White matter integrity alteration in mirror neurons of schizophrenic patients and their correlations With social cognition; DTI study

Thesis

Submitted for Partial Fulfillment of Master Degree
in Neuropsychiatry

By

Hadeer Hassan Ahmed Mohamed
(M.B.,B.Ch.)

Supervised by

Prof. Dr. Heba Hamed ElShahawi
Professor of Neurology and Psychiatry
Faculty of Medicine - Ain Shams University

Prof. Hossam Moussa Sakr
Professor of Diagnostic Radiology
Faculty of Medicine - Ain shams University

Dr. Mai Seif El-din Abdeen
Lecturer of Neurology and Psychiatry
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2019

Acknowledgement

I thank **ALLAH** from all my heart for His maintained grace and blessings in my life and my career and for this project to come to an end. Second, I would like to thank ***Prof. Dr. Heba Hamed ElShahawi***, ***Professor of Neurology and Psychiatry,*** for her encouragement and support in my career in general and in help accomplishing this work.

No words can describe my sincere gratitude and thankfulness to ***Prof. Hossam Moussa Sakr, Professor of Radiology,*** for his generous mentorship and education during my thesis. Without his expertise and guidance this work would have not been possible. Special thanks to ***Dr. Mai Seif El-din Abdeen, Lecturer of Neurology and Psychiatry,*** for her revision of the work and encouraging words and for her mentorship during this thesis.

Finally I would like to thank the patients contributed to this study.

Hadeer Hassan

List of Contents

List of Abbreviations

ADC	Apparent Diffusion Coefficient
MNS	Mirror Neuron System
WM	White Matter
DTI.....	Diffusion Tensor Imaging
FA	Fractional Anisotropy
MRI	Magnetic resonance imaging
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
WHO	World Health Organization
IRI	Interpersonal Reactivity Index
IQ	Intelligence Quotient
MATRICS	Measurement and Treatment Research to improve Recognition in Schizophrenia
WCST	Wisconsin Card Sorting Test
FAR	Facial Affective Recognition
IFG	Inferior Frontal Gyrus
ACC	Anterior Cingulate Cortex
MPFC	Medial Prefrontal Cortex
ToM	Theory of Mind
TT	Theory Theory
ST	Stimulation Theory
STS	Superio Temporal Sulcus
TPJ	Tempro-Parietal Junction
AIHQ	Ambiguous Intentions and Hostility Questionnaire

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AG	Angular Gyrus
AIP	Anterior Intraparietal Area
ASD	Autism Spectrum Disorder
ASQ	Attributional Style Questionnaire
BA	Broca's Area
CPT	Continuous Performance Test
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSST	Digit Symbol Substitution Task
DTMRI	Diffusion Tensor MRI
DWMRI	Diffusion Weighted MRI
EEG	Electroencephalography
EMG	Electromyography
F5	Mirror neurons in ventral premotor region
FEF	Frontal Eye Field
FG	Fusiform Gyrus
fMRI	Functional MRI
IF	Inferior Frontal Sulcus
IFOF	Inferior Fronto-Occipital Fasiculus
ILF	Inferior Longitudinal Fasiculus
IP	Inferior Precentral Sulcus
IPC	Inferior Parietal Cortex
IPSAQ	Internal Personal and Situational Attributions Questionnaire

List of Abbreviations

LIP	Lateral Intraparietal Area
LT ACC	Left Anterior Cingulate Cortex
LT IPL	Left Inferior Parietal Lobe
LT PMA	Left Premotor Area
M1	Primary motor cortex
MD	Mean Diffusity
MEG	Magnetoencephalography
MEPs	Motor Evoked Potential
MNA	Mirror Neuron Activity
PET	Positron Emission Tomography
PMC	Primary Motor Cortex
Pop	Pars Opercularis
PSSC	Primary Somatosensory Cortex
QoL	Quality of Life
RAIT	Rapid Approximate Intelligence Test
ROCF	Reye Osterrieth Complex Figure test
ROI	Region of Interest
RT ACC	Right Anterior Cingulate Cortex
RT IPL	Right Inferior Parietal Lobe
RT PMA	Right Premotor Area
rTMS	Repetitive Transcranial Magnetic Stimulation
RVIP	Rapid Visual Information Processing
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SMA	Supplementary Motor Area
SMG	Supramarginal Gyrus

