Brain Structure, Behavioural Phenotypes, and Emerging Mental Illness in Adolescence

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The Neural Maturation Gap: Understanding The Importance Of Brain Development

**Observation**
Early consolidation of limbic-sub-cortical reward processing networks.
Later consolidation of neocortical control networks.
Spike in drug use, psychotic and mood disorders in the neural maturation gap.

**Hypothesis**
Increased incidence of psychopathology in adolescence associated with different developmental rates for limbic and prefrontal systems.

**Proposed Mechanism**
Variation in rate of myelination of long distance cortico-cortical tracts predicts developmental reconfiguration of large scale brain networks.
Experience dependent synaptic plasticity and pruning of inactive connections are other plausible mechanisms.
Hypotheses

- Adolescent cortical shrinkage is coupled to intracortical myelination.

- That consolidation of [shrinkage~myelination] is concentrated anatomically on:
  1. association cortex
  2. the most anatomically strongly connected connected regions (hubs)

- Associated with a gene expression profile enriched for neuronal development and severe mental illness eg schizophrenia, psychoses.
Method

**Sample:** 297 of available 313 scans used after quality control checks

Stratified by 5 age bins: 14-15, 16-17, 18-19, 20-21, 22-24 with ~60 participants (m=f) in each.

**Measures:** CT = mm and MT = % units (PU) at 308 cortical regions for each participant.

**Gene Expression:** Allen Brain Institute – regional gene expression of 20,737 microarrays

**Analysis:** Linear models to estimate baseline CT and MT at 14 years. Age related changes ΔCT and ΔMT Degree closeness of each node PLS method to map gene patterns to regions
The cortex of the brain shrinks and becomes more myelinated in adolescence

Kirstie Whitaker

Cortical shrinkage: Intracortical Myelination ($r^2 = 0.43$)
Baseline MT increases monotonically with distance from the pial surface, Age-related increase in MT ($\Delta$MT) was greatest at 70% cortical depth. ($E$) Correlation between baseline MT and $MBP$ gene expression was also strongest at 70% depth.
Gene expression profiles
cortical shrinkage and myelination
Connectome hubs -> regions with faster rates of cortical consolidation.
Summary of sMRI Findings

- At 14 years association cortex thicker and less myelinated than primary cortex.

- Association cortex had faster rates of cortical shrinkage and intracortical myelination growth over adolescence.

- Age-related increases in cortical myelination were maximized approximately at the internal layer of projection neurons.

- Adolescent intracortical myelination and cortical shrinkage were coupled.

- Specifically associated with a dorsoventrally patterned gene expression profile enriched for synaptic, oligodendroglial- and schizophrenia-related genes.
Summary of sMRI Findings

• Topologically efficient and biologically expensive hubs of the brain anatomical network had greater rates of consolidation.

• Hubs of the connectome were associated with overexpression of the same transcriptional profile as cortical consolidation.

• Normative human brain maturation involves a genetically patterned process of consolidating anatomical network hubs.

• Developmental variation relevant both to normal cognitive and behavioral changes and the high incidence of severe mental illness such as schizophrenia.
Estimating Multidimensional relationships and symptom networks in the natural world
DSM Hierarchical Additivity: Unipolar Major Depression

A Symptoms (1 only) + B Symptoms (>=4)

No discrimination on the basis of location within depression syndromes.
No discrimination within population.
No accounting for chance.
IRT: A mathematical approach that accounts for location, discrimination and chance

\[ p_i(\theta) = c_i + \frac{1 - c_i}{1 + e^{-a_i(\theta - b_i)}} \]

**Item Discrimination**
between persons in different regions on the latent continuum

- **c = 0.25**
- **a = 1.0**
- **b = 0.0**

**Item Location**
One Item at medium strength on the trait

- **p (guess)**

**Latent Trait for depression**

- **Low**
- **High**
Some Longitudinal Modelling Principles

\[ p_i(\theta) = c_i + \frac{1 - c_i}{1 + e^{-\alpha_i(\theta-b_i)}} \]

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\[ p_i(\theta) = c_i + \frac{1 - c_i}{1 + e^{-\alpha_i(\theta-b_i)}} \]
Using 33 item MFQ and 28 item RMAS
D: Depression.
A: anxiety.
W: Worrying.
S: Somatic symptoms.
G: General distress factor.
Sp1-3: Specific factors.

1159 respondents aged 14 yrs.
Sex effects tested (ns)= set to zero.
8% Any Dep; 6% Any Anx by 14 yrs.
Incl. correlated errors >0.6 considerably improved the fit.
NS effects of instrument/method

Bifactor Model and Diagnostic Typologies

Distress
Worry
Hopeless
Somatic

DSM Diagnoses

Discovery -> replication and extension of the General Distress Factor

• Cross-sectional, Item-level Information From Measures Of Depression, Anxiety And Psychotic Experiences

• 6617 Participants Aged 13 Yrs From The Alspac Birth Cohort.

• 977 Participants Aged 18 Yrs From The Roots Schools-based Sample.

Adding a Psychotic Symptoms Component in the youth population

**Model A**
**Structure:** Unidimensional
**Hypothesis:** A single factor underlies depressive and anxiety symptoms and PE

**Model B**
**Structure:** Two uncorrelated factors
**Hypothesis:** Two distinct latent variables corresponding to depressive and anxiety symptoms and PE

**Model C**
**Structure:** Two correlated factors
**Hypothesis:** Two factors as for model B, but depressive and anxiety symptoms and psychotic experiences are correlated

**Model D**
**Structure:** Bi-factor
**Hypothesis:** A single latent variable underlies depressive and anxiety symptoms and PE, with two specific factors (one for depressive and anxiety symptoms and one for PE)
Revealing a General Mental Health Distress Latent Trait with a longer tail

Location of the items measuring psychotic experiences relative to depressive and anxiety symptoms on the latent continuum of common mental distress.
Symptom Characteristics on the general distress continuum

• Items with higher values on the ‘D factor’ were related to motor retardation, suicidality, and specific night time worries.

• Problems with concentration and decision-making were generally located at the less severe end of the latent distress trait.

• 'I didn't enjoy anything', 'I was very restless' and 'I felt miserable or unhappy' were associated with very high severity on the underlying distress dimension.

• Psychotic phenomenon are on the same continuum and also occur at the very severe end of distress.
Using The NSPN Cohort To Reveal A Comprehensive D Factor

• Depression
• Anxiety
• Obsessions/Compulsions
• Antisocial behaviour
• Psychotic/Schizotypy
• Well-being
Fitting A Bifactor Model From An Item Pool Reduced via EFA/CFA
In 2,000 NSPN participants

St. Clair, M (2017) et al PlosOne under review
Quantitative assay of neural, cognitive and/or behavioural “type” in typical and atypical development

A test of developmental acceleration/deceleration hypotheses of the neural and behavioural basis of psychopathology
Myelination and the General ‘D’ Factor

(unpublished ongoing analyses)
The Post Doctoral Scientists of NSPN

Kirstie Whitaker  Anne-Laura Van Harmelen  Michelle St. Clair

Jeannette Brodbeck  Petra Vertes
The Post Doctoral Scientists of NSPN

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NeuroScience in Psychiatry Network

Wellcome Trust Strategic Award