyn, DiGirolamo, Thompson, & Alpert, 1998; Parsons, 1994; Sirigu & Duhamel, 2001; J Williams, Pearce, Loporto, Morris, & Holmes, 2012) . Similar to the mental rotation of objects, increasing response times are evident with increasing angles of rotation through to 180º. Significantly, responses are also affected by the awkwardness of the movement required to physically bring one's hand into alignment

with the stimulus – for example, responses are slower and less accurate when a right hand is presented at 135° clockwise (physically more awkward posture) than at 135° counter-clockwise (physically more comfortable posture) (de Lange et al., 2006; J Williams et al., 2012). This reflection of biomechanical constraints in imagined movements is taken to indicate that the participant is engaging in motor, and not visual, imagery. The engagement of motor imagery in the hand rotation task is supported by neuroimaging studies that have identified a considerable overlap during motor imagery in regions known to be involved in movement planning and execution (de Lange et al., 2005, 2006; Kosslyn et al., 1998; Parsons, 1994). A recent meta-analysis of the neural networks engaged in motor imagery confirmed that for the hand rotation task, consistent activation was reported in the following regions: bilateral superior and left inferior parietal lobes, postcentral gyrus, cerebellum, right middle frontal gyrus and putamen (Hétu et al., 2013).

Neuroimaging studies in Friedreich's ataxia

Neuroimaging studies of FRDA are scarce. Only a limited number of functional MRI (fMRI) and DTI and diffusion weighted imaging (DTI) studies have been conducted in patients suffering from FRDA. (Ref 8, 108-110). Although the small sample sizes were small in these studies, the findings of these suggest some evidence of change in the cerebro-cerebellar loops.

Gilman et al. (111) investigated the changes in central nervous system of patients suffering FRDA compared to controls utilizing positron emission tomography (PET) to study the regional cerebral metabolism rate of glucose. The authors suggest that the basal ganglia, thalamus, cerebellum, mesencephalon, and the pons might be involved patients with FRDA.

In another study, Montavan et al., (2006) used a repetitive task of simple visual-reaction times to implicitly evaluate the cognitive status of patients with FRDA. For the fMRI investigation, six patients diagnosed with FRDA performed a simple self-paced finger tapping task. In addition, the participants' neural activation was examined using single photon emission computed tomography (SPECT) to assess regional cerebral perfusion. As expected, finger tapping by healthy controls resulted in activation of the controlateral sensorimotor cortex and supplementary motor cortex. However, in the

FRDA group the pattern of activation was heterogeneous including activation in the sensorimotor cortex in one patients and posterior parietal regions activation in three patients. In two patients the motor task did not produce any detectable neural activation. Montayan et al., (2006) suggested that inconsistent and unexpected cortical activations in FRDA group might arise because of the decreased cerebellar feedback and dysfunctional internal correction during fine motor movement.

Della Nave (112) and colleagues used DTI to investigate white matter changes in degenerative ataxias including FRDA. They examined 28 patients including individuals with spinocerebellar ataxia type 1 (SCA1), type 2 (SCA2), sporadic adult onset pure cerebellar ataxia and seven individuals with FRDA. Della Nave and colleagues found that variable patterns of WM alteration in the brainstem, cerebellum, and cerebral hemispheres which were consistent with the known distribution of neuropathological changes in degenerative ataxias. They concluded that DTI methods along with MR spectroscopy might be useful in assessing the severity and progression of degenerative ataxias including FRDA.

The extent of White Matter (WM) changes in individuals with FRDA have been evaluated using DTI in several studies (Della Nave et al., 2008; França et al., 2009; Pagani et al., 2010). Changes in white matter have been observed particularly in the brainstem, bilateral SCP, cerebellar peri-dentate region, the optic chiasm (Della Nave et al., 2008; França et al., 2009; Pagani et al., 2010).

In a study by Della Nave at el. (108), white matter tract changes have been assessed by a voxel-wise analysis and showed almost symmetric decrease of FA in many WM tracts of the corticospinal tract, the brainstem and the inferior and superior cerebellar peduncles. They observed a correlation between the International Cerebellar Ataxia Rating Scale (ICARS) score and decreased in WM integrity in the left superior cerebellar peduncle which is the main output pathway of the cerebellum. Intriguingly, this is the only factor has been found to be related to the severity of the FRDA. Della Nave et al. (108) proposed that the cerebello-cerebral component of the cerebro-cerebello-cerebral circuit is disrupted.

Aims of the project

The overarching aim of this research is to use MRI to elucidate functional and anatomical causes in movement disorders. We used these results to consolidate the neuroimaging findings of a DCD study with the 'internal model' theory of motor control. For this reason, we investigated two different movement disorders at the motor planning and execution levels. This helps us to better understand the mechanisms of each of the movement disorders and the contributions of different brain regions in motor symptoms of these disorders.

The specific aim of the fMRI study of DCD was to combine our behavioural findings in adults with the same impaired motor imagery capacity seen in children with DCD, with neuroimaging data and determine the nature of the dysfunction of motor imagery-related areas of the brain. We achieved this by comparing the activation patterns of the CNS in individuals with DCD and in a control group whilst they were performing a mental rotation of hand task. Specifically, we aimed to monitor the parieto-frontal, cerebello-cerebral and occipito-parietal regions. To verify the results of the fMRI study we also looked at the white matter integrity in individuals suffering DCD in comparison to their peers in a control group. Using this MRI technique, we measured WM integrity in both DCD and control group. We expected to see lower WM integrity in the DCD group compared with the control group in the same pathways we investigated in the first study.

Finally, we adopted an imaging approach to verify the computational models of human motor system. We investigated the physiopathology of the human motor system including motor planning and motor execution phases from the imaging perspective. To achieve this goal, we used new MRI technologies to investigate the main neural networks proposed to be disrupted in DCD and FRDA.

Chapter 3

Methodology

To investigate the impairment of human movement control and execution we used MRI to elucidate possible neurological contributors to two movement disorders, namely Freidreich's ataxia (FRDA) and Developmental Coordination Disorder (DCD). For each disorder, we collected imaging data from two groups, individuals with impairment and control groups. The MRI data for both studies were acquired using a Siemens Skyra 3Tesla scanner (SiemensAG, Erlangen, Germany) located at Monash Biomedical Imaging (Melbourne, Australia). In the DCD study, participants executed a behavioral task before MR imaging data acquisition.

DCD study

Recruitment

Participants

The study sample consisted of students and staff from local universities aged between 18 to 40 years (see Table 1). Brochures and emails were distributed in universities' campuses. (See index for the sample). The brochure included a brief explanation of the study. In the brochure individuals who felt clumsy as children and continue to have this feeling were asked to contact the study investigators if they were interested in participating in the study. The brochure also asked adults who felt their motor skills were in the average range to consider participating in the study as a member of the control group. Participants were asked to fill screening forms for ADHD (Attention Deficit Hyperactivity Disorder), autism, Asperger's Syndrome and intellectual disability (see Appendix for samples of screening questionaries) to exclude any comorbidity or predisposing conditions that could influence their motor performance. Participants with any psychological, neurological or physical condition that could affect their motor skill

were also excluded from the study as well as individuals with any history of head trauma. Normal levels of cognitive and intellectual function were shown and also confirmed by participants' adaptive occupational function in a tertiary education environment. Individuals suffering from claustrophobia or with magnetic or metallic materials within their body were also excluded. Participants with eyesight refraction problems (ametropia) that could influence their visual judgment during the functional MRI task were asked to wear MRI-safe eyeglasses with the same optical dioptre as their original eyeglasses.

Twenty-one adults with probable DCD (pDCD) volunteered for the study and were included in the motor skill impaired (pDCD) group if they indicated a developmental history of motor learning difficulties and their score on the McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997) indicated the presence of motor impairment. This was defined here as a standard score ≤ 85 on either the total score or the fine or gross motor components This cut-off is considered sensitive to motor skill issues in children and young adults (Tan, Parker, & Larkin, 2001). Twelve of the 21 volunteers were included on this basis. Fifteen adults volunteering for the control group were also screened using the MAND and were excluded if their standard scores were on or below 85 on the total, fine or gross motor components. Three adults were excluded on this basis and one further participant was excluded after data collection due to an error in the protocol.

Assessment

The McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997). This standardised test of motor skill was used to confirm the status of adults in both the control and pDCD groups. The test includes five fine-motor and five gross-motor items. Scores for 10 tasks are summed to provide a standardised total score, called Neuromuscular Development Index (NDI; M = 100; SD = 15). Age-appropriate comparisons are available for individuals aged between 3.5 to 18 years; the latter age is appropriate for referencing the performance of young adults. In addition, standard scores are also provided for fine and gross motor skills. This battery is often used to identify motor skill difficulties in children (Hyde et al., 2014; Piek, Dawson, Smith, & Gasson, 2008; J Williams, Omizzolo, Galea, & Vance, 2013) and young adults. The

test-retest reliability of the MAND (over a 1-month period) ranges between 0.67 to 0.98 (McCarron, 1997). The MAND has good criterion and concurrent validity (McCarron, 1997), as well as high levels of specificity and sensitivity (Swee Kheng Tan, Parker, & Larkin, 2001). Importantly, global performance scores [i.e., Neuromuscular Developmental Index (NDI) are considered a valid index of general motor competence (Hands et al., 2013), and are predictive of motor fitness (Hands et al., 2009). Demographic information and MAND standard scores are shown in Table 1.

There were no significant differences in age. However, the control group had significantly higher standard scores in both fine and gross motor performance compared to the pDCD group.

Table 3.1. Group Demographic Data for the Control and pDCD Groups.

	Control group	pDCD group	Test Result
N[a]	11	12	
Male/Female	6/5	5/7	
Age (years) [a]	26.7 (5.5)[M(SD)][a]	24.5(7.6)	t(21) = .0.8, p > .05
MAND [a] Fine Motor Scores	105.1 (11.3)	82.7 (8.0)	t(21) = -5.5, p < .001
MAND Gross Motor Scores	98.5 (6.3)	86.2 (9.5)	t(21) = 3.6, p = .002
MAND Total Scores	99.0 (4.1)	84.7(4.8)	t(21) = 7.6, p < .001

Note: [a] Values represent, N = Number; M = mean; SD = Standard Deviation; pDCD = probable Developmental Coordination Disorder; MAND = McCarron Assessment of Neuromuscular Development.

MRI data acquisition

The participants lay supine in the scanner and a 32 channel head coil was used to acquire high quality images. The participants' heads were fixed in the coil using foam pads to reduce any motion. A foam pad was also placed under their knees for their comfort. The structural MR acquisition sequence parameters were as follows: A T1 sagittal orientated anatomical scan was initially acquired (TR = 1900 mesc, TE = 2.7 mesc, image matrix 320×320, 128 slices, slice thickness = 0.8 mm). Functional MR

gradient echo echo-planar images were recorded for 98 brain volumes using the following imaging parameters: TR = 3020 ms, TE = 30ms, flip angle = 90º, FOV = 24cm, matrix size 128×128, 36 trans-axial slices, thickness = 4.0 mm, no gap. The first two volumes were discarded to allow for T1 saturation effects. To assist with spatial normalisation a T2 weighted image was acquired in the same orientation as the echo planar images.

3.2.4 MRI data analysis

After acquisition of the images, DICOM EPI files were converted to the ANALYZE format, and FSL software version 4.1.8 (FSL, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) was used for pre-processing steps and data analysis.

3.2.4.1 fMRI data analysis

MRI images were brain-extracted and corrected for head motion using FEAT v5.98. Each participant's functional images were normalised to the standard Montreal Neurological Institute (MNI) brain atlas. The registration process was performed in two stages. First, each participant's functional images were co-registered to the individual's high-resolution T1-weighted image, using FMRIB's Linear Image Registration Tool (FLIRT); (Mark Jenkinson & Smith, 2001) with seven degrees of freedom (DOF) transformation T1-weighted images were then linearly registered to MNI space using a twelve DOF affine transformation. The combination matrix of these two transformation matrices was used to register each individual's functional images to MNI standard space. Every participant's registration process was visually inspected to exclude registration errors. The images were also spatially smoothed with a 5 mm FWHM Gaussian kernel, and high-pass temporal filtering (50Hz) was applied to remove low-frequency BOLD signal artefacts.

Three regresses were defined to model easy (50˚), medium (100˚) and hard (150˚) rotation conditions compared to the rest state. A statistical t-test map was achieved by using a linear contrast to examine parametric increases of activation with the angle of rotation. At the group level, a higher level group analysis method (Mumford & Nichols, 2006) was performed to calculate intra-group average and inter-group comparison. Significant activations for both within- and between-group analyses were defined using a voxel-level probability threshold (Z.2.33) and a False Discovery Rate ($P_{FDR} < 0.05$) was used to correct for multiple comparisons.

FRDA study

Recruitment

Participants

The study sample consisted of twenty adults including ten patients with FRDA and ten healthy controls.

FRDA patients were referred from a Friedreich's ataxia clinic, Melbourne, Australia, and healthy controls were adults who had no history of the systemic disease or movement disorders. These individuals were selected from volunteer staff and students at Monash University which were recruited using advertisements on campus.

Assessment and diagnostic criteria

Several criteria for diagnosing patients suspected of suffering from FRDA (M B Delatycki, Williamson, & Forrest, 2000; Pandolfo, 2009) have been reported recently. Among these are two main clinical diagnostic criteria introduced by Geoffroy et al., (1976) and Harding, (1981) (see Table 2.1). Harding, (1981) criteria are reportedly more sensitive in detecting FRDA symptoms in early stages of the disease in comparison to criteria suggested by Geoffroy et al., (1976), (M B Delatycki et al., 2000).

Table 3.2. Two sets of diagnostic criteria for FRDA developed by Geoffroy et al., (1976) and Harding [Table reproduced from (M B Delatycki et al., 2000)]

Criteria	***Geoffroy et al., 1976***	***Harding, 1981***
Primary	(1) Onset before the end of puberty (never after the age of 20 years) (2) Progressive ataxic gait (3) Dysarthria (4) loss of the joint position or vibration sense (5) Absent tendon reflexes in the legs (6) Muscle weakness	(1) Age of onset of symptoms before the age of 25 years (2) Progressive unremitting ataxia of limbs and of gait (3)Absence of knee and ankle jerks
Secondary	(1) Extensor plantar responses (2) Pes cavus (high arch foot) (3)Scoliosis (4) Cardiomyopathy	(1)Dysarthria (2) Extensor plantar responses

It was not until 1996 that the discovery of the impaired gene in those with FRDA that a 'gold standard' test was developed to detect individuals affected by FRDA with almost 100% specificity (Campuzano et al., 1996). However, this test is not 100% sensitive.

FRDA Rating scales

Rating scales are a method of quantifying the progress of the disease and neurological morbidity in individuals with FRDA (Martin B. Delatycki, 2009; D. R. Lynch et al., 2006; David R. Lynch, Farmer, Wilson, & Balcer, 2005). Patients are scored for each item on the rating scale by experienced specialists the final scored is calculated by summing up all sub-total scores (Martin B. Delatycki, 2009). The two most widely used rating scales in FRDA are the International Cooperative Ataxia Rating Scale (ICARS) and the Friedreich Ataxia Rating Scale (FARS).

The ICARS was developed by a group of neurologists at World Federation of Neurology. In this scale patients are scored out of 100 (Martin B. Delatycki, 2009), and includes four main sub-groups: posture and gait disturbance, kinetic function (limb ataxia), dysarthria and oculomotor disorder (OD) (Trouillas et al., 1997). Friedreich Ataxia Rating Scale (FARS)

Friedreich Ataxia Rating Scale (FARS) was developed by the Cooperative Ataxia Group (Subramony et al., 2005). The FARS scoring system aims to reflect specific neural substrates in FRDA and consists of three sub-scales: ataxia, activities of daily living and neurological examination (Martin B. Delatycki, 2009) (see figure 3.1). In both FARS and ICARS, the highest scores are assigned to individuals with greater morbidity and disability (Storey, Tuck, Hester, Hughes, & Churchyard, 2004)

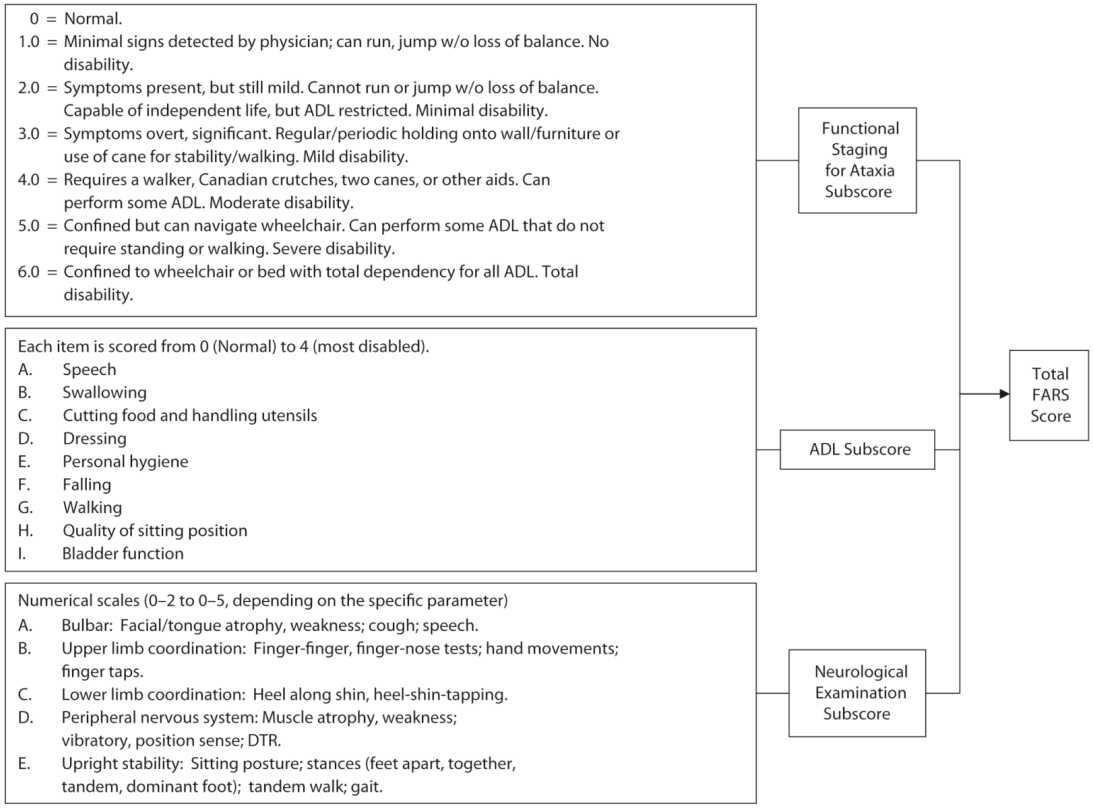


Figure 3.1. Three main sub-scales in FARS scoring system [Figure taken from (Martin B. Delatycki, 2009)].

Ten right-handed individuals homozygous for a GAA expansion in intron one of FXN (6 males) with a mean age of 37.7 years (SD = 11.2) participated in this study. An age and sex matched group of ten control participants (6 males) with no known neurological disorders and mean age of 38.2 years (SD = 7.9) also participated. There was no significant difference in age between the groups [f (1,180 = 0.013, p = 0.91]. See Table 3.3 for clinical and demographic details of participants.

Table 3.3. Demographic information and screening measures in individuals with FRDA and Controls.

Group Characteristics	FRDA			Controls			p value
Male/Female	6/4			6/4			-
Female	4			4			-
	M	SD	R	M	SD	R	

Age (y)	36.6	11.2	22-48	38.2	7.9	31-51	n/s
Age at Disease Onset (y)	20.1	7.6	8-34	-	-	-	-
Disease Duration (y)	16.5	7.1	6-25	-	-	-	-
FARS Score	95	17.4	69-124	-	-	-	-
GAA1	533	184	126-837	-	-	-	-
GAA2	950	216	462-1345	-	-	-	-

(M) = Mean, standard deviation (SD) and range (R) GAA1 = FXN GAA repeat size of the smaller allele; GAA2 = FXN GAA repeat size of the larger allele; FARS = Friedreich Ataxia Rating Scale; dashes indicate where descriptive was not applicable; MTR = Magnetisation Transfer Ratio, Superior Cerebellar Peduncle; MTR Magnetisation Transfer Ratio; n/s - not significant

Imaging data acquisition

MRI images were acquired using a 3 Tesla Siemens Skyra scanner (Siemens, Erlangen, Germany) at Monash Biomedical Imaging, Victoria, Australia. T2 weighted images were acquired using a 32 channel head coil (TE = 8.4ms, TR = 734ms, flip angle = 30°, voxel size = 0.9×0.9×3.3mm3, FOV = 230×172.5mm2, matrix size = 256×205, 46 slices). Images were acquired with and without saturation, using a magnetisation transfer pulse placed before each slice-selective excitation.

MRI data analysis

DICOM files were converted to ANALYZE format and processed using the FSL software tools (FSL version 4.1.8, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The brain images then were extracted from the whole head images using BET2 (Brain Exaction Tool version 2) in FSL and were registered to standard space , using non-linear registration with 7 degrees of freedom (DOF). Finally, the Superior Cerebellar Peduncle (SCP) mask was created for mean MTR calculation. To calculate MTR, the image acquired with the saturation pulse (MT image) for each participant was first linearly registered to the image without the saturation pulse (MT0 image) using FMRIB's linear image registration tool (FLIRT) (29). The MTR for each

voxel was calculated using the following formula: MTR = 100*(MT0-MT)/MT0 (Wolff & Balaban, 1994).

Chapter 4

Functional MRI study of individuals suffering probable developmental coordination disorder

The aim of this study was to elucidate the neuro-mechanisms underlying DCD in adults. We studied individuals suffering from ongoing motor skill impairment (pDCD) and we investigated whether this group exhibits the same behavioural deficits as those observed in children with Developmental Coordination Disorder (DCD) during their performance of a motor imagery task. We also examined whether these adults show any impairment in an atypical pattern of neural activation pattern when performing a motor imagery task. We used a mental rotation task to investigate motor imagery capability while performing imagery rotation of upper limbs. We scanned the participants whilst performing the task inside Magnetic Resonance Imaging machine.

The study samples comprised 12 adults with pDCD (5 male; age M = 24.5 yrs.) and 11 adults without pDCD (6 males; age M = 26.7 yrs.). We concluded that participants in both groups are using a motor imagery skill. This hypothesis was confirmed by demonstrating that performance during judgment of hand laterality, was influenced by biomechanical constraints of real movement. When we compared the response time and accuracy the data showed no significant group differences, but a significant parametric difference was observed between BOLD signal activation maps in controls compared to the pDCD group. The % BOLD signal change for increasing angle of rotation between two groups showed greater activation in the occipito-parietal and parieto-frontal and cerebellar networks. These involved cortical regions included the middle frontal gyrus bilaterally, the left superior parietal lobe and lobule VI of the cerebellum. The pattern of reduced activation in adults with pDCD is consistent with recent imaging studies of

DCD in children and adults. These studies exhibit atypical activation in frontal, parietal and cerebellar areas in individuals with DCD, and supports the hypothesis that the impairment observed in the pattern of cortical activation in DCD may be attributed to the disruption of parieto-frontal and parieto-cerebellar networks.

Introduction

Developmental Coordination Disorder (DCD) is a neurodevelopmental disorder that presents as a marked impairment in motor skills that interferes significantly with activities of daily living and/or education (APA, 2013). Like other neurodevelopmental disorders, DCD typically manifests early in development, and the onset of the symptoms occurs usually before school age. However, it normally remains undiagnosed until school age where the incidence is 5-10% of all children (Barnhart et al., 2003). Importantly, up to 50% of those diagnosed as children continue to experience motor problems into adulthood (Cantell, Smyth, & Ahonen, 2003), particularly during important transitions from adolescent to adult life, e.g., into occupational settings (Thomas, Williams, & Kirby, 2013).

While DCD is not explained by any known neurological condition and its aetiology remains unclear, the persistence of motor problems in some adults may suggest more fundamental issues of neuromotor control. Moreover, the study of adults with ongoing motor impairment presents a unique opportunity to exclude individuals whose motor impairment in childhood may be the result of a more benign developmental delay and who eventually 'catch-up' to their peers. Here, we will review evidence of the motor control deficits that have been observed at a behavioural level in children with DCD, but we will explore hypotheses in adults with ongoing motor impairment—individuals who are more likely to have underlying issues in motor control and learning that constrain the development of functional skills.

There are converging behavioural data that support the hypothesis that DCD may be underlain by a deficit in predictive control; this refers to the ability to internally model movements using feed forward control (see Wilson, 2005). An important component of

this is the ability to represent movements accurately at the neural level, as this helps predict the appropriate action to achieve a given goal. Typically, this is measured using motor imagery, which refers to the ability to imagine movements from an internal perspective, without any overt movement occurring (Crammond, 1997). Motor imagery has been shown to be constrained by the same biomechanical (e.g. Kosslyn, Digirolamo, Thompson, & Alpert, 1998; Parsons, 1987) and timing (e.g. Choudhury, 2007; Sirigu et al., 1996) constraints as an actual movement in healthy individuals. It has been repeatedly shown that this is not the case in DCD (Deconinck, Spitaels, Fias, & Lenoir, 2009; Gabbard, Cacola, & Bobbio, 2011; Lewis, Vance, Maruff, Wilson, & Cairney, 2008; Maruff, Wilson, Trebilcock, & Currie, 1999; Williams, Omizzolo, Galea, & Vance, 2013; Williams, Thomas, Maruff, Butson, & Wilson, 2006; Williams, Thomas, Maruff, & Wilson, 2008; Wilson et al., 2004; Wilson, Maruff, Ives, & Currie, 2001). Using the hand rotation task, which requires a laterality judgement of stimulus hands rotated around the frontal plane, it has been demonstrated that children with DCD are typically slower and/or less accurate to respond than their typically developing peers (Deconinck et al., 2009; Williams et al., 2011; Williams et al., 2013; Williams et al., 2006; Williams et al., 2008; Wilson et al., 2004).

Interestingly, the pattern has been seen in the performance of by individuals with DCD across different tasks (motor imagery, double-step saccades and covert orienting) is quite similar to the pattern that seen in patients with posterior parietal damage (e.g. Sirigu et al., 1996). This finding supports the theories that suggesting parietal lobe might be one of the main regions affected in individuals with DCD. One of the few fMRI studies of DCD which was conducted by (Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009). has shown a decrease in neural activation in parietal cortex during the performance of a motor sequencing task (Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009). Atypical activation in the parietal lobe, along with the frontal and temporal lobes, was also recently reported in a further DCD study, though on this trail-tracing task, the DCD group showed a significantly increased BOLD signal in these regions compared to controls (Zwicker, Missiuna, Harris, & Boyd, 2010). The cerebellum has also been posited to play a role in the forward internal modelling of movement (Kawato, 1999; Wolpert, Miall, & Kawato, 1998). In a recent fMRI study utilising a predictive motor timing task, Debraban, Gheysen, Caeyenberghs, Van Waelvelde and Vingerhoets (2013) compared neural activation in DCD and typically developing groups. They reported that while the control group, like adults, showed increased activation in the

dorsolateral prefrontal cortex (DLPC), left posterior cerebellum and the right temporo-parietal junction when responding to a variable inter-stimulus interval compared to a constant, predictable interval, the DCD group did not, resulting in significant group differences. In addition, Zwicker, Missiuna, Harris and Boyd, (2011) reported under-activation in the cerebellar–parietal and cerebellar–prefrontal networks in children with DCD during a motor learning activity. Taken together, the findings suggest that DCD likely stems from dysfunction across more than one brain region (Peters et al., 2013) and that poor coupling between parietal and cerebellar networks may underlie the deficits in internal movement simulation, and thereby motor skill development, in DCD.

A number of adult studies have used variants of the hand rotation task to investigate motor imagery ability (de Lange, Hagoort, & Toni, 2005; de Lange, Helmich, & Toni, 2006; Kosslyn et al., 1998; Parsons, 1994; Sirigu & Duhamel, 2001; Williams, Pearce, Loporto, Morris, & Holmes, 2012). Similar to the mental rotation of objects, increasing response times are evident with increasing angles of rotation through to 180º. Significantly, responses are also affected by the awkwardness of the movement required to physically bring one's hand into alignment with the stimulus – for example, responses are slower and less accurate when a right hand is presented at 135º clockwise (physically more awkward posture) than at 135º counter-clockwise (physically more comfortable posture; de Lange et al., 2006; Williams et al., 2012). This reflection of biomechanical constraints in imagined movements is taken to indicate that the participant is engaging in the motor, and not visual, imagery. The engagement of motor imagery in the hand rotation task is supported by neuroimaging studies that have identified a considerable overlap during motor imagery in regions known to be involved in movement planning and execution (de Lange et al., 2005; de Lange et al., 2006; Kosslyn et al., 1998; Parsons et al., 1995). A recent meta-analysis of the neural networks engaged in motor imagery confirmed that for the hand rotation task, consistent activation was reported in the following regions: bilateral superior and left inferior parietal lobes, postcentral gyrus, cerebellum, right middle frontal gyrus and putamen (Hétu et al., 2013).

The broad aim of this study was to extend our finding of motor imagery deficits in children with DCD to adults using both behavioural and functional neuroimaging techniques. To this end, we (i) analysed performance in an adult cohort with a history of ongoing motor skill impairment to ascertain whether deficits of this type remain associated with poor movement skill, suggesting a persistent delay in the ability to

represent movements internally, and (ii) used neuroimaging to determine whether adults with motor skill impairment (pDCD) show an atypical neural activation pattern during motor imagery. More specifically we aimed to (i) test at the behavioural level whether adults with pDCD could enlist motor imagery to solve the hand rotation task, taking into account the biomechanical constraints of the simulated action and, (ii) determine whether adults with pDCD show an atypical pattern of neural activation when performing tasks of motor imagery.

We predicted that at a behavioural level, adults with pDCD would display an atypical response pattern on measures of implicit motor imagery involving mental limb rotation when compared with adults without pDCD, and at a neural level, an atypical pattern of brain activation in motor pathways that support internal modelling and visual-motor coordinate transformation, specifically those involving posterior parietal cortex (PPC) and cerebellum.

Material and Methods

Participants

The current sample was composed of students and staff from local universities, aged 18-40 years (see Table 4.1). Brochures and emails were distributed asking individuals who felt that they were clumsy as a child and continue to feel clumsy to contact the researchers if they were interested in participating in the study. Adults who believed their motor skills were in the average range were also recruited through similar means. Participants were screened to exclude individuals with a diagnosis of Attention Deficit / Hyperactivity Disorder, intellectual disability, autism or Asperger's Syndrome, any physical or neurological condition that could cause motor skill impairment or with a history of neurological disease or head injury. Normal levels of cognitive and intellectual function were thus indicated, confirmed also by participants' adaptive occupational function in a tertiary education environment. Individuals suffering from claustrophobia or with magnetic or metallic materials within their body were also excluded.

Twenty-one adults with pDCD volunteered for the study and were included in the pDCD group if they indicated a developmental history of motor learning difficulties and

their score on the McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997) indicated the presence of motor impairment. This was defined here as a standard score ≤ 85 on either the total score or the fine or gross motor components. This cut-off is considered sensitive to motor skill issues in children and young adults (Tan, Parker, & Larkin, 2001). Twelve of the 21 volunteers were included on this basis. Fifteen adults volunteering for the control group were also screened using the MAND and were excluded if their standard scores were on or below 85 on the total, fine or gross motor components. Three adults were excluded on this basis and one further participant was excluded after data collection due to an error in the protocol.

2.2.1 The McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997). This standardised test of motor skill was used to confirm the status of adults in both the control and pDCD groups. The test includes five fine-motor and five gross-motor items. Scores for 10 tasks are summed to provide a standardised total score, termed the Neuromuscular Development Index (NDI; M= 100; SD = 15). Age-appropriate comparisons are therefore available for individuals aged between 3.5 to 18 years; the latter age is appropriate for referencing the performance of young adults. In addition, standard scores are also provided for fine and gross motor skills. This battery is often used to identify motor skill difficulties in children (Hyde & Wilson, 2011; Piek, Dawson, Smith, & Gasson, 2008; Williams et al., 2013) and young adults. The test-retest reliability of the MAND (over a 1-month period) ranges between .67 to .98 (McCarron, 1997). The MAND (McCarron, 1997), has high levels of specificity and sensitivity (Tan et al., 2001), and it appears to have current validity. Importantly, global performance scores (i.e., NDI) are considered a valid index of general motor competence (Hands et al., 2013), and are predictive of motor fitness (Hands et al., 2009).

Descriptive data including MAND fine and gross standard scores for the control group and adults with pDCD are presented in table 4.1.

Table 4.1. Group Descriptive Data and MAN scores for the Control and pDCD Groups.

	Control group	pDCD group	Test Result
N	11	12	
Male/Female	6/5	5/7	
% right handed	72.7	75.0	

Age (years) [a]	26.7 (5.5)	24.5(7.6)	t(21) = .0.8, p > .05
MAND Fine Motor SS [a]	105.1 (11.3)	82.7 (8.0)	t(21) = -5.5, p < .001
MAND Gross Motor SS [a]	98.5 (6.3)	86.2 (9.5)	t(21) = 3.6, p = .002
MAND Total SS [a]	99.0 (4.1)	84.7(4.8)	t(21) = 7.6, p < .001

Note: [a] Values reflect M (SD); SS = Standard Scores; pDCD:= Probable Developmental Coordination Disorder; MAND = McCarron Assessment of Neuromuscular Development.

Hand rotation task

We used E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) to produce the mental rotation task. Stimuli were projected onto a white screen. A mirror also was located in front of the participant's face on top of the head coil at the end of the scanner table so they could see the whole screen. Two button boxes were given to the participants and they were asked to keep the button boxes in their hands. They also were asked to respond by pressing the corresponding button, in each hand. Each participant was required to place their arms along their body with their elbows extended. They were also asked to remain still during the scanning process and not to move their hands. The stimulus images were pictures of left and right hands, presented so that the palm of the hand was facing participants (see Figure 4.1). Participants were provided with the following verbal instructions: "We're now going to start showing you the pictures of hands in different positions. We want you to try to imagine your hand in the position of the hand on the screen and decide whether the hand is a left or a right one. If it is a left hand, we want you to press the button in your left hand as quickly as you can. If it is a right hand, we want you to press the button in your right hand as quickly as you can". The stimuli were presented with the fingers pointing up (0° of rotation) or rotated in 20° increments between 40° and 160° in both clockwise and counter-clockwise directions. Stimuli were presented in blocks based on difficulty, presented at the greatest angle of rotation considered the most difficult. Four blocks were used – Baseline (0°), Easy (40-60°), Medium (80-120°) and Hard (140-160°). Within each block, stimulus presentation (left/right and at the various angles) was randomised through E-Prime, which recorded both response time and accuracy. Throughout scanning, participants responded to 15

baseline stimuli and 30 stimuli in each of the other three blocks (a total of 105 stimuli). To make sure participants are properly following the required task during the scanning, the participants' reactions to the stimuli were monitored. This was done by observing flashing lights on the response box during the task part of the scanning process. Each time the participant pressed the left or right button, the corresponding light flashed on the box. The participants' hand movements were also monitored visually to ensure there were no excessive movements during the scanning.

