Brain change trajectories across the stages of psychotic disorders:
Linking brain structure and function

Christos Pantelis
In this talk!

- **Lessons from the Asylum - Early studies with CANTAB**
  - interrogating frontal-subcortical circuits in schizophrenia and other psychoses

- **Brain changes are dynamic during early stages of psychosis**
  - trajectories of brain change in psychosis
  - trajectories and ‘resilience’
  - linking cognition to brain change

- **Ways forward**
  - Animal CANTAB
  - Melbourne study of childhood schizotypy
Lessons from the Asylum

‘Bedside-to-Bench’
Friern Hospital, London (Colney Hatch Asylum)
My Offices and Jobs might have changed a little since last year. I don’t know. I will write them now as best I can. My Titles are largely not included here. Put together, a whole page is required for them alone.

I am a Knight to Elizabeth, Duke of Byron, Member of the Privy Council, Chief Exchequer of the House of Lords, Junto of Australia, Genda of Victoria, (in the past I have been King of Australia and King of the Planet), Air Marshal in the Air Force, Major General in the Army, the equivalent of Captain in the Navy, member of Cerebus, Field Marshal for the War in Afghanistan, Field Marshal for the War with Jupiter, Venus and Pluto, senior member of the Australian Security and Intelligence Organization, Australian Federal Police Commissioner, Victorian Police Commissioner, Judge of life and death and body preparations, Hells Angel, Assassin, member or fellow of the Colleges of Physicians, Surgeons, Obstetrics and Gynecology, Pathology, Radiology and Psychiatry, member of the Medical Board of Victoria, Fellow of the Royal Society, Cardinal to the Pope, Chief of England Priest, Rastafarian Priest, Shiva Priest, Shinto Priest, Buddhist Lama, Kosovo Priest, Courier, Banker and Courier of Special Plants, Opiates and Meat Exports, that is a Mafia Don, a Musician, a Magistrate, teeth and muscle Microphone Broadcaster. Gene (Father) of 4,860, Forefather of 29.4 million, Forefather of 59% of the Australian Population and 45% of the Australian Aboriginal Population.

Positive symptoms
(disorder of thinking)

Movement Disorders:
Catatonia

Movement Disorders:
Echopraxia / Dystonia

Negative symptoms
& Cognitive Deficits

Cognitive Deficits across Stages of Psychosis

- Chronic schizophrenia more impaired than frontal lesioned patients on tasks of spatial working memory (SWM) and attentional set-shifting (EDID) (Pantelis et al, *Brain*, 1997, *Schizophr Res*, 1999)

- **SWM impaired from before illness onset but EDID not impaired in FEP** (Wood et al, 2003; Pantelis et al, 2009)
Trajectories of Adolescent Brain Maturation

- A context for understanding evolving mental disorder
Schizophrenia and other disorders (eg. Bipolar, depression)

Alzheimer’s and other disorders (eg. Parkinson’s)

The above figure (from Australian Institute of Health and Welfare (AIHW), burden of disease report 2003) shows how Incident Years Lost to Disability (YLD,Y axis) for mental diseases occurs in early adult years while neurological diseases occur much later in life.
Prefrontal / Temporal cortices - Later maturation

- Cortical thinning between age 4 - 21
- Posterior first, prefrontal and lateral temporal later

(Gogtay et al, PNAS, 2004)

(see: Gogtay, Vyas, Testa, wood, Pantelis, Schizophr Bull, 2011)
Inhibitory Control

Father - age 44

Son - age 16

LEADING MENTAL HEALTH RESEARCH ACROSS THE LIFESPAN
Progressive brain changes in psychosis

- changes at earliest stages of psychosis
- mapping brain change trajectories
- brain structure & cognition
- trajectories may be non-linear
• Ultra-High Risk (UHR) group criteria:
  • Attenuated psychotic symptoms
  • Transient psychotic symptoms
  • State and trait risk factors

• 37% transition rate to psychosis within 1-year (Yung et al 1996, 2004)

• Meta-analysis: 26% transition rate over mean 2.4 years (Fusar-Poli et al, AGP, 2012)

• Longterm followup of Melbourne UHR: 34.9% over a 10-year period (Nelson et al 2013)
Hippocampi reduced at later stages of Schizophrenia

