UNIVERSITY OF CAMBRIDGE

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.

Descriptive Psychopathology
Unipolar Major Depression

Irritability/anger

Depressed mood

Pervasive anhedonia

= 1

mood + 4 (or more) others

Executive Cognitive disturbance

Negative Self-perceptions

Suicide

Sleep disturbance

Weight/appetite disturbance

Psychomotor disturbance

Fatigue, lack of energy, tiredness

= 1

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

High Reliability but Low Validity

The Emergence Of The Depressions:

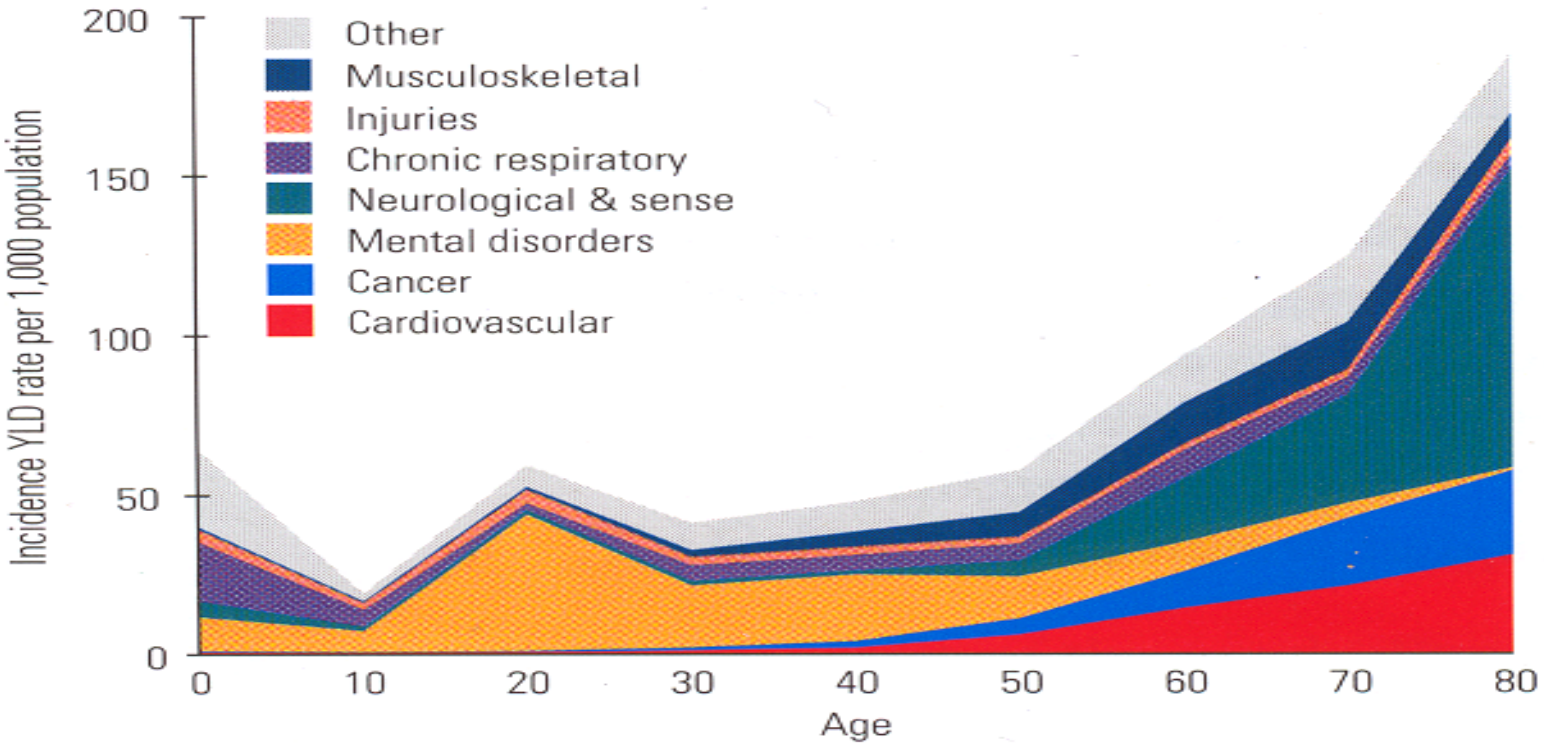
The Correlates of Age

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.

Developmental Epidemiology of disease

Figure 6 Incident YLD Rates per 1,000 Population by Age and Broad Disease Grouping, Victoria 1996



