INSTITUTE of MENTAL HEALTH
WOODBRIDGE HOSPITAL

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Probing White Matter Neurobiology in Psychosis Using Neuroimaging

Sim Kang
Senior Consultant Psychiatrist, IMH

NHG-NTU/LKCMedicine Research Seminar

13Nov14

Key Research Focus

- Psychiatric Epidemiology
- Mental Health Service Research
- Research in Bioethics of Psychiatric Research, Treatment & Policies

Programme for Mental Health Policy Research

- Clinical Phenotyping
- Psychiatric Genomics
- Neuro-imaging
- Neurocognition
- Clinical Trials

Programme for Translational & Clinical Research

Roadmap

- Why study white matter in psychosis?
- Perspectives of white matter pathology in psychosis
- What lies ahead

What is Psychosis?

- Affects 3% of population
- A form of severe mental disturbance where the individual loses touch with reality
- Characterised by delusions, hallucinations disorganised thinking and behaviour

Ten leading cause of years lost to disability (aged ≥15 years)

	Males			Females		
	Cause	YLD (millions)	Per cent of total YLD	Cause	YLD (millions)	Per cent of total YLD
1	Unipolar depressive disorders	24.3	8.3	Unipolar depressive disorders	41.0	13.4
2	Alcohol use disorders	19.9	6.8	Refractive errors	14.0	4.6
3	Hearing loss, adult onset	14.1	4.8	Hearing loss, adult onset	13.3	4.3
4	Refractive errors	13.8	4.7	Cataracts	9.9	3.2
5	Schizophrenia	8.3	2.8	Osteoarthritis	9.5	3.1
6	Cataracts	7.9	2.7	Schizophrenia	8.0	2.6
7	Bipolar disorder	7.3	2.5	Anaemia	7.4	2.4
8	COPD	6.9	2.4	Bipolar disorder	7.1	2.3
9	Asthma	6.6	2.2	Birth asphyxia and birth trauma	6.9	2.3
10	Falls	6.3	2.2	Alzheimer and other dementias	5.8	1.9

WHO, 2004

White Matter Matters!

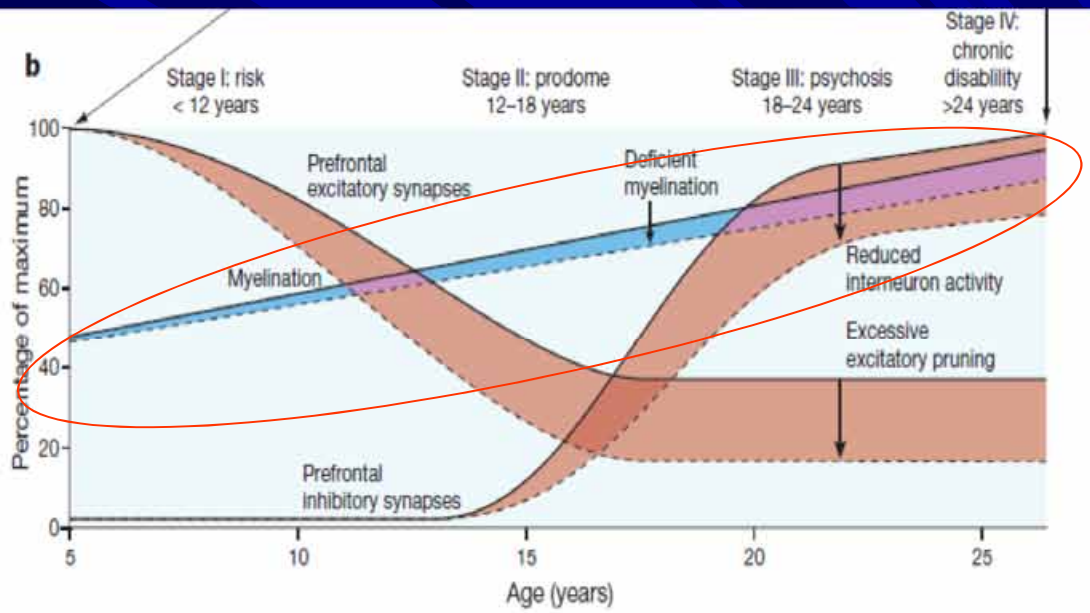

Figure 1 | Neurodevelopmental model of schizophrenia. a, Normal cortical development involves proliferation, migration, arborization (circuit formation) and myelination, with the first two processes occurring mostly during prenatal life and the latter two continuing through the first two post-natal decades. The combined effects of pruning of the neuronal arbor and myelin deposition are thought to account for the progressive reduction of grey-matter volume observed with longitudinal neuroimaging. Beneath this observed overall reduction, local changes are far more complex. Data from human and non-human primate brain indicate increases in inhibitory and decreases in excitatory synaptic strength occurring in prefrontal cortex throughout adolescence and early adulthood, during the period of prodrome and emergence of psychosis. b, The trajectory in children developing schizophrenia could include reduced elaboration of inhibitory pathways and excessive pruning of excitatory pathways leading to altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity. Although some data support each of these possible neurodevelopmental mechanisms for schizophrenia, none has been proven to cause the syndrome. Detection of prodromal neurodevelopmental changes could permit early intervention with potential prevention or preemption of psychosis.

