UNIVERSITY OF NEWCASTLE
SCHOOL OF MEDICINE & PUBLIC HEALTH

Thesis

NEURAL CORRELATES OF COGNITIVE IMPAIRMENT
IN A SAMPLE OF YOUNG PEOPLE AT RISK OF
DEVELOPING SCHIZOPHRENIA

by

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Doctor of Philosophy
2013
STATEMENT OF ORIGINALITY

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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____________________
Tim Ehlkes
STATEMENT OF COLLABORATION

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers. I have included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

... signed

____________________

Tim Ehlkes
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Last but not least I would like to thank all those who supported me throughout this study. In particular, I would like to thank the MinT consortium for their support and for making this research opportunity possible.
ABSTRACT

The reliable identification of the schizophrenia prodrome is a prerequisite for early intervention in young people considered “at-risk” of developing this severe mental illness. Clinical at-risk criteria, however, still lack predictive specificity to reliably predict outcome. Brain imaging research has added substantial evidence to the notion of emerging and progressive grey and white matter abnormalities in the early phase of illness. The purpose of this study was to investigate structural brain changes associated with the clinical profile of the At-Risk Mental State (ARMS) syndrome, along with cognitive and psychophysiological measures that have been linked schizophrenia.

Forty-two young individuals meeting ARMS criteria of the Comprehensive Assessment of At-risk Mental State (CAARMS) were included in the study. Surface-based methods were applied to quantify measures of cortical structure in high-resolution MRI scans. Participants underwent clinical and cognitive assessments. Event-related potentials (i.e. Mismatch Negativity and P3a) were recorded whilst study participants performed an auditory oddball task. A median-split of dividing the study participants into two groups with low versus high symptom expression (ARMS-LS vs. ARMS-HS) based on CAARMS symptom ratings revealed significantly reduced mean cortical grey matter thickness in the more symptomatic group. There was no significant group difference in total brain volume, grey or white matter volume, or pial or white matter surface areas. ARMS-HS presented significantly impaired in socio-occupational and social/role functioning, as well as performed lower in verbal fluency when compared to ARMS-LS.

Vertex-wise correlation analyses confirmed significant associations ($p<.05$ corrected) of CAAMRS symptom rating scores with reduced grey matter thickness in left and right superior frontal gyri, right anterior cingulate, and right medial occipito-temporal cortex (i.e. lingual gyrus). Reduced grey matter in frontal, prefrontal, and occipital cortical areas were associated with low function ratings. Verbal Fluency task performance largely overlapped with the
frontal brain areas identified for low function ratings by reduced regional grey matter thickness correlation maps.

These findings suggest that emerging psychopathology as defined by CAARMS for ARMS (i.e. low-grade psychotic symptom expression and functional impairment) is associated with reduced cortical grey matter thickness, a putative measure of brain pathology. Future research should investigate whether regional cortical grey matter reduction is associated with a higher risk of developing schizophrenia.
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GLOSSARY

ARMS  At-Risk Mental State
ARMS-HS  High-Symptom Group by CAARMS Composite Score Median-Split
ARMS-LS  Low-Symptom Group by CAARMS Composite Score Median-Split
BLIPS  Brief Limited Intermittent Psychotic Symptoms
BOLD  Blood Oxygenation Level-Dependent
BPRS  The Brief Psychiatric Rating Scale
CAARMS  Comprehensive Assessment of At-Risk Mental State
CCS  CAARMS Composite Score
CNSS  CAARMS Negative Symptom Score
CPSS  CAARMS Positive Symptom Score
CSF  Cerebrospinal Fluid (CSF)
CVLT-II  California Verbal Learning Test: Second Edition
CWIT  Colour-Word Interference Test
D-KEFS  Delis-Kaplan Executive Function System
DLPFC  Dorsolateral Prefrontal Cortex
DTI  Diffusion Tensor Imaging
DUP  Duration of untreated Psychosis
EEG  Electroencephalography
EF   Executive Functioning
ERP  Event-Related Potential
eTIV  Estimated Total Intracranial Volume
FA   Fractional Anisotropy
FEP  First-Episode Psychosis
FES  First Episode Schizophrenia
fMRI Functional Magnetic Resonance Imaging
GAF  Global Assessment of Functioning
GF:Role  Global Functioning: Role Scale
GF:Social  Global Functioning: Social Scale
GLM  General Linear Model
GM   Grey Matter
MC-Z  Monte-Carlo Simulation
MinT  Minds in Transition
MMN  Mismatch Negativity
MRI  Magnetic Resonance Imaging
N3   Non-Parametric Non-Uniform Intensity Normalization
NMDA  N-Methyl-D-Aspartate
PANSS  Positive and Negative Syndrome Scale
PET  Positron Emission Tomography
PPI  Prepulse Inhibition
SOFAS  Social and Occupational Functioning Scale
SWM  Spatial Working Memory
TMT  Trail Making Test
ToM  Theory of Mind
TT   Tower Task
UHR  Ultra High-Risk
VBM  Voxel-Based-Morphometry
VFT  Verbal Fluency Test
WASI  Wechsler Abbreviated Scale Of Intelligence
WM   White Matter
WMS-III  Wechsler Memory Scale: Third Edition