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

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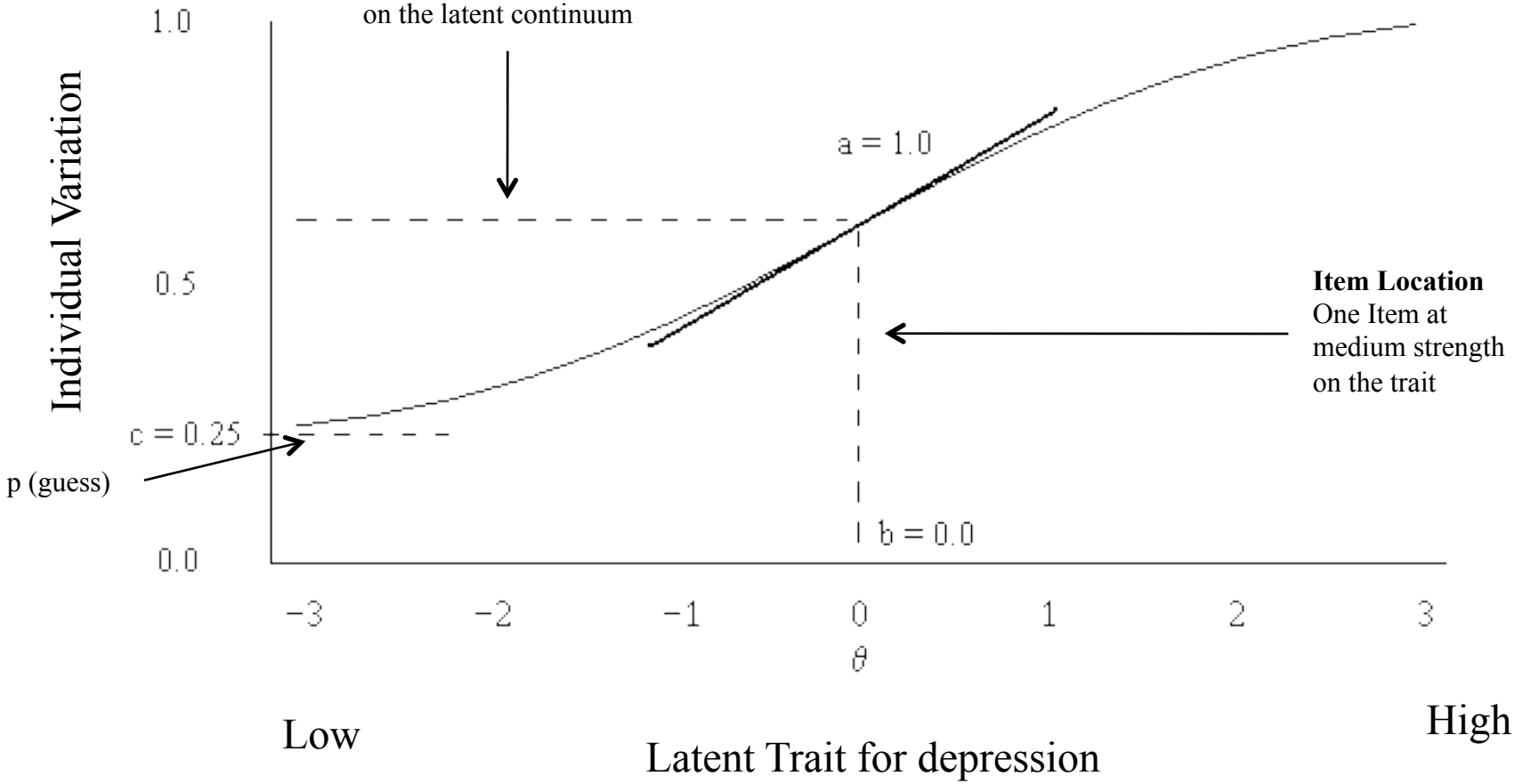
A Symptoms (1 only) + B Symptoms (>=4)

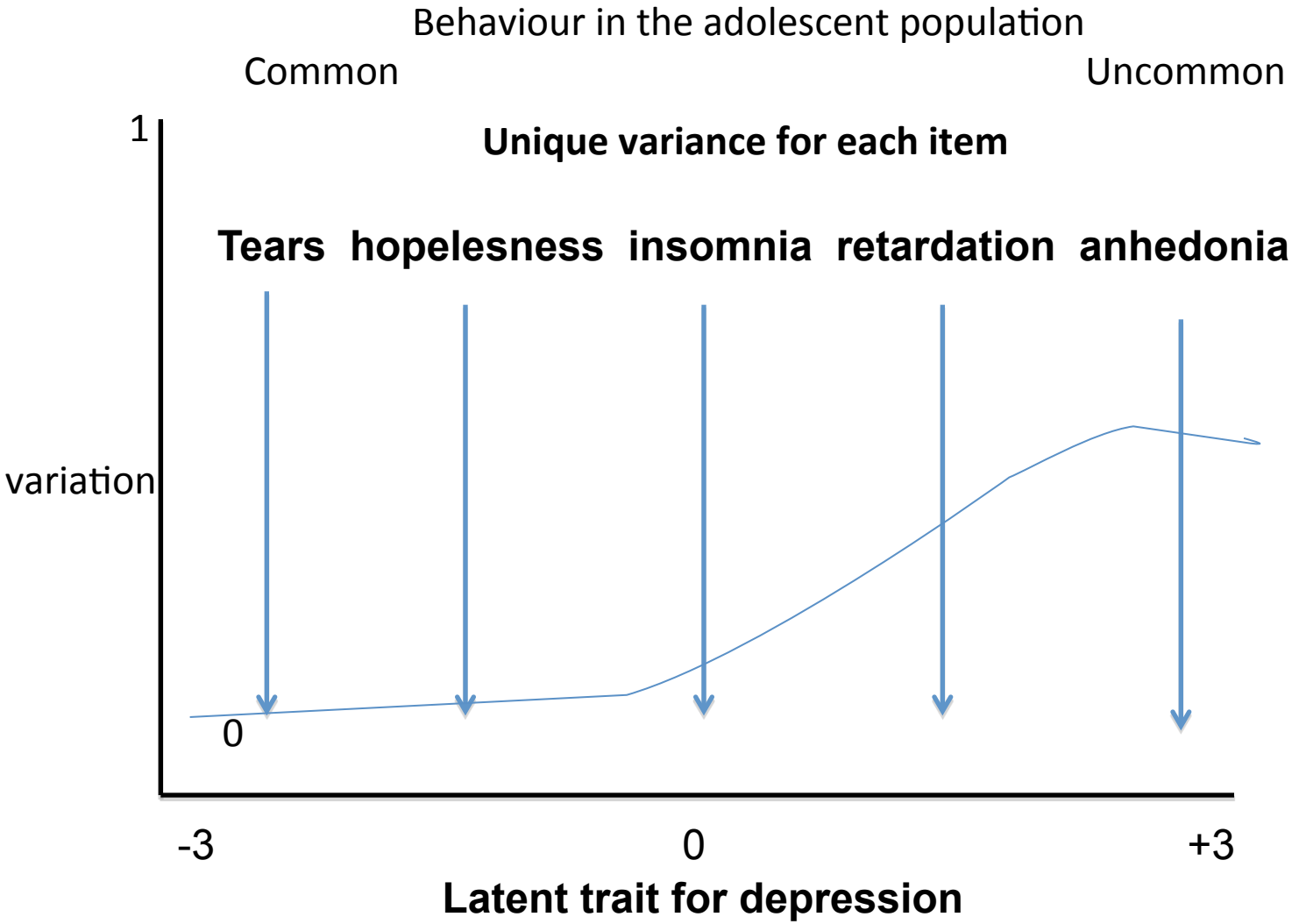
How many possible permutations are there ? >1,000
How many occur - not known
High Reliability BUT low validity