List of Abbreviations

SPSS	Statistical Package for the Social Science
SSD	Schizophrenia Spectrum Disorder
TBSS	Tract Based Spatial Statistics
TMS	Transcranial Magnetic Stimulation
TMT	Trail Making Test
US	United States
vPMA	ventral Premotor Area
WA	Wernicke's Area
WAIS	Wechselar Adult Intelligence Scale
WMS-R-III	Wechselar Memory Scale

List of Tables

List of Tables

List of Figures

List of Figures

Abstract

Abstract Objective: the aim of this study is to use Diffusion tensor imaging ***(Malcolm et al., 2009)*** to evaluate the white matter microstructure of the fiber tracks connecting the premotor cortex (PMC), the inferior parietal lobule (IPL) and the anterior cingulate cortex (ACC) in patients diagnosed with schizophrenia. **Conclusions:** We have demonstrated disrupted white mater microstructure within the white matter tracts subserving brain regions containing mirror neurons. We further showed that such structural disruptions might impact negative symptoms and, more specifically, contribute to the inability to feel intimacy (a measure conceptually related to theory of mind) in first episode and chronic schizophrenia;. Further studies are needed to understand the potential of our results for diagnosis, prognosis and therapeutic interventions.

ARTICLE INFO

Keywords: Mirror neurons, Schizophrenia, DTI studies, Social cognition.

INTRODUCTION

Schizophrenia is a severe mental disorder, affects approximately **1%** of the population and is characterized by disordered thought processes as well as impaired emotional responses ***(Wheeler & Voineskos, 2014).*** As well as a number of impairments that includes sensory and cognitive processing abnormalities ***(Kalkstein et al., 2010)***. However, in addition to these fairly well examined abnormalities, sometimes called 'cold cognition' abnormalities, schizophrenia patients experience a number of impairments in social cognition ***(Mehta et al., 2014).*** Indeed, it has been suggested that schizophrenia should be thought of as a 'social brain' disorder ***(Burns, 2006)***.

Social cognition defined as an ability to communicate feelings and attitudes and to understand signals that express these feelings and attitudes in other people ***(Adolphs, 2010)***. Social cognition skills are critical to successful functioning in social contexts and, in schizophrenia, their deficits contribute to poor functional outcomes ***(Pinkham, 2014).*** It is now understood that the social cognition is mediated by an interconnected network of cortical and subcortical brain regions, including orbitofrontal and ventromedial frontal cortex, cingulate cortex, insula, striatum and amygdala ***(Adolphs, 2010; McDonald et al., 2013).***

Mirror neurons (MNS) play a unique role in the brain architecture in relation to social cognition skills. These neurons are active not only during an action execution but also when an action of others is observed. Thus, it has been

proposed that they may confer not only the capacity to anticipate the actions of others but that they have contributed to the development of the theory of mind and empathy, as well as other important aspects of social cognition skills in non-human primates and humans ***(Ferrari, 2014; Bonini, 2016).***

As distributed structural circuits of cortical and subcortical areas serve normal brain functions, disrupted communication within and between brain regions may be the core pathology of schizophrenia. Two decades ago it was proposed that the symptoms of schizophrenia were due to alterations in cerebral connectivity ***(Friston & Frith, 1995)***, a hypothesis that has been gaining traction in recent years with the availability of advanced imaging techniques that can be used to address this theory ***(Kochunov & Hong, 2014)***. White matter in the brain consists of the axonal projections to other neurons and brain areas and forms the basis for connectivity in the brain ***(Wheeler & Voineskos, 2014).***

Although there have been functional imaging studies on the impairment of the MNS in schizophrenia, structural imaging studies are relatively scarce. Previously structural abnormalities have been reported in each of the components of the MNS individually ***(Tseng et al., 2015).*** Alterations as identified by magnetic resonance imaging (**MRI**) were reported in frontal and parietal lobes ***(Xiao et al., 2015)*** as well as fronto-parietal white matter (WM) connections ***(Sigmundsson et al., 2001; Burns et al., 2003).*** It is plausible to speculate that there are alterations