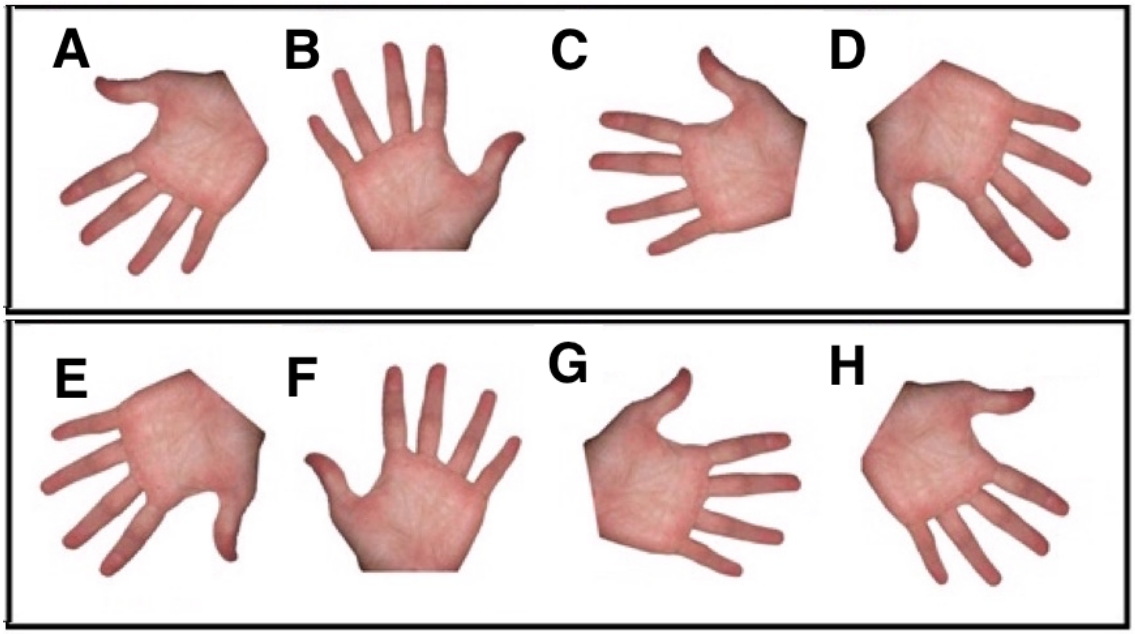


Figure 4. 1. Hand rotation stimuli showing views for (A-D) right hand: (A) rotated laterally 120°, (B) baseline 0°, (C) rotated medially 80°, and (D) right rotated laterally 140°.(E-H) Left hand: (E) rotated laterally 120°, (B) baseline 0°, (C) rotated medially 80°, and (D) right rotated medially 140°.

Procedure

All participants received an "Explanatory Statement" in which they could read comprehensive information on the research including reasons for the study, the method and techniques used and expected outcomes of the research. In the explanatory statement the term "incidental finding" was explained to participants, and they could nominate their medical professional to be contacted if the neuro-radiologist reported any incidental finding in their brain MRI scans. After having been apprised of the nature and details of the research all participants provided informed consent to participate in the

study. This study has been approved by the Human Research Ethics Committee at Monash University, Melbourne.

Participants were assessed using the MAND in a one-on-one setting and screened using an MRI safety checklist. The fMRI component of the study involved three scanning sequences conducted using a 3 Tesla MR scanner located at Monash Biomedical Imaging (Melbourne, Australia). The entire scanning protocol, in addition to functional runs, included structural T1 and T2 weighted images. Each functional sequence consisted of seven stimulus blocks (20 s each), with 20 s rest between blocks and a 12 sec blank screen lead in the period (total sequence time of 4 min 52 sec). The first block within each sequence consisted of baseline stimuli, with two blocks of easy, medium and hard stimuli making up the remaining six blocks (presented in a pseudo-randomised order, held consistent across participants). Within each block, five trials were completed, consisting of a 300 ms fixation (+ on a white screen), 100 ms blank screen, 3.5 sec stimulus presentation and 100 ms blank screen. Participants were provided with a minimum of 30 sec rest between scan sequences (see table 4.2).

Table 5.4.2 The rotation angle included in each category (easy, medium, hard) for mental rotation of hand task.

Rotation angle	0°	±40°	±60°	±80°	±100°	±120°	±140°	±160°
Stimulus category	Baseline	Easy		Medium			Hard	

Imaging data acquisition

The participant lay supine in the scanner and a 32 channel head coil was used to acquire high quality images. The participant's head was fixed in the coil using foam pads to reduce any motion. A foam pad was also placed under their knees for their comfort. The structural MR acquisition sequence parameters were as follows: A T1 sagittal orientated anatomical scan was initially acquired (TR = 1900 mesc, TE = 2.7 mesc, image matrix 320×320, 128 slices, slice thickness = 0.8 mm). Functional MR (gradient-echo echo-planar GE EPI)) images were recorded for 98 brain volumes using the following imaging parameters: TR = 3020 ms, TE = 30 ms, flip angle = 90°, FOV = 24 cm, matrix size 128×128, 36 transaxial slices, thickness = 4.0 mm, no gap. The first

two volumes were discarded to allow for T1 saturation effects. To assist with spatial normalisation a T2 weighted image was acquired in the same orientation as the echo planar images.

Data Analysis

Behavioural Data

For the hand task, anticipatory responses (less than 250 mesc!!) and those where participants failed to respond within the 2.5 s time limit were removed prior to analysis. Less than 1% of trials were removed. Mean response time (RT) and accuracy (proportion correct) were calculated for each participant at each angle of rotation. To determine whether groups conformed to biomechanical limitations of the task, we considered whether responses to hands rotated medially (left hands: 40-160°, right hands: 200-320°) were faster and more accurate than those rotated laterally (right hands: 40-160°, left hands: 200-320°). Mean response time (RT) and accuracy were calculated for each group in each direction, and at each degree of difficulty, and submitted to a 2 (direction; medial, lateral) × 3 (difficulty: easy, medium, hard) × 2 (group; pDCD, Control) repeated measures ANOVA. The multivariate approach was utilised to protect against violations of the assumption of sphericity and multivariate partial η^2 was calculated as a measure of effect size. Significant findings were followed up using pairwise comparisons of estimated marginal means with Bonferroni corrections.
To analyse RT and accuracy overall, data were analysed in each block (baseline, easy, medium and hard), regardless of the direction of rotation. Mean RT and accuracy were submitted to 4 (block) × 2 (group) repeated measures ANOVAs. The multivariate approach was used and significant findings were tested using pairwise comparisons of estimated marginal means.

fMRI data analysis

DICOM EPI files were converted to the ANALYZE format, and FSL software version 4.1.8 (FSL, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) was used for pre-processing steps and data analysis. Functional images were brain-extracted and corrected for head motion using FEAT version 5.98. Each participant's functional

images were normalised to the standard Montreal Neurological Institute (MNI) brain atlas. The registration process was performed in two stages. First, each participant's functional images were co-registered to the individual's high-resolution T1-weighted image, using FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson & Smith, 2001) with seven degrees of freedom (DOF) transformation. Then T1-weighted images were linearly registered to MNI space using a twelve DOF affine transformation. The combination matrix of these two transformation matrices was used to register each individual's functional images to MNI standard space. Every participant's registration process was visually inspected to exclude registration errors. The images were also spatially smoothed with a 5 mm FWHM Gaussian kernel, and high-pass temporal filtering (50Hz) was applied to remove low-frequency BOLD signal artefacts.
Three regresses were defined to rotation conditions including easy (50°), medium (100°) and hard (150°) were compared to the rest state. A statistical t-test map was achieved by using a linear contrast to examine parametric increases of activation with the angle of rotation. At the group level, a higher level group analysis method (Mumford & Nichols, 2006) was performed to calculate intra-group average and inter-group comparison. Significant activation for both within- and between-group analyses was defined using a voxel-level probability threshold (Z-score > 2.33) and a False Discovery Rate (P_{FDR} < 0.05) was used to correct for multiple comparisons.

Analysis of Percentage of change in BOLD signal

Responses induced by a hemodynamic change in oxygenation of brain tissue were analysed in regions with significantly higher activation in the controls compared with the pDCD group based on the factorial analysis. The brain statistical activation maps extracted were thresholded (Z-score > 3.0) and used as a mask to average mean BOLD signal response. The task-induced changes in the time courses of the BOLD signal were extracted from each subject using Peate software (http://www.jonaskaplan.com/peate/). One-time point (at t=-3 s) immediately before the presentation of the first stimulus at the beginning of each block was used as a baseline from which to calculate the change in the BOLD signal. Eight-time points measured from the start of each block of stimuli to one second after the finish of each active block (21 s) were selected for time course analysis.

Repeated-measures ANOVAs were performed to examine differences in the temporal characteristics of the hemodynamic response between the pDCD and control groups. The task-induced %BOLD signal change was investigated using three levels of the rotation angle and eight-time points repeated measures ANOVA as within-subject factors in control and pDCD group.

2.4.3 Conjunction analysis. A conjunction analysis was performed to determine the common areas of activation calculated from the parametric statistical maps for the control and pDCD groups, using a plug-in script for FSL (easythresh_conj.sh).

Functional connectivity analysis

Eight ROIs were selected for functional connectivity analysis. ROIs were chosen based on previously created maps of significant different between pDCD and control group. BOLD signal time course for each subject then was extracted using Featquery tool in FSL. Then mean BOLD signal for each group was exported to MATLAB software (version and pairwise correlation coefficient between time course vectors for each pair of ROIs was calculated for Controls and pDCD group

Results

Behavioural data

Repeated measures ANOVA to examine whether biomechanical constraints of real movement influenced response time identified a significant effect for stimulus difficulty [Wilks' $\Lambda = .30$, $F(2,20) = 22.86$, $p < .001$, $\eta_P^2 = .70$], and direction [Wilks' $\Lambda = .49$, $F(2,21) = 21.89$, $p < .001$, $\eta_P^2 = .51$] (see Figure 4.2). There was no effect of group, $p > .05$, and no significant interaction among the variables. The effects of difficulty and direction on accuracy showed a trend toward significance ($p = .064$ and .052 respectively), and there was no effect of group ($p = .19$). There were also no interactions among the variables.

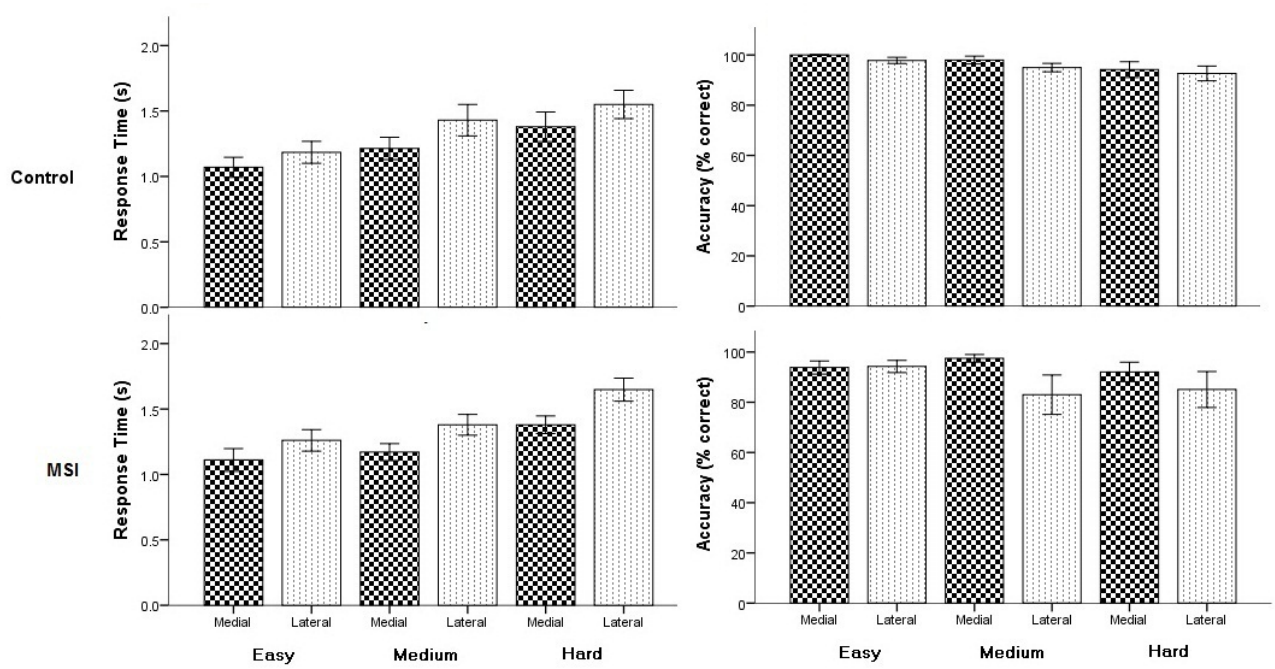


Figure 4. 2. Group means for response time and accuracy for hand stimuli presented in medial and lateral directions for easy, medium and hard angles of rotation.
Note: pDCD: probable Developmental Coordination Disorder; Significant effect for direction (medial vs. lateral) for response time, $p < .001$; Error bars represent 1SEM.

Figure 4.3 shows the overall RT and accuracy data for each group at each level of difficulty. Repeated measures ANOVA identified a significant effect for difficulty on response time [Wilks' $\Lambda = .25$, $F(3,19) = 19.00$, $p < .001$, $\eta_P^2 = .75$], but no effect for group or interaction among the variables (all $p > .05$). There was no effect of stimulus difficulty, group, or interaction (all $p > .05$) on accuracy.

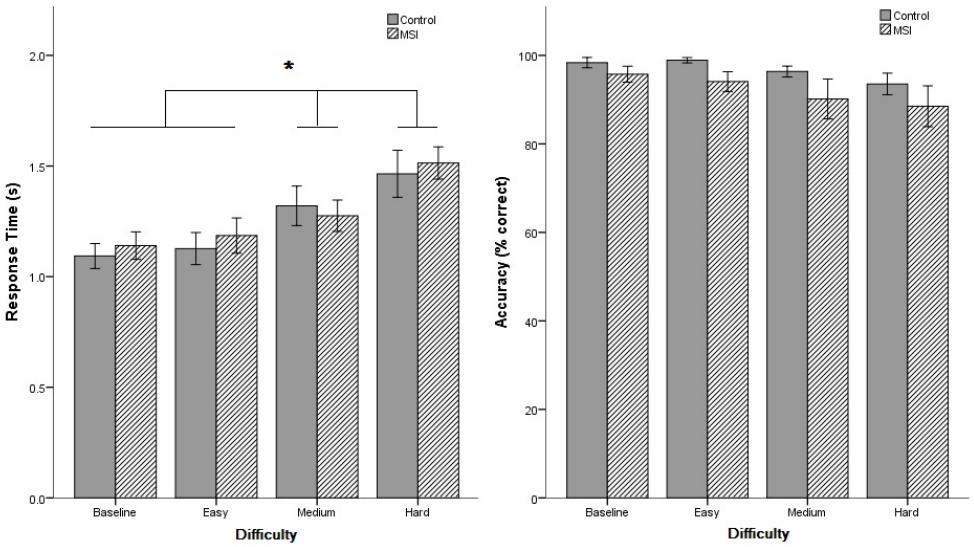


Figure 4. 3. Group means for response time and accuracy at the varying levels of response difficulty.

Note: pDCD: Probable Developmental Coordination Disorder; * p < .001; Error bars represent 1SEM.

fMRI Results

Analysis of statistical activation maps

Parametric analysis of the increasing angle of rotation with an increasing % BOLD signal difference using three conditions (50°, 100°, 150°), showed significant activation predominantly in occipito–parietal and parieto-frontal networks for both the control and pDCD groups (see Figure 4.4). However, the control group showed significantly higher activation in these networks compared with the pDCD group. In the control group, areas activated during the task included the bilateral middle frontal gyrus (MFG), bilateral superior frontal gyrus (SFG), bilateral inferior (IPL) and superior parietal lobules (SPL), bilateral anterior intra parietal sulcus (IPS), cingulate gyrus, bilateral lingual gyrus and cuneus in the occipital lobe, bilateral posterior lobe of the cerebellum and the right insula (Figures 4.4 and 4.6). In the pDCD group, activated areas included the bilateral SPL and the right MFG (Figure 4.5 and 4.6) Mean activation map showing parametric increases of activation with the angle of rotation in controls group

Comparisons between the groups demonstrated that the control group showed significantly greater activation than the pDCD group mainly in the left MFG, right MFG, left SPL and lobule VI of the cerebellum (see Figures 4.7 and 4.8). Table 4.2 shows the coordinates of the peak voxel Z-scores in regions that show significantly higher activation with increasing angle of rotation in the control group compared with the pDCD group.

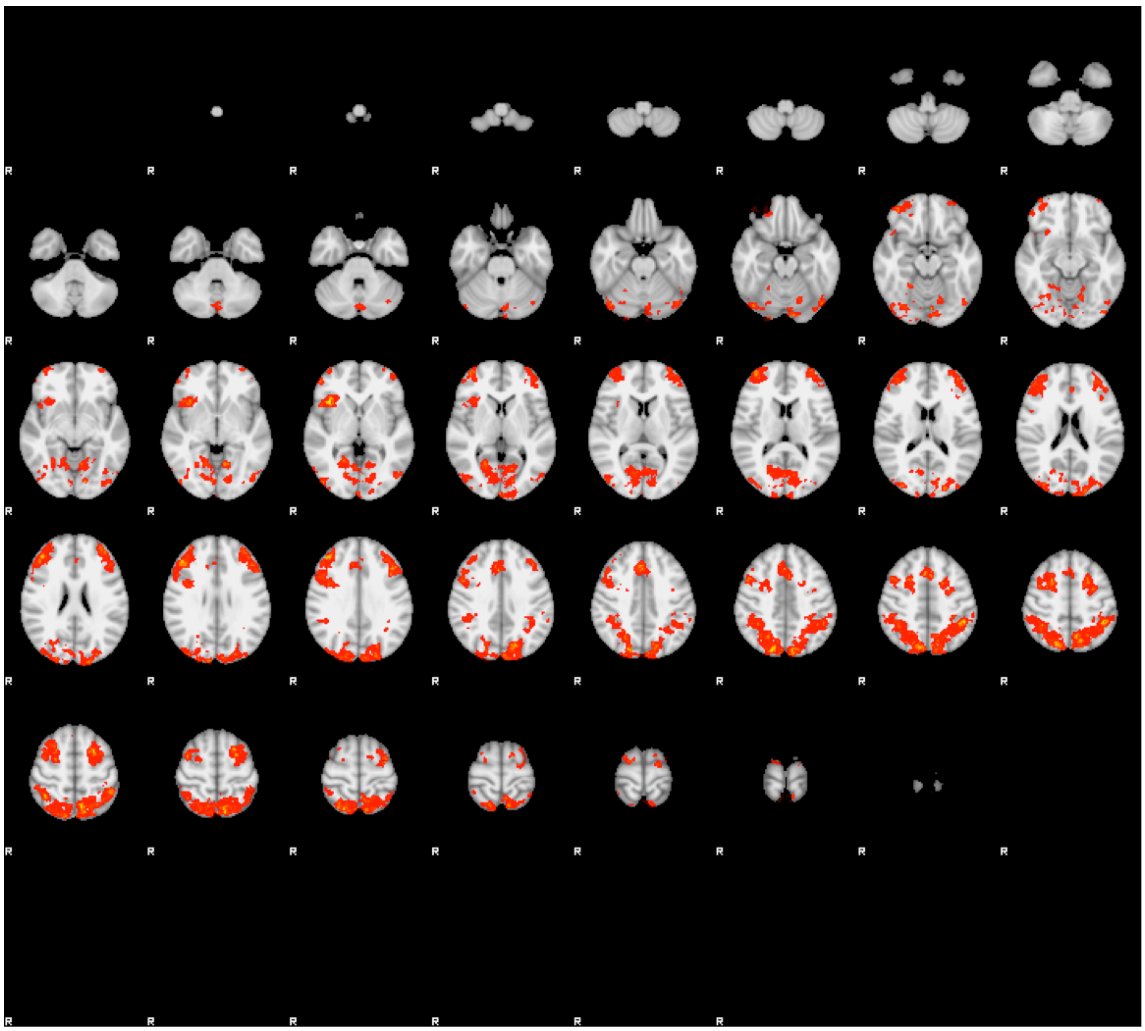


Figure 4. 4. Mean activation map showing parametric increases of activation with the angle of rotation in control group

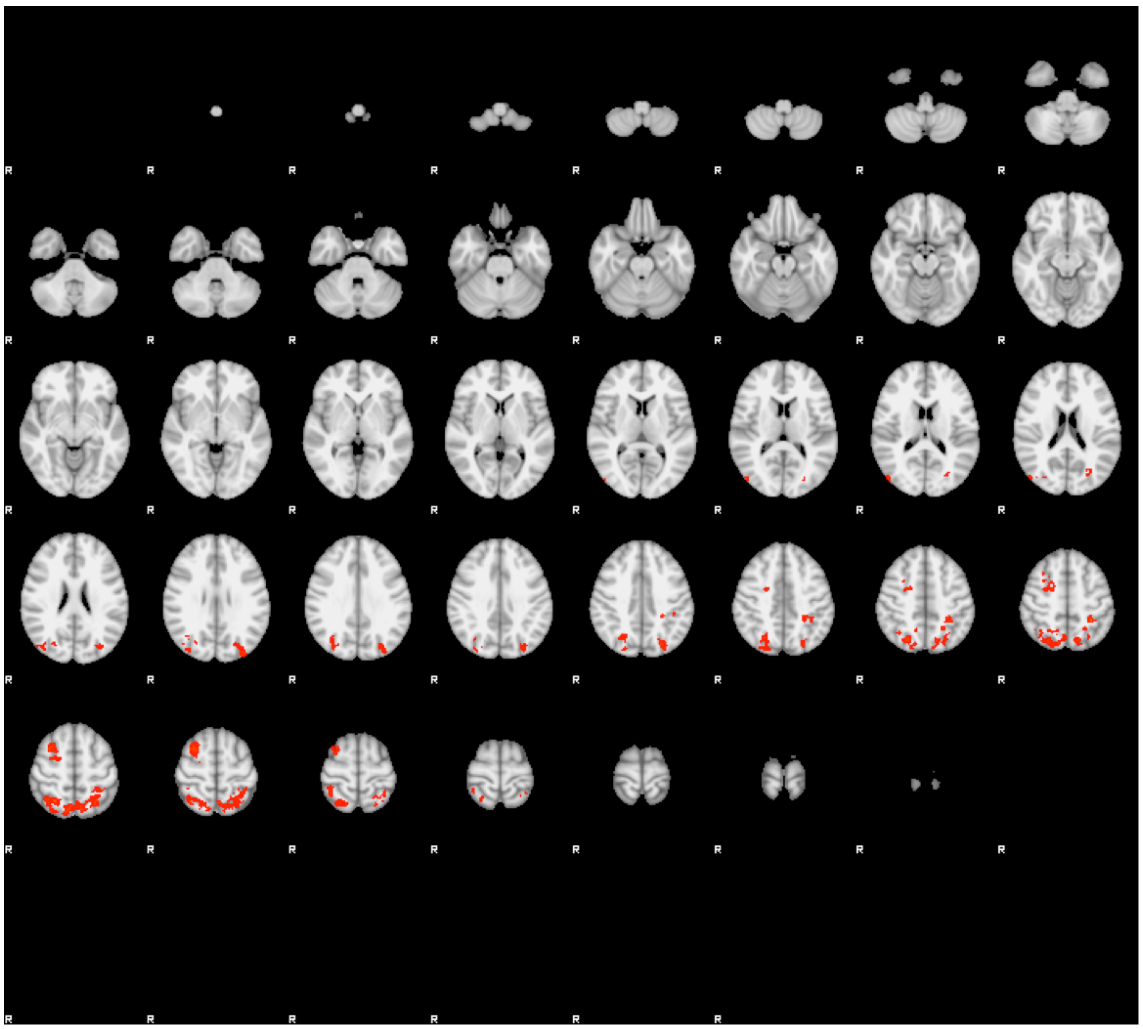


Figure 4. 5. Mean activation map showing parametric increases of activation with the angle of rotation in the pDCD group.

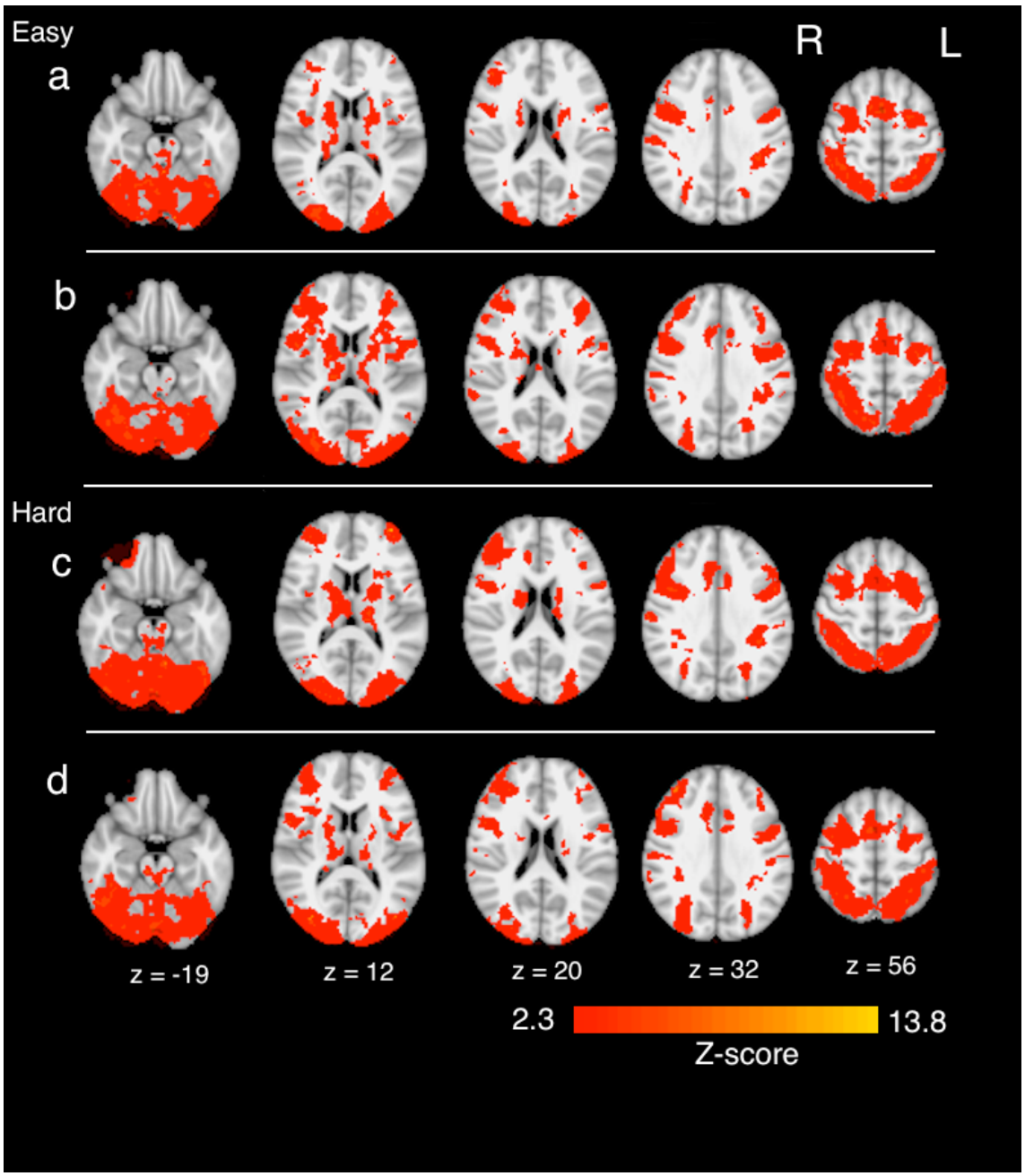


Figure 4. 6. Mean activation map showing activation in easy and hard rotation angles for the control group (a, c) and pDCD group (b, d).

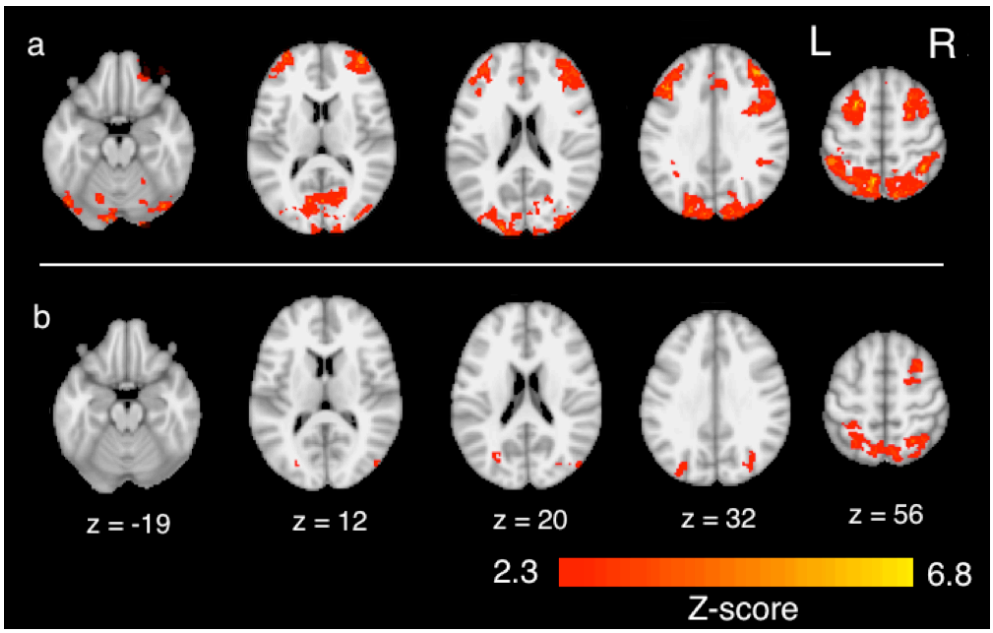


Figure 4.7. Mean activation map showing parametric increases of activation with the angle of rotation in (a) controls and (b) pDCD group.

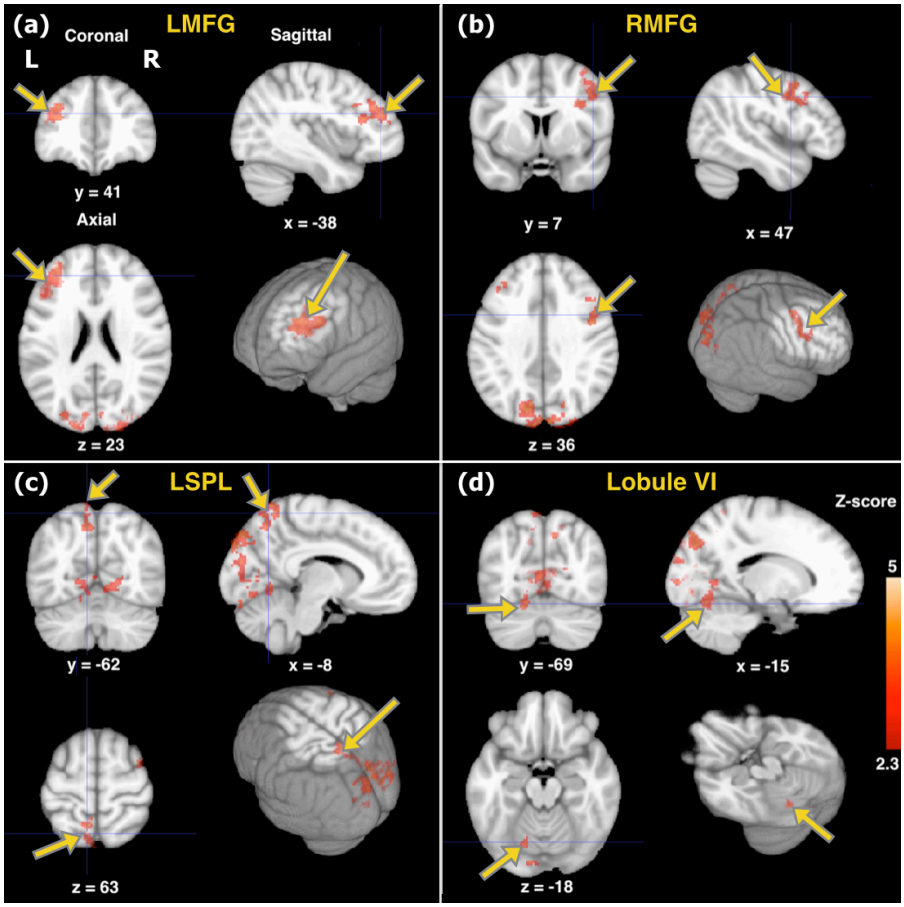


Figure 4.8. Regions where parametric increases of activation with the angle of rotation were significantly higher in the control group compared with the pDCD group: (a) left middle frontal gyrus, (b): right middle frontal gyrus, (c) left superior parietal lobe and (d) cerebellum, lobule VI.

Table 4.2. Regions Showing Significantly Higher Activation with Increasing Angle of Rotation in Control Group Compared with the pDCD Group.

Anatomical Location	BA	Co-ordinate (x,y,z)	Z-Score
L superior parietal lobule	7	-12,-52,66	4.04
R middle frontal gyrus	6	38,2,60	3.81
L middle frontal gyrus	9	-40,18,30	3.9
R occipital lobe, Cuneus	19	18,-88,32	4.38
L occipital lobe, Cuneus	19	-12,-80,36	3.89
Left Cerebellum lobule VI	_	36,22,0	3.40

Note: Coordinates of the peak voxel are expressed in stereotaxic x, y and z axes (Talairach Daemon Atlas and Cerebellar Atlas in MNI152 Space in FSL). BA= Brodmann Area; R: right hemisphere; L: left hemisphere

The task-induced change in the %BOLD signal for each group in the three conditions (easy, medium, hard) is shown in Figures 4.9-4.13. Analysis of task-induced change in the %BOLD signal showed a significant main effect of time [Wilks' $\Lambda = 0.07$, $F(7,15) = 30.43$, $\eta_P^2 = 0.93$, $p < .001$], reflecting the expected signal change over the recording interval. Rotation angle was also significant [Wilks' $\Lambda = 0.67$, $F(2,20) = 5.72$, $\eta_P^2 = 0.36$, $p < .05$]. However, there were no significant differences among groups ($p = .13$) and no significant interaction effects (each $p > .05$). Results of the conjunction analysis were mapped for both groups and can be seen in Figure 4.14.

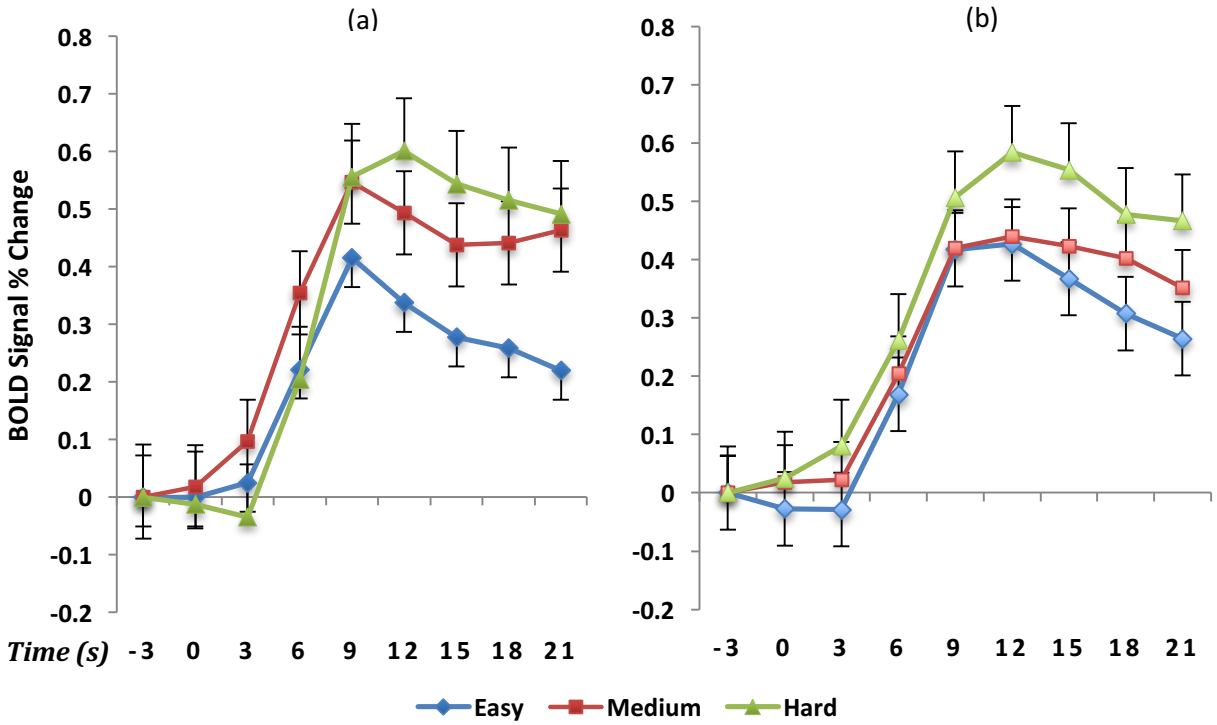


Figure 4.9. Mean task-induced change in the %BOLD signal during active blocks in all regions of interest identified by activation maps extracted from a comparison of pDCD group with controls and show the %BOLD response for the three conditions (easy, medium, hard) in (a) control group and (b) pDCD group.