Item Response Theory: A mathematical approach that accounts for location, discrimination and chance

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

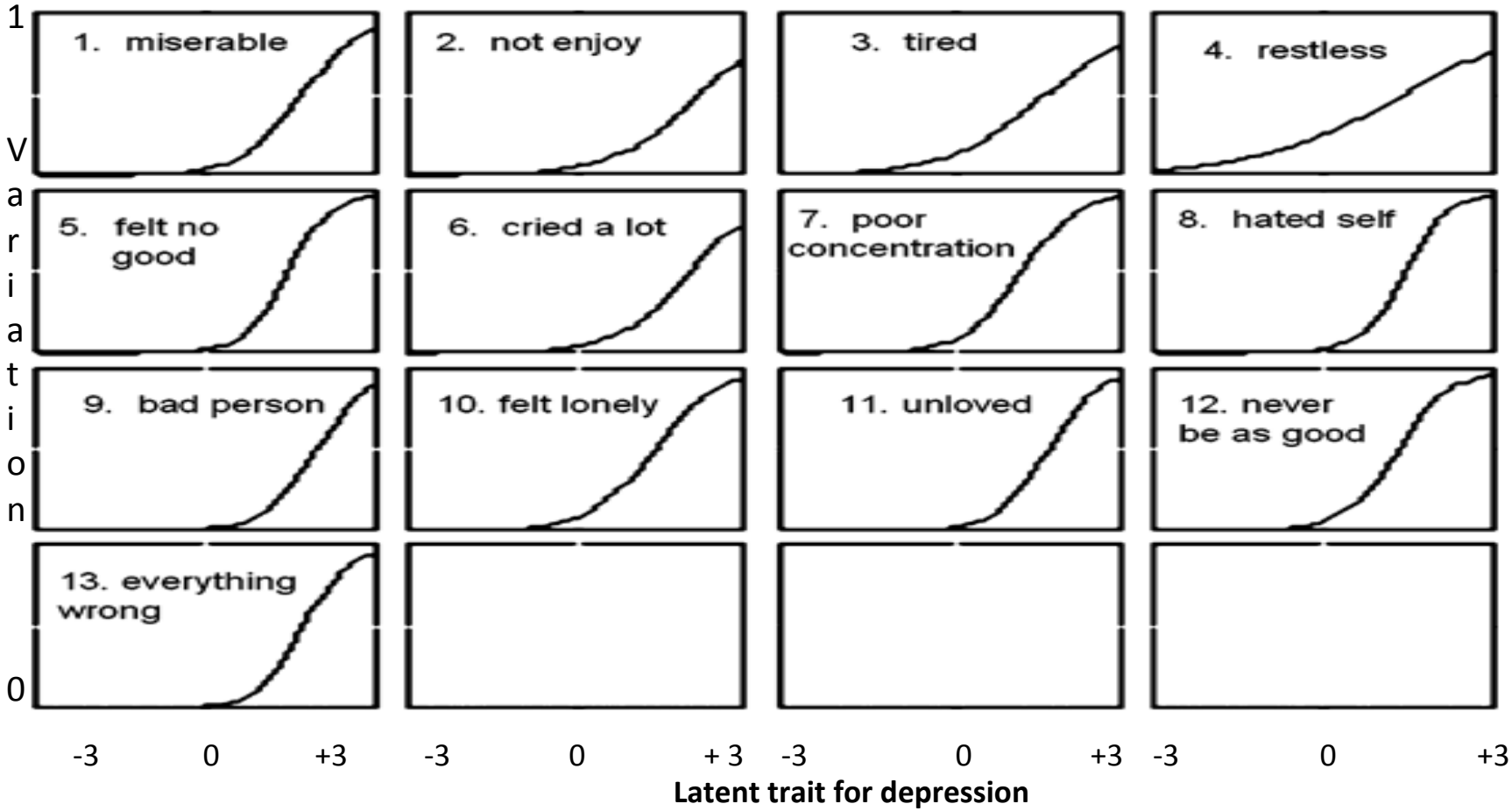


Latent Trait for Depression: Construct Validity



Common variance between items reveals the latent trait
Unique variance of the item reveals its singular importance

IRT For 657 Children 7-11 years for self reported depressive symptoms across the latent trait



- 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.

Sharp et al (2006) J Abnorm Child Psychol ;34(3):379-91.

IRT For 2,307 teens aged 11-18 years for depressive symptoms across the latent traits

Table 3

Item Parameter Estimates (and Standard Errors) for Bidimensional Graded Respor

Items	Discriminations		Thresholds	
	Dimension 1	Dimension 2	Threshold 1 (1 vs. 2 or 3)	Threshold
	Est. (*SE*)	Est. (*SE*)	Est. (*SE*)	E:
Depressed mood	**0.907** (0.011)	0.004 (0.016)	−0.273 (0.029)	0.3
Irritability	**0.794** (0.017)	0.015 (0.028)	−0.226 (0.029)	0.3
Anhedonia	**0.824** (0.016)	0.035 (0.030)	−0.081 (0.026)	0.2
Appetite decrease	**0.860** (0.078)	**30.649** (0.030)	0.597 (0.031)	0.9
Weight loss	**0.741** (0.077)	**30.606** (0.034)	1.246 (0.039)	1.5
Appetite increase	0.229 (0.118)	**0.832** (0.054)	0.905 (0.034)	1.2
Weight gain	0.136 (0.123)	**0.841** (0.056)	1.171 (0.038)	1.3
Initial insomnia	**0.689** (0.020)	−0.073 (0.034)	0.291 (0.029)	0.7
Middle insomnia	**0.723** (0.027)	−0.179 (0.036)	0.717 (0.032)	1.0

IRT Model gives 2 dimensions for depressive symptoms

Latent trait for depression and 2nd for maturation.