Adjusted hippocampal and amygdala volumes

Prepsychotic

Chronic FE Sz FE Szform FE Aff FE other UHRP UHRNP

Percent difference compared to control subjects

Right hipp Left hipp Right amyg Left amyg

Hippocampal and Amygdala Volumes According to Psychosis Stage and Diagnosis

A Magnetic Resonance Imaging Study of Chronic Schizophrenia, First-Episode Psychosis, and Ultra-High-Risk Individuals

Dennis Vahdati, MBBS, FRANZCP; Stephen J. Wood, MA(ANZC), PhD; Michael T. H. Wong, MBBS, MD, FRACGP; Alkove T. H. Wong, MBBS, MD, FRACGP; Patrick D. McCarry, MD, PhD, FRACGP; Alison Yang, MBBS, MD, MPM, FRANZCP; Lisa Phillips, PhD; Dr. Smith, GradDipPsych; Warrick Broom, BPsych(Hons), MA, PhD, Tina Pofflet, BPsych; Patricia Donegan, MSC, MD, FRACGP; Christos Pantelis, MBBS, FRANZCP

Arch Gen Psychiatry. 2006;63:139-149
Progressive brain changes in psychosis

• changes at earliest stages of psychosis
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• trajectories may be non-linear
It is widely accepted that most psychiatric disorders are associated with cognitive impairment and that neuropsychological approaches can help unravel the mechanisms underlying brain function and help us develop a better understanding of these disorders. In this book, a panel of the world's leading experts describe the development of neuropsychological approaches to the investigation, description, measurement, and management of a wide range of mental illnesses.

Section I explains the rationale for examining neuropsychological processes within clinical disorders, leading into a section summarizing and critiquing the methodological approaches to study. Section III covers each of the major psychiatric disorders and provides a summary of the neuropsychological finding for each condition. The final section brings together the perspectives of neuroscientists, psychiatrists, and philosophers.

This book is essential reading for all those studying the healthy as well as the disordered brain, from the fields of mental health, psychology, clinical neuroscience, and philosophy.
Dynamic changes at

(Wellcome Trust Centre for Human Neuroimaging, University of Cambridge)
Dynamic changes start before psychosis.

Frontal lobe shrinkage in controls.

Frontal lobe shrinkage in schizophrenia.

Frontal lobe shrinkage pre-psychosis.
Normal Development

Spatial Working Memory (SWM) from CANTAB

Dorsolateral Prefrontal Cortex is important for SWM ability

SWM is impaired from pre-psychosis onset

SWM is impaired across all illness stages (UHR -> chronic)

7-10 yrs follow-up: no change in SWM from earliest psychosis stages

Spatial Working Memory is improving until about age 30

*Psychosis onset interrupts this development (?)*

Attentional set-shifting (IDED) from CANTAB (cognitive flexibility)

**Orbitofrontal Cortex is important for IDED ability**

**First-episode psychosis**

*IDED is unimpaired at illness onset (FEP)*

(Pantelis et al, 2009; 2015 (however, see also: Murray et al, 2008; Leeson et al, 2009)
Attentional set-shifting (IDED) from CANTAB (cognitive flexibility)

EDID Task performance is normal at the beginning of psychosis

Schizophrenia patients have deteriorated at follow-up

IDED is unimpaired at illness onset (FEP)

(Pantelis et al, 2009; Pantelis, Wannan et al, 2015 / see also: Murray et al, 2008; Leeson et al, 2009)
• What about memory relevant to hippocampal integrity
  • CANTAB Visuo-Spatial Paired Associates task (VSPA)

• what happens in normal development and at different stages of psychosis?
Normal development of VSPA

Visuospatial Paired Associates Performance at Different Age Groups

- Stages completed
- 6 pattern errors

Psychosis onset

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<th>Age Group</th>
<th>No. of Errors</th>
<th>Stages Complete</th>
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<td>6-7</td>
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VSPA at Follow-up (2)

(Wannan et al, in preparation)