Note: Error bars represent 1SEM.

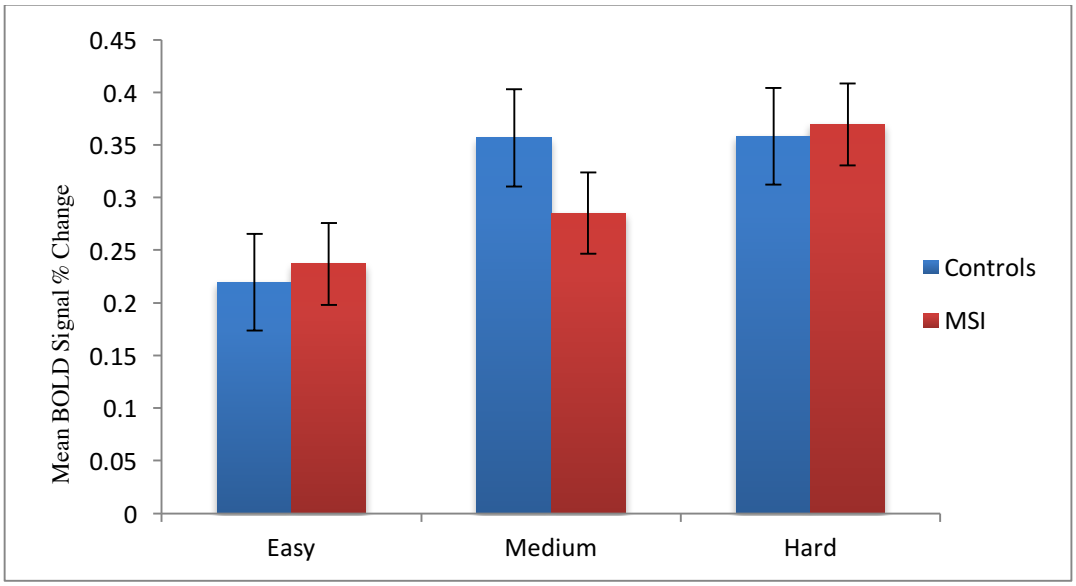


Figure 4.10. Average % BOLD signal change during task activation in ROI for three conditions for the control and pDCD groups. Note: Error bars represent 1SEM.

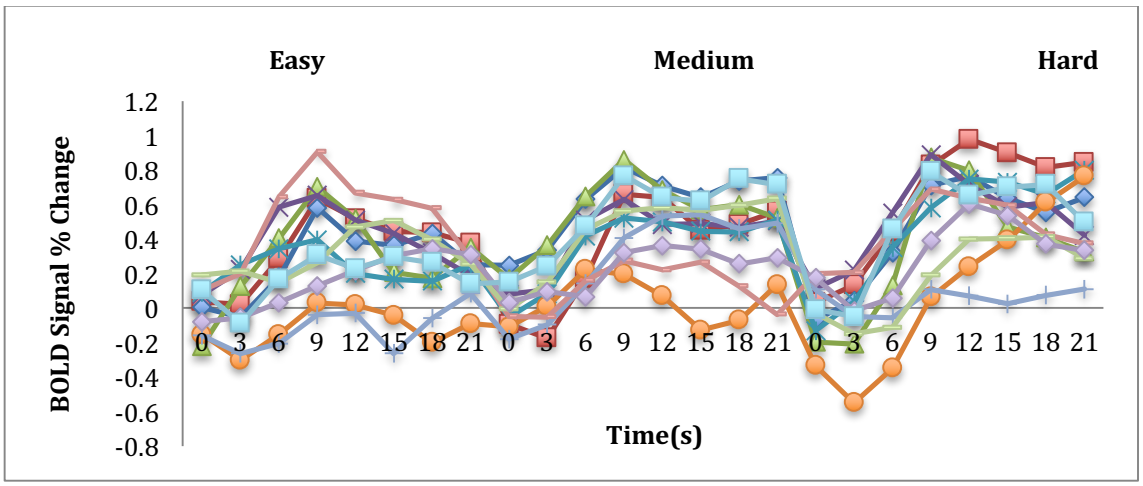


Figure 4.11. Time course of task-induced %BOLD signal change in control group

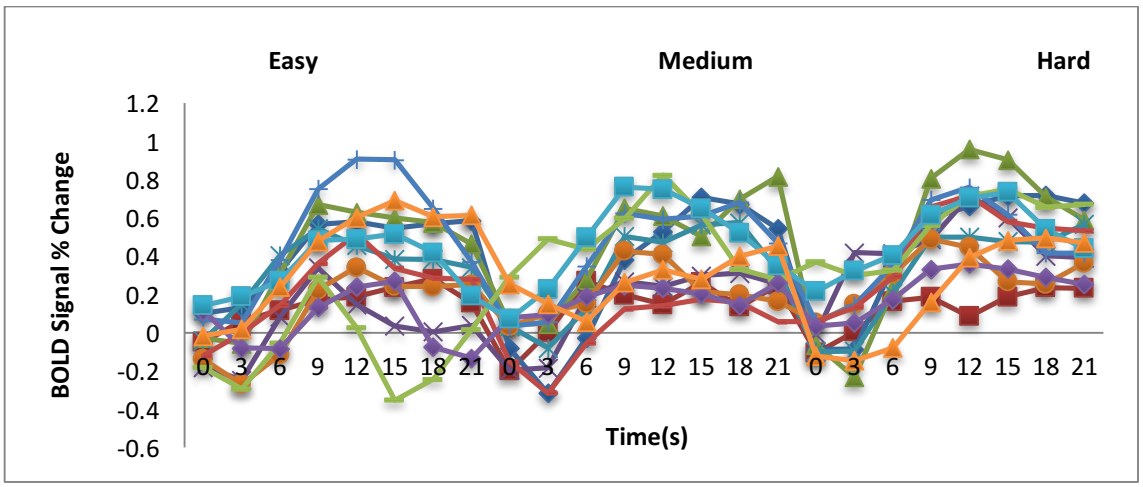


Figure 4.12.Time course of task-induced %BOLD signal change in pDCD group.

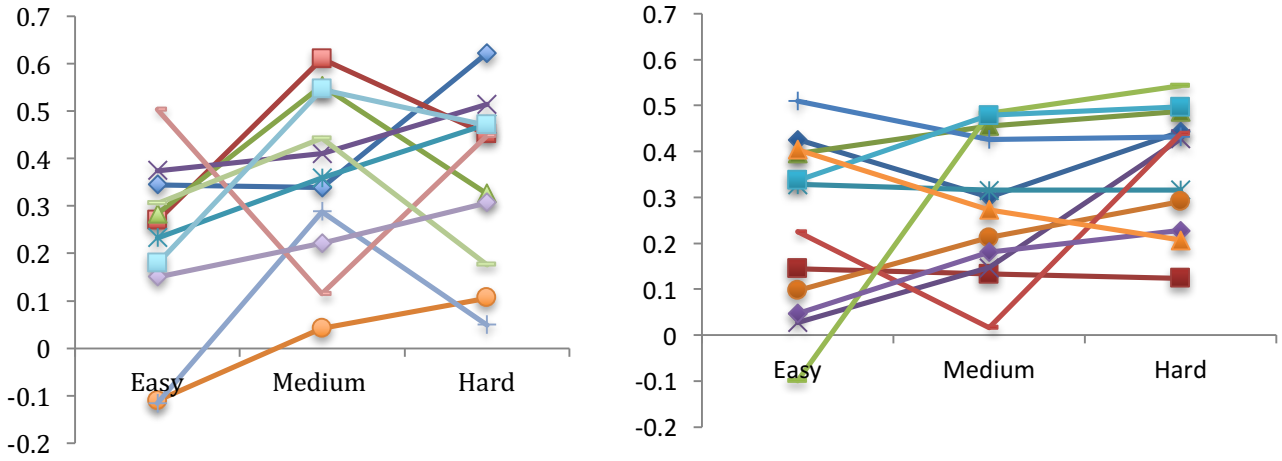


Figure 4.13. Mean BOLD % change in controls (right) and pDCD (left).

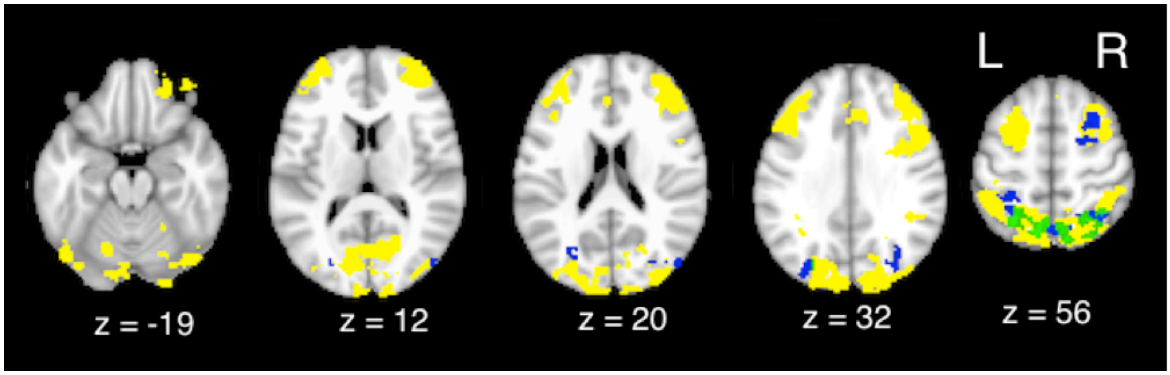


Figure 4.14. Parametric increases of activation with the angle of rotation in controls (yellow), pDCD (blue) and common area of activation (green) using conjunction analysis in both groups ($Z = 2.33$, $P_{FDR} < 0.05$).

Functional connectivity analysis:

The final results of functional connectivity analysis for pDCD and control group are presented as colour maps showing R-values as different colours.

Table 4.3 shows P-value for correlation analysis of BOLD signal time series between ROIs in the control and pDCD groups.

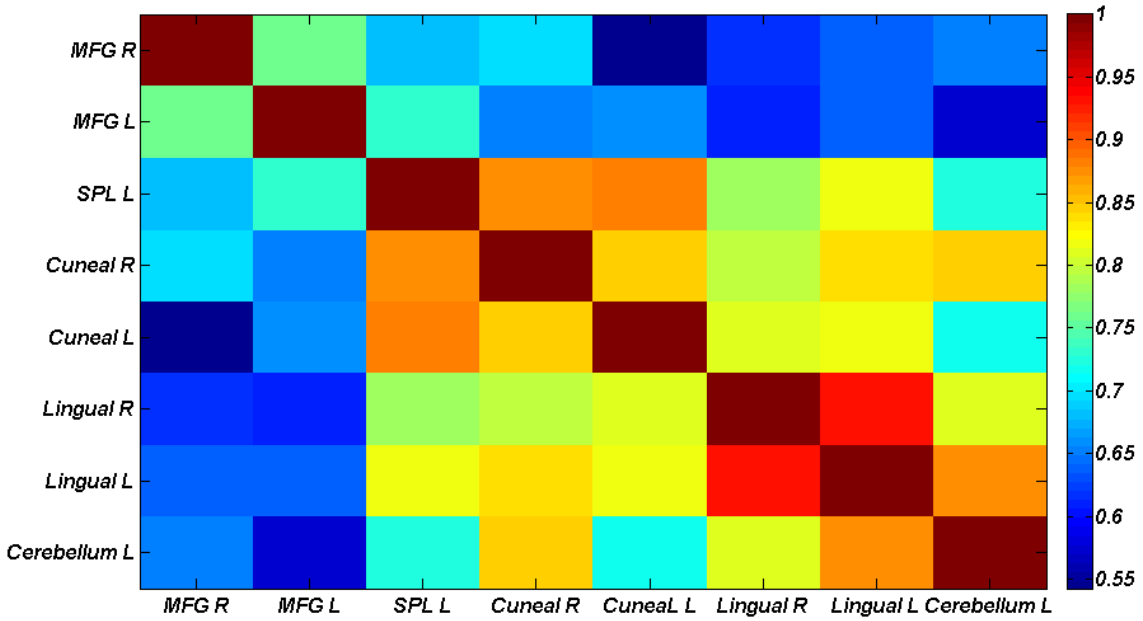


Figure 4. 15. Correlation matrix between BOLD signal time series in ROIs in control group.

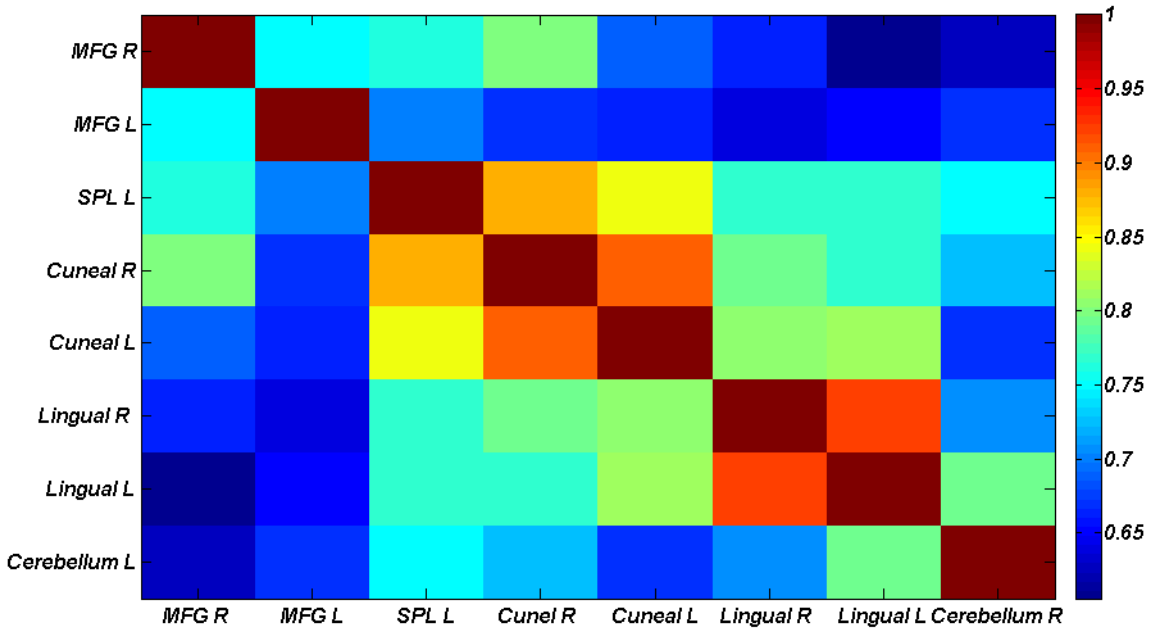


Figure 4.16. Correlation matrix between BOLD signal time series in ROIs in pDCD group.

Table 4.3 P-values for correlation matrix of BOLD signal time series for each region of interest in controls and pDCD group.

				Controls				
	MFG R	MFG L	SPL L	Cuneal R	Cuneal L	Lingual R	Lingual L	Cerebellum L
MFG R	1	0.76	0.68	0.7	0.54	0.61	0.64	0.65
MFG L	0.76	1	0.73	0.65	0.66	0.61	0.64	0.58
SPL L	0.68	0.73	1	0.87	0.88	0.78	0.82	0.73
Cuneal R	0.7	0.65	0.87	1	0.84	0.8	0.84	0.84
Cuneal L	0.54	0.66	0.88	0.84	1	0.81	0.82	0.72
Lingual R	0.61	0.61	0.78	0.8	0.81	1	0.93	0.81
Lingual L	0.64	0.64	0.82	0.84	0.82	0.93	1	0.88
Cerebellum L	0.65	0.58	0.73	0.84	0.72	0.81	0.88	1
				pDCD				
	MFG R	MFG L	SPL L	Cuneal R	Cuneal L	Lingual R	Lingual L	Cerebellum L
MFG R	1	0.75	0.76	0.8	0.69	0.67	0.6	0.63
MFG L	0.75	1	0.7	0.67	0.67	0.64	0.65	0.67
SPL L	0.76	0.7	1	0.88	0.84	0.77	0.77	0.75
Cuneal R	0.8	0.67	0.88	1	0.91	0.79	0.77	0.72
Cuneal L	0.69	0.67	0.84	0.91	1	0.81	0.81	0.67
Lingual R	0.67	0.64	0.77	0.79	0.81	1	0.92	0.71
Lingual L	0.6	0.65	0.77	0.77	0.81	0.92	1	0.79
Cerebellum L	0.63	0.67	0.75	0.72	0.67	0.71	0.79	1

Discussion

The aim of the study presented here was to determine whether adults with pDCD demonstrate a reduced ability to perform implicit motor imagery, which involves representing movements from an internal (or embodied) perspective, and whether an atypical pattern of neural activation is manifest during imagery performance. Behavioural data showed a similar pattern of performance among groups. For both pDCD and control groups, the biomechanical constraints that normally govern the performance of real movements were also shown to apply to the imagined transformation of limb stimuli; there was a significant increase in response time for laterally-rotated compared with medially-rotated stimuli. Similar results were reported in a recent study by Hyde et al. (2014). Response times also increased in line with stimulus difficulty for both the control and pDCD groups, while no effects were observed on accuracy. Parametric analysis of stimulus difficulty (angle of rotation) with BOLD signal increases showed activation in the occipito–parietal and parieto-frontal networks for both the control and pDCD groups, but, importantly, significantly reduced activation in these networks in the pDCD group.

Contrary to predictions, we failed to show an atypical performance pattern on a motor imagery task in the pDCD group. Studies of children with DCD have typically shown

slower and less accurate responses on mental (limb) rotation (Williams et al., 2013; Williams et al., 2006; Williams et al., 2008; Wilson et al., 2004). Like the study of probable DCD (pDCD) in adults by Hyde et al, (2014), our results showed that both impaired and unimpaired groups engaged in motor imagery to solve the task since responses conformed to the biomechanical constraints of real movements. While Hyde et al. (2013) reported reduced efficiency in the behavioural responses of adults with pDCD, our results suggest that the performance of adults with pDCD is relatively preserved for mental limb rotation. The disparity between studies may reflect the use of a slightly more impaired group in the study of Hyde et al., (2013) who screened for pDCD using a 10th percentile cut-off on the MAND plus high scores on the Adult Dyspraxia/DCD Checklist (ADC—Kirby et al., 2010). Taken together, however, the behavioural data do not show profound impairments in motor imagery in adults with motor difficulties, unlike children with DCD.

Figure 4.4 shows high levels of accuracy and little variability in the control group, indicating that many participants might have reached the ceiling level for the task. In contrast, accuracy was lower and more variable in the pDCD group. A task that demands more explicit control of imagery or one that uses a more complex configuration of limbs (Williams et al., 2006) may see this ceiling effect disappear and group differences emerge. This hypothesis remains to be tested.

Neuroimaging findings

The fMRI results demonstrated activation of both the occipito-parietal and parieto-frontal networks in both of our groups. Many of the areas activated are consistent with a recent meta-analysis of fMRI studies of motor imagery, in particular, those in the frontal and parietal regions (Hétu et al., 2013). Interestingly, our findings were more closely linked to those in the meta-analysis relating to explicitly imagined movements of the upper limb than to the findings relating specifically to upper limb judgement tasks such as the hand rotation task. A conjunction analyses study conducted by Hétu et al., (2013), demonstrated that both explicit motor imagery of the upper limb and limb judgement tasks resulted in consistent activation of the bilateral MFG and left IPL. There was consistently greater activation in the bilateral SMA and the left SMG in the explicit motor imagery than the limb judgement tasks and in contrast, consistently greater activation in the right SPL, MFG and postcentral gyrus during limb judgement

tasks when compared with explicit motor imagery of the upper limb. In addition, as in the current study, the explicit motor imagery of the upper limb activated the cingulate gyrus, anterior insula and lobule VI of the cerebellum (limb judgment tasks activated lobule VII of the cerebellum). The reason our results are more consistent with the explicit motor imagery tasks than the limb judgement tasks is likely due to our instruction set, which provided explicit instructions to "imagine your hand in the position of the hand on the screen". As pointed out in the review by Hétu et al., (2013), this type of instruction is rarely given in limb judgement tasks. It appears that the instruction has led to a more explicit motor imagery approach in the current study.

4.2 Brain regions involved in motor imagery

4.2.1 Posterior Parietal Cortex (PPC). Traditionally, neurophysiological findings have suggested that parietal regions, associated with perception and somatosensory transformations, play a pivotal role during spatial tasks like mental rotation (Deutsch, Bourbon, Papanicolaou, & Eisenberg, 1988; Ditunno & Mann, 1990; Mehta, Newcombe, & Damasio, 1987). Similarly, the importance of the PPC in motor imagery was highlighted by early studies demonstrating that patients with PPC damage do not perform motor imagery tasks as accurately as individuals without such damage (Sirigu & Duhamel, 2001; Sirigu et al., 1996). Further, disruption of the SPL during motor imagery via transcranial magnetic stimulation also results in reduced motor imagery performance (Fleming, Stinear, & Byblow, 2010). The role of the PPC in motor imagery is multi-faceted. It is responsible for coding the location of a body part and likely incorporates the somatosensory information on limb position into a motor plan (de Lange et al., 2005; de Lange et al., 2006). Hétu et al., (2013) also argue that the PPC, through its connections to other brain regions, plays a role in accessing the goal of a movement, preparation of simulated movements and ongoing updates to the representation of the limb whilst movement is being imagined.

Frontal region. The PPC is strongly connected to frontal areas of the brain and in particular, those in the supplementary motor (SMA) and premotor (PM) areas (Hétu et al., 2013) – both are reported to contribute to mental rotation of hand stimuli (Bonda, Petrides, Frey, & Evans, 1995; Parsons et al., 1995). In our study, activation of the Mfg. and SfG may reflect activation of the PM and SMA regions respectively. According to Hétu et al., (2013), motor imagery is likely to include a similar planning and

preparation phase prior to the movement simulation, in line with that required for overt movements to take place. However, this activation is not purely motor in origin, but reflects reciprocal activation between motor planning regions and the PPC, allowing the mapping of egocentric space to be incorporated into the simulated motor plan (Jackson & Husain, 1996; Jeannerod, 2006; Wise, di Pellegrino, & Boussaoud, 1996).

Cerebellum. The role of the cerebellum in motor imagery is not entirely clear. (Hétu et al., 2013) suggest that in the same way that motor execution requires integration of information not only from the networks thought to represent movement, but also those associated with those networks, such as the basal ganglia and cerebellum, so too does motor imagery. Decety (1996) also posited that motor imagery likely engages the full network of the motor system and that because of this, the cerebellar activity often recorded actually reflects an inhibitory mechanism, by which actual execution of the motor plan is prevented.

4.2.4 Occipital cortex. Interestingly, our results also demonstrated activation of the occipital cortex which was not reported by Hétu et al. (2013) to occur consistently during motor imagery. Although there was no evidence of consistent activation in the recent meta-analysis, previous studies have reported such activation and speculated on the role of occipital cortex. Thayer, Johnson, Corballis and Hamm (2001) showed, by EEG analysis, early occipital activation during the mental rotation of hands, reflecting stimulus recognition. Coupled with parietal activation, this allows the hand stimulus to be matched to the individual's own hand. Individuals with Parkinson's disease, for example, have shown increased activation through the occipto-parietal cortex during motor imagery of their affected hand (Helmich, de Lange, Bloem, & Toni, 2007), perhaps reflecting greater reliance on visual information during action planning.

Reduced neural activation in the pDCD group

Though there was some overlap in activated areas among groups, the pDCD group recorded significantly less activation in the PM (bilateral MfG), PPC (left SPL) and cerebellum (lobule VI). The reduced activation of these regions in the pDCD group concurs with an understanding of mechanisms that have been implicated in childhood DCD (Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2013). In a recent meta-analysis, showed converging evidence for poor predictive control in DCD, with possible links to the integrity of parieto-frontal and parieto-cerebellar networks.

Reduced activation in left SPL only in the pDCD group is also consistent with the crucial role of SPL in motor imagery (c.f. visual imagery), particularly that of the left hemisphere (Kosslyn et al., 1998). Disruptions of the parieto-frontal network would manifest behaviorally in poor movement planning, particularly when the integration of multisensory information is critical to performance. Further, disruption of parieto-cerebellar networks may compromise the use of incoming sensory input to update internal models of control being held within the cerebellum (Buneo & Andersen, 2012; Wolpert et al., 1998).

The current findings are in accord with some recent fMRI studies of DCD. Though not without limitations due to small sample sizes and non-comparable tasks (and no motor imagery studies), the studies have tended to show that DCD is unlikely to result from dysfunction of one neural region alone, but rather multiple regions and/or atypical functional connections between them. In these studies, atypical activation has been observed most commonly in the frontal and parietal areas (Debrabant et al., 2013; Kashiwagi et al., 2009; Querne et al., 2008; Zwicker et al., 2010, 2011), as well as some cerebellar regions (Debrabant et al., 2013; Zwicker et al., 2011). Importantly, like the current study, differences at a neural level are not always reflected in behavioural differences (Pangelinan, Hatfield, & Clark, 2013; Zwicker et al., 2010, 2011). One hypothesis is that individuals with DCD enlist compensatory strategies when performing simple motor and motor imagery tasks. These strategies are manifest by a different pattern of neural activation, while the behavioural outcome is preserved under relatively simple task constraints.

By comparison, using an overt sequential timing task, Debranant et al. (2013) have shown that poor predictive control in DCD was mirrored in a distinct pattern of neural activation compared with typically developing children. Controls showed higher activation in the left posterior cerebellum and the right temporo-parietal junction for trials that used non-predictive inter-stimulus intervals (compared with predictive). For DCD, there was no difference in the activation pattern for trials with predictive and non-predictive visual cuing, suggesting that they require more processing resources under conditions of predictive timing. Importantly, this study, like others cited above, also showed a more generalised pattern of hypoactivation in DCD in parieto-cerebellar and fronto-cerebellar networks. What are needed are additional neuroimaging studies that vary task constraints parametrically and/or utilise path modelling to examine inter-regional coupling. These approaches will enable a better understanding of neural

recruitment patterns in DCD as a function of motor, cognitive and perceptual load. For example, the effect of an inhibitory load on performance has been demonstrated in work by Querne et al. (2008); while children with DCD engage similar cortical regions to controls when performing a go-nogo task, coupling between prefrontal, anterior cingulate and inferior parietal cortex did not conform to a typical right hemispheric dominance for (inhibitory) attentional control. In addition to mapping the unique neurodynamics of atypical motor development, larger scale studies will provide a window to individual differences within and across age groups, and possible distinctions between DCD sub-types.

Limitations

The hand rotation task has been widely used to identify deficits in motor imagery ability in children with DCD on a number of occasions (Deconinck et al., 2009; Williams et al., 2013; Williams et al., 2006; Williams et al., 2008; Wilson, 2004), but this is the first study to use the task in adults with a similar form of motor skill impairment. In our study, the paradigm has enabled us to identify reduced patterns of neural activation in adults with pDCD. However, behavioural data suggested a ceiling effect on accuracy, despite a trend toward reduced accuracy in the pDCD group. A more complex task involving the explicit use of motor imagery, e.g. the visually-guided pointing task (Wilson et al., 2001), may be preferable in future studies, to investigate the effect of task and cognitive complexity on the pattern of neural recruitment.

Conclusions

In this study, we found that adults with pDCD were capable of engaging in motor imagery to solve the hand rotation task with no behavioural differences in response time and accuracy compared with control participants. Despite this, the adults with pDCD manifested an atypical pattern of neural activation when performing an implicit task of motor imagery. We conclude that the pattern of hypoactivation with respect to frontal, parietal, and cerebellar regions may reflect deficient coupling between zones in the service of action planning and the prospective control of movement. This is consistent with recent hypotheses proposed by Wilson and colleagues, (2013) based on a meta-analysis. These findings provide the motivation for a systematic evaluation using a

parametric experimental design incorporating motor and imagery tasks of varying complexity.

Chapter 5

White matter alterations in adults with probable Developmental Coordination Disorder

Introduction

Developmental Coordination Disorder (DCD) is defined as impairment of motor skills that significantly interferes with activities of daily living and/or education (DSM V). DCD affects 5-6% of children of school age (Blank, Smits-Engelsman, Polatajko, Wilson, & European Academy for Childhood, 2012). Although DCD is usually is diagnosed in early phases of development during childhood, the symptoms have been reported to persist into adulthood in up to 70% of cases (Blank et al., 2012). The aetiology of DCD and the exact neuromechanism behind the motor impairment in DCD remains ambiguous. However, recent studies in the field of cognitive neuroscience have suggested that neural dysfunction might play the essential role in producing sign and symptoms in individuals suffering from DCD. (Brown-Lum & Zwicker, 2015). Recent meta-analyses of behavioural data also suggest a distributed pattern of impairment across different aspects of motor and cognitive control in DCD (P H Wilson, Ruddock, Smits-Engelsman, Polatajko, & Blank, 2013). In the most recent studies, the main affected brain regions have been showed to include mainly the frontal and parietal lobes and the cerebellum (Brown-Lum & Zwicker, 2015). In a very recent structural connectivity study by Debrabant et al., (2016), significant positive correlations were observed between visual-motor behavioural scores and fractional anisotropy (FA) in the retro-lenticular limb of the internal capsule in a DCD group. Moreover, lower FA in sensorimotor tracts and altered structural connectivity were observed in children with DCD. Neuroimaging studies using Diffusion Tensor Imaging (DTI) have reported a reduction in white matter (WM) density, mainly in sensory-motor related pathways in

individuals with DCD (Debrabant et al., 2016; Langevin, MacMaster, Crawford, Lebel, & Dewey, 2014; Jill G. Zwicker, Missiuna, Harris, & Boyd, 2012). Although using a small sample, Zwicker et al., (2012) identified white matter paucity supported by a reduction in axial diffusivity in the corticospinal tract (CST) and posterior thalamic radiation in children suffering from DCD compared to a control group . Zwicker et al., (2012) also reported that there is a significant positive correlation between axial diffusivity values and the sensorimotor level of motor skill impairment in DCD group. In another study conducted in Canada, reduced fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF) and superior/parietal portion of the corpus callosum was reported in children with DCD (Langevin et al., 2014). Most recently, reduced FA was identified in the internal capsule (IC) of children with DCD (Debrabant et al., 2016). In summary, recent neuroimaging studies of DCD suggest there are persistent neurobiological alterations along WM tracts in the regions that are identified to be involved in motor planning, cognition and their association.

Aims and hypothesis

The above mentioned studies, have noted changes in white matter integrity in sensorimotor areas, in addition to potential dysfunction in the grey matter regions including fronto-parietal and cerebro-cerebellar networks, in subjects with DCD. This suggests that the disorder might result from microstructural abnormalities in the brain. Although the results from literature look very promising, it is important to bear in mind that the sample size in the studies involved in the current literature is quite small. Finding a perfect sample with considerable size for research could be challenging, particularly when studying a disorder such as DCD in which, the patients' sample is substantially heterogenic because of the nature of the disorder (J G Zwicker, Missiuna, & Boyd, 2009). Another issue in studying DCD is a lack of precision in the knowledge about the nature of DCD; because it is not clearly proven if microsturactural abnormalities in the brain white matter of individuals with DCD and resulting motor dysfunction is due to a maturational delay that is outgrown or persistent into adulthood. The current study aimed to explore the white matter integrity in adults suffered from motor skill impairment as children and continue to experience this impairment into adulthood, providing a more homogenous sample with persistent symptoms of DCD.

We expected to find structural abnormalities in white matter networks in adults with probable DCD (pDCD) along important pathways that are involved in motor planning, motor control and cognition.

Methods

Participants

This study was approved by Human Research Ethics Committee of Victoria University and Monash University. Participants with pDCD were individuals who responded to advertisements at local universities for adults aged 18-40 years who experienced motor skill difficulties presently and also during childhood. Childhood motor difficulties were confirmed via interview and the existing level of motor proficiency was assessed using the McCarron Assessment of Neuromuscular Development MAND (McCarron, 1997). Adults without motor impairment were recruited using similar means. They were also assessed using Adult Developmental Co-ordination Disorders/Dyspraxia Checklist (ADC) questionnaire and the McCarron Assessment of Neuromuscular Development (MAND) battery and were included in the study as control group if they met the criteria (As explained is the study reported in Chapters 4) The participants were excluded from the study if they diagnosed with any of the following conditions: Attention Deficit/Hyperactivity Disorder, autism or Asperger's Syndrome and intellectual disability, a history of neurological disease, head injury or any medical or neurological condition that could affect their motor skills, claustrophobia and having metallic objects installed within their body.

Of the 21 adults with possible motor impairment who volunteered for the study, 12 (6 males scored ≤ 85 on the MAND component or total scores. Of total 15 adults volunteering for the control group, three were excluded after scoring ≤85 on the MAND and one participant was excluded due to a technical error in the protocol after data collection, leaving eleven participants. Twelve adults with pDCD (5 male; age M = 24.5 yrs.) and 11 adults without pDCD (6 males; age M = 26.7 yrs.) participated in the study

Motor skill Measures

The MAND (McCarron, 1997) includes five fine- and five gross-motor items, summed to provide standardised component (fine- and gross-motor) and total standard scores (SS; all M= 100; SD = 15) and has been used to identify DCD in adult samples previously (Hyde et al., 2014). A score ≤ 85 on the total or scores for each component defines the motor impairment and was used to identify pDCD in adult volunteers. On the other hand, a score within the normal range (85-115) was determined inclusion criteria for selection of the control group.

Imaging data acquisition

As is the studies reported in Chapters 3 and 4 of this thesis participants lay supine in the scanner and a 32-channel head coil was used to acquire high quality images. Participants' heads were fixed using foam pads to reduce motion. The MR acquisition sequence parameters were as follows: DTI whole brain images were acquired using double spin echo diffusion weighted EPI sequence. The diffusion sensitising gradient encoding was applied in 64 independent directions with the b value of 2000 s/mm^2 (TR = 9900 ms, TE =100 ms, image matrix 128 ×128×128 slices, slice thickness = 2.2 mm). In addition, a DTI image was acquired with the same parameters and no gradient sensitising (b value = 0 s). An anatomical axial T1-weighted image was also acquired for registration purposes (TR = 1900, TE = 2.7 ms, image matrix 320 × 320, 128 slices, slice thickness = 0.8 mm).