Atypical depressive items load on the 2nd only

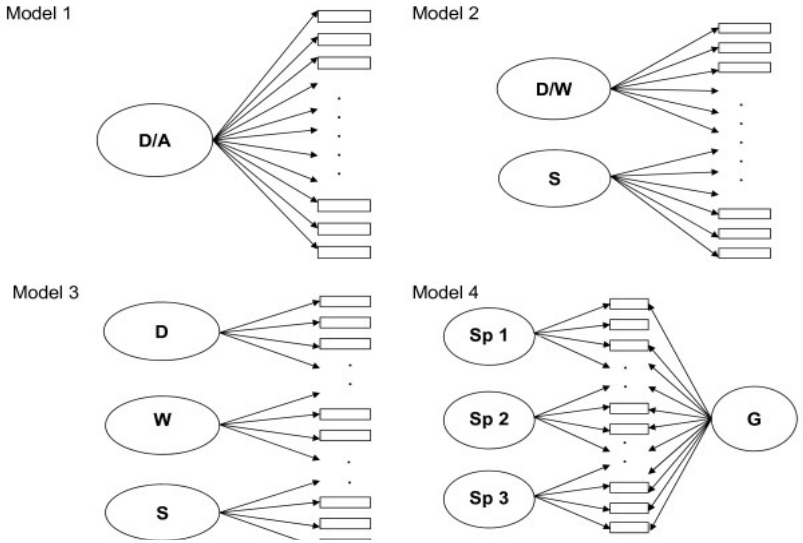
Cole D et al (2012) J Abnorm Psychol. 121(4):838-51

Summary

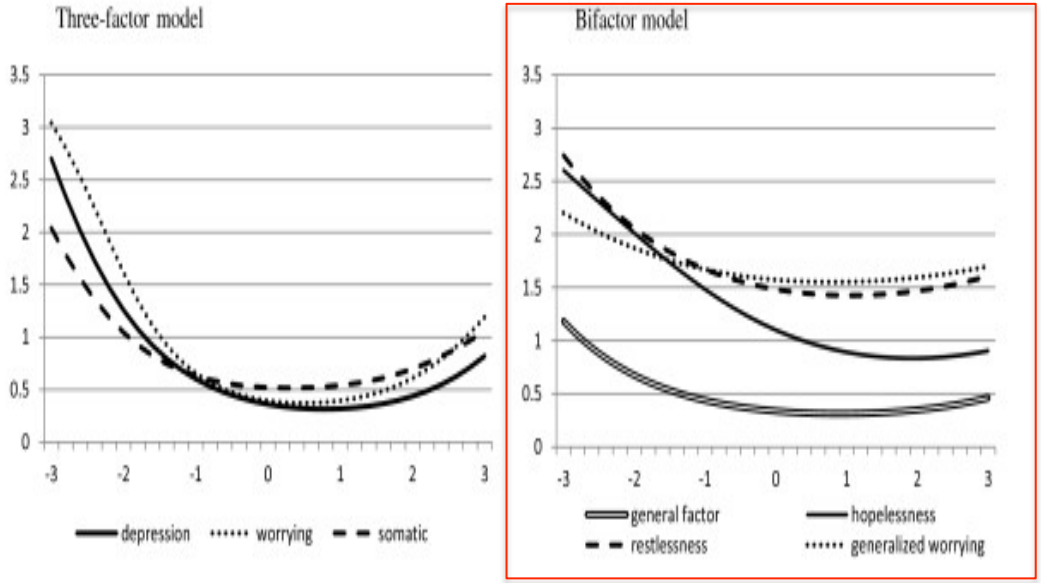
- The magnitude of individual item response for contributing to a clinical state vary with age.
- The importance of items varies with sample type.
- Metabolic effects during adolescence account for weight gain and appetite increases.
- Clinical diagnostic markers for primary care and hospital practice are likely to be different.

Revealing Structure of Clinical Phenotypes

IRT : Hierarchical Bi-Factor Modeling



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

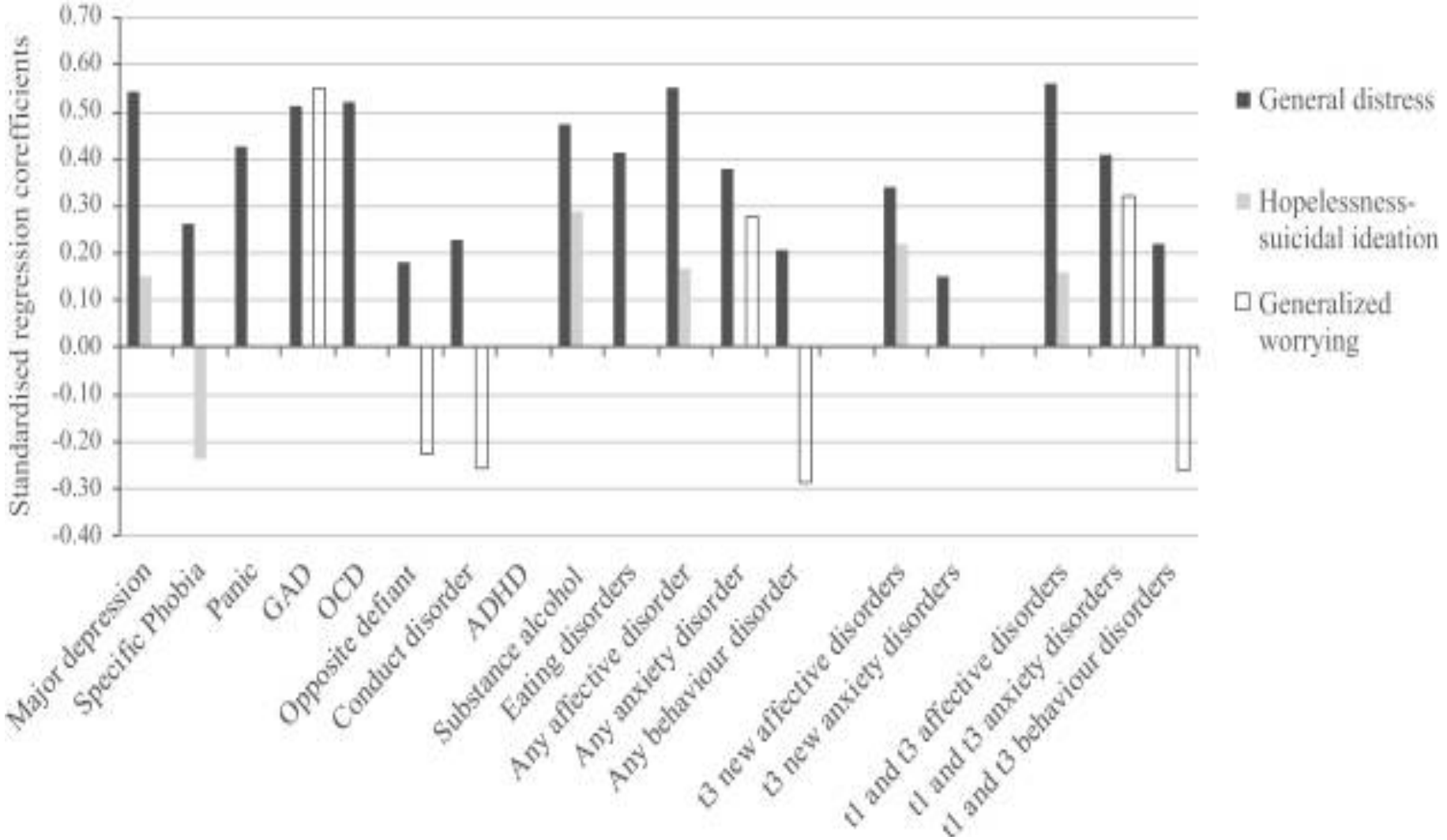
Brodbeck et al (2011) BMC Psychiatry 11:191