(Insel, Nature 2010)

ORIGINAL ARTICLE

Pathways That Make Voices

White Matter Changes in Auditory Hallucinations

Daniela Hubl, MD; Thomas Koenig, PhD; Werner Strik, MD; Andrea Federspiel, PhD; Roland Kreis, PhD; Chris Boesch, MD, PhD; Stephan E. Maier, PhD; Gerhard Schroth, MD; Karl Lovblad, MD; Thomas Dierks, MD

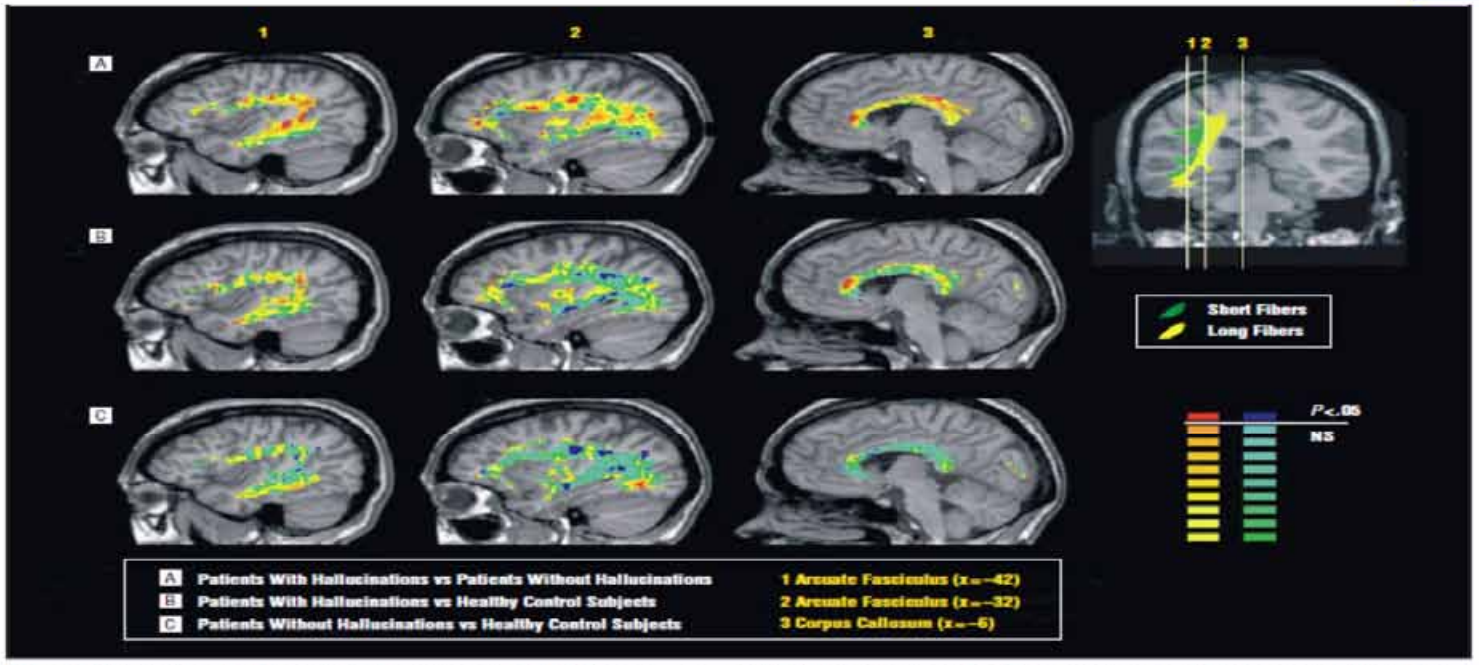

Figure 5. The medial part of the arcuate fasciculus contains long fibers connecting the frontal with the temporal cortex, whereas the lateral part, with its shorter

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Methods:
to acquire twelve 3-mm slices covering the Sylvian fis-
sure. Fractional anisotropy was assessed in 13 patients prone to auditory hallucinations, in 13 patients without auditory hallucinations, and in 13 healthy control subjects. Structural magnetic resonance imaging was conducted in the same session. Based on an analysis of vari-
activation in regions related to the acoustical processing
of external stimuli. This abnormal activation may account for the patients' inability to distinguish self-generated thoughts from external stimulation.