Data Analysis

MRI data analysis

DICOM EPI files were converted to ANALYZE format to be readable by FSL software version 4.1.8 (FSL, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) that was used for pre-processing steps and data analysis. An FSL package, called FDT (FMRIB's Diffusion Toolbox), was used to analyse diffusion-weighted images and extracting eigenvectors and eigenvalues. First, a mask of the brain was created for each participant's row DTI data using the BET2 algorithm (Smith, 2002). Images were corrected for head motion and eddy current distortion. Finally, eigenvalues and

eigenvectors for each voxel were calculated to create FA, mean diffusivity (MD), and axial and radial diffusivity maps for each participant.

TBSS Analysis

A further FSL package, Tract-based Special Statistics (TBSS version 1.1) (Smith et al., 2006), was used for statistical analysis of DTI processed data. TBSS is a voxel-wise statistical analysis approach for improving the sensitivity, objectivity and interpretability of analysis of multi-subject DTI studies (Smith, 2002; Smith et al., 2006). TBSS was used to explore gross differences between major white matter tracts in the pDCD group and controls. To gain better quality images, the first step in the TBSS analysis was run. This step includes the pre-processing script to slightly erode FA images and remove likely outliers. The next step was to align and register all images to a standard space by applying a non-linear registration algorithm.

The default image provided by FSL package as standard-space FA image was used as the target to register all FA images. The registration was performed in one step and it was found to result in good alignment. The target images were then linearly registered to 1×1×1 mm^3 MNI152 space. This resolution was chosen for two reasons: (i) the later skeletonisation and projection processes perform better at this resolution, and (ii) for convenience of display and coordinate reporting. The non-linear registration of the FA images to the target and the affine registration of the target into the MNI space were combined and applied to each subject's FA images to bring them into the standard space. Each participant's brain image was visually inspected to verify the automatic registration process and control for any potential errors occurred during the process. The resulting standard space FA images were merged into a 4-dimensional image file, averaged to create a mean FA image. For statistical comparison purposes FA images were thinned and thresholded to produce a skeleton for voxel-wise cross subject statistical analysis. The threshold of 0.2 was applied on the mean FA skeleton to eliminate the majority of noises while maintaining the major white matter tracts. Finally, a distance map was created to skeletonise all FA images onto the mean FA skeleton to perform voxel-wise statistical analysis.

WM tracts then were determined using the JHU (John Hopkins University) tractography atlas and the International Consortium for Brain Mapping (ICBM DTI-81) WM labels atlas, both of which are installed as part of FSL. The Jueliech histological and Talairach

Daemon atlas' were also used for more accurate labelling. A region of interest (ROI) analysis was conducted by initially creating a 5mm radius sphere around the centre voxel that showed maximal (significant) differences in FA or MD values between groups in each region. Within each region a mask was then created based on the JHU tractography atlas. Finally, common areas between spheres and these standard masks were used as final regions of interest.

A Regions of interest (ROI) analysis was conducted on clusters showing significant differences in FA or MD values between groups. Group mean FA or MD values for each ROI were submitted to a 2 (group) × 4 (region) ANOVA in SPSS. The relationship between each ROI and motor skill level was explored by submitting each participant's mean FA or MD values for each ROI to a Pearson's correlation with the MAND NDI score.

Results

Whole brain white matter skeleton FA and MD values for the two groups were compared using voxel-wise, statistical comparison. FA values were compared between groups in three regions bilaterally (CST, SLF and IC: internal capsule) and MD values were compared in two regions bilaterally (IFL: inferior longitudinal fasciculus and IC). Of these, four clusters with significant differences between groups were identified. FA in the internal capsule did not differ significantly between the groups ($p > .05$). There were no significant differences between groups identified in any region for AD or RD (all $p > .05$). Results for repeated measures ANOVA of comparison of white matter integrity values between pDCD and controls as well as their MNI coordinates can be viewed in Figure 5.1.

All four regions were strongly correlated to the total standard score (SS) from the MAND. Lower FA values in the right CST and left SLF were linked to poorer motor ability, as were lower MD values in the left IC and right ILF. The charts showing of Pearson's correlation between MAND scores and WM integrity values for each ROI in shown in Figure 5.2.

Table 5.1. Demographic information, and diffusion parameters, and ANOVA results are shown in regions with significant difference in

	pDCD		**Control**		**P value**	**Correlation with NDI**		**MNI coordinates**		
	Mean	S.D.	Mean	S.D.		r	p	x	y	z
Age (years)	24.5	7.6	26.7	5.5	>.05	-	-	-	-	-
MAND Fine Motor SS	82.7	8.0	105.1	11.3	<.001	-	-	-	-	-
MAND Gross Motor SS	86.2	9.5	98.5	6.3	.002	-	-	-	-	-
MAND Total SS	84.7	4.8	99.0	4.1	<.001	-	-	-	-	-
FA Right corticospinal tract	0.47 (.02)	.02	0.53	.20	<.001	.71	<.001	19	-18	55
FA Left superior longitudinal fasciculus	0.42 (0.32)	.32	0.48	.02	<.001	.68	<.001	-38	-11	27
MD Left internal capsule	5.68e-4	.20e-4	5.99e-4	.13e-4	<.001	.56	.005	-21	12	9
MD Right inferior longitudinal fasciculus	6.30 e-4	.31e-4	6.70e-4	.16e-4	<.001	.56	.005	30	-74	3

Note: pDCD: probable DCD; MAND: McCarron Assessment of Neuromuscular Development; SS: Standard Scores; FA: fractional anisotropy; MD: mean diffusivity.

The FA and MD values for the whole brain white matter skeleton in pDCD group were compared using voxel-vise statistical comparison model. Final statistical images were thresholded using a p-value of .05 (Figures 5.1 and 5.2). These results informed the ROI analysis: FA values were explored between groups in three regions bilaterally (CST, SLF and IC: internal capsule) and MD values were explored in two regions bilaterally inferior longitudinal fasciculus (ILF) and IC). Of these, four clusters with significant differences between groups were identified (Table 5.1). FA in the internal capsule did not differ significantly between the groups ($p > .05$). There were no significant differences between groups identified in any region for axial or radial diffusivity (all $p > .05$).

All four regions were strongly correlated to the total SS from the MAND. Lower FA values in the right CST and left SLF were linked to poorer motor ability, as were lower MD values in the left IC and right ILF (Table 5.1; Figure 5.1).

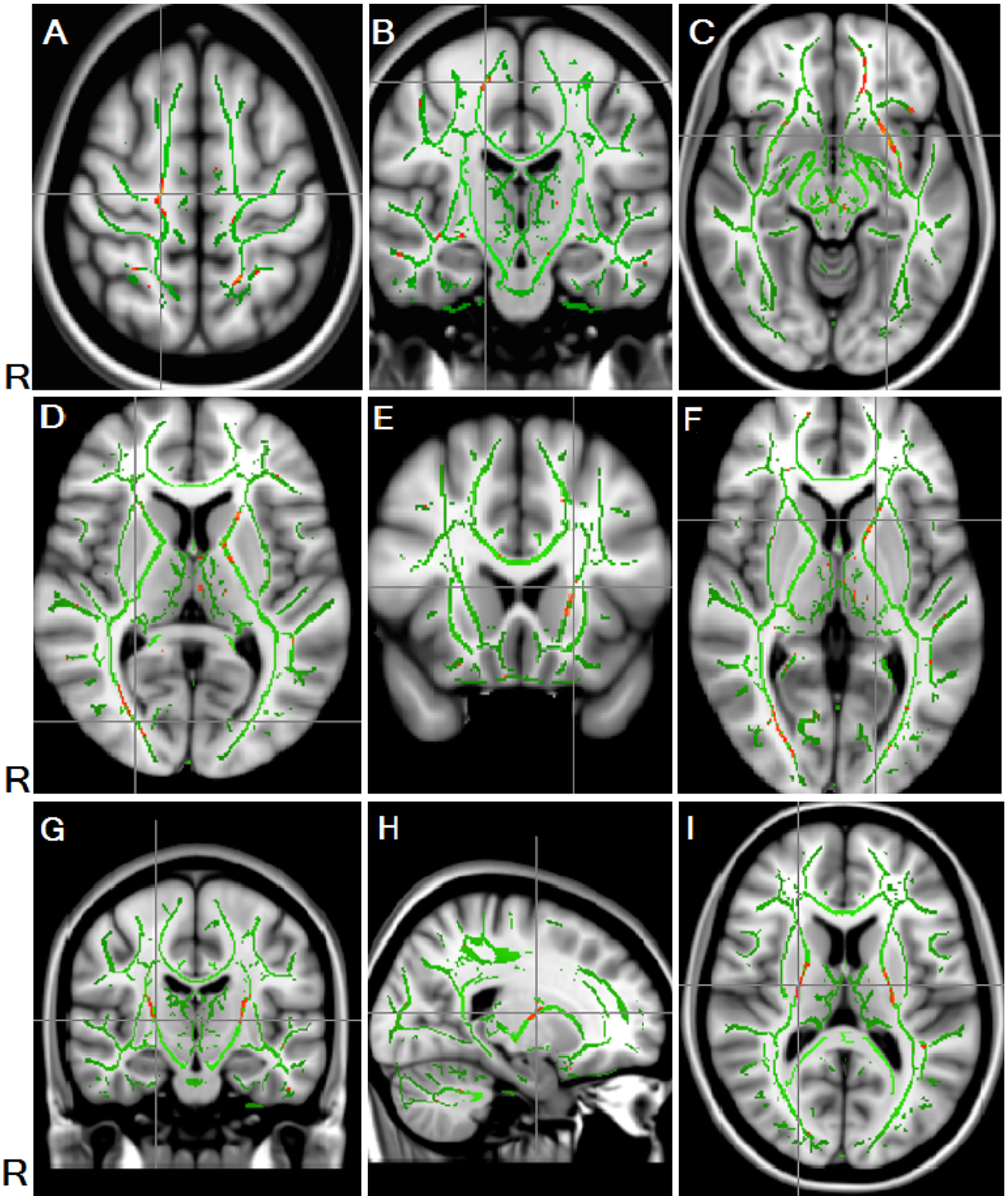


Figure 5.1. Areas with significant differences between groups in white matter density (green) using voxel wise comparisons. Red voxels show the regions with significant difference ($p < .05$). Lower fractional anisotropic values in pDCD compared with controls in the superior left corticospinal tract (a, b) and left superior longitudinal fasciculus (c); Lower mean diffusivity values in pDCD compared with controls in the right inferior longitudinal fasciculus (d) and anterior limb of internal capsule (e, f) and; Higher FA values in pDCD compared with controls in the posterior limb of internal capsule (g-i).

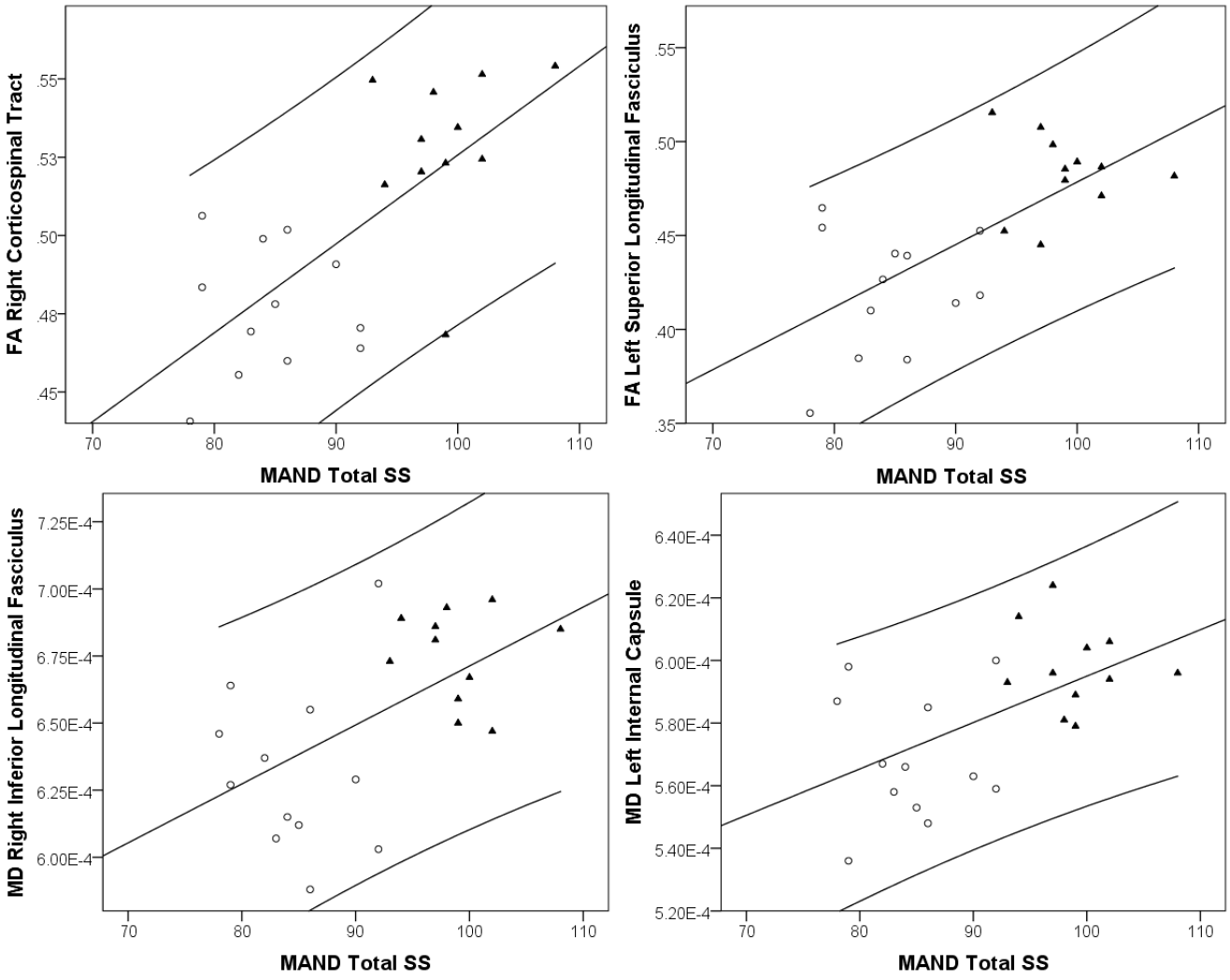


Figure 5.1. Correlations between white matter integrity and movement assessment scores. Key: open circles = pDCD; closed triangles = controls. FA: fractional

anisotropy; MD: mean diffusivity; MAND: McCarron Assessment of Neuromuscular Development; SS: Standard Score.

Limitations

A limitation of this study is the small sample size. Since DCD is generally diagnosed in childhood ages, screening and finding adults with DCD symptoms is a challenging task. a larger sample size would definitely improve the power of study and enables researchers to further investigate subtle alterations in neuroimaging aspects of DCD over time.

Discussion

This study identified changes in WM integrity in adults with pDCD along pathways important for motor planning, control and cognition. Some alterations, such as decreased FA in the SLF, are consistent with the previous research in DCD (Langevin et al., 2014), while our finding of decreased FA in the CST is in contrast to previous study conducted by Zwicker et al., (2012) reporting reduced MD in this tract. In addition, we showed a reduction in MD in the left IC and right ILF. Importantly, WM integrity was correlated highly with degree of motor skill impairment in these regions in our study. Reduced FA in the CST of the pDCD group in this study is in contrast to the results of study conducted by Zwicker et al., (2012) but it is consistent with studies conducted in other motor impaired populations (Caeyenberghs et al., 2011; Yoshida et al., 2010). In particular, reduced FA of the CST is one of the most reported WM tract abnormalities in cerebral palsy (Scheck, Boyd, & Rose, 2012). An alteration to the CST in a disorder where motor impairment is the defining feature, as in DCD, is not surprising, but the difference between this study and that of Zwicker et al., (2012) who propose that involvement of WM CST WM and level of contribution in motor impairment observed in DCD requires further examination. Whilst changes in the axonal make-up and/or myelination within the CST may contribute to the motor execution problems of children with DCD, it is likely that further alterations within the cortex also play a role. At a behavioral level, individuals with DCD have been shown to display deficits across a

range of higher order motor and cognitive functions, including motor planning, executive functioning and motor imagery (P H Wilson et al., 2013).

The finding of reduced FA in the parieto-frontal network is consistent with previous research in DCD (Langevin et al., 2014) and adolescents with very low birth weight displaying motor impairment similar to that of our pDCD group (Skranes et al., 2007). Atypical activation in regions connected by the SLF has also been identified using fMRI during visuo-motor and motor learning tasks (Kashiwagi et al., 2009; Jill G Zwicker, Missiuna, Harris, & Boyd, 2010; Jill G. Zwicker et al., 2011). At a behavioural level, individuals with DCD have repeatedly been shown to experience deficits in the ability to utilise predictive movement control and executive function (P H Wilson et al., 2013). Both of these, draw heavily on regions within the parieto-frontal network. SLF is a long fibre tract integral to reciprocal processing and inter-modal association across anterior-posterior cortical regions. Dysfunction in these regions would have important implications for attentional control, working memory (Vestergaard et al., 2010), action representation and movement planning. Together, these findings suggest that modifications of WM integrity within the SLF may highlight a number of deficits observed in DCD and have a critical role in motor impairment itself.

Alterations to WM within the left IC capsule in DCD was recently reported by Debrabant et al., (2016), in the form of reduced FA. Reduced FA in the IC has previously been linked with motor skill impairment, which includes preterm infants (Rose et al., 2007). Our findings confirm the role of the IC in motor control. Via the IC, the CST extends, carrying information from the primary and supplementary motor areas to lower motor regions (Sullivan, Zahr, Rohlfing, & Pfefferbaum, 2010). The posterior thalamic radiation also run through the IC (Cowan & de Vries, 2005), transmitting sensory information from the thalamus to the parietal lobe. Damage to this pathway has been shown to be related to reduction in sensory and motor function in children born preterm with cerebral palsy (Hoon Jr et al., 2009). Though we also identified alterations to WM within this region, our sample of adults with pDCD had significantly lower MD which typically indicates increased WM integrity (Soares, Marques, Alves, & Sousa, 2013). Therefore, our findings seem to conflict with what is expected to be observed in DCD. However, the findings of Debrabant et al., (2016) were specific to the retro-lenticular limb of the IC, whilst our comparisons suggest differences in the anterior limb (Figure 5.1 b-c).

Similarly, we identified lower MD within the ILF. The ILF connects the occipital and temporal lobes and is thought to represent the visual ventral stream (Ortibus et al., 2012). Recent research has also highlighted a significant overlap with the nearby inferior fronto-occipital fasciculus (Wahl et al., 2010) which suggests the ILF may also extend to frontal areas (Ashtari, 2012). Our finding here in relation to ILF is difficult to resolve in regard to often reported difficulties in DCD with processing visual perceptual information, whether or not a motor component is involved (P H Wilson & McKenzie, 1998). Interestingly, Zwicker et al., (2012) also showed reduced MD in some sensory-motor tracts in a small sample of children with DCD. One possibility is that the reduced WM integrity in the SLF of our pDCD group shows an impairment in visual dorsal, or 'vision for action', stream, as proposed by Milner and Goodale (Milner & Goodale, 2008). They suggest the dorsal stream is responsible for programming and controlling skilled movements, with damage to this pathway could result in various motor impairments. Despite the conventional view that claims the ventral tracts of the fronto-occipital pathway is responsible for object recognition (Milner & Goodale, 2008), more recent models suggest this pathway plays a supporting role in movement by its involvement in action planning phase of movement control (Milner & Goodale, 2008).We speculate that the increased WM integrity in the ILF and decreased WM integrity in the SLF in our pDCD group may reflect a compensatory mechanism whereby the ventral stream is required to play a more significant role in action planning due to impairment of the dorsal pathways. Our research is conflicted if individuals suffering from DCD (or dyspraxia) experience ventral pathway deficits (Grinter, Maybery, & Badcock, 2010), and further research in this area is required. Another explanation for our findings is that the increased WM density along selected tracts could be a compensatory mechanism for a more fundamental disruption of the parieto-frontal network. Because the superior pathways are compromised, inferior pathways may be enlisted to a greater degree to establish reciprocal connectivity to anterior (motor planning) regions. However, both hypotheses suggest that DCD may best be modelled using a network approach (instead of being perceived as a result of isolated dysfunction of specific grey matter regions or due to a global white matter/grey matter brain atrophy or hypo-activation in grey matter).

Conclusion

The results of this study suggest a disruption in white matter integrity, supported by reduction in fractional anisotropy (FA) in critical motor-related networks in adults with pDCD which are mainly observed in corticospinal tract and superior longitudinal fasciculus. There is also evidence of possible compensatory increases in white matter integrity along the ventral portions of fronto-occipital pathway, indicated by decreased mean diffusivity (MD) in the inferior longitudinal fasciculus (ILF). These results are consistent with behavioural data which shows a collection of motor deficits across motor planning, control and cognition in individuals suffering from DCD.

Chapter 6

Hypo-myelination of the superior cerebellar peduncle in individuals with Friedreich ataxia: an MRI magnetization transfer imaging study

Louise A Corben*[1,4], Saman Rassaei Kashuk*[2,3], Hamed Akhlaghi[2], Sharna Jamadar [2,4,] Martin B Delatycki [1,4,5], Joanne Fielding[4], Beth Johnson [2,4], Nellie Georgiou-Karistianis[4], Gary F Egan[2,4].

*Denotes equal first authors

[1] Bruce Lefroy Centre for Genetic Health Research, Murdoch Childrens Research Institute, Parkville 3052, Victoria, Australia

[2] Monash Biomedical Imaging, Monash University, Clayton 3800, Victoria, Australia

[3] School of Engineering and Science, Victoria University, Melbourne 8001, Victoria, Australia

[4] School of Psychology and Psychiatry, Monash University, Clayton 3800, Victoria, Australia

[5] Department of Clinical Genetics, Austin Health, Heidelberg 3084, Victoria, Australia

Abstract

The dentate nucleus (DN) is the major relay station for neural connection between the cerebellum and cortex, and is a significant component of the neuropathological profile of Friedreich ataxia (FRDA). We have previously shown that the size of the superior cerebellar peduncle (SCP), which links the DN to cortical and subcortical structures, is significantly reduced in individuals with FRDA compared to control participants. This study used magnetization transfer imaging (MTI) to examine and contrast the integrity of white matter (WM) in the SCP and the corpus callosum (CC) (control region) in ten individuals with FRDA and ten controls. Individuals with FRDA demonstrated a significant reduction in the magnetization transfer ratio (MTR) in the SCP compared to control participants. However, there was no significant difference between groups in MTR in the CC. When comparing regions within groups, there was a significant reduction in MTR in the SCP compared to CC in participants with FRDA only. We suggest that the reduction in MTR in the SCP may be indicative of hypo-myelination in WM tracts in individuals with FRDD

Introduction

Friedreich ataxia (FRDA) is the most common of the hereditary ataxias and is a complex multisystem autosomal recessive condition, characterized by progressive ataxia, spasticity, weakness, absent lower limb reflexes, impaired vibration sense and proprioception, scoliosis, foot deformity and cardiomyopathy. In 98% of cases, FRDA is due to homozygosity for an expansion of a GAA trinucleotide repeat in intron one of FXN (Campuzano et al., 1996). The remaining 2% are compound heterozygous for a GAA expansion and a point mutation or deletion in FXN (Voncken, Ioannou, & Delatycki, 2004). The GAA expansion in intron one of FXN leads to reduced levels of the encoded protein frataxin. Whilst the exact role of frataxin is still not fully understood, there is consensus that frataxin is a mitochondrial membrane protein involved in iron sulfur cluster synthesis and iron chaperone activity (Pandolfo & Pastore, 2009; Santos et al., 2010; Vaubel & Isaya, 2013).

The major sites of neuropathology in FRDA include the dorsal root ganglia (DRG) and posterior columns of the spinal cord, spinocerebellar tracts, corticospinal tracts and the dentate nucleus (DN) of the cerebellum (Koeppen, Davis, & Morral, 2011; Pandolfo, 2009). The DN is the major relay station for neural connections between the cerebellum and cortical areas (Kwon et al., 2011; Yamaguchi & Goto, 1997), via the superior cerebellar peduncle (SCP). Atrophy of the SCP in individuals with FRDA has been reported, and becomes more apparent in those individuals with earlier age of disease onset, greater disease severity and longer disease duration (Akhlaghi et al., 2011; Della Nave et al., 2008, 2011). However, the source of the reduction remains unclear (Akhlaghi et al., 2011).

Diffusion tensor imaging (DTI) has been widely used for in vivo investigation of micro-structural white matter (WM) changes, axonal degeneration and demyelination (Mori & Barker, 1999). A number of studies have mapped the extent of WM changes in individuals with FRDA using DTI (Della Nave et al., 2008; França et al., 2009; Pagani et al., 2010). In particular these studies have noted WM changes in the brainstem, bilateral SCP, cerebellar peri-dentate region, the optic chiasm and deep cerebral WM (Della Nave et al., 2008; França et al., 2009; Pagani et al., 2010). Disruption of WM tracts, linking the cerebellum to the cortex, may compromise cerebellar access to more distal structures critical to both motor and non-motor tasks. Indeed, a recent study reported disrupted cerebello-cerebral connectivity in several distant cortical and sub-cortical areas including the supplementary motor area, frontal cortices, putamen, pallidum, cingulate cortex and hippocampus in individuals with FRDA (Zalesky et al., 2013). Disruption to cerebello-cerebral connectivity may underlie the non-motor symptoms reported in individuals with FRDA and indicates that the neuropathology associated with FRDA has a far wider effect on neural networks than previously thought (Corben et al., 2010; Corben, Akhlaghi, et al., 2011; Corben, Georgiou-Karistianis, et al., 2011; Fielding et al., 2010; Klopper et al., 2011).

Magnetization transfer imaging (MTI) is a novel magnetic resonance imaging (MRI) technique that utilizes an off-resonance magnetization pulse in order to measure variation in the exchange of protons between free water and macromolecules (Wolff & Balaban, 1994). Neuropathological processes that result

in a reduction of macromolecular bound protons lead to a reduction in the magnetization transfer ratio (MTR) value. MTI changes in brain imaging studies, expressed as a reduction in MTR value, are indicative of changes in the degree of axonal myelination and this is thought to be a more specific measure of myelination status than provided by DTI techniques (Stanisz et al., 1999). Most of the published studies examining MTR values in the human brain have examined myelination in people with multiple sclerosis. These studies have investigated the demyelinating process of the disease and have established MTR is a sensitive biomarker for clinical trials (Dousset et al., 1992; Harrison et al., 2013). What remains elusive is an understanding of the pathological processes underlying WM changes in individuals with FRDA. MTI provides an important opportunity to semi-quantitatively examine myelination changes in major white matter tracts in vivo.

The aim of this study was to use MTI to examine the extent of myelination (characterized by the MTR value) in WM regions connecting cerebellum and cerebral structures. Given the previously documented reduction in size of the SCP, and the structural relevance of this region in terms of cerebro-cerebellar connectivity, we elected to examine the MTR values in the SCP and the CC in individuals with FRDA compared to control participants (Akhlaghi et al., 2011; Della Nave et al., 2011). Consistent with previous findings we hypothesized that individuals with FRDA would have reduced MTR in the SCP compared to control participants; however, there would be no difference in the MTR value in the CC between groups. In addition, we hypothesized that the degree of MTR reduction in the SCP would correlate with clinical measures of disease severity.

Methods

Participants

Ten right-handed individuals homozygous for a GAA expansion in intron one of FXN (6 males) with a mean age of 37.7 years (SD=11.2) participated in this study. An age and sex matched group of ten control participants (6 males) with no known neurological disorders and mean age of 38.2 years (SD=7.9) also participated.

There was no significant difference in age between the groups (f[1,18 = 0.013, p = 0.91). See Table 6.1 for clinical and demographic details of participants.

Table 6.1. Mean (M), standard deviation (SD) and range (R) of group characteristics and screening measures for participants with FRDA and Controls.

Group Characteristics	FRDA			Controls			p value
Male	6			6			-
Female	4			4			-
	M	SD	R	M	SD	R	
Age (y)	36.6	11.2	22-48	38.2	7.9	31-51	n/s
Age at Disease Onset (y)	20.1	7.6	8-34	-	-	-	-
Disease Duration (y)	16.5	7.1	6-25	-	-	-	-
GAA1	553	184	126-837	-	-	-	-
GAA2	339	216	462-1345	-	-	-	-
FARS Score	95	17.4	69-124	-	-	-	-
MTR SCP	4	1.9	46.5-52.6	54.9	2.6	51.8-60	p < 0.001
MTR CC	9.3	0.9					
ΔMTR	35	2.2	54.4-57.6	56.5	2	52.4-56.7	n/s

	5.7 6.4	3-9	1.6	.2 2.7	-3.2-5.4	p < 0.001

GAA1 = FXN GAA repeat size of the smaller allele; GAA2 = FXN GAA repeat size of the larger allele; FARS = Friedreich Ataxia Rating Scale; dashes indicate where descriptive were not applicable; MTR SCP = Magnetization Transfer Ratio, Superior Cerebellar Peduncle; MTR CC = Magnetization Transfer Ratio, Corpus Callosum; ΔMTR = difference between MTR in SCP and CC; n/s - not significant

Imaging data acquisition

MRI images were acquired using a 3 Tesla Siemens Skyra scanner (Siemens, Erlangen, Germany) at Monash Biomedical Imaging, Victoria, Australia. T2 weighted images were acquired using a 32 channel head coil (TE = 8.4ms, TR = 734ms, flip angle = 30°, voxel size = 0.9×0.9×3.3mm^3, FOV = 230x172.5mm^2, matrix size = 256×205, 46 slices). Images were acquired with and without saturation, using a magnetization transfer pulse placed before each slice-selective excitation.

MR Image Analysis

DICOM files were converted to ANALYZE format and processed using the FSL software tools (FSL version 4.1.8, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) for brain extraction, registration, mask creation and mean MTR calculation. To calculate MTR, the image acquired with the saturation pulse (MT image) was first linearly registered to the image without the saturation pulse (MT_0 image) using FMRIB's linear image registration tool (FLIRT) (M Jenkinson, Bannister, Brady, & Smith, 2002). The MTR for each voxel was calculated using the following formula: MTR = 100*(MT_0-MT)/MT_0 (Wolff & Balaban, 1994) (see Figure 6.1).

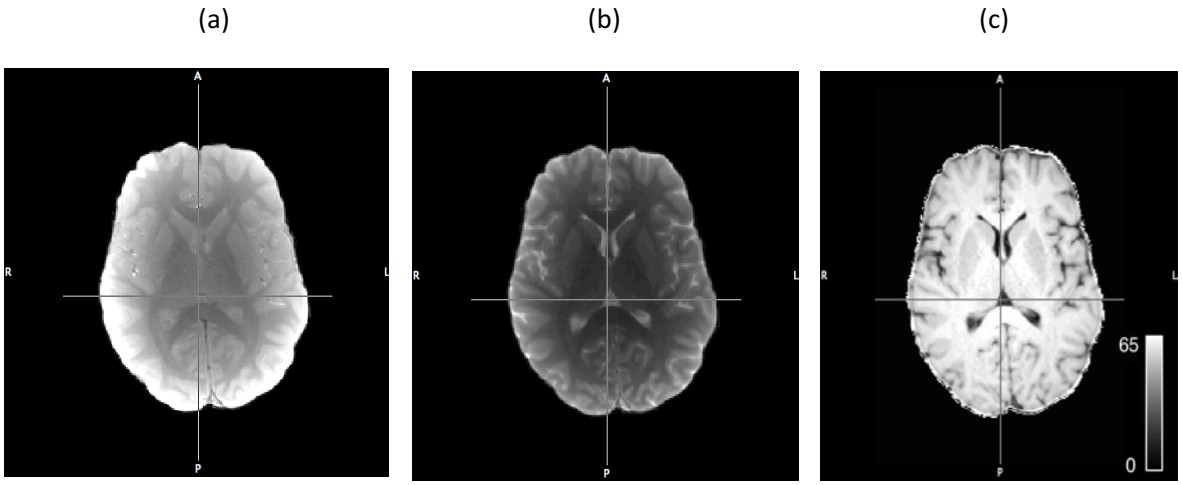


Figure 6.1. One slice from a multislice data set: (a) MT_0 image: without MT pulse, (b) MT image: with MT pulse, (c) calculated MTR image: $100*(MT_0-MT)/MT_0$

Our primary region of interest (ROI) was the SCP. We also examined the CC as a control region in order to compare changes in MTR values between individuals with FRDA and controls and also between the ROI within each group. The boundaries of the SCP were defined according to the following visual criteria: the posterior border of the pons defined the inferior border, the Cerebrospinal fluid (CSF) within the fourth ventricle defined the medial and lateral borders, and the inferior colliculus defined the superior border. A 3D mask was subsequently created manually for each individual in the central part of the SCP and the mean MTR was calculated for the masked area (see Figure 6.2).

(a) (b) (c)

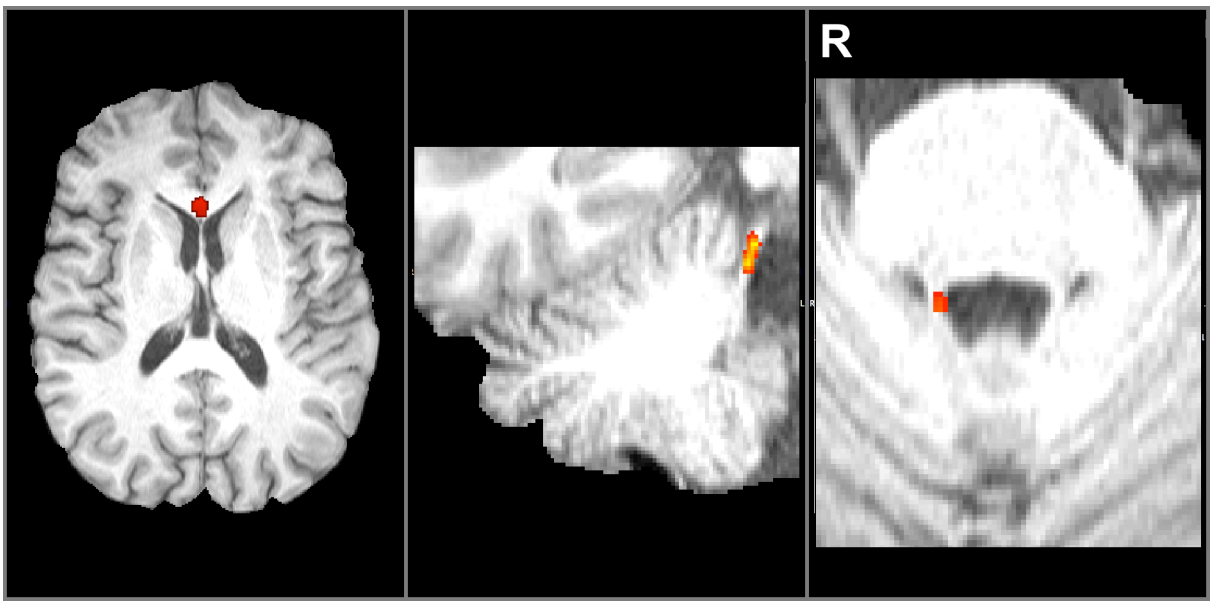


Figure 6.2. ROIs used to measure MTR value of the genu of the CC (a) and the right SCP (b and c) in one individual with FRDA, overlaid on the T1-weighted image of the patient.

We compared the mean MTR values in the SCP and CC between individuals with FRDA and control participants using a two-way repeated measure ANOVA with the factors of Group (FRDA, controls) and ROI (SCP, CC). Separate paired t-tests explored the significant Group by ROI interaction by comparing MTR values in the SCP and CC for each group. The analysis was conducted using SPSS Statistics V.20 software (IBM Corporation, NY, USA).