Bifactor Model and Diagnostic Typologies

Distress
Worry
Hopeless
Somatic

Currently & 3 years later

DSM Diagnoses



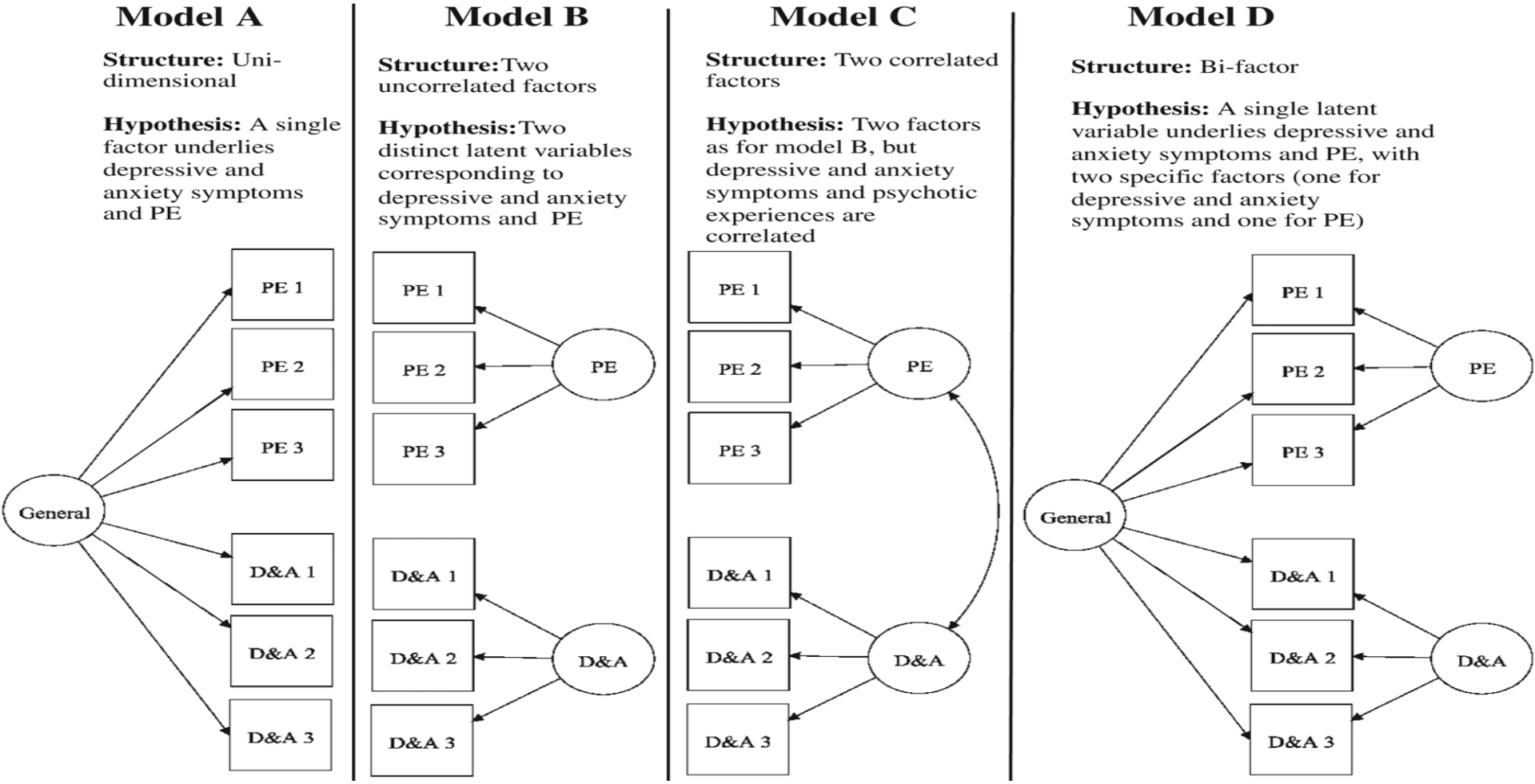
Brodbeck et al (2014) J Affect Disord.52-154:299-305

