

A longitudinal study of brain structure in the early stages of schizophrenia

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Doctor of Philosophy*

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DECLARATION OF ORIGINALITY

To the best of my knowledge, this thesis contains no copy or paraphrase of work published by another person, except where duly acknowledged in the text. This thesis contains no material that has been presented for a degree at the University of Sydney or any other university.

Thomas J. Whitford

Date

ABSTRACT

Schizophrenia is a severe mental illness that affects approximately 1% of the population worldwide, and which typically has a devastating effect on the lives of its sufferers. The characteristic symptoms of the disease include hallucinations, delusions, disorganized thought and reduced emotional expression. While many of the early theories of schizophrenia focused on its psychosocial foundations, more recent theories have focused on the neurobiological underpinnings of the disease. This thesis has four primary aims: 1) to use magnetic resonance imaging (MRI) to identify the structural brain abnormalities present in patients suffering from their first episode of schizophrenia (FES), 2) to elucidate whether these abnormalities were static or progressive over the first 2-3 years of patients' illness, 3) to identify the relationship between these neuroanatomical abnormalities and patients' clinical profile, and 4) to identify the normative relationship between longitudinal changes in neuroanatomy and electrophysiology in healthy participants, and to compare this to the relationship observed between these two indices in patients with FES.

The aim of Chapter 2 was to use MRI to identify the neuroanatomical changes that occur over adolescence in healthy participants, and to identify the normative relationship between the neuroanatomical changes and electrophysiological changes associated with healthy periadolescent brain maturation. MRI and electroencephalographic (EEG) scans were acquired from 138 healthy participants between the ages of 10 and 30 years. The MRI scans were segmented into grey matter (GM) and white matter (WM) images, before being parcellated into the frontal, temporal, parietal and occipital lobes. Absolute

EEG power was calculated for the slow-wave, alpha and beta frequency bands, for the corresponding cortical regions. The age-related changes in regional tissue volumes and regional EEG power were inferred with a regression model. The results indicated that the healthy participants experienced accelerated GM loss, EEG power loss and WM gain in the frontal and parietal lobes between the ages of 10 and 20 years, which decelerated between the ages of 20 and 30 years. A linear relationship was also observed between the maturational changes in regional GM volumes and EEG power in the frontal and parietal lobes. These results indicate that the periadolescent period is a time of great structural and electrophysiological change in the healthy human brain.

The aim of Chapter 3 was to identify the GM abnormalities present in patients with FES, both at the time of their first presentation to mental health services (baseline), and over the first 2-3 years of their illness (follow-up). MRI scans were acquired from 41 patients with FES at baseline, and 47 matched healthy control subjects. Of these participants, 25 FES patients and 26 controls returned 2-3 years later for a follow-up scan. The analysis technique of voxel-based morphometry (VBM) was used in conjunction with the Statistical Parametric Mapping (SPM) software package in order to identify the regions of GM difference between the groups at baseline. The related analysis technique of tensor-based morphometry (TBM) was used to identify subjects' longitudinal GM change over the follow-up interval. Relative to the healthy controls, the FES patients were observed to exhibit widespread GM reductions in the frontal, parietal and temporal cortices and cerebellum at baseline, as well as more circumscribed regions of GM increase, particularly in the occipital lobe. Furthermore, the FES patients lost

considerably more GM over the follow-up interval than the controls, particularly in the parietal and temporal cortices. These results indicate that patients with FES exhibit significant structural brain abnormalities very early in the course of their illness, and that these abnormalities progress over the first few years of their illness.

Chapter 4 employed the same methodology to investigate the white matter abnormalities exhibited by the FES subjects relative to the controls, both at baseline and over the follow-up interval. Compared to controls, the FES patients exhibited volumetric WM deficits in the frontal and temporal lobes at baseline, as well as volumetric increases at the fronto-parietal junction bilaterally. Furthermore, the FES patients lost considerably more WM over the follow-up interval than did the controls in the middle and inferior temporal cortex bilaterally. While there is substantial evidence indicating that abnormalities in the maturational processes of myelination play a significant role in the development of WM abnormalities in FES, the observed longitudinal reductions in WM were consistent with the death of a select population of temporal lobe neurons over the follow-up interval.

The aim of Chapter 5 was to investigate the clinical correlates of the GM abnormalities exhibited by the FES patients at baseline. The volumes of four distinct cerebral regions where 31 patients with FES exhibited reduced GM volumes relative to 30 matched controls were calculated and correlated with patients' scores on three primary symptom dimensions: Disorganization, Reality Distortion and Psychomotor Poverty. The results indicated that the greater the degree of atrophy exhibited by the FES patients in three of

these four ‘regions-of-reduction’, the less severe their degree of Reality Distortion. These results suggest that an excessive amount of GM atrophy may in fact preclude the formation of hallucinations or highly systematized delusions in patients with FES.