Arch Gen Psychiatry. 2004;61:658-668

Passivity phenomenon

Psychiatry Research: Neuroimaging 172 (2009) 121–127

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

White matter abnormalities and neurocognitive deficits associated with the passivity phenomenon in schizophrenia: A diffusion tensor imaging study

Kang Sim[a,*], Guo Liang Yang[b], Donus Loh[c], Lye Yin Poon[d], Yih Yian Sitoh[e], Swapna Verma[d], Richard Keefe[f], Simon Collinson[g], Siow Ann Chong[d], Stephan Heckers[h], Wieslaw Nowinski[b], Christos Pantelis[i]

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ABSTRACT

The passivity phenomenon is a distressing Schneiderian first rank symptom in patients with schizophrenia. Based on extant data of functional and structural cerebral changes underlying passivity, we sought to examine cerebral white matter integrity in our subjects. We hypothesised that the passivity phenomenon would be associated with white matter changes in specific cortical (frontal, parietal cortices, and cingulate gyrus) and subcortical regions (thalamus and basal ganglia) and correlated with relevant neurocognitive deficits, compared with characteristics in those without the passivity phenomenon. Thirty-six subjects (11 with

Passivity:

- ↑ FA in frontal cortex, cingulate gyrus, basal ganglia
- ↓ FA within the thalamus

Negative symptoms

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Hippocampal-cortical structural connectivity disruptions in schizophrenia: An integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles

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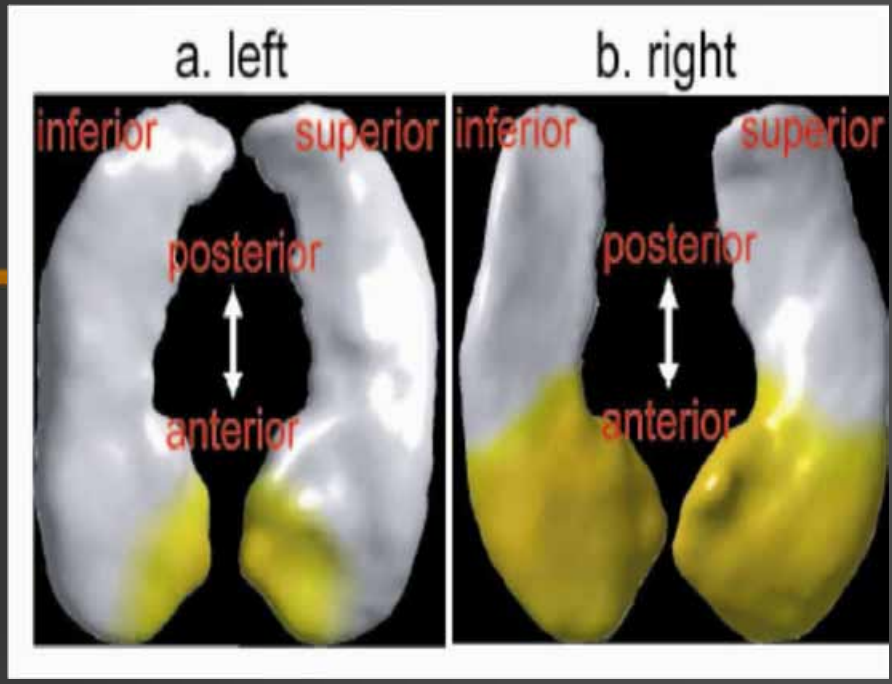
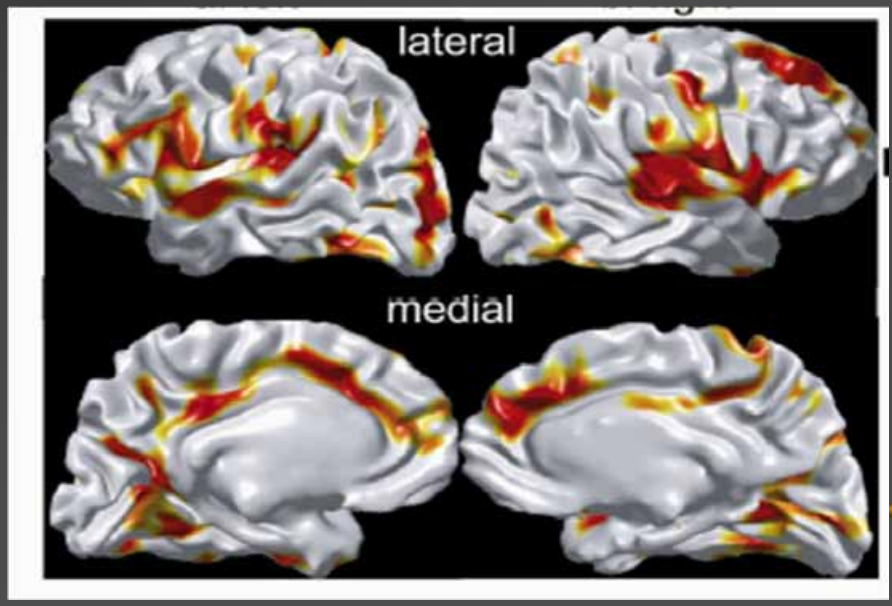
ABSTRACT