Depressions and Psychotic Experience

Psychotic Experiences (PE) and Depression

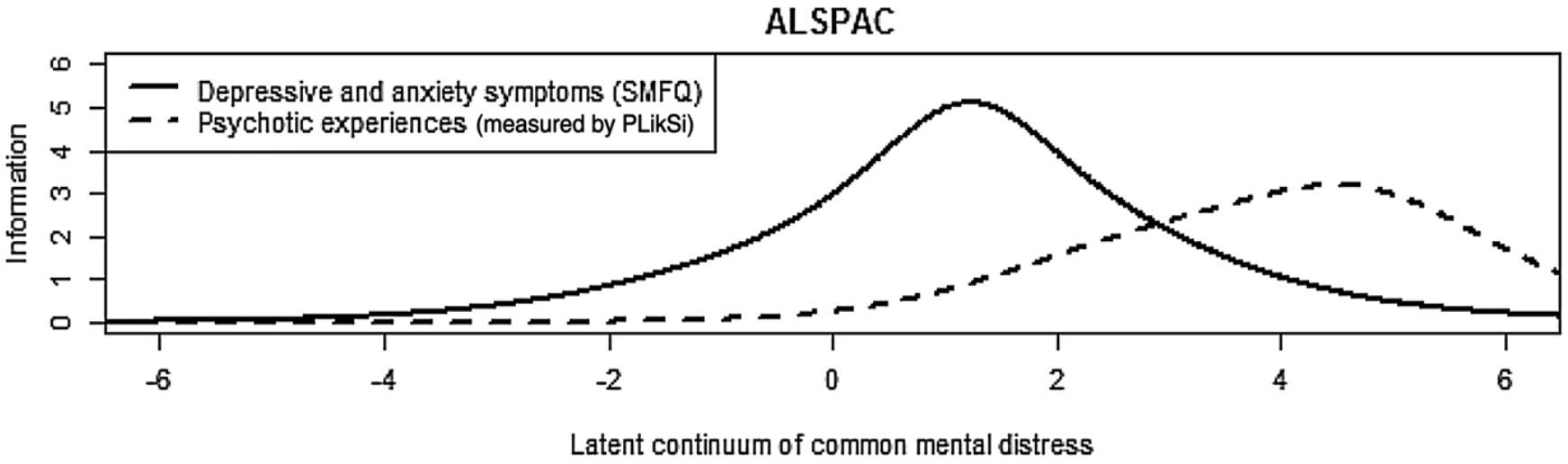
- PE are common in the general population (3%=5%).
- PE and MDD are co-occurring.
- Share the same risk factors.
- Conceptual, clinical and causal links exist.
- No clear cut validity for distinction in clinical typology.
- Excluded from diagnostic criteria for MDD.

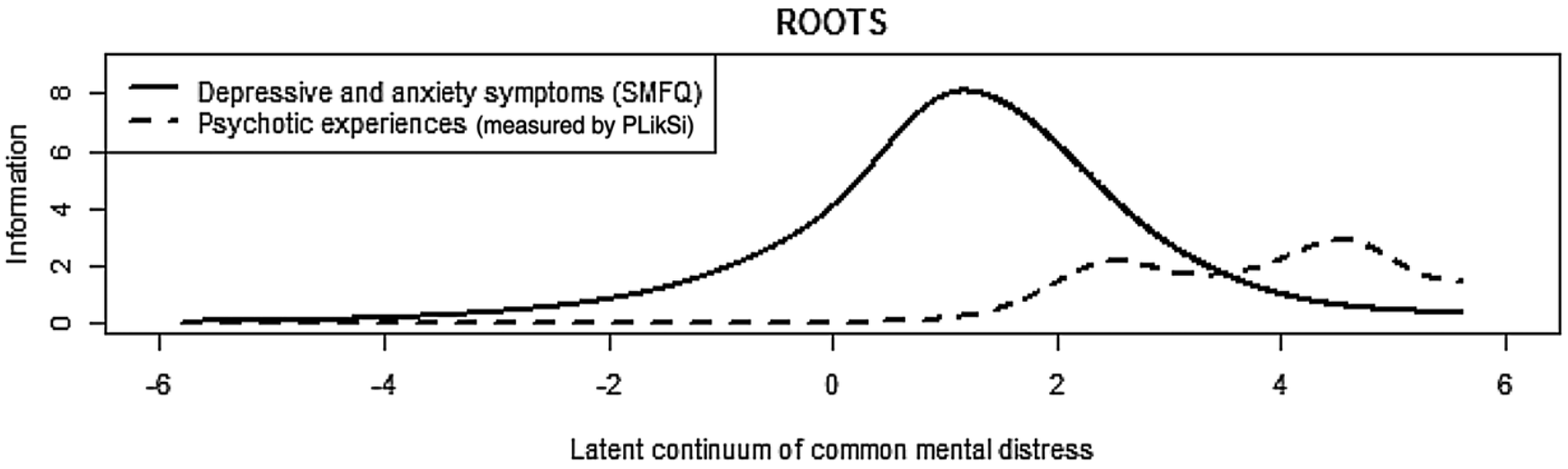
Psychotic Experiences (PE), Depressive And Anxiety (D&A) Symptoms



Stochl , J., et al (2015) Psychological Medicine, 45 :07, 1483-1493

Location Of Psychotic Experiences Relative To Depressive And Anxiety Symptoms





Stochl , J., et al (2015) Psychological Medicine, 45 :07,1483-1493

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’