Correlation between MTR and clinical parameters

To determine whether MTR measures are related to clinical parameters, we analyzed the correlations between the MTR data in SCP with clinical parameters in individuals with FRDA using Pearson correlation coefficients. To remove potential confounding by individual differences in the global MTR between individuals with FRDA, we calculated the difference between the SCP and CC MTR values for each individual and correlated this MTR difference (ΔMTR) score against clinical

parameters. The clinical parameters included in the correlational analyses were age at disease onset (defined as the age in years at which clinical symptoms of FRDA were first noticed by the individual or parents); disease duration (age when tested minus age at disease onset); GAA1 (smaller repeat size) and GAA2 (larger repeat size); and the Freidreich's Ataxia Clinical Rating Scale (FARS) score, a scale of disease severity (Subramony et al., 2005).

Results

MTR

The two way repeated measures ANOVA revealed a main effect of Group ($F(1,18) = 19.80$, $p<0.001$). The mean MTR values in individuals with FRDA ($M=52.5$, $SD=4.6$) were significantly lower than in control participants ($M=55.7$, $SD=1.2$). There was also a main effect of ROI ($F(1,18) = 53.58$, $p<0.001$), with MTR in the CC ($M=56.1$, $SD= 1.2$) being significantly higher than the MTR value in the SCP ($M=52.1$, $SD=3.6$). Finally, there was a significant Group by ROI interaction ($F(1,18) = 19.07$, $p<0.001$). Paired t-tests examining differences between the MTR values in the SCP and CC for each group revealed the source of this interaction to be the significant difference in MTR values [$t(9) = -9.18$, $p<0.001$] between the SCP ($M=54.9$, $SD=2.6$) and CC ($M=56.5$, $SD=2.2$) in individuals with FRDA. There was no significant difference in MTR values between the SCP and CC in control participants.

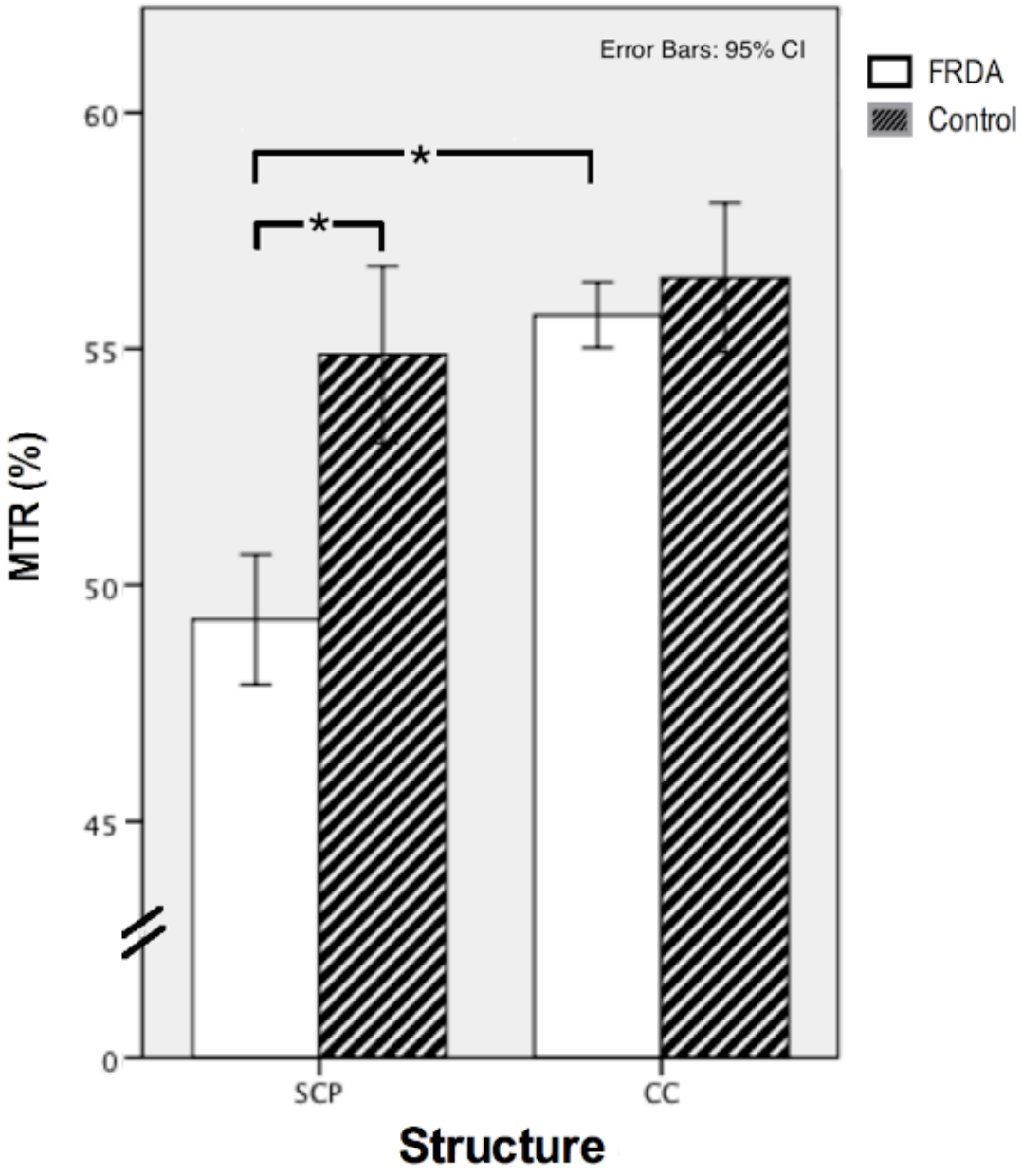


Figure 6.3. Comparison of mean MTR results between patients and control groups in superior cerebellar peduncle (SCP) and corpus callosum (CC).

Correlations between MTR and clinical parameters

There were significant correlations between the MTR values in the SCP region and GAA2 ($r=-0.72$, $p<0.05$), and between the MTR score and GAA2 ($r=0.66$, $p<0.05$) in individuals with FRDA (see figures 6. 4 and 6.5). There were no other significant correlations.

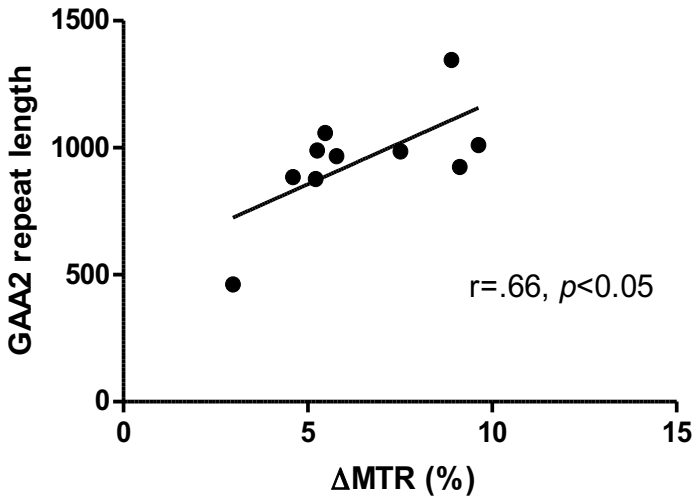


Figure 6.4. Scatter plot indicating the relationship between ΔMTR in the SCP and GAA2 repeat length.

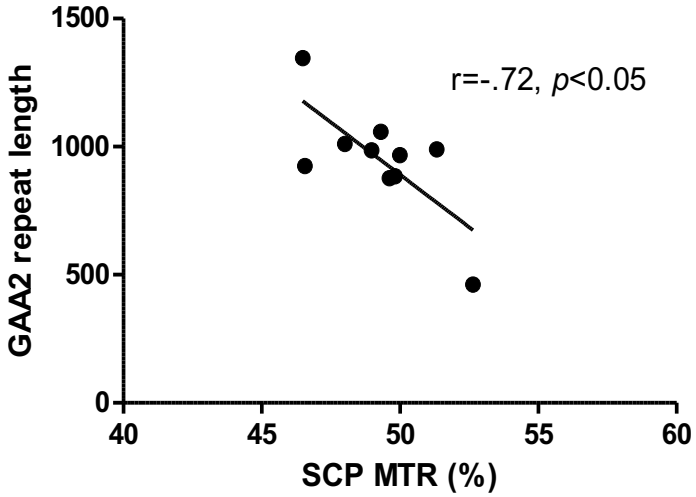


Figure 6.5. Scatter plot indicating the relationship between the MTR in the SCP and GAA2 repeat
size.

Discussion

We used MTI to examine the integrity of WM tracts in individuals with FRDA compared with control participants. Consistent with our hypotheses, individuals with FRDA demonstrated a significant reduction in MTR value in the SCP, but not in the CC when compared with control participants. Furthermore, there was a significant reduction in the MTR value in the SCP compared with the CC in participants with FRDA. MTR values in the SCP and MTR both demonstrated a significant correlation with GAA2 in participants with FRDA. Our results provide the first evidence for a reduction in the myelination signal from the WM tracts in the SCP in individuals with FRDA.

Previous neuropathological MTR studies (Dousset et al., 1992; Gass et al., 1994; Mottershead et al., 2003) have interpreted reduced MTR values as evidence of demyelination. Although demyelination is not considered a cardinal feature of FRDA, there are reports of changes to the pattern of myelination in peripheral sensory neurons in FRDA (Morral, Davis, Qian, Gelman, & Koeppen, 2010; Nolano et al., 2001; Said, Marion, Selva, & Jamet, 1986). Examination of the dorsal roots of the lumbar spinal cord in post mortem studies of FRDA indicated that the density of axonal fibers is not visibly different compared to control participants (Koeppen, 2011). However, a lack of larger myelinated fibers is apparent with the preserved axonal fibers being organized in a compact manner and having reduced cross-sectional area (Koeppen et al., 2009). Immunocytochemical analysis of the dentate nucleus in post mortem studies of FRDA revealed selective atrophy of large neurons, with sparing of the smaller GABA-ergic neurons with the underlying cause of the selective degradation of the larger neurons not yet apparent (Koeppen, 2011). There have been no published comparative analyses of myelinated fibers in areas other than the DRG in individuals with FRDA (Koeppen, 2011).

Based on inference from recent findings by Koeppen and colleagues and Morral and colleagues, MTR changes observed in FRDA could be related to hypo-myelination rather than demyelination (Koeppen, Morral, McComb, & Feustel, 2011; Morral et al., 2010). Both studies examined DRG and sural nerve biopsies and found that whilst axonal count remains relatively similar between individuals with and without FRDA, there is a significant difference in the number of myelinated axons. Notably in individuals with FRDA, only 11% of sural nerve axons were reported to be myelinated whereas 36% were myelinated in controls (Morral et al., 2010). Consistent with this observation, the group difference obtained in this study may reflect the presence of smaller and less myelinated fibers with a reduction in the proportionate number of larger myelinated fibers in WM tracts in individuals with FRDA. Thus the neuropathological process associated FRDA may be one of hypo-myelination rather than demyelination. Morral and co-workers suggested that hypomyelination in the sural nerves in individuals with FRDA may be a consequence of impaired interaction between axons and Schwann cells in the peripheral nervous system, increasing with disease progression (Morral et al., 2010). This may well also be the case in the central nervous system. Della Nave and colleagues also observed lower fractional anisotrophy and increase in both axial and radial diffusivity in the area corresponding to the decussation of the SCPs; and hypothesized that changes to axial diffusivity may reflect degeneration in distal WM fibers and noted the structural and biophysical mechanism underlying this degeneration remains unknown (Della Nave et al., 2011).

The MTR study findings also showed that there is a significant negative correlation between MTR values in the SCP and GAA2 repeat length in DNA of individuals with FRDA. GAA1 repeat length has been previously noted to correlate more often and to a greater degree with severity of motor impairement than GAA2 (M B Delatycki et al., 2000). However, Koeppen and colleagues challenged the historical emphasis placed on the relationship between GAA1 and measures of disease severity by suggesting GAA2 may also have a role to play in the neuropathological phenotype (Koeppen, Davis, et al., 2011).

The GAA expansion associated with FRDA is thought to cause partial silencing of FXN and thus reduction of the production of frataxin. However, the effect of frataxin deficiency on the production of healthy myelin is still unclear. Individuals

with FRDA are able to synthesize between 4% and 29% of the normal levels of structurally and functionally normal frataxin (Campuzano et al., 1997). However, as has been demonstrated in mouse studies, the complete lack of frataxin production leads to embryonic lethality (Cossee et al., 2000). FXN expression is highest in the heart and spinal cord, lower in the cerebellum, liver, pancreas and skeletal muscle and lowest in the cerebral cortex (Campuzano et al., 1996). Whilst the regions with higher FXN expression in unaffected individuals are consistent with the regions most affected by the FRDA disease process, FXN expression does extend beyond these sites (Santos et al., 2010). Santos and colleagues proposed that the areas specifically affected by FRDA are highly dependent on mitochondrial metabolism (Santos et al., 2010). In particular, neuronal cells are seen to be more vulnerable to apoptotic cell-death as a result of reduced frataxin than non-neuronal cells (Palomo, Cerrato, Gargini, & Diaz-Nido, 2011). In addition, diminished frataxin levels place neuronal cells under considerable stress, which may lead to dysfunction of brain cells such as glial cells which are critical to production and maintenance of healthy myelin in the central nervous system (Diaz-Nido et al., 2012). Despite the burgeoning understanding of the effect of diminished frataxin on neuronal cells, the impact of reduced frataxin on the production of health myelin remains speculative and requires further examination.

Contrary to our expectation, the FARS score, an index of clinical severity, did not correlate with MTR in either ROI. Regner and colleagues (Regner et al., 2012) reported younger individuals with FRDA or those with longer GAA repeat lengths had a more rapid decline over time in measures of clinical severity such as the FARS. Our participants had a relatively later mean age of onset of disease than average at 20 years, compared to the more typical onset during late childhood or early adolescence (Pandolfo, 2009). The later mean age of onset and the relatively low mean FARS score both indicate that this cohort may be on the “milder” end of the disease spectrum, with low variability in disease parameters. Furthermore, the relatively low number of participants in the study may have contributed to the correlational analysis with clinical parameters having insufficient statistical power to identify significant correlations. Della Nave and colleagues made a similar observation regarding their lack of correlation between clinical parameters and an increase in axial or radial diffusivity in the SCP decussation in individuals with

FRDA (Della Nave et al., 2011). We note that the study by Morral and colleagues also did not report a significant correlation between the number or percentage of myelinated fibers and age of onset or disease duration (Morral et al., 2010). Future studies with a greater number of participants would enable further exploration of the relationships between clinical parameters and MTR changes in FRDA.

Conclusions

This is the first study to demonstrate reduced MTR in the SCP of individuals with FRDA when compared to control participants. These findings may reflect a process of hypo-myelination or myelin loss and provides significant new insight into the neurodegenerative pathology of FRDA. Despite an improvement in our understanding of the neuropathology associated with FRDA, the details and mechanisms of the microstructural degradation that underlies these observations remains speculative. Future studies using larger cohorts and advanced quantitative imaging techniques such as composite hindered and restricted model of diffusion (CHARMED) may enable further examination of myelination changes in the SCP in individuals with FRDA (Assaf & Basser, 2005).

Acknowledgements

The authors thank the participants for their involvement in this study and the staff at Monash Biomedical Imaging, Monash University, Victoria. Funding for this study was from a Monash Biomedical Imaging Psychology Department Grant. LAC is an Early Career Fellow, MBD is a Practitioner Fellow, GE is Research Fellow all of the National Health and Medical Research Council. SRK is in receipt of a Victoria University Postgraduate Research Scholarship. The authors also wish to acknowledge the support of the Friedreich Ataxia Research Alliance (USA) and the Friedreich Ataxia Research Association (Australasia).

Chapter 7

Discussion

DCD study

The aim of the fMRI study was to determine whether at behavioural level, adults with pDCD demonstrate a decreased ability to perform implicit motor imagery. In addition, we investigated the brain cortical activity in adults with DCD to determine if they would demonstrate the same pattern of cortical dysfunction observed in children with DCD during performance of a motor imagery task. Our data demonstrate that the pDCD group exhibit greater response time and lower accuracy compared to control group. However, this difference did not reach level of significance, probably because of the ceiling effect. The use of implicit motor imagery was also confirmed in both group by indicating that there was a significant increase in response time for laterally-rotated compared with medially-rotated stimuli imagery; this suggests that the biomechanical constraints that normally affect the performance of real movements also apply to the imagined movement. The results were consistent with the finding of the recent study conducted by (Hyde et al., 2014). Furthermore, the imaging data analysis demonstrated parametric increase in the BOLD signal with task difficulty in the occipito–parietal and parieto-frontal networks for both the control and pDCD groups. More importantly, significantly reduced activation in these networks was observed in the pDCD group compared to controls.

Neuroimaging findings and brain regions involved in motor imagery

The the results of a functional MRI study, revealed activation in the parieto-frontal and occipito-parietal loops in both of our groups. Activation in these networks is consistent

with a recent meta-analysis of fMRI studies of motor imagery, those in the frontal and parietal regions (Hétu et al., 2013), in particular. Intriguingly, despite using implicit imagery in our study, our results are more closely linked to those in this meta-analysis relating to explicit imagined movements of the upper limb than to the findings of studies limited specifically to upper limb judgement tasks such as the hand rotation task. Hétu et al., (2013) demonstrated that explicit motor imagery of both the upper limb and limb judgement tasks resulted in consistent activation of the bilateral MFG and left IPL. However, there was greater activation in the bilateral SMA and the left SMG in the explicit motor imagery studies than the limb judgement tasks. On the other hand, greater activation was shown consistently in the right SPL, MFG and postcentral gyrus during limb rotation judgement tasks when compared with explicit motor imagery of the upper limb. Probably, the reason our results are more consistent with the explicit motor imagery tasks than the limb judgement tasks is because of our instruction set. We specifically provided explicit instructions to the participants to imagine their hand in the position of the hand on the screen. This type of instruction is rarely given in limb judgement tasks (Hétu et al., 2013).

Fronto-parietal network

Traditionally, parietal regions, are associated with perception and somatosensory transformations and play a critical role during spatial tasks like mental rotation (Deutsch, Bourbon, Papanicolaou, & Eisenberg, 1988; Ditunno & Mann, 1990). As mentioned in chapter 2, the role of the posterior parietal cortex in motor imagery was initially suggested in studies of patients with PPC damage, which showed that motor imagery capabilities are diminished after PPC damage (Sirigu & Duhamel, 2001; Sirigu et al., 1996). A recent study also reported motor imagery impairment in individuals with superior parietal lobe (SPL) damage (Fleming et al., 2010). The brain's parietal lobe in humans is responsible for receiving the somatosensory signals and transformation of limb position information into a motor plan using internal models (de Lange, Hagoort, & Toni, 2005; de Lange, Helmich, & Toni, 2006). Hétu et al., (2013) also propose that the parietal cortex and PPC in particular, plays an essential role in motor planning and control, through its connections to other brain regions particularly the frontal lobe and the cerebellum. The frontal lobe is traditionally known to be the main area involved in human voluntary movement and the parietal cortex is strongly connected to frontal areas within the brain and particularly, those in the supplementary motor areas (SMA) and

premotor (PM) cortex (Hétu et al., 2013). These regions are both suggested to contribute to mental rotation of hand stimuli (Bonda et al., 1995; Parsons et al., 1995). The PM cortex and SMA are the function based names areas that anatomically are mainly placed in the SFG and MFG regions. Therefore, in our study, activation of the MFG and SFG may reflect activation of the PM and SMA regions respectively. Hétu et al., (2013) suggest that motor imagery might include a similar planning phase prior to the simulation of movement, in line with that required for performing overt movements. However, this activation is not purely motor in nature, and reflects reciprocal activation between motor planning regions and the parietal cortex, allowing the mapping of egocentric space to be incorporated into the simulated motor plan (Jackson & Husain, 1996; Jeannerod, 2006; Wise et al., 1996).

Cerebellum

The role cerebellum plays in motor imagery is not exactly clear. Hétu et al., (2013) suggest that in the same way that motor execution requires integration of information not only from the networks thought to represent movement, but also those associated with those networks, such as the basal ganglia and cerebellum, so too does motor imagery. Decety et al., (1996) also posited that motor imagery likely involves the full network of the motor system and that because of this, actual execution of the motor plan is prevented and the cerebellar activity usually presents an inhibitory mechanism.

Occipital cortex

Interestingly, our results also demonstrated activation of the occipital cortex which was not reported to occur consistently during motor imagery by Hétu et al., (2013). Although there was no evidence for consistent activation in the recent meta-analysis, such activation and conjectured on the role of occipital cortex have been previously reported. An EEG study conducted by Thayer, Johnson, Corballis and Hamm, (2001) demonstrated occipital activation during the mental rotation of hands, reflecting stimulus recognition. Coupled with parietal activation, this allows the hand stimulus to be matched to the individual's own hand. For example, increased activation through the occipto-parietal cortex during motor imagery have shown in affected hand of

Individuals suffering Parkinson's disease (Helmich, 2007). This might reflect greater reliance on visual information during action planning.

Decreased cortical activation in the adults with pDCD

The pDCD group recorded significantly less activation in the PM (bilateral MFG), PPC (left SPL) and cerebellum (lobule VI). This pattern of decreased cortical activation is consistent with our understanding of mechanisms that have been implicated in childhood DCD (Wilson et al., 2013). Impaired predictive control in DCD was demonstrated in a recent meta-analysis (Reynolds et al., 2015), which was linked to the integrity of parieto-frontal and parieto-cerebellar networks. Reduced activation in left SPL only in the pDCD group is also consistent with a recent brain MRI connectomics study which showed SPL is one of the regions involved in motor impairment in children suffering DCD (Debrabant et al., 2016).

The DTI study if individuals with DCD identified alterations to WM integrity in adults with pDCD along pathways important for motor planning, control and cognition. Some alterations, such as reduced FA in the SLF, are in line with previous research in DCD (Langevin et al., 2014), while our finding of reduced FA in the CST is in contrast to previous work demonstrating reduced MD in this tract (Jill G. Zwicker et al., 2012). In addition, we identified reduced MD in the left IC and right ILF. Importantly, WM integrity was correlated highly with motor skill level across each of these regions in our study.

Reduced FA in the CST of the pDCD group in this study is in contrast to the findings of (Jill G. Zwicker et al., 2012), but in line with work with other motor impaired populations (Caeyenberghs et al., 2011; Yoshida et al., 2010). In particular, reduced FA of the CST is one of the most regularly reported WM tract abnormalities in cerebral palsy (Scheck et al., 2012). An alteration to the CST in a disorder where motor impairment is the defining feature, as in DCD, is not surprising, but the contrasting results between the current study and that of Zwicker et al. (Jill G. Zwicker et al., 2012) suggests the WM make-up of the CST in DCD requires further examination. Whilst changes in the axonal make-up and/or myelination within the CST may contribute to the motor execution difficulties of children with DCD, it is likely that further alterations within the cortex also play a role.

Alterations to WM within the left IC capsule in DCD was recently reported by (Debrabant et al., 2013), in the form of reduced FA. Reduced FA in the IC has been linked with motor skill impairment previously, including in preterm infants (Rose et al., 2007). Our findings support the role of the IC in motor control. Via the IC, the CST extends, carrying information from the primary and supplementary motor areas to lower motor neurons (Sullivan et al., 2010). The posterior thalamic radiation also runs through the IC (Cowan & de Vries, 2005), transmitting sensory information from the thalamus to the parietal lobe. Damage to this pathway has been linked to reduced sensory and motor function in children born preterm with cerebral palsy (Hoon Jr et al., 2009). Though we also identified alterations to WM within this region, our sample of adults with pDCD had significantly lower MD which typically indicates increased WM integrity (Soares et al., 2013); hence, our findings seem to contradict what would be expected in DCD. However, the findings of Debrabant et al., (2016) were specific to the retro lenticular limb of the IC, whilst our comparisons suggest differences in the anterior limb (Figure 2b-c).

Similarly, we identified lower MD within the ILF. The ILF connects the occipital and temporal lobes and is thought to represent the visual ventral stream (Ortibus et al., 2012). Recent research has also highlighted a significant overlap with the nearby inferior fronto-occipital fasciculus (Wahl et al., 2010), which suggests the ILF may also extend to frontal areas (Ashtari, 2012). Our finding here in relation to ILF is difficult to resolve given the often reported difficulties in DCD with processing visual perceptual information, whether or not a motor component is involved (P H Wilson & McKenzie, 1998). Interestingly, Zwicker et al., (2012) also showed reduced MD and reduced WM integrity in some sensory-motor networks in children with DCD. One possibility is that the reduced WM integrity in the SLF of our pDCD group represents an impairment in visual dorsal, or 'vision for action', stream, as proposed by Milner and Goodale, (2008). They suggest the dorsal stream is responsible for programming and controlling skilled movements, with damage to this stream resulting in various motor impairments. Unlike the traditional view of the ventral stream acting as the pathway for object recognition, Milner and Goodale's more recent model suggests this stream plays a supporting role in movement by its involvement in the planning of action. Intriguingly, in the fMRI study we showed that that occipital lobe is one of the regions involved in adults with pDCD. This is consistent with the results of our DTI study which show significant differences in WM integrity in networks connect occipital cortex to frontal lobe (SLF and ILF)

between pDCD group and controls. We suggest that the increased WM integrity in the ILF and decreased WM integrity in the SLF in our pDCD group might reflect a compensatory mechanism in which due to impairment of the dorsal pathway, the ventral pathway is required to play a more significant role in action planning. Alternatively, another explanation for our findings is that increased WM density along selected tracts could be a compensatory mechanism for a more major disruption of the parieto-frontal network. Because the superior (dorsal) pathways are compromised, inferior (ventral) pathways may be enlisted to a greater degree to establish reciprocal connectivity to anterior regions, which are involved in motor planning. Although both hypotheses are speculative, they suggest that DCD may best be modelled using a network approach (rather than being seen as a result of a global brain dysfunction or hypoactivation).

Generally, our findings from fMEI and DTI studies are in accord with recent studies of DCD that indicate that DCD is unlikely to result from dysfunction of one neural region alone, but rather multiple regions and/or networks. In these studies, atypical activation has been observed most commonly in the frontal and parietal regions (Debrabant et al., 2013; Debrabant et al., 2013; Kashiwagi et al., 2009; Zwicker, 2010; Zwicker, 2011; Querne et al., 2008), as well as some cerebellar regions (Debrabant et al., 2013; Jill G. Zwicker et al., 2011). Importantly, like the current study, differences at a neural level are not always reflected in behavioural differences (Pangelinan et al., 2013; Zwicker et al., 2010; Zwicker et al., 2011). One hypothesis is that individuals with DCD enlist compensatory strategies when performing simple motor and motor imagery tasks. These strategies are manifest by a different pattern of neural activation, while the behavioural outcome is preserved under relatively simple task constraints.

FRDA study

We used MTI to examine the integrity of WM tracts in individuals with FRDA compared with control participants. As we expected, individuals with FRDA demonstrated a significant reduction in MTR value in the SCP, but not in the CC when compared with control participants. Additionally, there was a significant reduction in the MTR value in the SCP compared with the CC in participants with FRDA. Our

results provide the first evidence for a reduction in the myelination signal from the WM tracts in the SCP in individuals with FRDA.

Previous neuropathological MTR studies (Dousset et al., 1992; Gass et al., 1994; Mottershead et al., 2003) have interpreted reduced MTR values as evidence of demyelination. Although demyelination is not considered a cardinal feature of FRDA, there are reports of changes to the pattern of myelination in peripheral sensory neurons in FRDA (Morral et al., 2010; Nolano et al., 2001; Said et al., 1986). Examination of the dorsal roots of the lumbar spinal cord in post mortem studies of FRDA indicated that the density of axonal fibers is not visibly different compared to control participants (Koeppen, 2011). However, a lack of larger myelinated fibers is apparent with the preserved axonal fibers being organized in a compact manner and having reduced cross-sectional area (Koeppen et al., 2009).

The recent findings by Koeppen and colleagues, (2011) and Morral et al., (2010), indicate that MTR changes observed in FRDA could arise as a result of hypo-myelination rather than demyelination. Both studies examined DRG and sural nerve biopsies and found that whilst axonal count remains relatively similar between individuals with and without FRDA, there is a significant difference in the number of myelinated axons. Notably in individuals with FRDA, only 11% of sural nerve axons were reported to be myelinated whereas 36% were myelinated in controls (Morral, 2010). Consistent with this observation, the group difference obtained in this study may reflect the presence of smaller and less myelinated fibers with a reduction in the proportionate number of larger myelinated fibers in WM tracts in individuals with FRDA. Thus the neuropathological process associated FRDA may be one of hypo-myelination rather than demyelination. Morral and co-workers suggested that hypomyelination in the sural nerves in individuals with FRDA may be a consequence of impaired interaction between axons and Schwann cells in the peripheral nervous system, increasing with disease progression (Morral, 2010). This may well also be the case in the central nervous system. Della Nave and colleagues also observed lower fractional anisotropy and increase in both axial and radial diffusivity in the area corresponding to the decussation of the SCPs; and hypothesized that changes to axial diffusivity may reflect degeneration in distal WM fibers and noted the structural and biophysical mechanism underlying this degeneration remains unknown (Della Nave et al., 2011)

This study reported a significant negative correlation between MTR values in the SCP and GAA2 repeat length in the DNA of individuals with FRDA. However, GAA1 repeat length has been previously noted to correlate more often and to a greater degree with measures of disease severity than GAA2 (M B Delatycki et al., 2000).

This is the first study to demonstrate reduced MTR in the SCP of individuals with FRDA when compared to control participants. These findings may reflect a process of hypo-myelination or myelin loss and provides significant new insight into the neurodegenerative pathology of FRDA. Despite an improvement in our understanding of the neuropathology associated with FRDA, the details and mechanisms of the microstructural degradation that underlies these observations remains speculative. Future studies using larger cohorts and advanced quantitative imaging techniques such as composite hindered and restricted model of diffusion (CHARMED) may enable further examination of myelination changes in the SCP in individuals with FRDA (49).

Chapter 8

Conclusion

DCD study

The results of the fMRI study in adults with pDCD showed that members of this group were capable of engaging in motor imagery to solve the hand rotation task with no behavioural differences in response time and accuracy compared with control participants. Despite this, the adults with pDCD demonstrated an atypical pattern of neural activation when performing an implicit task of motor imagery. We conclude from these findings that the pattern of decreased activation with respect to frontal, parietal, and cerebellar regions may represent signs of deficient coupling between zones in the service of action planning and the prospective control of movement. This is consistent with recent hypotheses proposed by Wilson and colleagues (P H Wilson et al., 2013) based on a meta-analysis. These findings provide the motivation for a systematic evaluation using a parametric experimental design incorporating motor and imagery tasks of varying complexity.

Our results of DTI study suggest disruption to the microstructure of critical WM networks in adults with pDCD (most notably the left SLF), with some tentative evidence for maturational compensation along inferior sections of the LF. These biological markers are broadly consistent with behavioural data showing a constellation of deficits across motor planning, control and cognition in DCD.

FRDA study

The MTR study of SCP in FRDA is the first study that shows reduced MTR in the SCP of individuals with FRDA in comparison to control group. These findings confirm the crucial role of cerebro-cerebellar loops, particularly, SCP in motor impairment observed in FRDA. SCP includes afferent tracts caring information from CNS lower regions

toward cerebral cortex. The results of this study are consistent with previous studies of FRDA and demonstrate the significance of cerebro-cerebellar loop in interpretation of movement impairment observed in FRDA. This might reflect a process of hypo-myelination or myelin loss and it provides significant new insights into the neurodegenerative pathology of FRDA. Despite an improvement in our understanding of the underlying neuromechanism associated with FRDA, the details and mechanisms of the microstructural degradation that underlay these observations remain unclear.

Final conclusion

In general, the results of our research on DCD and FRDA emphasise the role of novel imaging technologies, such as MRI, in understanding both the theoretical aspects and practical application in individuals with motor dysfunction, especially in movement disorders such as DCD and FRDA in which conventional methods such as traditional imaging methods and laboratory biochemistry laboratory tests are of very limited value. This research also suggests that MRI findings could be considered as a potential biomarker for determining the severity of motor disorders, following up the clinical progression and evaluating the effectiveness of therapeutic interventions in movement disorders with neurological causes at CNS level.

Limitations and future work

DCD study

To ensure that any differences in motor imagery performance in subjects with DCD and healthy volunteers are distinguished, further motor imagery research would benefit from a tasks that demand more explicit control over imagery or one that uses a more complex configuration of limbs to prevent the consequent ceiling effect. Also, since there is evidence that suggests the positive relationship between motor imagery competence and motor skill development increases with age (Caeyenberghs et al., 2009), an investigation of the relationship between imitation skills and efficiency in performing motor imagery tasks would be highly beneficial.

From the interventional perspective, as most daily motor skills are complex, motor imagery interventions often require imagery of complex movements to assist in motor skill acquisition and development. An exploration of motor imagery competence using a complex hand rotation task would be beneficial, to explore whether individuals with DCD are still able to use a motor imagery. Additionally, more advanced neuroimaging studies are required to identify the main regions and circuits responsible for clinical manifestations of DCD. A longitudinal study is also required to assess temporal alterations of the MRI findings including both functional and structural changes in individuals with DCD and eventually to identify *in vivo* biomarkers to assess severity and duration of the disorder. Additionally, a larger sample group would increase the power of the study and would help in detecting subtle changes over the time, however a large homogeneous sample of DCD cases is difficult to achieve because of lack of a "gold standard" test for DCD and also controversies in the guidelines as to how great an impairment should be considered a "marked impairment" (S. E. Henderson & Barnett, 1998). These contentions, in addition to social taboos associated with acknowledgment of clumsiness as a developmental "disorder", have left a substantial number of DCD cases undiagnosed.

We need additional neuroimaging studies that vary task constraints parametrically and/or use path modelling to examine inter-regional coupling. These approaches will enable a better understanding of neural recruitment patterns in DCD as a function of motor, cognitive and perceptual load.

Moreover, a longitudinal study would be useful in following up children suffering DCD from the early stages until adulthood and to assess the temporal course of MRI including structural and functional findings. This would shed a light on the underlying neuro-mechanism and the course of progression/remission of the disorder in individuals suffering from DCD. This would eventually lead to identifying *in vivo* biomarkers to assess severity and progression of the DCD. Additionally, a larger sample group would definitely be useful in improving the power of study and enables researchers to further investigate subtle alterations in behavioural and neuroimaging aspects of DCD over time. Through understanding of neuro-mechanism and aetiology of DCD plays crucial role in development of new therapeutic approaches in management of DCD including physiotherapy and even potential pharmaceutical treatments that would have a significant impact in improving the quality of life in individual with DCD.

FRDA study

A longitudinal study is required to assess of the fMRI findings in individuals with FRDA during time and eventually to detect *in vivo* biomarkers for assessment of the severity and progression of the disease sign and symptoms. A larger sample group, although difficult to achieve due to the rarity of the disease, would be useful in improving the value of study and enable researchers to further investigate subtle changes that might have been overlooked in our study because of the limited sample size. This might warrant conducting a multi-centre study. Moreover, future studies with greater sample sizes, would enable further exploration of the relationships between clinical parameters and MTR changes in FRDA.

REFERENCES

Akhlaghi, H., Corben, L. A., Georgiou-Karistianis, N., Bradshaw, J. L., Storey, E., Delatycki, M. B., & Egan, G. F. (2011). Superior Cerebellar Peduncle Atrophy in Friedreich's Ataxia Correlates with Disease Symptoms. *Cerebellum*, *10*, 81–87.