Disruptions in the hippocampal-cortical functional connectivities have been implicated in schizophrenia but less is known about their anatomical disconnectivities and association with clinical symptoms. We assessed the anatomical relationships between hippocampal shape, cortical thickness, and integrity of white matter bundles interconnecting them in this study. A brain mapping technique, large deformation diffeomorphic metric mapping, was used to analyze structural magnetic resonance imaging and diffusion tensor imaging scans of 126 schizophrenia patients and 77 matched healthy controls. We found that schizophrenia patients had surface inward deformation in bilateral anterior hippocampi and cortical thinning in the regions of bilateral prefrontal, temporal, and occipital cortices compared with healthy controls. Anterior hippocampal shape deformity was associated with cortical thinning in the brain regions involved in visuo-spatial and verbal memory pathways. Canonical analysis revealed that greater disruptions in the hippocampal-cortical connectivity were associated with more severe negative symptoms in schizophrenia. Furthermore, fractional anisotropy in the fornix and cingulum bundles were reduced, indicating abnormal integration of white matter between hippocampus and cortex in schizophrenia. Our findings suggested that aberrant structural hippocampal-cortical connectivities may serve as a marker of the illness and provide further structural evidence to support the notion of schizophrenia as a disorder of brain connectivity.

- Negative symptoms associated with impairment of social functioning
- Correlation between hippocampal shape deformity and cortical thinning
- Greater the abnormality, more severe the negative symptoms





Precise WM tract changes

OPEN ACCESS Freely available online

PLoS one

Regionally Specific White Matter Disruptions of Fornix and Cingulum in Schizophrenia

Muhammad Farid Abdul-Rahman[1], Anqi Qiu[1,2,3]*, Kang Sim[4,5]

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Abstract

Limbic circuitry disruptions have been implicated in the psychopathology and cognitive deficits of schizophrenia, which may involve white matter disruptions of the major tracts of the limbic system, including the fornix and the cingulum. Our

OPEN ACCESS Freely available online

PLoS one

Arcuate Fasciculus Abnormalities and Their Relationship with Psychotic Symptoms in Schizophrenia

Muhammad Farid Abdul-Rahman[1], Anqi Qiu[1,2,3]*, Puay San Woon[4], Carissa Kuswanto[4], Simon L. Collinson[4,5], Kang Sim[4,6]