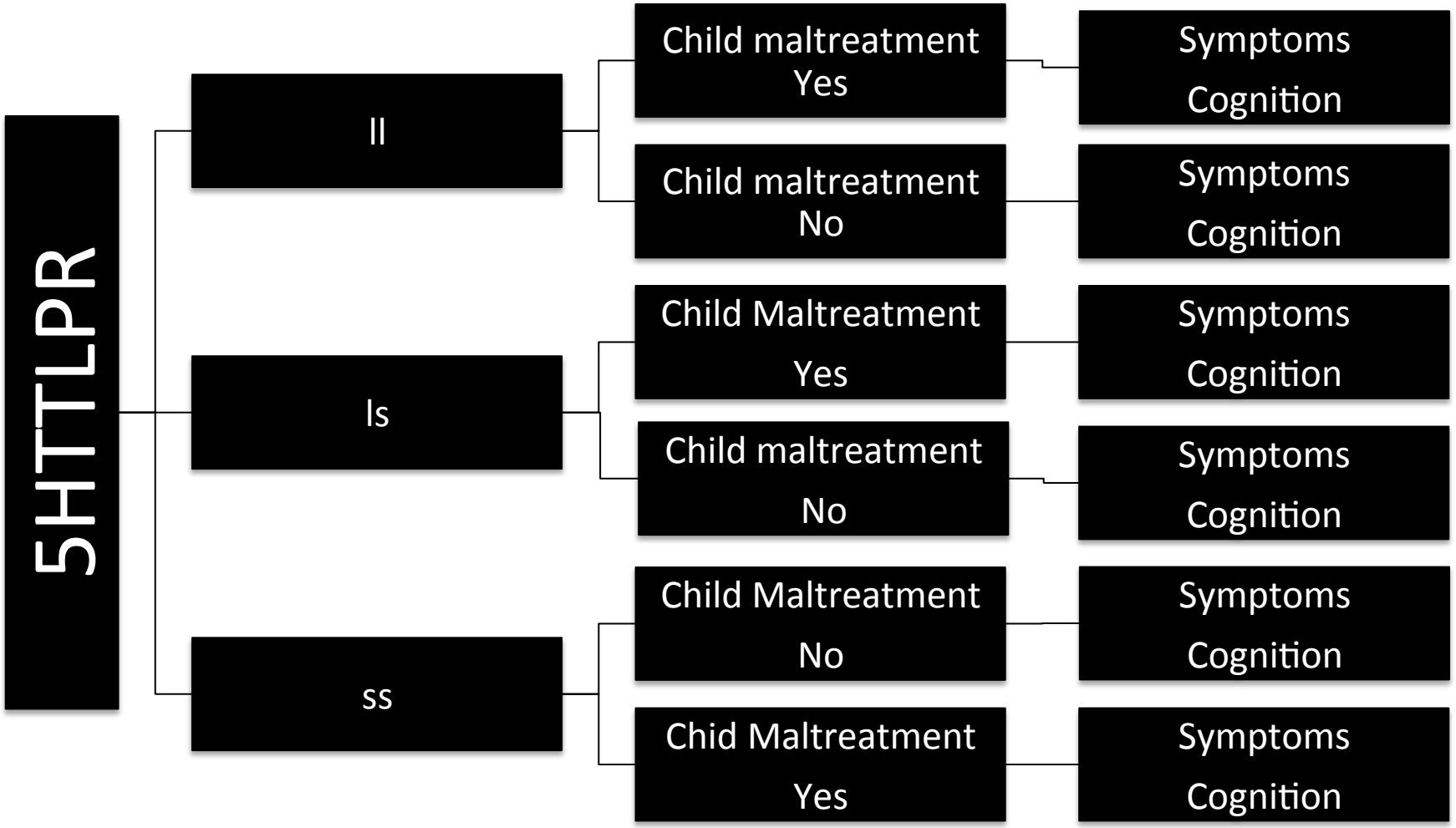
First step in creating new valid clinical typologies.

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."

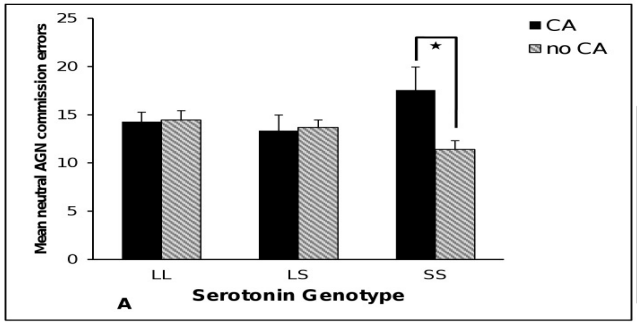
Gene-Environment Population Markers For The Presence of Depressions

Multilevel Gene–environments And Symptoms
A Longitudinal Perspective



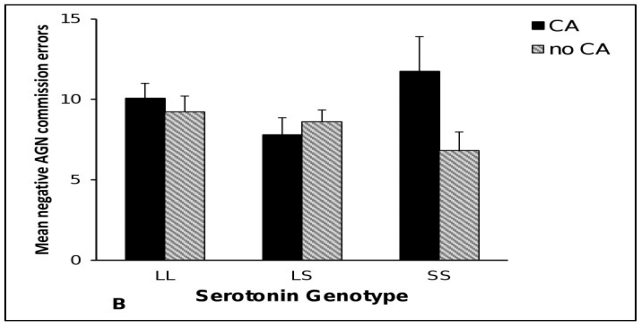
Multiple SEM tests the effects simultaneously via GLM regression whilst controlling the covariance for each equation.

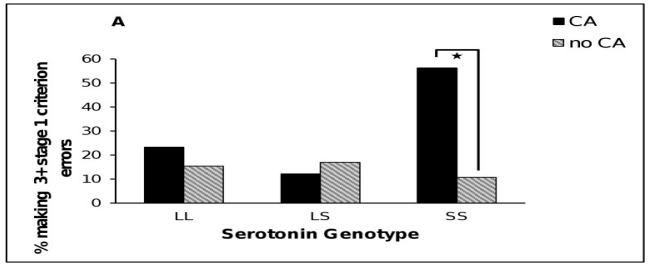
Moderation-mediation of Cognition and Symptoms in 277 16-17 yr olds