Akhlaghi, H., Corben, L., Georgiou-Karistianis, N., Bradshaw, J., Delatycki, M. B., Storey, E., & Egan, G. F. (2012). A functional MRI study of motor dysfunction in Friedreich's ataxia. *Brain Research*, *1471*, 138–154. http://doi.org/10.1016/j.brainres.2012.06.035

Alper, G., & Narayanan, V. (2003). Friedreich's ataxia. *Pediatric Neurology*. http://doi.org/10.1016/S0887-8994(03)00004-3

Amaro, E., & Barker, G. J. (2006). Study design in fMRI: Basic principles. In *Brain and Cognition* (Vol. 60, pp. 220–232). http://doi.org/10.1016/j.bandc.2005.11.009

American Psychiatric Association. (2013). *DSM-V*. *American Journal of Psychiatry*. http://doi.org/10.1176/appi.books.9780890425596.744053

Ashtari, M. (2012). Anatomy and functional role of the inferior longitudinal fasciculus: a search that has just begun. *Developmental Medicine & Child Neurology*, *54*(1), 6–7. http://doi.org/10.1111/j.1469-8749.2011.04122.x

Assaf, Y., & Basser, P. J. (2005). Composite hindered and restricted model of diffusion (CHARMED) MR imaging of the human brain. *NeuroImage*, *27*(1), 48–58. http://doi.org/10.1016/j.neuroimage.2005.03.042

Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., … Smith, S. M. (2003). Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. *Magnetic Resonance in Medicine*, *50*(5), 1077–1088. http://doi.org/10.1002/mrm.10609

Blakemore, S. J., & Sirigu, A. (2003). Action prediction in the cerebellum and in the parietal lobe. In *Experimental Brain Research* (Vol. 153, pp. 239–245). http://doi.org/10.1007/s00221-003-1597-z

Blank, R., Smits-Engelsman, B., Polatajko, H., Wilson, P., & European Academy for Childhood, D. (2012). European Academy for Childhood Disability (EACD): recommendations on the definition, diagnosis and intervention of developmental

coordination disorder (long version). *Dev Med Child Neurol*, *54*, 54–93. http://doi.org/10.1111/j.1469-8749.2011.04171.x

Brown-Lum, M., & Zwicker, J. (2015). Brain Imaging Increases Our Understanding of Developmental Coordination Disorder: a Review of Literature and Future Directions. *Current Developmental Disorders Reports*, *2*(2), 131–140. http://doi.org/10.1007/s40474-015-0046-6

Caeyenberghs, K., Leemans, A., Geurts, M., Linden, C. V, Smits-Engelsman, B. C. M., Sunaert, S., & Swinnen, S. P. (2011). Correlations Between White Matter Integrity and Motor Function in Traumatic Brain Injury Patients. *Neurorehabilitation and Neural Repair*, *25*, 492–502. http://doi.org/10.1177/1545968310394870

Campuzano, V., Montermini, L., Lutz, Y., Cova, L., Hindelang, C., Jiralerspong, S., … Koenig, M. (1997). Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Human Molecular Genetics*, *6*(11), 1771–1780.

Campuzano, V., Montermini, L., Molto, M. D., Pianese, L., Cossee, M., Cavalcanti, F., … Monticelli, A. (1996). Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science*, *271*(5254), 1423–1427.

Corben, L. A., Akhlaghi, H., Georgiou-Karistianis, N., Bradshaw, J. L., Egan, G. F., Storey, E., … Delatycki, M. B. (2011). Impaired inhibition of prepotent motor tendencies in Friedreich ataxia demonstrated by the Simon interference task. *Brain and Cognition*, *76*(1), 140–145. http://doi.org/doi:10.1016/j.bandc.2011.02.002

Corben, L. A., Delatycki, M. B., Bradshaw, J. L., Horne, M. K., Fahey, M. C., Churchyard, A. C., & Georgiou-Karistanis, N. (2010). Impairment in motor reprogramming in Friedreich ataxia reflecting possible cerebellar dysfunction. *Journal of Neurology*, *257*(5), 782–791.

Corben, L. A., Georgiou-Karistianis, N., Bradshaw, J. L., Hocking, D. R., Churchyard, A. J., & Delatycki, M. B. (2011). The Fitts task reveals impairments in planning and online control of movement in Friedreich ataxia: reduced cerebellar-cortico connectivity? *Neuroscience*, *192*(382-390).

Cossee, M., Puccio, H., Gansmuller, A., Koutnikova, H., Dierich, A., LeMeur, M., … Koenig, M. (2000). Inactivation of the Friedreich ataxia mouse gene leads to early embryonic lethality without iron accumulation. *Human Molecular Genetics*, *9*(8), 1219–1226.

Cowan, F. M., & de Vries, L. S. (2005). The internal capsule in neonatal imaging.

Seminars in Fetal and Neonatal Medicine, *10*(5), 461–474. http://doi.org/http://dx.doi.org/10.1016/j.siny.2005.05.007

de Lange, F. P., Hagoort, P., & Toni, I. (2005). Neural topography and content of movement representations. *Journal of Cognitive Neuroscience*, *17*, 97–112.

de Lange, F. P., Helmich, R. C., & Toni, I. (2006). Posture influences motor imagery: An fMRI study. *NeuroImage*, *33*, 609–617.

Debrabant, J., Gheysen, F., Caeyenberghs, K., Van Waelvelde, H., & Vingerhoets, G. (2013). Neural underpinnings of impaired predictive motor timing in children with Developmental Coordination Disorder. *Research in Developmental Disabilities*, *34*(5), 1478–1487. http://doi.org/10.1016/j.ridd.2013.02.008

Debrabant, J., Vingerhoets, G., Van Waelvelde, H., Leemans, A., Taymans, T., & Caeyenberghs, K. (2016). Brain Connectomics of Visual-Motor Deficits in Children with Developmental Coordination Disorder. *The Journal of Pediatrics*, *169*, 21–27.e2. http://doi.org/10.1016/j.jpeds.2015.09.069

Delatycki, M. B. (2009). Evaluating the progression of Friedreich ataxia and its treatment. *Journal of Neurology*. http://doi.org/10.1007/s00415-009-1007-y

Delatycki, M. B., Williamson, R., & Forrest, S. M. (2000). Friedreich ataxia: an overview. *Journal of Medical Genetics*, *37*(1), 1–8.

Della Nave, R., Ginestroni, A., Diciotti, S., Salvatore, E., Soricelli, A., & Mascalchi, M. (2011). Axial diffusivity is increased in the degenerating superior cerebellar peduncles of Friedreich's ataxia. *Neuroradiology*, *53*(5), 367–372.

Della Nave, R., Ginestroni, A., Tessa, C., Salvatore, E., Bartolomei, I., Salvi, F., … Mascalchi, M. (2008). Brain white matter tracts degeneration in Friedreich ataxia. An in vivo MRI study using tract-based spatial statistics and voxel-based morphometry . *NeuroImage*, *40*(1), 19–35.

Desmurget, M., & Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. *Trends in Cognitive Sciences*. http://doi.org/10.1016/S1364-6613(00)01537-0

Deutsch, G., Bourbon, W. T., Papanicolaou, A. C., & Eisenberg, H. M. (1988). Visuospatial tasks compared via activation of regional cerebral blood flow. *Neuropsychologia*, *26*(3), 445–452. http://doi.org/10.1016/0028-3932(88)90097-8

Diaz-Nido, J., Loría, F., Oberdoerfer, D., Katsu, Y., Yang, O., Moreno, J., & Pérez-Luz, S. (2012). Are Glial Cells an Unrecognized Contributor to Neurodegeneration in Friedreich's ataxia? In *Ataxia Research Conference*. London.

Ditunno, P. L., & Mann, V. A. (1990). Right Hemisphere Specialization for Mental Rotation in Normals and Brain Damaged Subjects. *Cortex*, *26*(2), 177–188. http://doi.org/10.1016/S0010-9452(13)80349-8

Dousset, V., Grossman, R. I., Ramer, K. N., Schnall, M. D., Young, L. H., Gonzalez-Scarano, F., … Cohen, J. A. (1992). Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging. *Radiology*, *182*(2), 483–91. http://doi.org/10.1148/radiology.182.2.1732968

Fielding, J., Corben, L., Cremer, P., Millist, L., White, O., & Delatycki, M. (2010). Disruption to higher order processes in Friedreich ataxia. *Neuropsychologia*, *48*(1), 235–242.

França, A. E., D'Abreu, A., Yasuda, C. L., Bonadia, L. C., Santos da Silva, M., Nucci, A., … Cendes, F. (2009). A combined voxel-based morphometry and 1H-MRS study in patients with Friedreich's ataxia. *Journal of Neurology*, *256*, 1114–1120.

Frith, C. D., Blakemore, S. J., & Wolpert, D. M. (2000). Abnormalities in the awareness and control of action. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *355*(1404), 1771–1788. http://doi.org/10.1098/rstb.2000.0734

Gass, A., Barker, G. J., Kidd, D., Thorpe, J. W., MacManus, D. G., Brennan, A., … Miller, D. H. (1994). Correlation of magnetisation transfer ratio with clinical disability in multiple sclerosis . *Annals of Neurology*, *32*, 62–67.

Geoffroy, G., Barbeau, A., Breton, G., Lemieux, B., Aube, M., Leger, C., & Bouchard, J. P. (1976). Clinical description and roentgenologic evaluation of patients with Friedreich's ataxia. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*.

Georgiou-Karistianis, N., Akhlaghi, H., Corben, L. A., Delatycki, M. B., Storey, E., Bradshaw, J. L., & Egan, G. F. (2012). Decreased functional brain activation in Friedreich ataxia using the Simon effect task. *Brain and Cognition*, *79*(3), 200–208. http://doi.org/10.1016/j.bandc.2012.02.011

Gerardin, E., Sirigu, A., Lehéricy, S., Poline, J. B., Gaymard, B., Marsault, C., … Le Bihan, D. (2000). Partially overlapping neural networks for real and imagined hand movements. *Cerebral Cortex (New York, N.Y. : 1991)*, *10*(11), 1093–1104. http://doi.org/10.1093/cercor/10.11.1093

Grinter, E. J., Maybery, M. T., & Badcock, D. R. (2010). Vision in developmental disorders: Is there a dorsal stream deficit? *Brain Research Bulletin*, *82*(3–4), 147–

160. http://doi.org/http://dx.doi.org/10.1016/j.brainresbull.2010.02.016

Harding, A. E. (1981). Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain*, *104*(3), 589–620.

Harrison, D. M., Shiee, N., Bazin, P. L., Newsome, S. D., Ratchford, J. N., Pham, D., … Reich, D. S. (2013). Tract-specific quantitative MRI better correlates with disability than conventional MRI in multiple sclerosis. *Journal of Neurology*, *260*(2), 397–406.

Hétu, S., Grégoire, M., Saimpont, A., Coll, M. P., Eugène, F., Michon, P. E., & Jackson, P. L. (2013). The neural network of motor imagery: An ALE meta-analysis. *Neuroscience and Biobehavioral Reviews*. http://doi.org/10.1016/j.neubiorev.2013.03.017

Hoon Jr, A. H., Stashinko, E. E., Nagae, L. M., Lin, D. D., Keller, J., Bastian, A. M. Y., … Johnston, M. V. (2009). Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. *Developmental Medicine & Child Neurology*, *51*(9), 697–704. http://doi.org/10.1111/j.1469-8749.2009.03306.x

Hyde, C., Fuelscher, I., Buckthought, K., Enticott, P. G., Gitay, M. A., & Williams, J. (2014). Motor imagery is less efficient in adults with probable developmental coordination disorder: Evidence from the hand rotation task. *Research in Developmental Disabilities*, *35*(11), 3062–3070. http://doi.org/http://dx.doi.org/10.1016/j.ridd.2014.07.042

Jackson, S. R., & Husain, M. (1996). Visuomotor functions of the lateral pre-motor cortex. *Current Opinion in Neurobiology*. http://doi.org/10.1016/S0959-4388(96)80029-8

Jeannerod, M. (2006). *Motor Cognition*. *Motor Cognition: What Actions Tell the Self*. http://doi.org/10.1093/acprof:oso/9780198569657.001.0001

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robustand accurate linear registration and motion correction of brain images. *Neuroimage*, *17*, 825–841.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*(2), 143–156. http://doi.org/10.1016/S1361-8415(01)00036-6

Kashiwagi, M., Iwaki, S., Narumi, Y., Tamai, H., & Suzuki, S. (2009). Parietal

dysfunction in developmental coordination disorder: a functional MRI study. *Neuroreport*, *20*(2), 1319–1324. http://doi.org/10.1097/WNR.0b013e32832f4d87

Kawato, M. (1999). Internal models for motor control and trajectory planning. *Current Opinion in Neurobiology*. http://doi.org/10.1016/S0959-4388(99)00028-8

Kirby, A., Edwards, L., Sugden, D., & Rosenblum, S. (2010). The development and standardization of the Adult Developmental Co-ordination Disorders/Dyspraxia Checklist (ADC). *Res Dev Disabil*, *31*(1), 131–139. http://doi.org/10.1016/j.ridd.2009.08.010

Klopper, F., Delatycki M.B, Corben L, A., Bradshaw, J. L., Rance, G., & N., G.-K. (2011). The Test of Everyday Attention Reveals Significant Sustained Volitional Attention and Working Memory Deficits in Friedreich Ataxia. *Journal of International Neuropsychology Society*, *17*, 196–200.

Koeppen, A. H. (2011). Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. *Journal of the Neurological Sciences*, *303*(1-2), 1–12.

Koeppen, A. H., Davis, A. N., & Morral, J. A. (2011). The cerebellar component of Friedreich's ataxia. *Acta Neuropathologica*, *122*(3), 323–330.

Koeppen, A. H., Morral, J. A., Davis, A. N., Qian, J., Petrocine, S. V, Knutson, M. D., … Danhong, L. (2009). The dorsal root ganglion in Friedreich's ataxia. *Acta Neuropathologica*, *118*(6), 763–776.

Koeppen, A. H., Morral, J. A., McComb, R. D., & Feustel, P. J. (2011). The neuropathology of late-onset Friedreichs' ataxia. *Cerebellum*, *10*(1), 96–103. http://doi.org/DOI 10.1007/s12311-010-0235-0

Kosslyn, S. M., DiGirolamo, G. J., Thompson, W. L., & Alpert, N. M. (1998). Mental rotation of objects versus hands: neural mechanisms revealed by positron emission tomography. *Psychophysiology*, *35*(2), 151–161. http://doi.org/10.1017/s0048577298001516

Kwon, H. G., Hong, J. H., Hong, C. P., Lee, D. H., Ahn, S. H., & Jang, S. H. (2011). Dentatorubrothalamic tract in human brain: diffusion tensor tractography study. *Neuroradiology*, *53*, 787–791.

L.H.J., P., C.G.B., M., & M., H.-A. (2013). Neural correlates of developmental coordination disorder. *Developmental Medicine and Child Neurology*, *55*(SUPPL.4), 59–64.

Langevin, L. M., MacMaster, F. P., Crawford, S., Lebel, C., & Dewey, D. (2014). Common White Matter Microstructure Alterations in Pediatric Motor and

Attention Disorders. *The Journal of Pediatrics*, *164*(5), 1157–1164.e1. http://doi.org/http://dx.doi.org/10.1016/j.jpeds.2014.01.018

Lauterbur, P. C. (1973). Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. *Nature*, *242*(5394), 190–191. http://doi.org/10.1038/242190a0

Lotze, M., & Halsband, U. (2006). Motor imagery. *Journal of Physiology, Paris*, *99*(4-6), 386–395.

Luypaert, R., Boujraf, S., Sourbron, S., & Osteaux, M. (2001). Diffusion and perfusion MRI: Basic physics. *European Journal of Radiology*, *38*(1), 19–27. http://doi.org/10.1016/S0720-048X(01)00286-8

Lynch, D. R., Farmer, J. M., Tsou, A. Y., Perlman, S., Subramony, S. H., Gomez, C. M., … Balcer, L. J. (2006). Measuring Friedreich ataxia: Complementary features of examination and performance measures. *Neurology*, *66*(11), 1711–1716. http://doi.org/10.1212/01.wnl.0000218155.46739.90

Lynch, D. R., Farmer, J. M., Wilson, R. L., & Balcer, L. J. (2005). Performance measures in Friedreich ataxia: Potential utility as clinical outcome tools. *Movement Disorders*, *20*(7), 777–782. http://doi.org/10.1002/mds.20449

Mantovan, M. C., Martinuzzi, A., Squarzanti, F., Bolla, A., Silvestri, I., Liessi, G., … Angelini, C. (2006). Exploring mental status in Friedreich's ataxia: A combined neuropsychological, behavioral and neuroimaging study. *European Journal of Neurology*. http://doi.org/10.1111/j.1468-1331.2006.01363.x

McCarron, L. T. (1997). *McCarron Assessment of Neuromuscular Development: Fine and Gross Motor Abilities*. (revised). Dallas, TX: Common Market Press.

Milner, A. D., & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia*, *46*(3), 774–785. http://doi.org/10.1016/j.neuropsychologia.2007.10.005

Mori, S., & Barker, P. B. (1999). Diffusion magnetic resonance imaging: its principle and applications. *The Anatomical Record*, *257*(3), 102–9. http://doi.org/10.1002/(SICI)1097-0185(19990615)257:3<102::AID-AR7>3.0.CO;2-6 [pii]

Morral, J. A., Davis, A. N., Qian, J., Gelman, B. B., & Koeppen, A. H. (2010). Pathology and pathogenesis of sensory neuropathy in Friedreich's ataxia. *Acta Neuropathologica*, *120*, 97–108.

Mottershead, J. P., Schmierer, K., Clemence, M., Thornton, J. S., Scaravilli, F., Barker,

G. J., … Miller, D. H. (2003). High field MRI correlates of myelin content and axonal density in multiple sclerosis-a post-mortem study of the spinal cord. *Journal of Neurology*, *250*(11), 1293–1301.

Mukherjee, P., Chung, S. W. W., Berman, J. I. I., Hess, C. P. P., & Henry, R. G. G. (2008). Diffusion tensor MR imaging and fiber tractography: technical considerations. *AJNR. American Journal of Neuroradiology*, *29*(5), 843–852. http://doi.org/10.3174/ajnr.A1052

Mulkern, R. V., & Chung, T. (2000). From signal to image: Magnetic resonance imaging physics for cardiac magnetic resonance. *Pediatric Cardiology*. http://doi.org/10.1007/s002469910003

Mumford, J. A., & Nichols, T. (2006). Modeling and inference of multisubject fMRI data. *IEEE Engineering in Medicine and Biology Magazine*, *25*(2), 42–51. http://doi.org/10.1109/MEMB.2006.1607668

Nolano, M., Provitera, V., Crisci, C., Saltalamacchia, A. M., Wendelschafer-Crabb, G., Kennedy, W. R., … Caruso, G. (2001). Small fibers involvement in Friedreich's ataxia. *Annals of Neurology*, *50*(1), 17–25.

Ortibus, E. L. S., Verhoeven, J., Sunaert, S., Casteels, I., De Cock, P., & Lagae, L. (2012). Integrity of the inferior longitudinal fasciculus and impaired object recognition in children: a diffusion tensor imaging study. *Developmental Medicine & Child Neurology*, *54*(1), 38–43. http://doi.org/10.1111/j.1469-8749.2011.04147.x

Pagani, E., Ginestroni, A., Della Nave, R., Agosta, F., Salvi, F., De Michele, G., … Mascalchi, M. (2010). Assessment of brain white matter fiber bundle atrophy in patients with Friedreich ataxia. *Radiology*, *255*(3), 882–889.

Palomo, G. M., Cerrato, T., Gargini, R., & Diaz-Nido, J. (2011). Silencing of frataxin gene expression triggers p53-dependent apoptosis in human neuron-like cells. *Human Molecular Genetics*, *20*(14), 2807–2822.

Pandolfo, M. (2009). Friedreich Ataxia: the clinical Picture. *Journal of Neurology*, *256*, 3–8. http://doi.org/10.1007/s00415-009-1002-3

Pandolfo, M., & Pastore, A. (2009). The pathogenesis of Friedreich ataxia and the structure and function of frataxin. *Journal of Neurology.*, *256*(Suppliment 1), 9–17.

Parsons, L. M. (1994). Temporal and kinematic properties of motor behavior reflected in mentally simulated action. *Journal of Experimental Psychology: Human Perception and Performance*, *20*, 709–730.

Piek, J. P., Dawson, L., Smith, L. M., & Gasson, N. (2008). The role of early fine and gross motor development on later motor and cognitive ability. *Human Movement Science*, *27*(5), 668–681. http://doi.org/http://dx.doi.org/10.1016/j.humov.2007.11.002

Regner, S. R., Wilcox, N. S., Friedman, L. S., Seyer, L. A., Schadt, K. A., Brigatti, K. W., … Lynch, D. R. (2012). Friedreich ataxia clinical outcome measures: natural history evaluation in 410 participants. *J Child Neurol*, *27*(9), 1152–1158. http://doi.org/10.1177/0883073812448462088307381244846208830738124484 62 [pii]

Reynolds, J. E., Thornton, A. L., Elliott, C., Williams, J., Lay, B. S., & Licari, M. K. (2015). A systematic review of mirror neuron system function in developmental coordination disorder: Imitation, motor imagery, and neuroimaging evidence. *Research in Developmental Disabilities*, *47*, 234–283. http://doi.org/10.1016/j.ridd.2015.09.015

Rose, J., Mirmiran, M., Butler, E. E., Lin, C. Y., Barnes, P. D., Kermoian, R., & Stevenson, D. K. (2007). Neonatal microstructural development of the internal capsule on diffusion tensor imaging correlates with severity of gait and motor deficits. *Developmental Medicine & Child Neurology*, *49*(10), 745–750. http://doi.org/10.1111/j.1469-8749.2007.00745.x

Ryding, E., Decety, J., Sjoholm, H., Stenberg, G., Ingvar, D. H., Sj??holm, H., … Ingvar, D. H. (1993). Motor imagery activates the cerebellum regionally. A SPECT rCBF study with 99mTc-HMPAO. *Cognitive Brain Research*, *1*(2), 94–99. http://doi.org/10.1016/0926-6410(93)90015-W

Said, G., Marion, M. H., Selva, J., & Jamet, C. (1986). Hypotrophic and dying-back nerve fibers in Friedreich's ataxia. *Neurology*, *36*(10), 1292–1299.

Santos, R., Lefevre, S., Sliwa, S., Seguin, A., Camadro, J., & Lesuisse, E. (2010). Friedreich Ataxia:Molecular mechanisms, redox considerations, and therapeutic opportunities. *Antioxidants & Redox Signaling*, *13*(5), 651–690.

Scheck, S. M., Boyd, R. N., & Rose, S. E. (2012). New insights into the pathology of white matter tracts in cerebral palsy from diffusion magnetic resonance imaging: a systematic review. *Developmental Medicine & Child Neurology*, *54*(8), 684–696. http://doi.org/10.1111/j.1469-8749.2012.04332.x

Siegel, A., & Sapru, H. N. (2006). *Essential Neuroscience*. *Mayo Clinic Proceedings* (Vol. 81). http://doi.org/10.4065/81.10.1405-c

Sirigu, A., & Duhamel, J. R. (2001). Motor and visual imagery as two complementary

but neurally dissociable mental processes. *Journal of Cognitive Neuroscience*, *13*, 910–919.

Sirigu, A., Duhamel, J. R., Cohen, L., Pillon, B., Dubois, B., & Agid, Y. (1996). The mental representation of hand movements after parietal cortex damage. *Science*, *273*, 1564–1568.

Skranes, J., Vangberg, T. R., Kulseng, S., Indredavik, M. S., Evensen, K. A. I., Martinussen, M., … Brubakk, A.-M. (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain*, *130*, 654–666.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. http://doi.org/10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., … Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487–1505. http://doi.org/http://dx.doi.org/10.1016/j.neuroimage.2006.02.024

Smyth, T. R. (1992). Impaired motor skill (clumsiness) in otherwise normal children: A review. *Child: Care, Health and Development*, *18*(5), 283–300. http://doi.org/10.1111/j.1365-2214.1992.tb00360.x

Soares, J., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to Diffusion Tensor Imaging. *Frontiers in Neuroscience*, *7*. http://doi.org/10.3389/fnins.2013.00031

Stanisz, G. J., Kecojevic, A., Bronskill, M. J., & Henkelman, R. M. (1999). Characterizing white matter with magnetization transfer and T2. *Magnetic Resonance in Medicine*, *42*(6), 1128–1136. http://doi.org/10.1002/(SICI)1522-2594(199912)42:6<1128::AID-MRM18>3.0.CO;2-9

Stephan, K., Fink, G., Passingham, R., Silbersweig, D., Ceballosbaumann, A., Frith, C., & Frackowiak, R. (1995). Functional-Anatomy of the Mental Representation of Upper Extremity Movements in Healthy-Subjects. *Journal of Neurophysiology*, *73*(1), 373–386.

Storey, E., Tuck, K., Hester, R., Hughes, A., & Churchyard, A. (2004). Inter-rater reliability of the International Cooperative Ataxia Rating Scale (ICARS). *Movement Disorders*, *19*(2), 190–192. http://doi.org/10.1002/mds.10657

Subramony, S. H., May, W., Lynch, D., Gomez, C., Fischbeck, K., Hallett, M., … Ashizawa, T. (2005). Measuring Friedreich ataxia: Interrater reliability of a

neurologic rating scale. *Neurology*, *64*(7), 1261–2. http://doi.org/10.1212/01.WNL.0000156802.15466.79

Sullivan, E. V, Zahr, N. M., Rohlfing, T., & Pfefferbaum, A. (2010). Fiber tracking functionally distinct components of the internal capsule. *Neuropsychologia*, *48*(14), 4155–4163. http://doi.org/10.1016/j.neuropsychologia.2010.10.023

Swee Kheng Tan, Parker, H. E., & Larkin, D. (2001). Concurrent validity of motor tests used to identify children with motor impairment. *Adapted Physical Activity Quarterly*, *18*(2), 168–182.

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R. D., Subramony, S. H., Wessel, K., … Manyam, B. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. *Journal of the Neurological Sciences*. http://doi.org/10.1016/S0022-510X(96)00231-6

Vaubel, R. A., & Isaya, G. (2013). Iron-sulphur cluster synthesis, iron homeostatis and oxidative stress in Friedreich ataxia. *Molecular and Cellular Neuroscience*, *55*, 50–61.

Vestergaard, M., Madsen, K. S., Baaré, W. F. C., Skimminge, A., Ejersbo, L. R., Ramsøy, T. Z., … Jernigan, T. L. (2010). White Matter Microstructure in Superior Longitudinal Fasciculus Associated with Spatial Working Memory Performance in Children. *Journal of Cognitive Neuroscience*, *23*, 2135–2146. http://doi.org/10.1162/jocn.2010.21592

Voncken, M., Ioannou, P., & Delatycki, M. B. (2004). Friedreich ataxia-update on pathogenesis and possible therapies. *Neurogenetics*, *5*(1), 1–8.

Wahl, M., Li, Y.-O., Ng, J., LaHue, S. C., Cooper, S. R., Sherr, E. H., & Mukherjee, P. (2010). Microstructural correlations of white matter tracts in the human brain. *NeuroImage*, *51*(2), 531–541. http://doi.org/http://dx.doi.org/10.1016/j.neuroimage.2010.02.072

Williams, J., Omizzolo, C., Galea, M., & Vance, A. (2013). Motor imagery skills of children with Attention Deficit Hyperactivity Disorder and Developmental Coordination Disorder. *Human Movement Science*, *32*, 121–135.

Williams, J., Pearce, A. J., Loporto, M., Morris, T., & Holmes, P. S. (2012). The relationship between corticospinal excitability during motor imagery and motor imagery ability. *Behavioural Brain Research*, *226*, 369–375.

Williams, J., Thomas, P. R., Maruff, P., Butson, M., & Wilson, P. H. (2006). Motor, visual and egocentric transformations in children with Developmental

Coordination Disorder. *Child: Care, Health and Development*, *32*(6), 633–647. http://doi.org/10.1111/j.1365-2214.2006.00688.x

Williams, J., Thomas, P. R., Maruff, P., & Wilson, P. H. (2008). The link between motor impairment level and motor imagery ability in children with developmental coordination disorder. *Human Movement Science*, *27*(2), 270–285. http://doi.org/10.1016/j.humov.2008.02.008

Wilson, P. H., Maruff, P., Butson, M., Williams, J., Lum, J., & Thomas, P. R. (2004). Internal representation of movement in children with developmental coordination disorder: a mental rotation task. *Developmental Medicine and Child Neurology*, *46*, 754–759. http://doi.org/10.1017/S001216220400129X

Wilson, P. H., Maruff, P., Ives, S., & Currie, J. (2001). Abnormalities of motor and praxis imagery in children with DCD. *Human Movement Science*, *20*(1-2), 135–159. http://doi.org/10.1016/S0167-9457(01)00032-X

Wilson, P. H., & McKenzie, B. E. (1998). Information processing deficits associated with developmental coordination disorder: A meta-analysis of research findings. *Journal of Child Psychology and Psychiatry*, *39*, 829–840.

Wilson, P. H., Ruddock, S., Smits-Engelsman, B., Polatajko, H., & Blank, R. (2013). Understanding performance deficits in developmental coordination disorder: a meta-analysis of recent research. *Developmental Medicine & Child Neurology*, *55*, 217–228.

Wise, S. P., di Pellegrino, G., & Boussaoud, D. (1996). The premotor cortex and nonstandard sensorimotor mapping. *Canadian Journal of Physiology and Pharmacology*, *74*(4), 469–482. http://doi.org/10.1139/y96-035

Wolff, S. D., & Balaban, R. S. (1994). Magnetization transfer imaging: Practical aspects and clinical applications. *Radiology*, *192*, 593–599.

Wolpert, D. (1997). Computational approaches to motor control. *Trends in Cognitive Sciences*, 655–662. http://doi.org/10.1016/S1364-6613(97)01070-X

Wolpert, D. M., & Ghahramani, Z. (1995). An internal model for sensorimotor integration. *Science*, *269*, 1880–1882. http://doi.org/10.1126/science.7569931

Wolpert, D. M., & Ghahramani, Z. (2000). Computational principles of movement neuroscience. *Nature Neuroscience*, *3 Suppl*(november), 1212–1217. http://doi.org/10.1038/81497

Wolpert, D. M., Ghahramani, Z., & Flanagan, J. R. (2001). Perspectives and problems in motor learning. *Trends in Cognitive Sciences*. http://doi.org/10.1016/S1364-

6613(00)01773-3

Wolpert, D. M., & Kawato, M. (1998). Multiple paired forward and inverse models for motor control. *Neural Networks*. http://doi.org/10.1016/S0893-6080(98)00066-5

Wolpert, D. M., Miall, R. C., & Kawato, M. (1998). Internal models in the cerebellum. *Trends in Cognitive Sciences*, *2*(9), 338–347. http://doi.org/10.1016/S1364-6613(98)01221-2

Yamaguchi, K., & Goto, N. (1997). Three-dimensional structure of the human cerebellar dentate nucleus: a computerized reconstruction study. *Anatomical Embryology*, *196*, 343–348.

Yoshida, S., Hayakawa, K., Yamamoto, A., Okano, S., Kanda, T., Yamori, Y., … Hirota, H. (2010). Quantitative diffusion tensor tractography of the motor and sensory tract in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *52*, 935–940. http://doi.org/10.1111/j.1469-8749.2010.03669.x

Yurkanis Bruice, P. (1998). Organic chemistry. *Chem. Eur. J.*, 1256.

Zalesky, A., Akhlaghi, H., Corben, L. A., Bradshaw, J. L., Delatycki, M. B., Storey, E., … Egan, G. F. (2013). Cerebello-cerebral connectivity deficits in Friedreich ataxia. *Brain Structure and Function*, in press.

Zwicker, J. G., Missiuna, C., & Boyd, L. A. (2009). Neural correlates of Developmental Coordination Disorder: A review of hypotheses. *Journal of Child Neurology*, *24*, 1273–1281.