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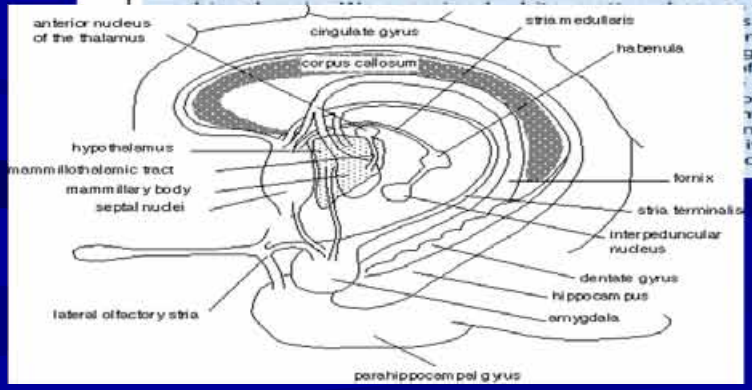
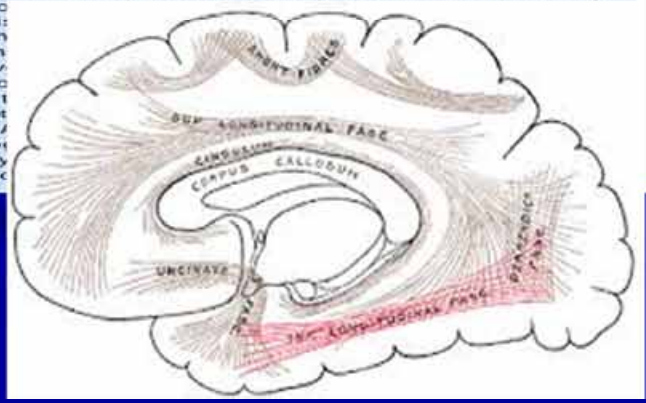
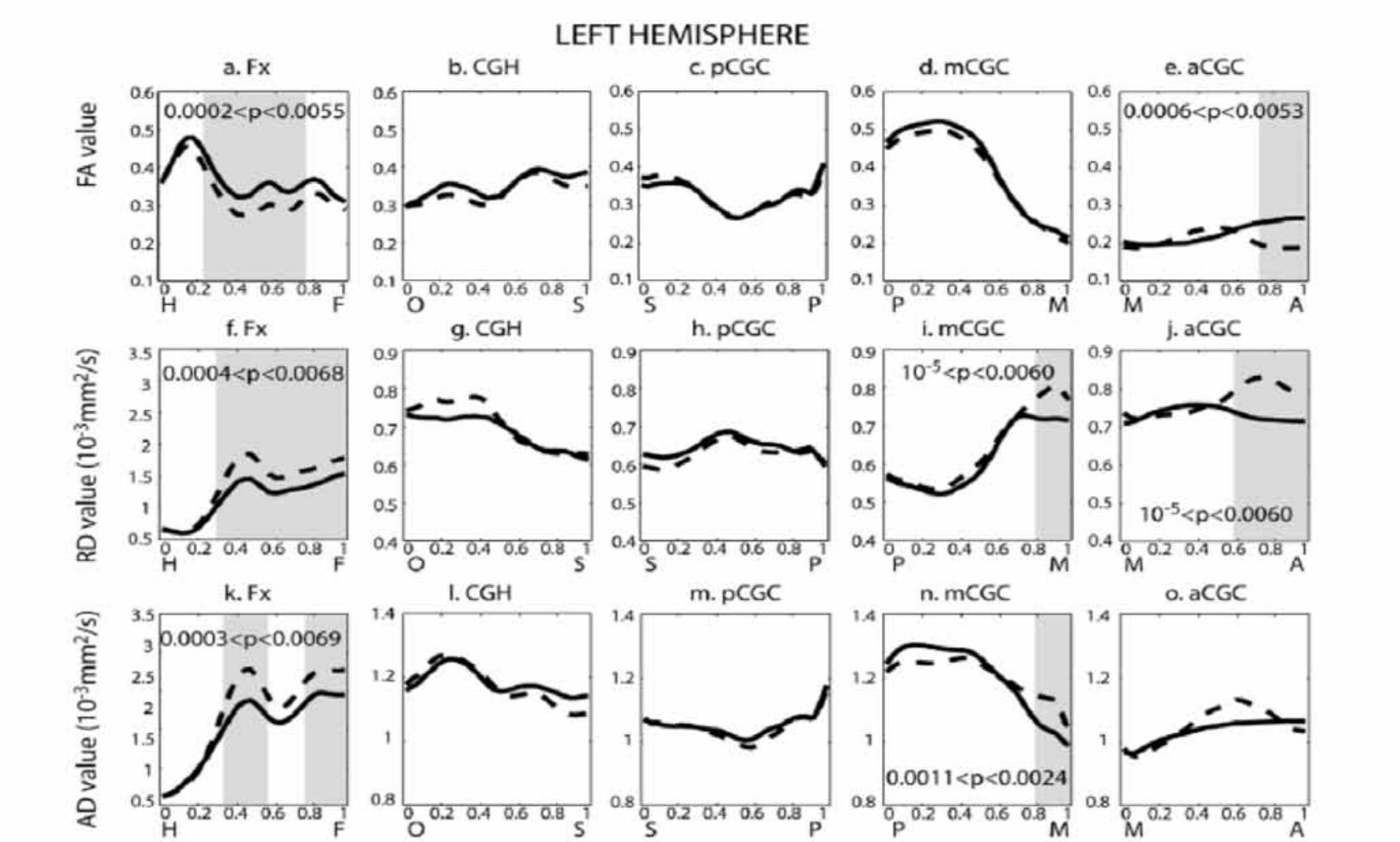
Abstract

Disruption of fronto-temporal connections involving the arcuate fasciculus (AF) may underlie language processing anomalies and psychotic features such as auditory hallucinations in schizophrenia. No study to date has specifically investigated abnormalities of white matter integrity at particular lo