Group x Time: Wald $\chi^2(2) = 13.64$, $p = .001$

Sz Spectrum(Time): Wald $\chi^2(1) = 18.12$, $p < .001$

Affective (Time): Wald $\chi^2(1) = .030$, $p = .861$

Control (Time): Wald $\chi^2(1) = 3.67$, $p = .055$
• The brain is changing in structure in early psychosis, associated with functional (cognitive) changes
  • neuroprogressive changes in temporal and orbitofrontal regions
  • accelerated normal changes of development in dorsal frontal regions

• is there evidence of improved trajectories?
• what factors modulate these trajectories?
Developmental Lag: Findings COS & Siblings

A. COS - GM loss Declines and is Circumscribed to Prefrontal and Temporal Cortices By Age 24

(Greenstein et al. JCPP 2006)

B. Healthy COS Siblings show cortical GM Deficits in Early Ages that Normalise by Age 18

(see: Gogtay, Vyas, Testa, wood, Pantelis, Schizophr Bull, 2011)

(Gogtay et al, AGP, 2007; Mattai et al, submitted)
Childhood Onset Schizophrenia (COS) - GM loss Declines and is Circumscribed to Prefrontal and Temporal Cortices By Age 24

Healthy COS Siblings show cortical GM Deficits in Early Ages that Normalize by Age 18 - resilience factors (?)

(see: Gogtay, Vyas, Testa, wood, Pantelis, Schizophr Bull, 2011)
Developmental Lag: Findings COS & Siblings

Progressive brain changes in psychosis

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- trajectories may be non-linear
ACC thickness in UHR & cognition


- normal leftward asymmetry of ACC is lost in schizophrenia (males)
- leftward asymmetry associated with better performance on SWM
- no effect for verbal fluency

(see also: Gutiérrez-Galve et al, Psychol Med, 2014; Gutiérrez-Galve et al, Biol Psych, 2010)
ACC thickness in UHR & symptoms

- **UHR-P group**: reduced thickness of rostral paralimbic ACC associated with more negative symptoms \((r=0.465, p<0.05)\)

- **UHR-NP group**: increased thickness of rostral limbic ACC associated with higher anxiety symptoms \((r=0.54, p=0.01)\)

(Fornito et al, Biological Psychiatry, 2008)
Progressive brain changes in psychosis

- changes at earliest stages of psychosis
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Dynamic changes early in psychosis

Results shown for Left Planum Temporale
(similar for PP & STG; L>R)

Anterior Insula volume changes
(similar for other regions)

(Takahashi et al, AGP, 2009; Schizophr Res, 2009a, 2009b, 2010)
Developmental Trajectories

(Shaw et al, J Neurosci, 2008; also, Lenroot & Giedd, Neurosci & Biobehv Rev, 2006)

In Summary

- Dynamic brain structural changes are evident from before illness onset
- Neurocognitive and functional outcomes can be understood in the context of brain maturation (Pantelis et al, 2009; Gogtay et al & Pantelis, 2011; Pantelis, Wannan et al, 2015)
  - early versus late maturing abilities
  - improvement in brain structural integrity may be associated with improvement in symptoms and function
- linking function to brain structure requires
  - mapping trajectories (linear/non-linear) from before illness onset
- Emergence of mental disorders is affected by a dynamic balance between factors that confer risk and those that are protective (Pantelis & Bartholomeusz, *World Psychiatry*, 2014)

(see also: Pantelis & Bartholomeusz, *World Psychiatry*, 2014)
Ways Forward

• Trajectories of Acute Relapse
  • role of neuroinflammation

• Translational studies with the animal CANTAB

• Mapping the brain in developmental disorders of childhood
  • Melbourne Study of Schizotypy in Children
  • Autism Spectrum Disorders
Childhood Schizotypy

- present with unusual features, esp. in their thinking / patterns of thought
  - Often not the cause of the referral
  - unusual preoccupations with an internal imaginary worlds
  - Imaginary friends and characters that they interact with within an internal world
  - Vivid imaginations
  - Guarded and Secretive
  - Elaborate ‘world’
Typically developing children, n=TD 32 (17 M)

Autism spectrum disorder (ASD), n=15 (10 M)

Schizotypal disorder (SD), n=8 (5 M)

ASD+SD, n=10 (4 M)

Children with features of schizotypal disorder and ASD are better on attentional set-shifting task (p<0.001)

(Jones et al, 2015; Abu-Akel et al, submitted)
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VLSCI Peak Computing Facility

Austin PET Centre