Zwicker, J. G., Missiuna, C., Harris, S. R., & Boyd, L. a. (2010). Brain Activation of Children With Developmental Coordination Disorder Is Different Than Peers. *Pediatrics*, *126*(3), e678–e686. http://doi.org/10.1542/peds.2010-0059

Zwicker, J. G., Missiuna, C., Harris, S. R., & Boyd, L. A. (2011). Brain activation associated with motor skill practice in children with developmental coordination disorder: an fMRI study. *International Journal of Developmental Neuroscience*, *29*(2), 145–152. http://doi.org/10.1016/j.ijdevneu.2010.12.002

Zwicker, J. G., Missiuna, C., Harris, S. R., & Boyd, L. A. (2012). Developmental coordination disorder: A pilot diffusion tensor imaging study. *Pediatric Neurology*, *46*(3), 162–167. http://doi.org/10.1016/j.pediatrneurol.2011.12.007

APPENDICES

Appendix A. DCD study Scanning full MRI protocol

Scan	Gradient field map	Functional task runs	T1	T2	64 directions DTI
Sequence name	gre_field_mapping	Run 1-3_moco	t1_mprage_sag_p2_iso_1mm	T2_axial_tse_576_3.5mm	ep2d_diff_mddw_64
Acq time (mins)	1:43	4:51	5:25	2:02	11:31
FOV (mm)	240x240	240x240	250x250	210x210	276x276
Matrix	120x120	120x120	320x320	448x448	128x128
Voxel size (mm)	2x2x4	2x2x4	0.8x0.8x0.8	0.5x0.5x3.5	2.2x2.2x2.2
Slices	36	36	208	40	44
Slice thickness(mm)	4.0	4.0	0.8	3.5	3.0
Gap	no	no	no	no	no
TR (ms)	420	3020	1900	4000	9900
TE (ms)	5.19	30	2.69	98	100
TI (ms)	-	-	-	900	-
Flip angle	60	90	9	136	-
ETL	-	-	-	-	-
Turbo factor	-	-	166	17	-
Echo spacing (ms)	-	0.7	8.1	10.9	-
IPAT factor	off	2(GRAPPA)	2(GRAPPA)	2(GRAPPA)	2(GRAPPA)
Averages	1	1	1	1	1
Prescan Normalize	off	On	on	on	on
Other					Phase partial fourier =6/8

Head Coil: 32 channels

SCAN PROTOCOL

1. Gradient field map
2. 3x BOLD epi for hand rotation task
3. T1
4. T2
5. DTI

```
                  SIEMENS MAGNETOM Skyra syngo MR D11
--------------------------------------------------------------------------------
              \\USER\Saman\DCD\DCD MR094 Adult\localizer
          TA:0:13  PAT:Off  Voxel size:0.5√ó0.5√ó7.0 mm Rel. SNR:1.00   :fl
--------------------------------------------------------------------------------
Properties
     Prio Recon                          On
     Before measurement
     After measurement
     Load to viewer                      On
     Inline movie                        Off
     Auto store images                   On
     Load to stamp segments              On
     Load images to graphic segments     On
     Auto open inline display            Off
     Wait for user to start              Off
     Start measurements                  single
Routine
     Nr. of slice groups                 3
     Slices                              1
     Dist. factor                        20 %
     Position                            Isocenter
     Orientation                         Sagittal
     Phase enc. dir.                     A >> P
     AutoAlign                           ---
     Phase oversampling                  0 %
     FoV read                            250 mm
     FoV phase                           100.0 %
     Slice thickness                     7.0 mm
     TR                                  8.6 ms
     TE                                  4.00 ms
     Averages                            2
     Concatenations                      3
     Filter                              Prescan Normalize, Elliptical filter
     Coil elements                       HEA;HEP
Contrast
     TD                                  0 ms
     MTC                                 Off
     Magn. preparation                   None
     Flip angle                          20 deg
     Fat suppr.                          None
     Water suppr.                        None
     SWI                                 Off
     Averaging mode                      Short term
     Measurements                        1
     Reconstruction                      Magnitude
     Multiple series                     Each measurement
Resolution
     Base resolution                     256
     Phase resolution                    90 %
     Phase partial Fourier               Off
     Interpolation                       On
     PAT mode                            None
```

Image Filter	Off
Distortion Corr.	Off
TD	0 ms
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	On
Mode	Inplane
Geometry	
Nr. of slice groups	3
Slices	1
Dist. factor	20 %
Position	Isocenter
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Sequential
Series	Interleaved
Saturation mode	Standard
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Water suppr.	None
Special sat.	None
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	REF
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Off
Shim mode	Tune up
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm
Frequency 1H	123.247600 MHz
Correction factor	1
SRFExcit 1H	54.702 V
Gain	High

Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Segments	1
Tagging	None
Magn. preparation	None
Dark blood	Off
Resp. control	Off
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Dimension	2D
Phase stabilisation	Off
Averaging mode	Short term
Multi-slice mode	Sequential
Asymmetric echo	Allowed
Contrasts	1
Bandwidth	320 Hz/Px
Flow comp.	No
Allowed delay	0 s
RF pulse type	Normal
Gradient mode	Normal
Excitation	Slice-sel.
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
Mode	Off
BOLD	
Subtract	Off
Liver registration	Off
Save images	On
Autoscaling	Off
Scaling factor	1
Offset	0
Subtrahend	1
Subtraction indices	
StdDev	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Radial MIP	Off
Save original images	On
Distortion Corr.	Off
MapIt	None
Contrasts	1
Save original images	On
Wash - In	Off
Wash - Out	Off
TTP	Off
PEI	Off
MIP - time	Off
Number of radial views	1
Axis of radial views	L-R
MPR Sag	Off
MPR Cor	Off
MPR Tra	Off

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\gre_field_mapping

TA:1:43 Voxel size:2.0√ó2.0√ó4.0 mm Rel. SNR:1.00 :fm_r

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single
Routine	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	240 mm
FoV phase	100.0 %
Slice thickness	4.0 mm
TR	420.0 ms
TE 1	5.19 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	HEA;HEP
Contrast	
MTC	Off
Flip angle	60 deg
Fat suppr.	None
Averaging mode	Long term
Measurements	1
Reconstruction	Magn./Phase
Multiple series	Each measurement
Resolution	
Base resolution	120
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
Image Filter	Off
Distortion Corr.	Off
Prescan Normalize	Off
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	Off
Geometry	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Special sat.	None
Special sat.	None

Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P18.2 F1.8 mm
Rotation	1.50 deg
R >> L	240 mm
A >> P	240 mm
F >> H	144 mm
Frequency 1H	123.247600 MHz
Correction factor	1
01GreFCE 1H	164.105 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Dimension	2D
Averaging mode	Long term
Multi-slice mode	Interleaved
Asymmetric echo	Off
Contrasts	2
Bandwidth	260 Hz/Px
Flow comp.	Yes
RF pulse type	Normal
Gradient mode	Normal
RF spoiling	On
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
Mode	Off
BOLD	
Distortion Corr.	Off

Contrasts	2

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\RUN 1 moco

TA:4:51 PAT:2 Voxel size:2.0√ó2.0√ó4.0 mm Rel. SNR:1.00 :epfid

---

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	On
Start measurements	single
Routine	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	240 mm
FoV phase	100.0 %
Slice thickness	4.0 mm
TR	3020 ms
TE	30.0 ms
Averages	1
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP
Contrast	
MTC	Off
Flip angle	90 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Measurements	93
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off
Resolution	
Base resolution	120
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Separate
Distortion Corr.	Off
Hamming	Off
Unfiltered images	Off
Prescan Normalize	On
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Geometry	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm

Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	---
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P18.2 F1.8 mm
Rotation	1.50 deg
R >> L	240 mm
A >> P	240 mm
F >> H	144 mm
Frequency 1H	123.247600 MHz
Correction factor	1
SincRFPulse 1H	350.306 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1894 Hz/Px
Free echo spacing	Off
Echo spacing	0.7 ms
EPI factor	120
RF pulse type	Normal
Gradient mode	Fast*
TX/RX delta frequency	0 Hz

TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
BOLD	
GLM Statistics	Off
Dynamic t-maps	On
Starting ignore meas	2
Ignore after transition	0
Model transition states	Off
Temp. highpass filter	Off
Threshold	4.00
Paradigm size	20
Motion correction	On
Spatial filter	Off
Delay in TR	0 ms
Distortion Corr.	Off
Interpolation	3D-K-space

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\RUN 2 moco

TA:4:51 PAT:2 Voxel size:2.0√ó2.0√ó4.0 mm Rel. SNR:1.00 :epfid

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	On
Start measurements	single
Routine	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	240 mm
FoV phase	100.0 %
Slice thickness	4.0 mm
TR	3020 ms
TE	30.0 ms
Averages	1
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP
Contrast	
MTC	Off
Flip angle	90 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Measurements	93
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off
Resolution	
Base resolution	120
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off

PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Separate
Distortion Corr.	Off
Hamming	Off
Unfiltered images	Off
Prescan Normalize	On
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Geometry	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	---
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P18.2 F1.8 mm
Rotation	1.50 deg
R >> L	240 mm
A >> P	240 mm
F >> H	144 mm
Frequency 1H	123.247600 MHz
Correction factor	1
SincRFPulse 1H	350.306 V
Gain	High
Table position	0 mm

Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1894 Hz/Px
Free echo spacing	Off
Echo spacing	0.7 ms
EPI factor	120
RF pulse type	Normal
Gradient mode	Fast*
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
BOLD	
GLM Statistics	Off
Dynamic t-maps	On
Starting ignore meas	2
Ignore after transition	0
Model transition states	Off
Temp. highpass filter	Off
Threshold	4.00
Paradigm size	20
Motion correction	On
Spatial filter	Off
Delay in TR	0 ms
Distortion Corr.	Off
Interpolation	3D-K-space

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\RUN 3 moco

TA:5:00 PAT:2 Voxel size:2.0√ó2.0√ó4.0 mm Rel. SNR:1.00 :epfid

---

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	On
Start measurements	single
Routine	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	240 mm
FoV phase	100.0 %
Slice thickness	4.0 mm
TR	3020 ms
TE	30.0 ms
Averages	1

Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP
Contrast	
MTC	Off
Flip angle	90 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Measurements	96
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off
Resolution	
Base resolution	120
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Separate
Distortion Corr.	Off
Hamming	Off
Unfiltered images	Off
Prescan Normalize	On
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Geometry	
Nr. of slice groups	1
Slices	36
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	---
Auto Coil Select	Default

Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P18.2 F1.8 mm
Rotation	1.50 deg
R >> L	240 mm
A >> P	240 mm
F >> H	144 mm
Frequency 1H	123.247600 MHz
Correction factor	1
SincRFPulse 1H	350.306 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1894 Hz/Px
Free echo spacing	Off
Echo spacing	0.7 ms
EPI factor	120
RF pulse type	Normal
Gradient mode	Fast*
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
BOLD	
GLM Statistics	Off
Dynamic t-maps	On
Starting ignore meas	2
Ignore after transition	0
Model transition states	Off
Temp. highpass filter	Off
Threshold	4.00
Paradigm size	20
Motion correction	On
Spatial filter	Off
Delay in TR	0 ms
Distortion Corr.	Off
Interpolation	3D-K-space

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\t1_mprage_sag_p2_iso_1mm

TA:5:25 PAT:2 Voxel size:0.8√ó0.8√ó0.8 mm Rel. SNR:1.00 :tfl

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off

Wait for user to start	Off
Start measurements	single
Routine	
Nr. of slab groups	1
Slabs	1
Dist. factor	50 %
Position	R0.6 P7.9 F1.2 mm
Orientation	S > C-4.6 > T-0.3
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
Slice oversampling	0.0 %
FoV read	250 mm
FoV phase	100.0 %
Slice thickness	0.80 mm
TR	1900.0 ms
TE	2.69 ms
Averages	1
Concatenations	1
Filter	Prescan Normalize, Elliptical filter
Coil elements	HEA;HEP
Contrast	
Magn. preparation	Non-sel. IR
TI	900 ms
Flip angle	9 deg
Fat suppr.	None
Water suppr.	None
Averaging mode	Long term
Measurements	1
Reconstruction	Magnitude
Multiple series	Each measurement
Resolution	
Base resolution	320
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
Accel. factor 3D	1
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	On
Mode	Inplane
Slice resolution	80 %
Slice partial Fourier	Off
Geometry	
Nr. of slab groups	1
Slabs	1
Dist. factor	50 %
Position	R0.6 P7.9 F1.2 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Slice oversampling	0.0 %
Slices per slab	208
Multi-slice mode	Single shot
Series	Ascending
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Water suppr.	None
Special sat.	None
Set-n-Go Protocol	Off

Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Default
Shim mode	Tune up
Adjust with body coil	On
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	Isocenter
Rotation	0.00 deg
R >> L	350 mm
A >> P	263 mm
F >> H	350 mm
Frequency 1H	123.247600 MHz
Correction factor	1
SLoopIRns1 1H	516.861 V
Gain	Low
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Magn. preparation	Non-sel. IR
TI	900 ms
Dark blood	Off
Resp. control	Off
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	Off
Dimension	3D
Elliptical scanning	Off
Averaging mode	Long term
Multi-slice mode	Single shot
Reordering	Linear
Asymmetric echo	Allowed
Bandwidth	160 Hz/Px
Flow comp.	No
Echo spacing	8.1 ms
Turbo factor	166
RF pulse type	Fast
Gradient mode	Fast
Excitation	Non-sel.
RF spoiling	On

TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
Mode	Off

BOLD

Subtract	Off
Save images	On
Autoscaling	Off
Scaling factor	1
Offset	0
Subtrahend	1
Subtraction indices	
StdDev	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off
Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Radial MIP	Off
Save original images	On
Distortion Corr.	Off
Save original images	On
Number of radial views	1
Axis of radial views	L-R
MPR Sag	Off
MPR Cor	Off
MPR Tra	Off

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\T2_axial_tse_576_3.5mm

TA:2:02 PAT:2 Voxel size:0.5√ó0.5√ó3.5 mm Rel. SNR:1.00 :tse_rs

---

Properties

Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	On
Load images to graphic segments	On
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single

Routine

Nr. of slice groups	1
Slices	40
Dist. factor	0 %
Position	R7.3 P16.4 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	R >> L
AutoAlign	---
Phase oversampling	20 %
FoV read	210 mm
FoV phase	100.0 %
Slice thickness	3.5 mm
TR	4000.0 ms
TE	98.0 ms
Averages	1
Concatenations	2
Filter	Prescan Normalize, Elliptical filter
Coil elements	HEA;HEP

Contrast	
TD	0.0 ms
MTC	Off
Magn. preparation	None
Flip angle	136 deg
Fat suppr.	None
Water suppr.	None
Restore magn.	Off
Averaging mode	Long term
Measurements	1
Reconstruction	Magnitude
Multiple series	Each measurement
Resolution	
Base resolution	448
Phase resolution	80 %
Phase partial Fourier	Off
Trajectory	Cartesian
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	46
Reference scan mode	Integrated
Image Filter	Off
Distortion Corr.	Off
TD	0.0 ms
Unfiltered images	Off
Prescan Normalize	On
Normalize	Off
B1 filter	Off
Raw filter	Off
Elliptical filter	On
Mode	Inplane
Geometry	
Nr. of slice groups	1
Slices	40
Dist. factor	0 %
Position	R7.3 P16.4 F1.8 mm
Phase enc. dir.	R >> L
Phase oversampling	20 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	None
Water suppr.	None
Special sat.	None
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
Restore magn.	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L

Coronal	A >> P
Transversal	F >> H
Save uncombined	Off
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Off
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P16.4 F1.8 mm
Rotation	91.50 deg
A >> P	210 mm
R >> L	210 mm
F >> H	140 mm
Frequency 1H	123.247600 MHz
Correction factor	1
VExcit 1H	286.224 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	
1st Signal/Mode	None
Magn. preparation	None
Dark blood	Off
Trajectory	Cartesian
Resp. control	Off
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	On
Dimension	2D
Compensate T2 decay	Off
Averaging mode	Long term
Multi-slice mode	Interleaved
Reduce Motion Sens.	On
Contrasts	1
Bandwidth	189 Hz/Px
Flow comp.	Slice
Allowed delay	60 s
Echo spacing	10.9 ms
Define	Turbo factor
Turbo factor	17
Echo trains per slice	14
RF pulse type	Fast
Gradient mode	Fast
Hyperecho	Off
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
Mode	Off
BOLD	
Subtract	Off
Save images	On
Autoscaling	Off
Scaling factor	1
Offset	0
Subtrahend	1
Subtraction indices	
StdDev	Off
Std-Dev-Sag	Off
Std-Dev-Cor	Off
Std-Dev-Tra	Off

Std-Dev-Time	Off
MIP-Sag	Off
MIP-Cor	Off
MIP-Tra	Off
MIP-Time	Off
Radial MIP	Off
Save original images	On
Distortion Corr.	Off
Contrasts	1
Save original images	On
Number of radial views	1
Axis of radial views	L-R
MPR Sag	Off
MPR Cor	Off
MPR Tra	Off

SIEMENS MAGNETOM Skyra syngo MR D11

\\USER\Saman\DCD\DCD MR094 Adult\ep2d_diff_mddw_64

TA:11:13 PAT:2 Voxel size:2.2√ó2.2√ó2.2 mm Rel. SNR:1.00 :epse

---

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Wait for user to start	Off
Start measurements	single
Routine	
Nr. of slice groups	1
Slices	64
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Orientation	T > C-3.3 > S0.2
Phase enc. dir.	A >> P
AutoAlign	---
Phase oversampling	0 %
FoV read	276 mm
FoV phase	100.0 %
Slice thickness	2.2 mm
TR	9900 ms
TE	100.0 ms
Averages	1
Concatenations	1
Filter	Raw filter, Prescan Normalize
Coil elements	HEA;HEP
Contrast	
MTC	Off
Magn. preparation	None
Fat suppr.	Fat sat.
Fat sat. mode	Weak
Averaging mode	Long term
Delay in TR	0 ms
Reconstruction	Magnitude
Multiple series	Off
Resolution	
Base resolution	128
Phase resolution	100 %
Phase partial Fourier	6/8
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	30

Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	On
Normalize	Off
Raw filter	On
Intensity	Weak
Slope	25
Elliptical filter	Off
Dynamic Field Corr.	Off
Geometry	
Nr. of slice groups	1
Slices	64
Dist. factor	0 %
Position	R7.3 P18.2 F1.8 mm
Phase enc. dir.	A >> P
Phase oversampling	0 %
Multi-slice mode	Interleaved
Series	Interleaved
Nr. of sat. regions	0
Position mode	L-P-H
Fat suppr.	Fat sat.
Special sat.	None
Fat sat. mode	Weak
Special sat.	None
Set-n-Go Protocol	Off
Table position	P
Inline Composing	Off
System	
Body	Off
HEP	On
HEA	On
SP5	Off
SP6	Off
SP7	Off
SP8	Off
SP1	Off
SP2	Off
SP3	Off
SP4	Off
Position mode	L-P-H
Positioning mode	FIX
Table position	H
Table position	0 mm
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Adaptive Combine
AutoAlign	---
Auto Coil Select	Default
Shim mode	Advanced
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Dominant Fat	Off
Assume Silicone	Off
Adjustment Tolerance	Auto
? Ref. amplitude 1H	0.000 V
Position	R7.3 P18.2 F1.8 mm
Rotation	1.50 deg
R >> L	276 mm
A >> P	276 mm
F >> H	141 mm
Frequency 1H	123.247600 MHz
Correction factor	1
AddCSaCSatNS 1H	85.046 V
Gain	High
Table position	0 mm
Img. Scale. Cor.	1.000
Physio	

1st Signal/Mode	None
Magn. preparation	None
Resp. control	Off
Inline	
Inline Composing	Off
Distortion correction	Off
Sequence	
Introduction	Off
Averaging mode	Long term
Multi-slice mode	Interleaved
Bandwidth	1860 Hz/Px
Optimization	None
Free echo spacing	On
Echo spacing	0.66 ms
EPI factor	128
RF pulse type	Normal
Gradient mode	Fast
TX/RX delta frequency	0 Hz
TX Nucleus	None
TX delta frequency	0 Hz
Coil elements	HEA;HEP
Acquisition duration	0 ms
BOLD	
Delay in TR	0 ms
Diffusion mode	MDDW
Diff. weightings	2
b-value 1	0 s/mm¬≤
Diff. weighted images	On
Trace weighted images	On
ADC maps	On
FA maps	On
Mosaic	On
Tensor	On
Distortion Corr.	Off
b-Value >=	0 s/mm¬≤
Exponential ADC Maps	Off
Invert Gray Scale	Off
Calculated Image	Off
Calculated bValue	1400 s/mm¬≤

SIEMENS MAGNETOM Skyra syngo MR D11

Table Of Contents

\\USER
|Saman
| |DCD
| | |DCD MR094 Adult
| | | |localizer
| | | |gre_field_mapping
| | | |RUN 1 moco
| | | |RUN 2 moco
| | | |RUN 3 moco
| | | |t1_mprage_sag_p2_iso_1mm
| | | |T2_axial_tse_576_3.5mm
| | | |ep2d_diff_mddw_64

Appendix B. Adult DCD Checklist (ADC)

The Adult Developmental Coordination Disorder/ Dyspraxia Checklist (ADC) for Further and Higher Education
(Kirby and Rosenblum, 2008)

Please complete the following questionnaire giving as much information as you can.
Please tick boxes as appropriate. It will take you about 10-15 minutes to complete this.
All information given is dealt with in the strictest confidence.

Name: **Completed by:**	**Date of Birth:** **Date completed:**
Address: **Post Code:** **Tel no. or mobile phone no:** **E-mail:** **Name of School/College/University/workplace:**	

Course being studied/place of employment:
……

Year of study (e.g. first year)
……

Are you a: **Part-time student?** ☐ **Full-time student?** ☐

Are you in receipt of:
Disability Student Allowance? ☐ Disability Living Allowance? ☐

Have you been diagnosed with any of the following?
Dyspraxia, Developmental Co-ordination Disorder, Clumsy Child Syndrome ☐
Dyslexia ☐
Attention Deficit Hyperactivity Disorder (ADHD), or ADD ☐
Asperger's Syndrome, Autism Spectrum Disorder ☐
Learning Difficulties, Disabilities ☐
Other ☐

Who diagnosed you?..... Don't know ☐

When were you diagnosed?.....

Section 1: As a child, did you:				
	Never	**Sometimes**	**Frequently**	**Always**
1. Have difficulties with self-care tasks, such as tying shoelaces, fastening buttons and zips?	☐	☐	☐	☐
2. Have difficulty eating without getting dirty?	☐	☐	☐	☐
3. Have difficulty learning to ride a bike compared to your peers?	☐	☐	☐	☐
4. Have difficulties with playing team games, such as football, volleyball, catching or throwing balls accurately?	☐	☐	☐	☐
5. Have difficulty writing neatly (so others could read it)?	☐	☐	☐	☐
6. Have difficulty writing as fast as your peers?	☐	☐	☐	☐
7. Bump into objects or people, trip over things more than others?	☐	☐	☐	☐
8. Have difficulty playing a musical instrument (e.g. violin, recorder)?	☐	☐	☐	☐
9. Have difficulties with organising/finding things in your room?	☐	☐	☐	☐
10. Have others comment about your lack of coordination or call you clumsy?	☐	☐	☐	☐
Total				

Section 2: Do you <u>currently</u> have difficulties with the following items:				
	Never	**Sometimes**	**Frequently**	**Always**
1. Self-care tasks such as shaving or make up?	☐	☐	☐	☐
2. Eating with a knife and fork/spoon?	☐	☐	☐	☐
3. Hobbies that require good coordination?	☐	☐	☐	☐
4. Writing neatly when having to write fast?	☐	☐	☐	☐
5. Writing as fast as your peers?	☐	☐	☐	☐
6. Reading your own writing?	☐	☐	☐	☐
7. Copying things down without making mistakes?	☐	☐	☐	☐
8. Organising/finding things in your room?	☐	☐	☐	☐
9. Finding your way around new buildings or places?	☐	☐	☐	☐
10. Have others called you disorganised?	☐	☐	☐	☐
11. Do you have difficulties sitting still or appearing fidgety?	☐	☐	☐	☐
12. Do you lose or leave behind possessions?	☐	☐	☐	☐
13. Would you say that you bump into things, spill or break things?	☐	☐	☐	☐
14. Are you slower than others getting up on the morning and getting to work or college?	☐	☐	☐	☐
15. Did it take you longer than others to learn to drive? (if you do not drive, please indicate on the paper and describe why you chose not to drive)	☐	☐	☐	☐
16. Do others find it difficult to read your writing?	☐	☐	☐	☐
17. Do you avoid hobbies that require good coordination?	☐	☐	☐	☐
18. Do you choose to spend your leisure time more on your own than with others?	☐	☐	☐	☐
19. Do you avoid team games/sports?	☐	☐	☐	☐
20. If you do a sport, is it more likely to be on your own, e.g. going to the gym, than with others?	☐	☐	☐	☐

	Never	Sometimes	Frequently	Always
21. Do you/did you in your teens/twenties avoid going to clubs/dancing?	☐	☐	☐	☐
22. If you are a driver, do you have difficulty parking a car?	☐	☐	☐	☐
23. Do you have difficulty preparing a meal from scratch?	☐	☐	☐	☐
24. Do you have difficulty packing a suitcase to go away?	☐	☐	☐	☐
25. Do you have difficulty folding clothes to put them away neatly?	☐	☐	☐	☐
26. Do you have difficulty managing money?	☐	☐	☐	☐
27. Do you have difficulties with performing two things at the same time (e.g. driving and listening or taking a telephone message)?	☐	☐	☐	☐
28. Do you have difficulties with distance estimation (e.g. with regard to parking, passing through objects)?	☐	☐	☐	☐
29. Do you have difficulty planning ahead?	☐	☐	☐	☐
30. Do you feel you are losing attention in certain situations?	☐	☐	☐	☐
Section two total				
Section one total				
Questionnaire total [section one + section two]				

Can you describe any compensatory strategies or approaches that you have developed over the years in order to deal with coordination difficulties in your everyday life?

_____

_____

_____

_____

The Dyscovery Centre often conducts research with adults.
Please let us know if you would like to take part in future projects.

Prof Amanda Kirby
The Dyscovery Centre
University of Wales, Newport
Allt-yr-yn Campus
Newport
NP20 5DA
01633 432330 / dyscoverycentre@newport.ac.uk

Appendix C. The Adult DCD/Dyspraxia Checklist (ADC) Instructions for use

(Kirby & Rosenblum, 2008)

Revision of scoring (2011)

About DCD in adults

Developmental Co-ordination Disorder (DCD), also known as Dyspraxia in the UK, is a developmental disorder affecting motor co-ordination. The American Psychiatric Association (APA; 2000) cites the prevalence at 6% for children in the age range of 5–11 years. Having reasonable co-ordination skills is a necessary requisite for nearly all activities of daily living and for full participation in school. The child with DCD usually has difficulties undertaking a range of self-care tasks at home such as feeding and dressing and has difficulties in school with tasks such as handwriting and playing team sports. Presentation of signs and symptoms may vary depending on the age of the child and the demands presented to him or her. As the child grows up new skills may present new challenges. In teen years greater academic and sporting demands may lead in a child who has managed well in primary school to start to have difficulties. Difficulties may include recording information at speed and playing team games. The difficulties may result in lowered self esteem and greater social isolation (Poulsen, Ziviani & Cuskelly, 2007) and increasing peer relationship problems (Dewey et al, 2002).

The diagnostic criteria for Developmental Coordination Disorder (APA, 2000) describe a childhood developmental disorder and may not be appropriate for an older age group. The adult presentation of motor symptoms and signs may have altered because the individual has received intervention or can now adapt or avoid situations or specific tasks. For example, as adults they may avoid playing team games or may use a computer to record information rather than having to write by hand. However, this does not mean the individual no longer has difficulties and these may be seen when he or she tries to acquire new skills such as learning to drive a car.

What is the Adult DCD/Dyspraxia Checklist (ADC)?

The ADC is a useful tool to help identify Developmental Co-ordination Disorder/ Dyspraxia/ movement difficulties in adulthood. There are currently many DCD/Dyspraxia checklists for children but few have been extended to DCD/Dyspraxia in adulthood.

The questionnaire

The ADC has been trialled with over 100 students and young adults in both the U.K. and Israel

and has been shown to effectively identify DCD/Dyspraxia type difficulties in adults. The ADC is divided into three parts.

Background information

The aim of the first part of the questionnaire is to gather background and contact information. Information regarding other/past diagnoses is useful as it allows an understanding of other areas of difficulty that may impact on the individual such as attention or reading difficulties.

Section 1: Childhood history

In order to meet criterion B of the DSM-IV (i.e. having difficulties interfering with activities of daily living and education since childhood), ten questions relate specifically to past motor difficulties in childhood.

Section 2: Current functioning

Section 2 contains items about current functioning. These questions look at areas that have been associated with DCD in childhood such as daily living skills, self organisation, learning new skills, sporting behaviour, leisure behaviour and handwriting. These questions were selected from information gathered from clinical practice working with adults with DCD and with discussion with occupational therapists working with adults with DCD.

Who can use the ADC?

The ADC can be completed by any adult over 16 years of age. Employers or Higher/Further Education staff may wish employees or students to complete the ADC in order to identify areas of strengths, weakness and areas that need further support. Additional information from other sources such as parent, teacher or employer may be useful also to gain a more complete picture and to corroborate information and /or difficulties.

How do I complete the ADC?

The ADC should take 10-15 minutes to complete. The checklist is simple to complete and contains instructions throughout. Once complete, the checklist can be scored using the attached scoring sheet. It is not a diagnostic tool but can be useful in highlighting areas of difficulty and identifying the need for further diagnosis, assessment or support.

Scoring and interpretation of the ADC

In order to get a joint score the adult needs to complete Section 1 (as a child) and Section 2 (current functioning)

Each question is allocated a score as follows:

Never = 0

Sometimes = 1

Frequently = 2

Always = 3

Add Section 1 and Section 2 to give an overall total

The individual requires a score of at least 17 in Section 1 in order to meet the criteria of having past difficulties in childhood.

If this is the case, then the combined score can be calculated.

A score of:

56 + = DCD at risk 65+ =Probable DCD

Additional note:

Differential Diagnosis

Some individuals may score high on the ADC but may not have DCD. Individuals with visual impairment and visual perceptual difficulties alone may have difficulties with co-ordination. Look at the pattern of difficulties in the answers.

Someone who has Cerebral Palsy could have similar scores on many of the questions.

Some individuals have poor motor function but may have Joint Hypermobility Syndrome-these individuals often have pain on writing, and flexible fingers.

Individuals with cognitive impairments will have a marked increased risk of motor impairments, especially if it is below 70. Be aware someone that presents with a global pattern of difficulties in a number of domains, this may not be representing a specific learning difficulty. For this reason, the diagnosis is usually not given below 70 as there is a much higher frequency of motor difficulties.

Deteriorating motor ability is a 'red flag' and advice should be sought from a GP, or neurologist.

Pain on movement should also seek additional guidance.

*****Gaining a multiple informant view point**

Always try to look at the pattern of difficulties being presented. Take a past history in childhood. Seek additional information from individual, parent (where possible), school, and/or present employer/lecturer to gain as full history as possible. There is not one test that will diagnose DCD in adults but best practice suggests the need for triangulation of information.

Someone who has scored low in past difficulties in childhood is very unlikely to have DCD. Their recall may be poor and seeking past historical information on childhood functioning should be sought through from enquiry from parents, old school reports etc.

Additional sources of information to assist with screening

Look at handwriting *quality, speed, accuracy*- usually individuals with DCD have poor control in writing, variable letter formation, poor spacing and difficulty maintaining writing along a line leading to poor legibility.

Co-existing difficulties

Dyslexia, ASD, Dyscalculia and ADHD commonly coexist with DCD.

Consider ADHD where the individual has poor organisation, and time management difficulties as well as impulsive behaviour and poor attention skills.

Consider Dyslexia where there are writing difficulties alone. Some individuals will present with poor handwriting who have Dyslexia, because of difficulty in spelling words. In a copy task these individuals should perform better than in a free writing task. The form of the letter formation is usually more consistent in these individuals than in those with a predominant motor difficulty, even though it may appear 'untidy' and slower to produce.

Consider ASD where an individual has difficulties socialising with others, has poor group interaction,

Appendix D. Adult ADHD Self Report checklist (ASR-V1.1)

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions

The questions on the back page are designed to stimulate dialogue between you and your patients and to help confirm if they may be suffering from the symptoms of attention-deficit/hyperactivity disorder (ADHD).

Description: The Symptom Checklist is an instrument consisting of the eighteen DSM-IV-TR criteria. Six of the eighteen questions were found to be the most predictive of symptoms consistent with ADHD. These six questions are the basis for the ASRS v1.1 Screener and are also Part A of the Symptom Checklist. Part B of the Symptom Checklist contains the remaining twelve questions.

Instructions:

Symptoms

1. Ask the patient to complete both Part A and Part B of the Symptom Checklist by marking an X in the box that most closely represents the frequency of occurrence of each of the symptoms.

2. Score Part A. If four or more marks appear in the darkly shaded boxes within Part A then the patient has symptoms highly consistent with ADHD in adults and further investigation is warranted.

3. The frequency scores on Part B provide additional cues and can serve as further probes into the patient's symptoms. Pay particular attention to marks appearing in the dark shaded boxes. The frequency-based response is more sensitive with certain questions. No total score or diagnostic likelihood is utilized for the twelve questions. It has been found that the six questions in Part A are the most predictive of the disorder and are best for use as a screening instrument.

Impairments

1. Review the entire Symptom Checklist with your patients and evaluate the level of impairment associated with the symptom.

2. Consider work/school, social and family settings.

3. Symptom frequency is often associated with symptom severity, therefore the Symptom Checklist may also aid in the assessment of impairments. If your patients have frequent symptoms, you may want to ask them to describe how these problems have affected the ability to work, take care of things at home, or get along with other people such as their spouse/significant other.

History

1. Assess the presence of these symptoms or similar symptoms in childhood. Adults who have ADHD need not have been formally diagnosed in childhood. In evaluating a patient's history, look for evidence of early-appearing and long-standing problems with attention or self-control. Some significant symptoms should have been present in childhood, but full symptomology is not necessary.

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date					
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.			Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?							
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?							
3. How often do you have problems remembering appointments or obligations?							
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?							
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?							
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?							
							Part A
7. How often do you make careless mistakes when you have to work on a boring or difficult project?							
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?							
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?							
10. How often do you misplace or have difficulty finding things at home or at work?							
11. How often are you distracted by activity or noise around you?							
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?							
13. How often do you feel restless or fidgety?							
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?							
15. How often do you find yourself talking too much when you are in social situations?							
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?							
17. How often do you have difficulty waiting your turn in situations when turn taking is required?							
18. How often do you interrupt others when they are busy?							

The Value of Screening for Adults With ADHD

Research suggests that the symptoms of ADHD can persist into adulthood, having a significant impact on the relationships, careers, and even the personal safety of your patients who may suffer from it.[1-4] Because this disorder is often misunderstood, many people who have it do not receive appropriate treatment and, as a result, may never reach their full potential. Part of the problem is that it can be difficult to diagnose, particularly in adults.

The Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist was developed in conjunction with the World Health Organization (WHO), and the Workgroup on Adult ADHD that included the following team of psychiatrists and researchers:

- **Lenard Adler, MD**
  Associate Professor of Psychiatry and Neurology
  New York University Medical School

- **Ronald C. Kessler, PhD**
  Professor, Department of Health Care Policy
  Harvard Medical School

- **Thomas Spencer, MD**
  Associate Professor of Psychiatry
  Harvard Medical School

As a healthcare professional, you can use the ASRS v1.1 as a tool to help screen for ADHD in adult patients. Insights gained through this screening may suggest the need for a more in-depth clinician interview. The questions in the ASRS v1.1 are consistent with DSM-IV criteria and address the manifestations of ADHD symptoms in adults. Content of the questionnaire also reflects the importance that DSM-IV places on symptoms, impairments, and history for a correct diagnosis.[4]

The checklist takes about 5 minutes to complete and can provide information that is critical to supplement the diagnostic process.

References:
1. Schweitzer JB, et al. Med Clin North Am. 2001;85(3):10-11, 757-777.
2. Barkley RA. Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 2nd ed. 1998.
3. Biederman J, et al. Am J Psychiatry.1993;150:1792-1798.
4. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association. 2000: 85-93.

Appendix E. Adult Participant Explanatory Statement and Consent form for DCD study

ADULT PARTICIPANT EXPLANATORY STATEMENT
AND CONSENT FORM

Study Title: Understanding the neural basis of motor skill impairment.

Study Investigators: Dr Jacqueline Williams, Lecturer/Research Fellow, Victoria University; Prof Gary Egan, Monash University

Study Site Address:
Monash Biomedical Imaging
Monash University
770 Blackburn Road, Clayton
VIC 3800

Thank you for taking the time to read this Explanatory Statement. This Explanatory Statement and Consent Form is 7 pages long. Please make sure you have all the pages.

1. Introduction

You are invited to participate in a research project that is explained below. This Explanatory Information and Consent Form contain detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Explanatory Information and Consent Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Participation in this research project is voluntary. If you don't want to take part, you don't have to. You can withdraw from the project at any time without explanation.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form (page 6). By signing the Consent Form, you

indicate that you understand the information and that you give your consent to participate in the research project.
You will be given a copy of the Participant Information and Consent Form to keep as a record.

2. Purpose of the study.

This project is about individuals with Developmental Coordination Disorder (DCD). In Australia, DCD can also be referred to as Dyspraxia. DCD is mostly diagnosed in children who have trouble with their motor skills – everyday tasks such as writing, cutting, throwing, running and balancing are difficult to do smoothly. They appear to be healthy children but are described as 'clumsy'. Because they appear healthy, many children are not ever given a diagnosis and are simply considered clumsy. Approximately 50% of children with motor skill problems continue to be 'clumsy' into adulthood. Because DCD is a relatively new diagnosis, there are many adults who, as children, were considered 'clumsy' but never given any official diagnosis and these adults continue to have difficulty with their motor skills today.
Unfortunately, the causes of DCD are not known, but the motor problems are thought to be linked to the way the brain plans and controls movements.
When we plan movements, we first play the movement out in our minds at a subconscious level, to ensure we pick the right movement to achieve a given goal. It is thought that individuals with DCD have difficulty playing this movement out accurately in their brains. We can measure this by asking them to imagine performing particular movements and looking at how accurately they can do this.
We have found that children with DCD are less accurate at imagining movements than other children their age. We would like to find out if adults who are clumsy have the same difficulty imagining movements accurately. Also, to understand why individuals with DCD are less accurate, we need to look at how the brain is working when they are imagining movements. This study will allow us to do this by asking children and adults to imagine movement whilst in a brain scanner and comparing it to the brain activity of children and adults without motor skill impairment.
We hope a total of 10 children, aged 8-12 years, and 20 adults, aged 18-40, will take part in this study.

3. Who is funding this research project?

This research is being funded by the Victoria University Research Development Grant Scheme.

4. Why am I being asked to be in this research project?

We are asking you because you are aged 18-40 years and you have indicated that either you believe that your motor skills are typically developed or they are below that expected for your age.

5. What do I need to do to be in this research project?

We will gather information from you about your medical history and motor skill development, to ensure you are suitable for the study. This can be done over the phone or by mail and will take approximately 20 minutes to complete.

If you are suitable, we would like to complete a screening and behavioural assessment with you. This will take place at Monash University, Clayton. The assessment will take approximately 45 minutes and will involve the following tasks:

Movement skill tasks: There are 10 tasks that assess aspects of fine and gross motor skills. The tasks involve movements like those you would do in everyday life; such as picking up objects, balancing and strength activities. The results of these tasks will allow us to determine if you are suitable for the rest of the study. If you are, you will also complete the tasks below.

