UNIVERSITY OF NEWCASTLE

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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

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STATEMENT OF ORIGINALITY

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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.

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Tim Ehlkes

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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
ТМТ	Trail Making Test
ТоМ	Theory of Mind
ТТ	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