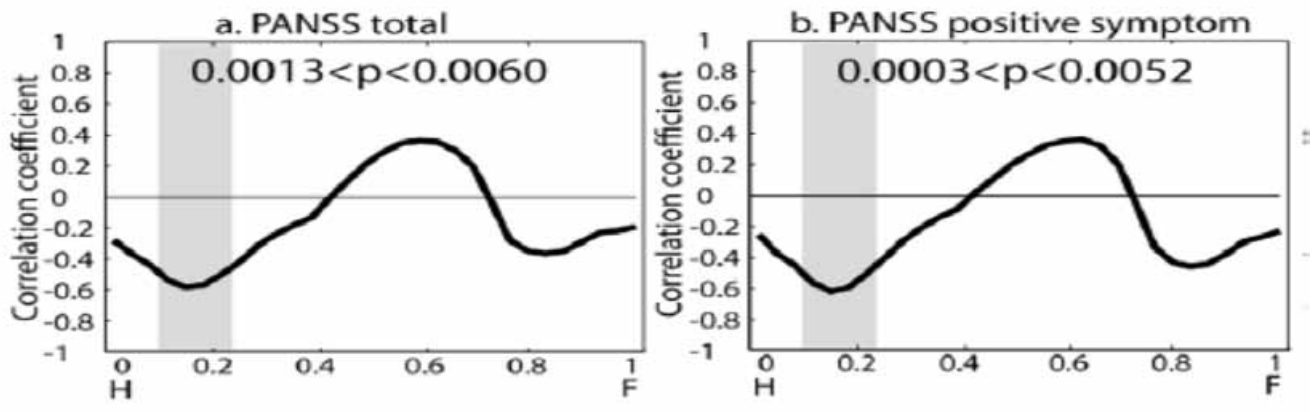


Reductions of FA along fornix, cingulum

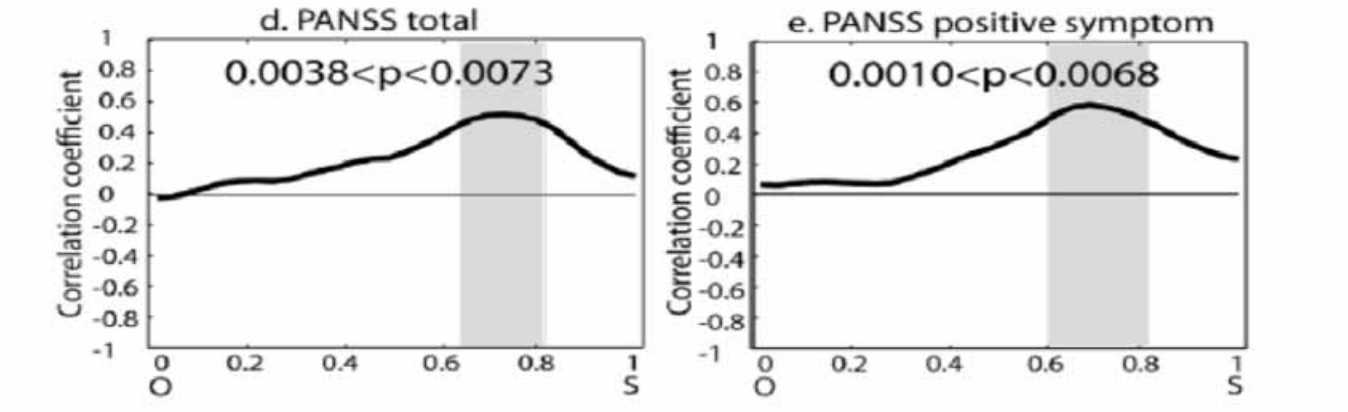


WM disruptions and symptoms

FA along Left fornix



AD along Left Cingulum



(b) Imaging Genetics

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Review

Genome wide association studies (GWAS) and copy number variation (CNV) studies of the major psychoses: What have we learnt?

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ABSTRACT

Schizophrenia (SZ) and bipolar disorder (BPD) have high heritabilities and are clinically and genetically complex. Genome wide association studies (GWAS) and studies of copy number variations (CNV) in SZ and BPD have allowed probing of their underlying genetic risks. In this systematic review, we assess extant genetic signals from published GWAS and CNV studies of SZ and BPD up till March 2011. Risk genes associated with SZ at genome wide significance level (p value $< 7.2 \times 10^{-8}$) include zinc finger binding protein 804A (*ZNF804A*), major histocompatibility (*MHC*) region on chromosome 6, neurogranin (*NRGN*) and transcription factor 4 (*TCF4*). Risk genes associated with BPD include ankyrin 3, node of Ranvier (*ANK3*), calcium channel, voltage dependent, L type, alpha 1C subunit (*CACNA1C*), diacylglycerol kinase eta (*DGKH*), gene locus on chromosome 16p12, and polybromo-1 (*PBRM1*) and very recently neurocan gene (*NCAN*). Possible common genes underlying psychosis include *ZNF804A*, *CACNA1C*, *NRGN* and *PBRM1*. The CNV studies suggest that whilst CNVs are found in both SZ and BPD, the large deletions and duplications are more likely found in SZ rather than BPD. The validation of any genetic signal is likely confounded by genetic and phenotypic heterogeneities which are influenced by epistatic, epigenetic and gene-environment interactions. There is a pressing need to better integrate the multiple research platforms including systems biology computational models, genomics, cross disorder phenotyping studies, transcriptomics, proteomics, metabolomics, neuroimaging and clinical correlations in order to get us closer to a more enlightened understanding of the genetic and biological basis underlying these potentially crippling conditions.

