The Emergence Of Clinical Depressions In The Human Life Cycle

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This Lecture

• The Scope and Characteristics of the Problem.
• Depression Severity and Psychotic Experiences.
• Mathematical approaches to phenotypes.
• Discovering Biomarkers.
• The Maturing brain.
Depressed mood
Irritability/anger
Pervasive anhedonia

Executive Cognitive disturbance
Negative Self-perceptions
Suicide
Sleep disturbance
Weight/appetite disturbance
Psychomotor disturbance
Fatigue, lack of energy, tiredness

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

High Reliability but Low Validity
The Emergence Of The Depressions: The Correlates of Age
Prevalence Of Youth Diagnostic Depressions In The First 2 Decades Of Life

• <1% in Pre-pubertal Children: B=G.

• 3%-6% in post-pubertal adolescents: G >B 2:1.

• ~70% -> premorbid non specific difficulties.

• Higher symptoms -> more severity -> lower T response.

• Clinical typology is top down and heterogeneous.

• High reliability but low validity.
Common mental illnesses are emergent between 10 and 30 years. Endophenotypes likely to be formed by the first two decades of life. In contrast activation processes may occur proximal to illness emergence.
The Emergence Of The Depressions: Illness Severity
Descriptive Psychopathology
Unipolar Major Depression

- Depressed mood
- Irritability/anger
- Pervasive anhedonia
- Executive Cognitive disturbance
- Negative Self-perceptions
- Suicide
- Sleep disturbance
- Weight/appetite disturbance
- Psychomotor disturbance
- Fatigue, lack of energy, tiredness

= 1 mood + 4 (or more) others

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

How many possible permutations are there? >1,000
How many occur - not known
High Reliability BUT low validity
Item Response Theory: 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

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

\( p \) (guess)

\( a = 1.0 \)

\( b = 0.0 \)

**Individual Variation**
Latent Trait for Depression: Construct Validity

Behaviour in the adolescent population

Common variance between items reveals the latent trait

Unique variance of the item reveals its singular importance

Tears hopelessness insomnia retardation anhedonia

Common Uncommon

Unique variance for each item

variation

-3 0 +3

Latent trait for depression

Common variance between items reveals the latent trait

Unique variance of the item reveals its singular importance
The y-axis is the probability that the SMFQ symptom is endorsed.

All items function at more or less the same level on the latent trait.

All items are located towards the more severe end—to the right of the figures.

The probability of endorsing any item is very low.

IRT Model gives 2 dimensions for depressive symptoms
Latent trait for depression and 2nd for maturation.
Atypical depressive items load on the 2nd only

Summary

• The magnitude of individual item response for contributing to a clinical state vary with age.

• The importance of items varies with sample type.

• Metabolic effects during adolescence account for weight gain and appetite increases.

• Clinical diagnostic markers for primary care and hospital practice are likely to be different.
Revealing Structure of Clinical Phenotypes
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

Currently & 3 years later

Distress
Worry
Hopeless
Somatic

DSM Diagnoses

Standardised regression coefficients

-0.40 -0.30 -0.20 -0.10 0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70

-0.40 -0.30 -0.20 -0.10 0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70

General distress
Hopelessness-suicidal ideation
Generalized worrying

Major depression
Specific Phobia
Panic
GAD
OCD
Opposite defiant
Conduct disorder
ADHD
Substance alcohol
Eating disorders
Any affective disorder
Any anxiety disorder
13 new affective disorders
13 new anxiety disorders
11 and 13 affective disorders
11 and 13 anxiety disorders
t1 and t3 affective disorders
t1 and t3 anxiety disorders
t1 and t3 behaviour disorders

Depressions and Psychotic Experience
Psychotic Experiences (PE) and Depression

• PE are common in the general population (3%-5%).

• PE and MDD are co-occurring.

• Share the same risk factors.

• Conceptual, clinical and causal links exist.

• No clear cut validity for distinction in clinical typology.

• Excluded from diagnostic criteria for MDD.
Psychotic Experiences (PE), Depressive And Anxiety (D&A) Symptoms

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)

Location Of Psychotic Experiences Relative To Depressive And Anxiety Symptoms

Summary

Bifactor models reveal a common general latent trait that links behaviourally different items.

This is likely to account for covariance at the factor level; comorbidity at the clinical level.