Computer based tasks: In the first task, you will need to imagine a movement to allow you to answer a question about a picture on the screen. In the second task, you will need to imagine a letter or number rotating from a rotated position to an upright one, to determine whether it is facing in its correct direction or mirror-reversed. For these tasks, you will sit at a desk in front of a computer screen and press one of two buttons in response to the picture on the screen.

Imagined pointing task: This task will require you to perform a tapping movement back and forth between two targets and then imagine performing the same movement – we will use a stopwatch to time how long it takes to actually perform it and compare it to how long it takes to imagine it.

MRI scan: Following this assessment, we would like you to have an MRI brain scan. This will take place in MRI Centre at the Monash Biomedical Imaging, Monash University, Clayton and will take about 1.5 hours.

MRI stands for magnetic resonance imaging. A MRI scanner is a machine that uses electromagnetic radiation (radio waves) in a strong magnetic field to take clear pictures of the inside of the body. Electromagnetic radiation is not the same as ionising radiation used, for example, in X-rays. The pictures taken by the machine are called MRI scans.

You may first take part in a mock MRI session to familiarise you with the MRI process. We will then complete an actual MRI scan whilst you complete a computer-based movement imagination task, so that we can learn how the brain is active during the

imagination of movement.

We will ask you to lie on a table inside the MRI scanner. The scanner will record information about your brain while you complete the movement imagination task. It is very important that you keep very still during the scanning. When you lie on the table we will make sure you are in a comfortable position so you can keep still. The scanner is very noisy and we can give you some earphones to reduce the noise.

6. What are the possible risks, side-effects and/or discomforts?

The motor skill tasks you will be asked to do as part of this project carries a minor risk of injury, no greater than when you move around your natural environment. All of the tasks will be completed indoors in a secure environment, with staff that have extensive experience in assessing movement abilities.

MRI information and risks:

An MRI scan does not use any ionising radiation; instead it relies on magnetic fields and radio waves. Currently there are no known adverse effects of MRI magnetic fields and radio waves on humans.

MRI is considered a safe procedure when performed at a centre with appropriate guidelines. However, the magnetic attraction for some metal objects can pose a safety risk, so it is important that metal objects are not taken into the scanner room. We will thoroughly examine you to make sure there is no reason for you not to have the scan. You must tell us if you have metal implanted in your body, such as a pacemaker, or metal pins after being involved in an accident.

The MRI scan could be inconvenient because you must remain very still while in the scanner. There is also a lot of machine noise during scanning.

Some people (approximately 3-5%) find lying in the MRI scanner claustrophobic; if you do experience discomfort during your scan, you will be able to communicate immediately with MRI operators to ask to be removed from the scanner.

Some people may notice warmth and/or minor tingling during some scans. This is nothing to worry about, and is caused by the magnetic fields generated by the scanner. Once again if you feel uncomfortable you can ask to be removed from the scanner.

What happens if something unusual is found in my scans?

The scans we are taking are for research purposes. They are not intended to be used like scans taken for a full clinical examination. The scans will not be used to help diagnose, treat or manage a particular condition. We cannot guarantee that we will find any/all unusual features.

Very occasionally (in approximately 2% of cases), the images of participants may show anatomical abnormalities. It may be necessary to do further tests to establish whether an abnormality is truly present. Some findings may have no negative implications for your health, and are called incidental. However, in about 1% of scans, the imaging abnormality may represent a risk to your health, and are called adverse findings. In many cases, there are effective treatments available for adverse findings, but sometimes there are adverse findings for which no effective treatment is currently available. Knowledge of an adverse finding may have implications for your private health insurance. All of the scans obtained will be reviewed by a radiologist and their report will be held securely and confidentially at Monash Biomedical Imagining.

In the unlikely event that the radiologist does find an adverse or incidental finding, they will contact your nominated doctor to communicate this.

Please take time to consider the advantages and disadvantages of discovery of a health risk before deciding to take part in this research project.

7. What are the possible inconveniences?

Time is the major inconvenience associated with participating in this study. We will try our best to arrange appointments at times that suit you.

8. What are the possible benefits for me?

There is no direct benefit to you. We will send you a written report on how you performed on the movement skill tasks in the weeks following you assessment. If there are any concerns about your assessment results, we will contact you by telephone to discuss them.

9. What are the benefits for other people in the future?

We hope to use the information from this project to develop a training program that will improve the ability of children and adults with DCD to plan movements. We hope that this will improve their movement skills, and that in time, these training programs will be readily available for children and adults with motor skill difficulties.

10. What happens to the information collected about me as part of the study and will it be kept private?

Any information we collect for this research project that can identify you will be treated as confidential. We can disclose the information only with your permission, except as required by law.

Motor assessment data will be stored securely in the Institute of Sport, Exercise and Active Living at Victoria University and brain imaging data will be stored securely at Monash Biomedical Imaging.

The following people may access information collected as part of this research project:

- the research team involved with this project
- The Monash University Human Research Ethics Committee

The information will be re-identifiable. This means that we will remove your name and give the information a special code number. Only the research team can match your name to your code number, if it is necessary to do so.
We will keep the information until the youngest participant in this project turns 25 years old. After this time, it will be destroyed.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to access and correct the information we collect and store about you. Please contact us if you would like to access your information.

When we write or talk about the results of this project, information will be provided in such a way that you cannot be identified. If you would like, the results of the study can be sent to you by newsletter or summary format. It is important to know that results may not be known until well after your participation in the study is completed.

11. What are the costs of taking part in the study?

You will not be expected to pay for any of the tests being conducted. The only expense to you will be the cost of transport to MBI, Clayton. You will not be required to pay for parking at MBI.

12. Will I be paid for taking part in the study?

You will not be paid for your participation in this study.

13. What are my alternatives to taking part in this project? Can the Study Researcher remove me from the study if I ask?

Participation in any research project is voluntary. You do not have to take part if you do not want to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do so, you may also ask to have any information relating to you collected so far to be removed from the project.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. It is important that you sign the consent form (page 6) only after you have had a chance to ask your questions and have received satisfactory answers. If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

Non participation will not affect your ability to participate in further research.

14. Who has reviewed the study?

This project has been reviewed and approved by **Monash University Human Ethics Research Committee.**

15. What if I have questions about the study?

If you would like more information about the project or if you need to speak to a member of the research team in an emergency please contact:

Name: **Dr Jacqueline Williams**

Victoria University

Contact telephone: **03 9919 4025**

Name: **Prof Gary Egan**

Monash University

Contact telephone: **03 9902 9750**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact;

Monash University Human Ethics Research Committee,
Executive Officer
Monash University Human Research Ethics Committee (MUHREC)
Building 3e Room 111
Research Office
Monash University VIC 3800
Tel: +61 3 9905 2052
Email: muhrec@monash.edu

CONSENT FORM

Title: Understanding the neural basis of motor skill impairment.

NOTE: **Signed written consent will remain with the Monash University researcher for their records.**

1. **The study has been explained to me. I have read and understand the information provided in this Informed Consent Form. I have had the opportunity to ask questions and have had these questions answered satisfactorily.**

2. **I have had time to consider the information provided in this Informed Consent Form to consider answers to my questions, and to consider whether I wish to take part in the study.**

3. **I understand that taking part in the study is voluntary and that I am free to leave the study at any time, without giving any reason.**

4. **I agree to the use and release of study-related information about me for the purposes described in this Informed Consent Form.**

5. **I understand that my consent continues forever but that I can withdraw my consent at any time by giving notice to the Study Doctor. I understand that if I withdraw my consent I will not be**

able to continue to take part in the study.

6. **I understand that if I withdraw consent, the study researchers will no longer use or release information that has been collected about me prior to my withdrawal.**

7. **I understand that I will receive a copy of this signed and dated Informed Consent Form.**

I agree to take part in the above Monash University research project. The project has been explained me, and I have read the Explanatory Statement, which I will keep for my records.
I understand that agreeing to take part means that I am willing participate in all stages of the research including behavioural tasks and MRI scanning

☐**Yes** ☐**No**

Full name: _____

Signature: _____ Date: _____

Researcher:

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

_____ _____ _____

Name **Signature** **Date**

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

Disclosure of MRI results

I would like to be advised of:

Please tick appropriate box

(a) Any incidental finding that may require treatment, or may have implications for my future health ☐

(b) Only those adverse findings that require that I have urgent treatment ☐

In the event of there being an incidental or adverse finding, I would like the following doctor to be advised:

Name _____.

Address _____

Phone _____

Appendix F. Noticeboard flyer for DCD study recruitment

Did you feel clumsy as a child?

Do you still feel clumsy?

VICTORIA UNIVERSITY | A NEW SCHOOL OF THOUGHT

We are conducting a research study examining motor skill planning.
We are looking for **adults aged 18-40**, who felt clumsy as a child and still experience motor problems in daily life, as well as adults in the same age range who think their motor skills are fairly typical to participate in our research study.

What does participation involve?

You will be asked to complete some questionnaires your motor development and developmental history.
You will complete a motor skill assessment and some tasks where they are required to imagine movements.
Eligible participants will undergo a MRI (magnetic resonance image) scan whilst imagining movements, to allow us to look at brain activity during this task.

If you would like more information about the study or would like to participate, please contact
Dr Jacqueline Williams on **9919 4025**
or email jacqueline.williams@vu.edu.au

Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025; jacqueline.williams@vu.edu.au	Adult Motor Skills Project Dr Jacqueline Williams: 9919 4025;

Appendix G. E-bulletin information

MONASH University Biomedical Imaging

VICTORIA UNIVERSITY | A NEW SCHOOL OF THOUGHT

Did you feel clumsy as a child? Do you still feel clumsy?

We are conducting a research study examining motor skill planning.

We are looking for **adults aged 18-40**, who felt clumsy as a child and still experience motor problems in daily life, as well as adults in the same age range who think their motor skills are fairly typical to participate in our research study.

What does participation involve?

You will be asked to complete some questionnaires your motor development and developmental history.

You will complete a motor skill assessment and some tasks where they are required to imagine movements.

Eligible participants will undergo a MRI (magnetic resonance image) scan whilst imagining movements, to allow us to look at brain activity during this task.

If you would like more information about the study or would like to participate, please contact **Dr Jacqueline Williams** on **9919 4025** or email jacqueline.williams@vu.edu.au.

Appendix G. MRI Pre-scanning screening questionnaire

MONASH University Biomedical Imaging

VICTORIA UNIVERSITY | A NEW SCHOOL OF THOUGHT

Understanding the neural basis of motor skill impairment.

Study eligibility questionnaire.

This questionnaire is designed to help us ensure you are eligible to participate in our study.

Please answer all of the questions to the best of your knowledge.

Your name:

_____

Your date of birth: ___/___/____ (dd/mm/yy)

Your gender (please tick): Male ___ Female ___

What is the main language spoken at home?

_____

Have you ever been diagnosed with, or suspected of having, any of the following:

	Diagnosed		Suspected
Attention Deficit / Hyperactivity Disorder			
Developmental Coordination Disorder or Dyspraxia			
Intellectual Disability			
Pervasive Development Disorder / Autism / Asperger's Syndrome			
Any other physical or neurological condition that could cause motor skill impairment,(e.g. cerebral palsy, muscular dystrophy, Tourette's syndrome)*			
Any neurological disease or history of head injury*			

* If yes, please provide details of the condition:

_____

__

	Yes		No
Do you suffer from claustrophobia (fear of confined spaces)?			
Do you have any magnetic implants and/or metallic materials in their body?			

We would appreciate you filling out the attached questionnaires.

Appendix H. MBI MRI Safety form

MONASH University
Biomedical Imaging

Telephone: 9902 9752

SUBJECT RESPONSE FORM & MRI SAFETY QUESTIONNAIRE

These questions are asked for your safety. Your answers will help us decide if there is anything in your body which might make it unsafe for you to have an MRI scan. Please read and answer the questions carefully; please ask us if there is anything that is not clear to you.

Subject's Name .....

Address .....

..... Phone .....

Date of birth .....

Approx. weight ..... (kgs) Approx. height .....(cm)

GENERAL QUESTIONS

Do you feel uncomfortable in enclosed spaces? (Are you claustrophobic?) ..... Yes / No

Do you suffer from asthma? ..... Yes / No
or kidney disease? ..... Yes / No

In the **last six weeks**, have you had any operations? ..... Yes / No

Please list any medications you are taking

.....

Do you take any medicines as a patch placed on your skin? ..... Yes / No

Are there any medicines to which you are allergic? ..... Yes / No

Please list .....

HAVE YOU EVER:

Been injured by a bullet, pellet or shrapnel? ..... Yes / No

At **any** time in your life, have you had an injury to your eyes with metal..... Yes / No
- if Yes, was the metal removed? .....

By whom? .....

Worked as a welder? ..... Yes / No

Had any surgical operations that involved metal? ..... Yes / No

If yes. nature and date .....

FEMALE PATIENTS ONLY:

Is there any chance that you may be pregnant? ..... Yes / No

Are you breastfeeding? ..... Yes / No

Do you have a breast implant/expander ? Yes / No

DO YOU HAVE ANY OF THE FOLLOWING

Heart pacemaker ..... Yes / No

Defibrillator ..... Yes / No

Neurostimulator ..... Yes / No

Cochlear implant ("bionic ear") ..... Yes / No

Other electronic or magnetic implant ..... Yes / No

Aneurysm clip (inside your head) ..... Yes / No

Heart valve ..... Yes / No

Pacing wires ..... Yes / No

Vascular stents, filters, coils ..... Yes / No

Brain shunt tube ..... Yes / No
If yes, is it programmable ..... Yes / No

Internal or external (eg Graseby) infusion pumps ..... Yes / No

Vascular access device (Swan-Ganz catheter etc.) ..... Yes / No

Penile prosthesis ..... Yes / No
Yes / No
Joint prosthesis/replacement ..... Yes / No

Metal pins, rods, nails or screws in your bones? ..... Yes / No

Hearing aid ..... Yes / No

Denture ..... Yes / No

Tattooed eyelids, tattoos or body piercing ..... Yes / No

Intrauterine device (IUD) ..... Yes / No

OFFICE USE ONLY:

MBI Subject Code .....

Date received .....

Form completed by: .....
(subject)

Reviewed by: .....
(radiologist/MIT)

MONASH University
Biomedical Imaging

Telephone: 9902 9752

MRI SERVICE – SUBJECT INFORMATION

WHAT IS MRI? ARE THERE ANY RISKS?

Magnetic Resonance Imaging (MRI) uses radio waves and very strong magnetic fields to make detailed pictures of the inside of your body.

There are no known harmful effects, from the either the radio waves or the magnetic field, on your body.
However, some people have electronic devices (such as cardiac pacemakers), metal fragments in the eye, or surgically implanted metal objects, which could be badly affected by the strong magnetic field. You will be given a detailed safety questionnaire about such objects, to help us decide if there would be any risk to you during an MRI scan.

PREPARATION

Except for special cases (scans with sedation, MRCP scans), no preparation is necessary – please eat, drink and take usual medications normally.

Please do not use makeup or hairspray if you are having a scan of the head, face, or neck.

Please do bring films of any previous MRI or CT scans, ultrasounds, or X-rays of the body part that is to be scanned.

WHAT WILL HAPPEN?

We will review the questionnaire sheet with you, to double-check any possible risks.

We will then explain the scanning procedure to you, and will be happy to answer any questions you may have.
You can also ring us in advance – 9902 9752

Before you enter the MRI scan room, you will be asked to take off your watch and any metallic jewellery, and to change into a hospital gown. Items such as CREDIT CARDS, PAGERS, and MOBILE PHONES MUST NOT be brought into the scan room – they may be severely damaged, and may also be hazardous to other persons in the room. A locker will be provided for safekeeping of such objects, other valuables, and clothing.

The MRI machine looks like a large metal doughnut. The table on which you lie passes through the middle of the doughnut; the part of the body being scanned must be positioned at the centre of the doughnut. Cushions and pillows will be provided to make you comfortable on the table, and mirrors will allow you to see out of the "doughnut".

During the scan, it is important that you keep as still as possible - particularly when the scanner is making noises. You will hear various clicking, tapping, buzzing and banging noises during the scan - these are quite normal. They are sometimes quite loud, and headphones or earplugs will be provided to protect your ears. If you wish, music of your choice can be played through the headphones during the scan. The scan will take between 15 and 45 minutes. At all times, you will be able to talk to us through an intercom system built into the MRI machine. We will speak to you periodically, through this system, throughout the scan.

ARE THERE ANY INJECTIONS?

A minority of subjects will need an injection of a "contrast agent" during the scan, to help us best assess your condition. This injection is usually made through a small needle in an arm vein, and is painless, apart from the initial slight needle-sting. The contrast agent is rapidly excreted, and side effects are very rare.

Some people do not tolerate the confined space of the MRI machine.

It is almost always possible for such people to have scans with the assistance of a mildly sedating injection. If you know that you find enclosed spaces uncomfortable, please let us know in advance, so that we can have things ready for an injection if needed. If you do need an injection, you should not drive, operate heavy machinery, or make significant decisions for the rest of that day. You will need a friend, colleague or relative to accompany you home.

AFTER THE TEST

Once the scan is completed, you will be free to get dressed and go, unless you needed a sedating injection (after which a short period of observation may be required).

There will be no after-effects from the scan. The MRI scans will be interpreted and reported by an MRI radiologist on the day the test is performed, and the results sent to your doctor thereafter.

Appendix I. MRI sequence parameters in for MTR pilot study

T1 weighted vs T2 weighted images used to acquire MTR images results for finding optimum MTI protocol with higher MTR (Magnetic Transfer Ratio) values

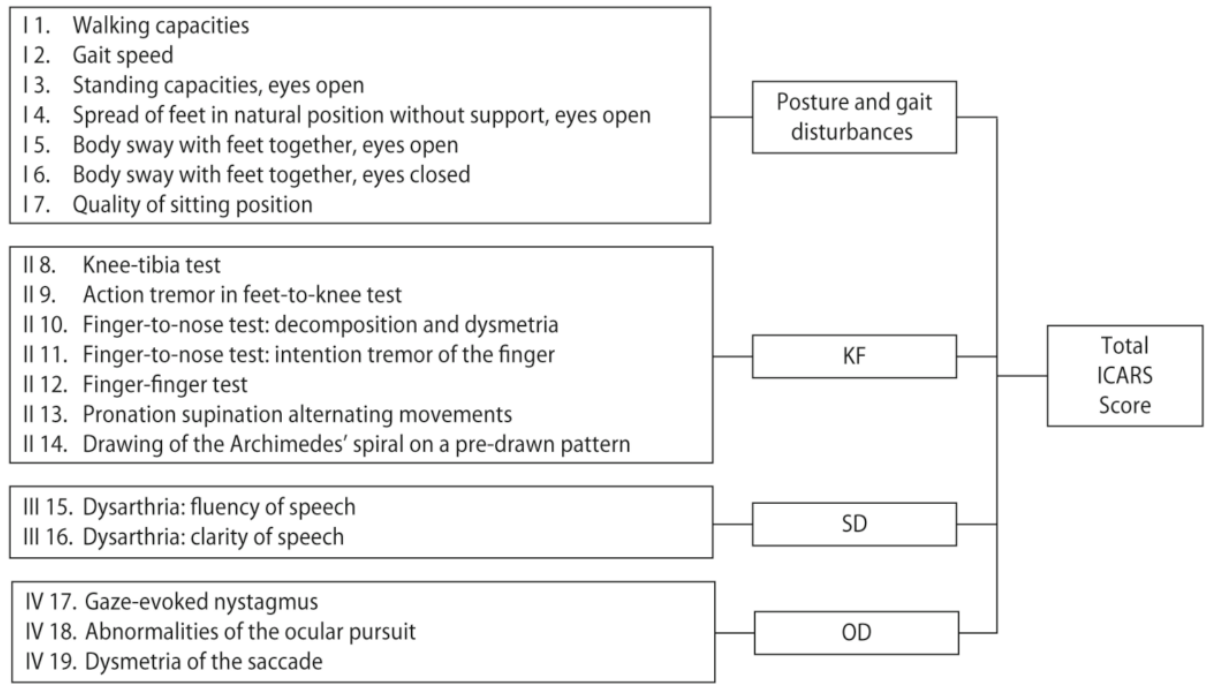
T1 Weighted imaging protocol

Scan	MT T2_2d	MT M0 T2_2d
Sequence name	t2_fl2d_tra_ MT IPat2	t2_fl2d_tra_I Pat2
Acq time (mins)	4:23	4:23
FOV (mm)	230x172.5	230x172.5
Matrix	256x205	256x192
Voxel size (mm)	0.9x0.9x3.0	0.9x0.9x3.0
Slices	46	46
Slice thickness(mm)	3.0	3.0
Gap(mm)	no	no
TR (ms)	734	734
TE (ms)	8.40	8.40
TI (ms)	-	-
Flip angle	30	30
ETL	-	-
Turbo factor	-	-
Echo spacing (ms)	-	-
IPAT factor	2(GRAPPA)	2(GRAPPA)
Averages	2	2
Prescan Normalize	off	off

T2 Weighted imaging protocol

MT T1_3d	MT M0 T1_3d
T1_fl3d_tra_MT IPat2	T1_fl3d_tra IPat2
2:56	2:56
240x202.5	240x202.5
320x270	320x270
0.9x0.9x3.0	0.9x0.9x3.0
52	52
3.0	3.0
10	10
36	36
4.9	4.9
-	-
25	25
-	-
-	-
-	-
2(GRAPPA)	2(GRAPPA)
1	1
off	off

Appendix J. International Cooperative Ataxia Rating Scale (ICARS) for Friedreich's Ataxia



Appendix K. FRDA MRI Protocol

Scan	Gradient field map	Functional OM task runs	Accelerated MT	Accelerated MT N0	12 Directions DTI	T1	Rest fMRI
Sequence name	gre_field_mapping 3mm	Run1-4_ep2d_p2_3mm	t2_fl2d_tra_MT IPat2	t2_fl2d_tra_IPat2	ep2d_diff_b3000_12_	t1_mprage_sag_p2_iso_0.6	Run 5 REST_eyes open
Acq time (mins)	1:00	5:42	4:23	4:23	4:16	6:06	4:59
FOV (mm)	192x192	192x192	230x172.5	230x172.5	256x256	240x240	192x192
Matrix	64x64	64x64	256x205	256x205	128x128	192x192	64
Voxel size (mm)	3x3x3	3x3x3	0.9x0.9x3.0	0.9x0.9x3.0	2x2x2	0.6x0.6x0.6	3x3x3
Slices	44	44	46	46	70	256	44
Slice thickness(mm)	3.0	3.0	3.0	3.0	2.0	0.6	3.0
Gap	no	no	no	no	no	no	no
TR (ms)	447	2500	734	734	15900	1900	2500
TE (ms)	4.92	30	8.40	8.40	111	2.43	30
TI (ms)	-	-	-	-	-	900	-
Flip angle	60	90	30	30	-	9	90
ETL	-	-	-	-	-	-	-
Turbo factor	102	-	-	-	-	256	-
Echo spacing (ms)	10.6	0.65	-	-	0.66	6.3	0.65
IPAT factor	off	2(GRAPPA)	2(GRAPPA)	2(GRAPPA)	2(GRAPPA)	off	2(GRAPPA)
Averages	1	1	2	2	1	1	1
Prescan Normalize	on	On	off	off	on	on	on
Other					Phase partial fourier = 6/8		

Appendix L. Adult Participant Explanatory Statement and Consent form for FRDA study

PARTICIPANT INFORMATION STATEMENT

AND CONSENT FORM

MONASH University
Biomedical Imaging

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

FRDA participant information and consent form

The Royal Children's Hospital, Melbourne

Flemington
Road, Parkville
Victoria, Australia, 3052

Telephone (03) 9345 5522
ISD (+613) 9345
5522

Facsimile (03) 9345 5789
Web
www.rch.org.au

STANDARD PARTICIPANT INFORMATION STATEMENT

AND CONSENT FORM

Project Number: EHRC 26147 A

Title of Project: A functional magnetic resonance imaging (fMRI) study addressing cognitive function in individuals with Freidreich's Ataxia.

Investigators: Professor Nellie Georgiou-Karistianis, Professor Martin Delatycki, Professor Gary Egan, Professor Elsdon Storey, Dr Hamed Akhlaghi, Dr Louise Corben and Dr Saman Kashuk

Thank you for taking the time to read this Information Statement.
This information statement and consent is 6 pages long. Please make sure you have all the pages.

For people who speak languages other than English:
If you would also like information about the research and the Consent Form in your language, please ask the person explaining this project to you.

You are invited to participate in a Research Project that is explained below.

What is an Information Statement?

These pages contain information about a research project we are inviting you to take part in. The purpose of this information is to explain to you clearly and openly all the steps and procedures of this project. The information is to help you to decide whether or not you would like to take part in the research.

Please read this information carefully. You can ask us questions about anything in it. You may also wish to talk about the project with your parents or guardians, friends or health care worker. Once you have understood what the project is about, if you wish to take part please sign the consent form at the end of this information statement. You will be given a copy of this information and consent form to keep

What is the Research Project about?
This research project aims to use functional magnetic resonance imaging (fMRI) to identify what brain regions are active as participants perform a simple computer task. fMRI is a type of brain imaging which provides pictures of brain function, rather than just brain structure, and is often used by doctors to localise areas of the brain that control language and limb movement prior to surgery. Brain imaging studies to date in Friedreich Ataxia have been very limited. The aim of this project is to use fMRI to find which parts of the brain are activated in response to the task.

We are studying people with Friedreich Ataxia (FRDA) so as to obtain a better understanding of how the brain functions in people with this condition. We plan to include approximately twenty people with Friedreich Ataxia. We also plan to include ten

people with Spinocerebellar Type 6 (SCA6) in order to further study effect of cerebellar changes on brain function. We will also include twenty age and sex matched control participants so as to obtain images of brain functioning in people without Friedreich Ataxia which will enable comparison with the images from people with Friedreich Ataxia and Spinocerebellar Type 6.

Who are the Researchers?
The researchers are doctors and scientists who have expertise in Friedreich ataxia and fMRI, from;
Monash University;
Professor Nellie Georgiou-Karistianis (Experimental Neuropsychology Research Unit, School of Psychology and Psychiatry,) a neuroscientist who has particular interest and expertise in the cognitive aspects of neurological conditions;
Professor Gary Egan (Director, Monash Biomedical Imaging) a neuroscientist with expertise in brain imaging in neurodegenerative diseases.
the Bruce Lefroy Centre for Genetic Health Research at the Murdoch Childrens Research Institute;
Professor Martin Delatycki, who is a clinical geneticist with expertise in FRDA;
Dr Louise Corben who is undertaking post-doctoral research examining aspects of cognitive function in FRDA.
Professor Elsdon Storey who is a Neurologist with expertise in cerebellar disorders.
Howard Florey Research Institute - Dr Hamed Akhlaghi is undertaking his Masters research in neuroimaging

Why am I being asked to be in this research project?
We are asking you to take part in this project either as someone with FRDA, Spinocerebellar Type 6 or as a control participant. We would like the opportunity to study how your brain functions in response to various tasks. This will assist in understanding what happens in people who have Friedreich Ataxia and may provide simpler and better means to develop and assess future therapies to benefit this area.

What are the alternatives to participating in this project?

If you choose not to take part in this project it will not affect any standard or normal treatment that you receive (such as attendance at the Friedreich Ataxia Clinic held at Monash Medical Centre)

What do I need to do to be in this research project?

If you choose to participate in this research project, you will be visited at home (or attend either the Murdoch Childrens Research Institute or Monash Biomedical Imaging (MBI) research centre if you would prefer) to practice the task you will perform while you are in the MRI scanner. For the fMRI scanning you will have a total of 2 visits to either the Royal Childrens Hospital in Parkville or Monash Biomedical Imaging research centre in Clayton. The second visit will occur 2 years after the first fMRI scan. At each visit the fMRI scanning will be conducted over two sessions lasting from 45 to 60 minutes, with an hour break in between.

Prior to commencing the scanning you will be given a questionnaire to complete which will identify if you have symptoms of depression. If you are identified as showing symptoms of depression you will be advised to seek medical advice. You will also be given some pen and paper activities to complete. These activities will examine how you go about solving problems and concentrating. The questionnaire will ask you questions about how you are feeling. These activities should take around 5 minutes to complete and will then be followed by scanning.

The fMRI session will take two 45- 60 minute sessions with a break in between. During this time you must remain still on a comfortable padded table that goes inside a large tube that is the imaging magnet. Because of the powerful magnetic field you must not bring any metal into the instrument. For you comfort we suggest the following:

Wear loose- fitting, comfortable clothing with no metal zippers or other fittings. You will need to remove your jewelry prior to entering the scanner so wear minimal jewelry. For several hours before the scan it is advisable to avoid drinking tea, coffee and large volumes of other fluid that may require you to go the restroom often (as you will be unable to do so during the duration of the scan). Very rarely, people feel uncomfortable or claustrophobic as a result of lying inside the scanner. If you do feel claustrophobic in the scanner you will be able to communicate this to the researcher and be moved out of the scanner immediately. If you are concerned this may be the case for you please discuss your concerns with the investigator requesting your participation.

Procedure

While you are in the scanner you will be asked to complete a finger tapping task with your right hand. During this time a series of brain recordings will be taken of your head using the fMRI imaging scanner. You will then have an opportunity to get out of the scanner and have a rest period. In the second session you will be asked to perform a simple task that involves responding by pressing a button to the direction of arrows displayed on a computer screen. You will also be asked to complete a mental arthrimetic task while a series of brain recordings are taken.

Is there likely to be a benefit to me?

Whilst there is no direct benefit to you, this technology may assist in assessing therapies which may ultimately benefit those with Friedreich Ataxia.

Is there likely to be a benefit to other people in the future?

We anticipate that this research may result in a technique to assess brain function in Friedreich Ataxia. If those with Friedreich Ataxia have changes in the way their brain functions, treatments may be identified that can reverse these changes or assist those people to manage these changes in their daily lives.

What are the possible risks and side effects for me?

There are no known risks from the fMRI scanning except for dangers associated with metal implants. Bringing metal into the scanner can be dangerous because of the very strong magnetic field. **You must not bring any metal into the MRI scanner**. If you have metal implants, you may not be able to participate. Prior to going into the MRI scanner, you will be asked questions by the MRI technologist to make sure that you can safely be put into the scanner. The MRI scanner is noisy, so you will wear special headphones to reduce the noise. There is no harmful radiation and no need for injections with fMRI scanning.

What are the possible discomforts and/or inconveniences?

The MRI scanner is shaped like a tunnel and is a bit tight for space. It also makes a loud hammering sound. You will wear headphones to lessen the scanner noise. Foam cushioning and Velcro straps are used to keep your head relatively still during scanning. While the cushions and straps are restraining, they should not be uncomfortable. We will be able to see and communicate with you during the scanning. If you are becoming uncomfortable or having difficulty concentrating during the session,

we can stop the scanning and if desired, continue at another time. You can also request that the scanning be stopped at any time by pushing on a button.

The possible inconveniences to you relate mostly to the time that the test takes. We will try to perform the fMRI study at a time of convenience. Free parking is available at the MBI, and
we will reimburse you for the costs of parking at the Royal Childrens Hospital as well as travelcosts.

What happens if something abnormal is found in my scans?

In this study, we will take a limited number of pictures of your brain. These will be for research purposes, not to diagnose or to help manage or treat any particular condition. After your scan, a specialist will examine these pictures. This will not be done on the day of your scan.

Minor changes are sometimes found in completely healthy people. You should be aware that because our pictures are taken for a specific research purpose, not all abnormalities that might be detected by other MRI scans are necessarily seen. On extremely rare occasions, we might find an abnormality in your brain. If this happens one of our doctors will call you at the contact number you supply and discuss the findings with you. Usually, this contact will be made within 2 weeks of your scan. Although detecting a significant abnormality is extremely unlikely, you should be aware that if an abnormality is detected and you are told about it, then this knowledge may have consequences for you. Knowing about an abnormality may affect your ability to work in certain professions, obtain life or health insurance and other facets of daily living. Please take the time to consider carefully what it would mean to you if we told you an abnormality in your brain that might, or might not, affect you in later life. If you do not want to know, then it is better not to participate.

What will be done to make sure the information is confidential?

We will not use your name to identify the test results. Instead, we will use a numeric code to identify participants in our study. We will store all test results in a locked area and on CD-ROMs. We hope to publish the results of our study in a scientific journal and will display any fMRI scans with no references to the identity of individuals. The records dealing with your participation will be kept under safe storage for 7 years after completion, and these records may be inspected for purposes of data audit by authorized persons within the institution (eg; Ethics Committee).

In accordance with relevant Australian and/or Victorian privacy and other relevant laws you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with which you disagree be corrected. Please contact one of the researchers named below if you would like to access your information.

Will I be informed of the results when the research project is finished?
If you wish to know the results of the research project once it has been completed, we would be happy to send you a letter explaining our overall findings

You can decide whether or not to take part in this research project. You can decide whether or not you would like to withdraw at any time without explanation.

You may like to discuss participation in this research project with your family and with your doctor. You can ask for further information before deciding to take part.

If you would like more information about the study or if you need to contact a study representative in an emergency, the person to contact is:

Name: Professor Nellie Georgiou-Karistianis **Contact telephone:** (03) 9905 1575

What are my rights as a participant?

I am informed that except where stated above, no information regarding my medical history will be released. This is subject to legal requirements.

I am informed that the results of any tests involving me will not be published so as to reveal my identity. This is subject to legal requirements.

The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.

It has also been explained that my involvement in the research may not be of any benefit to me personally. I understand that the purpose of this research project is to improve the quality of medical care in the future.

I have been asked if I would like to have a family member or a friend with me while the project is explained to me.

I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).

I understand that this research project has been approved by The Royal Children's Hospital Ethics in Human Research Committee on behalf of The Royal Children's Hospital Board, and by the Monash University Human Research Ethics Comittee.

I have received a copy of this document.

If you have any concerns about the study, and would like to speak to someone independent of the study, please contact;
The RCH Consumer Liaison
Clinical Support Services Team at the Executive Office.
Telephone 9345 5676 (Monday to Friday 9am-5pm),

Or

Executive Officer

Monash University Human Research Ethics Committee (MUHREC)

Building 3e Room 111

Research Office, Monash University VIC 3800

Tel: 03 9905 2052 / Fax: 03 9905 3831 / Email: muhrec@monash.edu

MONASH University
Biomedical Imaging

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

The Royal Children's Hospital, Melbourne

Flemington Road, Parkville
Victoria, Australia, 3052

Telephone (03) 9345 5522
ISD (+613) 9345 5522
Facsimile (03) 9345 5789
Web www.rch.org.au

STANDARD INFORMED CONSENT
FOR PARTICIPANT TO PARTICIPATE IN A RESEARCH PROJECT

Project Number

EHRC 26147 A

Title of Project

A functional magnetic resonance imaging (fMRI) study addressing cognitive function in individuals with Friedreich Ataxia.

Principal Investigator(s)

Professor Nellie Georgiou-Karistianis

I (Participant name) _____

voluntarily consent to take part in the above titled Research Project, explained to me by Mr/Ms/Dr/Professor _____

I have received a Participant Information Statement to keep and I believe I understand the purpose, extent and possible effects of my involvement

I have been asked if I would like to have a family member or friend with me while the project was explained

I have had an opportunity to ask questions and I am satisfied with the answers I have received

I understand that the researcher has agreed not to reveal results of any information involving me, subject to legal requirements

If information about this project is published or presented in any public form, I understand that the researcher will not reveal my identity

I understand that if I refuse to consent, or if I withdraw from the study at any time without explanation, this will not affect my access to the best available treatment options and care from The Royal Children's Hospital
I understand I will receive a copy of this consent form

SIGNATURE _____ Date _____

I have explained the study to the participant who has signed above, and believe that they understand the purpose, extent and possible effects of their involvement in this study.

RESEARCHER'S SIGNATURE _____ Date _____

Note: All parties signing the Consent Form must date their own signat