RAPID PUBLICATION

AMERICAN JOURNAL OF
medical genetics
Neuropsychiatric Genetics

Genome-Wide Supported Psychosis Risk Variant in ZNF804A Gene and Impact on Cortico—Limbic WM Integrity in Schizophrenia

Carissa Nadia Kuswanto,[1] Puay-San Woon,[1] Xue Bin Zheng,[1] Anqi Qiu,[2] Yih-Yian Sitoh,[3] Yiong Huak Chan,[4] Jianjun Liu,[5] Hywel Williams,[6] Wei Yi Ong,[7] and Kang Sim[1]*

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[2]

Effects of the Neurogranin Variant rs12807809 on Thalamocortical Morphology in Schizophrenia

Jamie Yu Jin Thong[1], Anqi Qiu[1,2,3*], Min Yi Sum[4], Carissa Nadia Kuswanto[4], Ta Ahn Tuan[1], Gary Donohoe[5], Yih Yian Sitoh[6], Kang Sim[4,7]

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ORIGINAL RESEARCH

CACNA1C Genomewide Supported Psychosis Genetic Variation Affects Cortical Brain White Matter Integrity in Chinese Patients With Schizophrenia

Puay San Woon, BSc; Min Yi Sum, BA; Carissa Nadia Kuswanto, BSc, MSc; Guo Liang Yang, PhD; Yih Yian Sitoh, MBBS; Tuck Wah Soong, PhD; Tih Shih Lee, MD, PhD; Wieslaw Lucjan Nowinski, PhD; and Kang Sim, MBBS, MMed

ARTICLE

doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

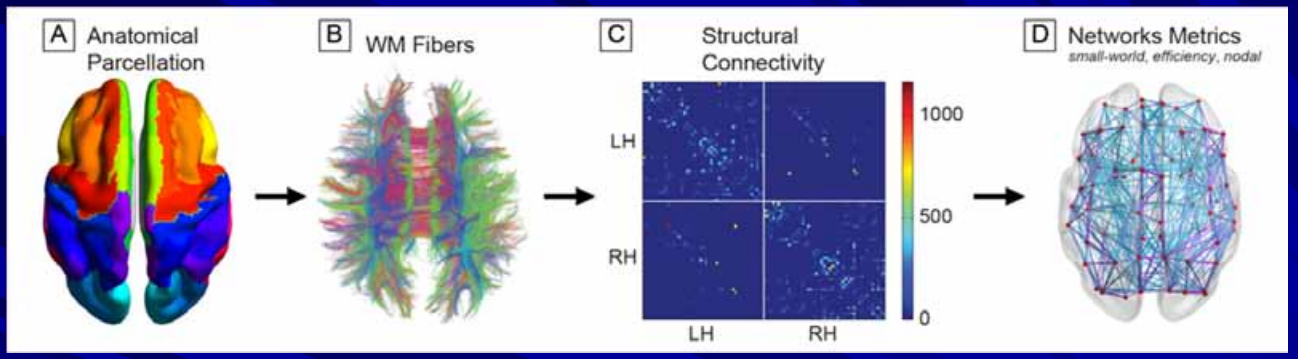
Schizophrenia is a highly heritable disorder. Genetic risk is conferred by a large number of alleles, including common alleles of small effect that might be detected by genome-wide association studies. Here we report a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls. We identify 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which have not been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into aetiology, but associations at *DRD2* and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

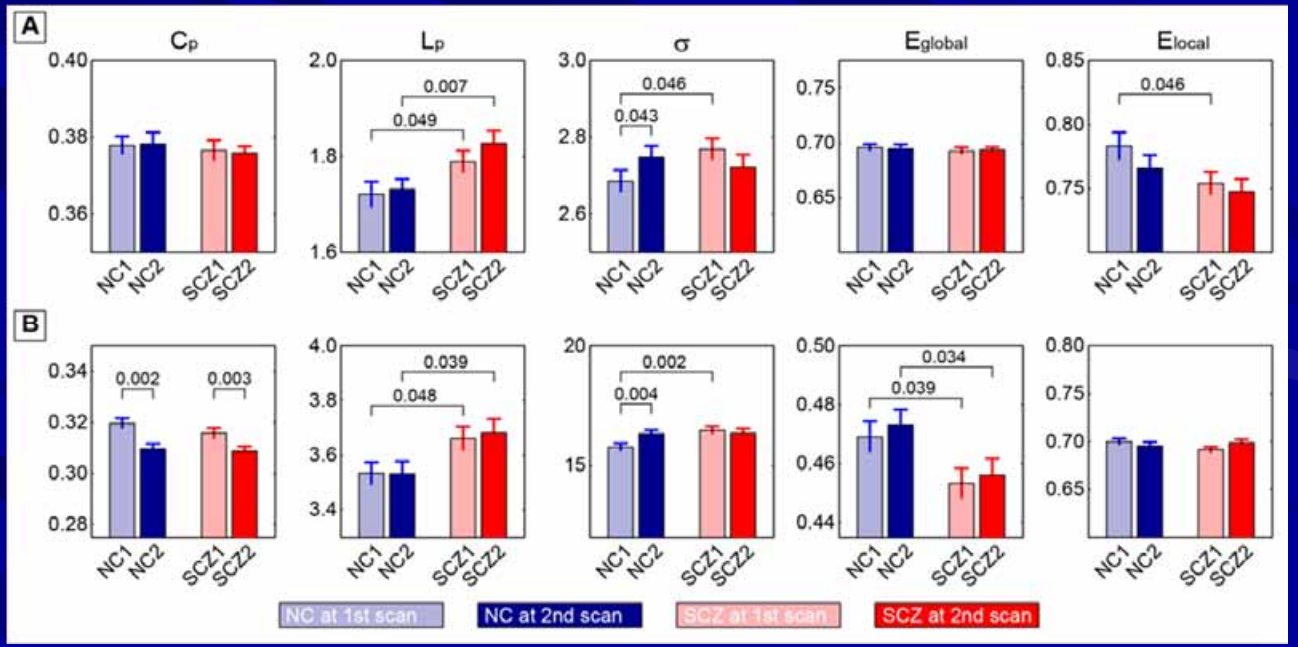
Schizophrenia has a lifetime risk of around 1%, and is associated with substantial morbidity and mortality as well as personal and societal costs[1–3]. Although pharmacological treatments are available for schizophrenia, their efficacy is poor for many patients[4]. All available antipsychotic drugs are thought to exert their main therapeutic effects through blockade of the type 2 dopaminergic receptor[5,6] but, since the discovery of this mech-