The aim of Chapter 6 was to identify the relationship between the longitudinal changes in brain structure and brain electrophysiology exhibited by 19 FES patients over the first 2-3 years of their illness, and to compare it to the normative relationship between the two indices reported in Chapter 2. The methodology employed for the parcellation of the MRI and EEG data was identical to Chapter 2. The results indicated that, in contrast to the healthy controls, the longitudinal reduction in GM volume exhibited by the FES patients was not associated with a corresponding reduction in EEG power in any brain lobe. In contrast, EEG power was observed to be maintained or even to increase over the follow-up interval in these patients. These results were consistent with the FES patients experiencing an abnormal elevation of neural synchrony. Such an abnormality in neural synchrony could potentially form the basis of the dysfunctional neural connectivity that has been widely proposed to underlie the functional deficits present in patients with schizophrenia.

The primary aim of Chapter 7 was to assimilate the findings from the preceding empirical chapters with the theoretical framework provided in the literature, into an integrated and testable model of schizophrenia. The model emphasized dysfunctions in brain maturation, specifically in the normative processes of synaptic ‘pruning’ and axonal myelination, as playing a key role in the development of disintegrated neural activity and the subsequent

onset of schizophrenic symptoms. The model concluded with the novel proposal that disintegrated neural activity arises from abnormal *elevations* in the synchrony of synaptic activity in patients with first-episode schizophrenia.

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PUBLICATIONS RELATING TO THIS THESIS

Listed below are the details for the papers on which Chapters 2 to 6 are based. Also listed are two additional papers on which I was involved that were closely related to the work presented in this thesis, and which were included as Appendices 1 and 2.

Chapter 2

Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology

Whitford TJ, Rennie CJ, Grieve SM, Clark CR, Gordon E, Williams LM

Published in *Human Brain Mapping*, 28: 228-237 (2007)

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I was primarily responsible for this work, with an overall contribution of about 90%.

Chapter 3

Progressive grey matter atrophy over the first 2-3 years of illness in first-episode schizophrenia: a tensor-based morphometry study

Whitford TJ, Grieve SM, Farrow TF, Gomes L, Brennan J, Harris AW, Gordon E, Williams LM

Published in *NeuroImage*, 32: 511-519 (2006)

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I was primarily responsible for this work, with an overall contribution of about 90%.

Chapter 4

Volumetric white matter abnormalities in first-episode schizophrenia: a longitudinal, tensor-based morphometry study

Whitford TJ, Grieve SM, Farrow TF, Gomes L, Brennan J, Harris AW, Gordon E, Williams LM

Published in the *American Journal of Psychiatry*, 164: 1082-1089 (2007)

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I was primarily responsible for this work, with an overall contribution of about 90%.

Chapter 5

Grey matter deficits and symptom profile in first episode schizophrenia

Whitford TJ, Farrow TF, Gomes L, Brennan J, Harris AW, Williams LM

Published in *Psychiatry Research: Neuroimaging*, 139: 229-238 (2005)

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Chapter 6

Longitudinal changes in neuroanatomy and neural activity in early schizophrenia

Whitford TJ, Farrow TF, Rennie CJ, Grieve SM, Gomes L, Brennan J, Harris AW, Williams LM

Published in *NeuroReport*, 18: 435-439 (2007)

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I was primarily responsible for this work, with an overall contribution of about 90%.

Appendix 1

Longitudinal study of neuropsychological and neuropathological changes in first-episode schizophrenia

Zipparo L, Whitford TJ, Redoblado MA, Lucas S, Farrow TFD, Brennan J, Gomes L, Williams LM, Harris AWF

Submitted to *Progress in Neuro-Psychopharmacology and Biological Psychiatry*

My contributions, which amounted to about 20% of this work, were in acquiring the MRI data, building the masks used to parcellate the images, pre-processing and analysing the MR images, and in writing the section on the MRI methodology in the manuscript.

Appendix 2

Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder

Farrow TF, Whitford TJ, Williams LM, Gomes L, Harris AWF

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My contributions, which amounted to about 20% of this work, were in acquiring the MRI data, pre-processing and analysing the MR images with voxel-based morphometry in conjunction with the Statistical Parametric Mapping (SPM) software package, assistance with writing the manuscript and suggesting a number of ideas in relation to the interpretation of the results.

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LIST OF ABBREVIATIONS

AAL – Automated Anatomical Labelling
BRID – Brain Resource International Database
CNS – central nervous system
CSF – cerebro-spinal fluid
CT – Computer Assisted Tomography
EEG – electroencephalography
FEED – first-episode bipolar disorder
FES – first-episode schizophrenia
FFT – fast Fourier transform
fMRI – functional magnetic resonance imaging
FOV – field-of-view
FU – follow-up
GM – grey matter
HVA – homovanillic acid
ICBM – International Consortium for Brain Mapping
MEG – magnetoencephalography
MNI – Montreal Neurological Institute
MRI – magnetic resonance imaging
PET – positron emission tomography
PFC – prefrontal cortex
RD – Reality Distortion
RF – radio frequency
ROI – region-of-interest
ROIs – regions-of-interest
SI – statistical imaging
SMA – supplementary motor area
SPM – Statistical Parametric Mapping
SPSS – Statistical Package for the Social Sciences
TBM – tensor-based morphometry
TE – time-to-echo
TI – inversion-time
TR – time-to-repeat
VBM – voxel-based morphometry
WM – white matter