Need a much greater scientific understanding of the behavioural repertoire in the ‘natural world’

First step in creating new valid clinical typologies.
Discovering Biomarkers in the Adolescent Population:

“a biologic feature that can be used to measure the presence or progress of disease or the effects of treatment.”
Gene-Environment Population Markers For The Presence of Depressions
Multiple SEM tests the effects simultaneously via GLM regression whilst controlling the covariance for each equation.
Moderation-mediation of Cognition and Symptoms in 277 16-17 yr olds

Affective G-NG
SS/CA+ve -> more commission errors on the neutral task (p=0.01)

Probabilistic Reversal
More errors (p=0.004) & switching in SS (CA+ve) (p=0.02).

SS( CA+ve) -> higher mean depression and anxiety scores at 14 yrs.

Longitudinal prediction from cognition to symptoms at 18-19 years

AGN Neutral commission errors (OR=1.82, p=0.006)

Psychoendocrine Population Markers Depressive Cognitions and Clinical Disorders
Psychoendocrine Subgroups In 2 Distinct Adolescent Community Populations in Cambridge

Depression symptoms and morning cortisol level from 3 assessments over time

Define subgroups using latent class analysis

Low D scores
Low Cortisol

High D scores
Low Cortisol

Low D Scores
High Cortisol

High D Scores
High Cortisol

Classes created from a discovery sample n=666 with both measures at 0,8 and 12 months Replicated in a 2nd sample, n=1198 with D measures at 0, 18,36 months but Cort at only
Clinical Depression Cases By Class

- Each Statistically derived sub type or class has a % of depressed cases by 17 years of age.
- Theoretically these depressed cases from each sub-type will have different mechanisms Accounting for the emergence of depressions.

Owens M et al. PNAS 2014;111:3638-3643
The odds ratios for MD in each class by sex

Owens M et al. PNAS 2014;111:3638-3643

The odds ratios for MD in each class by sex. The reference group is class 1 (n = 539). Adjusted for cohort, age, and pubertal status.

Owens M et al. PNAS 2014;111:3638-3643

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LCA 4 classes and overgeneral memory (OGM)

N=660

Class 4 > OGM responses than all other classes (4>1, P < 0.01), (4>2, P < 0.001) and (4>3, P = 0.01). No sex x classes interaction (P = 0.83).

Owens M et al. PNAS 2014;111:3638-3643
Summary

- 5HTTLPR ‘s’ carriers + child maltreatment at risk for high anxiety and depressive symptoms.

- Impaired bottom up emotion processing and/or difficulties in top down ‘learning through uncertainty’.

- **Dual processing cognitive deficits hypothesis.**

- High depression/distress traits + high morning trait cortisol defines a very high risk population sub type of adolescents.

- Characterised by impairments in autobiographical memory for both sexes and in boys only for clinical depressions.

- **Corticoid mediated cognitive hypothesis.**
Timing And The Developing Human Brain:

Implications Of Timing Of Experiences And The Emergence Of Depression
Gray Matter Changes
Cortical And Subcortical Brain Regions: 6-23 Years

Brain development proceeds in stages that vary across regions. Hippocampal volumes are 85% of adult values by adrenarche. Comparatively occurs in all mammalian species. Rates similar across species including the onset of puberty and higher-level cognition.

Based on Data from Jay Giedd: published in Andersen and Teicher 2008 TINS
Grey Matter Reduction And Affective Disorders
Meta-Analysis Findings

• Meta-analysis of 23 studies: GM reduction in bilateral rostral ACC.

• Reduction in rostral ACC the most consistent.

• Reductions in other regions within fronto-subcortical and limbic regions was less consistent.

• Related positively to illness duration.

• Chronic/persistent MDD has a deleterious and perhaps focal effect on brain structure.
The Depressed But Still Developing Brain

• X-Sectional structural neuroimaging.

• 109 MDD 36 healthy controls Case-control comparison.

• F>M (3:1) ; 11-17 years.

• GMV in ACC and across the whole-brain.
Main effect of age on GMV: controls>MDD. Age differences are dissimilar between MDD and controls.

Hagan et al 2015, Neuroimage: Clinical
Age and Depressive Symptom GMV decreases in the Thalamus

Opposite to ACC: MDD > CON.
MDD only: GMV in thalamus (not ACC) 1/symptoms. Unpublished Results
Summary
The Depressed And Developing Adolescent Brain

• Dissimilar age-related and symptom-sensitive patterns of GMV differences compared with controls.

• The thalamus and ACC may comprise distinctive neural markers for detecting these effects in youth.

• Critical to disaggregate antecedent neural vulnerabilities for MDD from the effects of MDD on the developing brain.
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.
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