These comprise the primary PGC GWAS data set. We processed the genotypes from all studies using unified quality control procedures followed by imputation of SNPs and insertion-deletions using the 1000 Genomes Project reference panel[25]. In each sample, association testing was conducted using imputed marker dosages and principal components (PCs) to control for population stratification. The results were combined

SZ PGC, 2014, Nature

Longitudinal approach





Peering ahead---Cross diagnostic examination

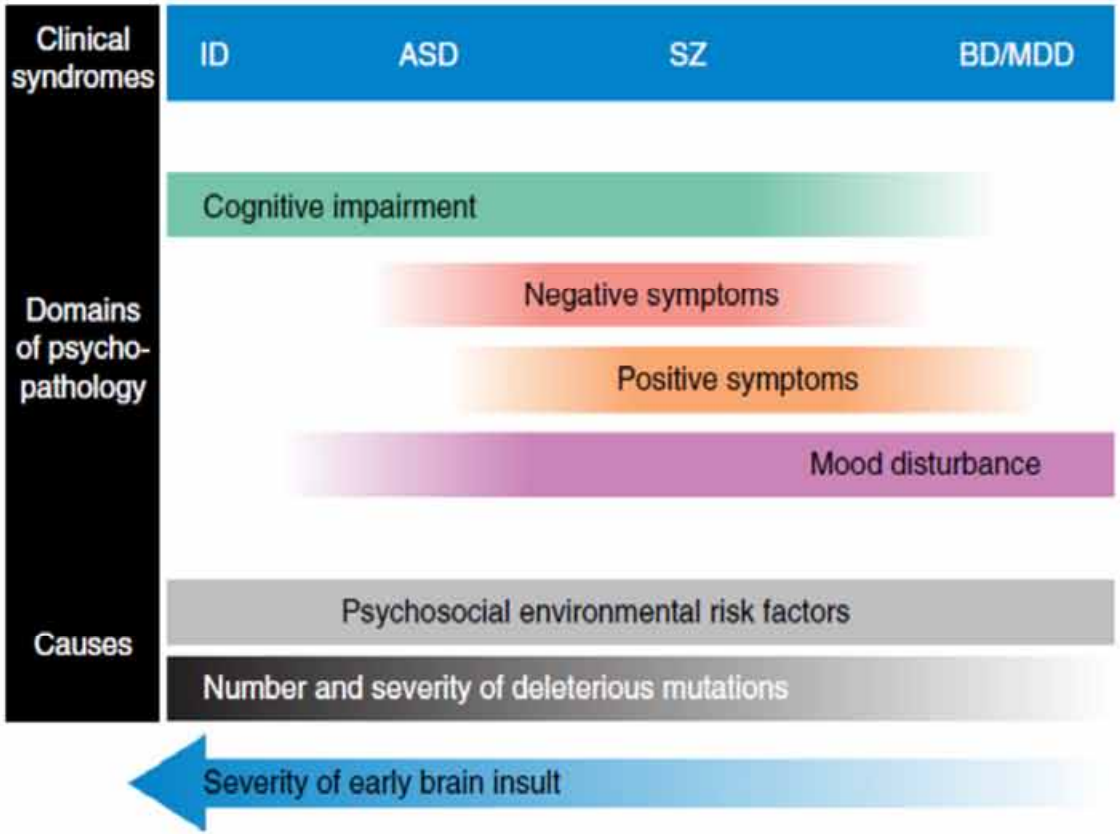


Figure 1 Simplified representation of the hypothesized relationship between the number and severity of deleterious genetic mutations and clinical syndromes. Psychiatric disorders as currently classified are shown as a neurodevelopmental continuum, with intellectual disability (ID) at one extreme and mood disorders at the other (see [130]). Domains of psychopathology overlap between the clinical syndromes, with

(Doherty and Owen, 2014, Genomic Medicine)