B

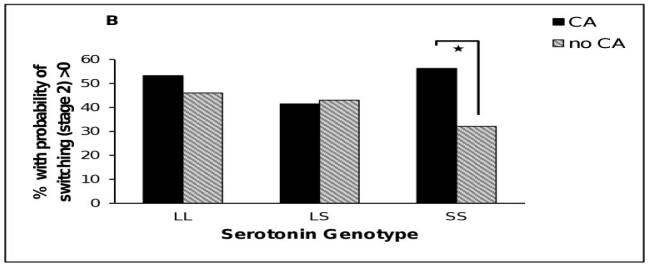
Affective G-NG
SS/CA+ve ->more commission errors on the neutral task(p=0.01)



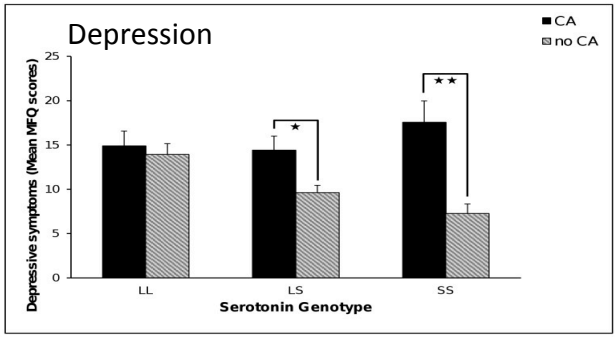


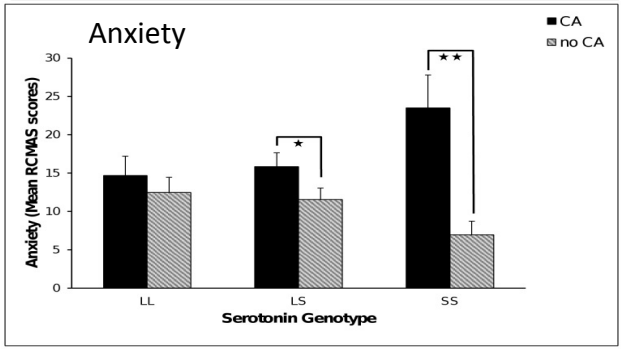
C

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



A





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

D

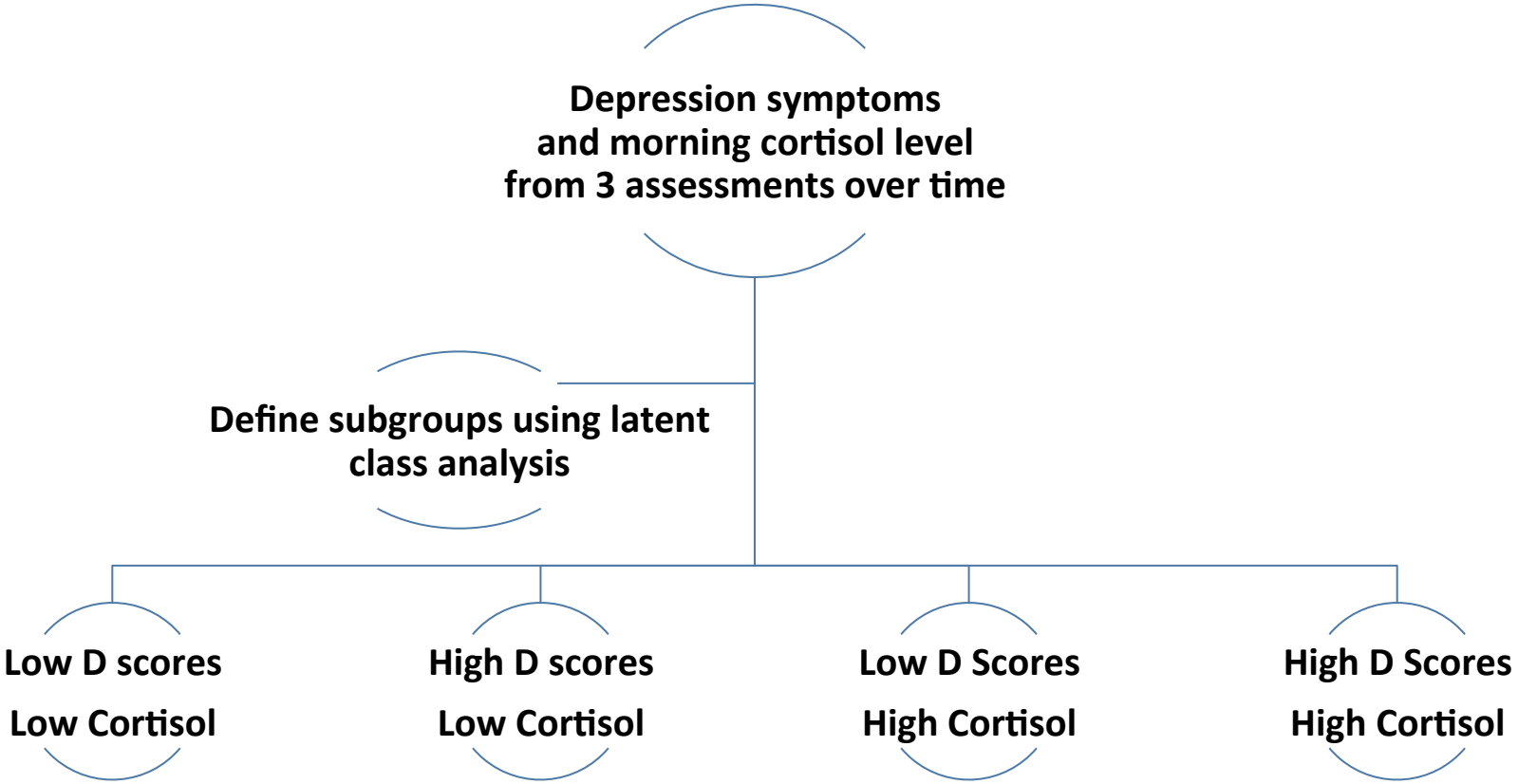
Longitudinal prediction from cognition to symptoms at 18-19 years

AGN Neutral commission errors (OR=1.82, p=0.006) → Anxiety Depressive Disorders

Owens et al (2012) PLoS One. 7(11):e48482

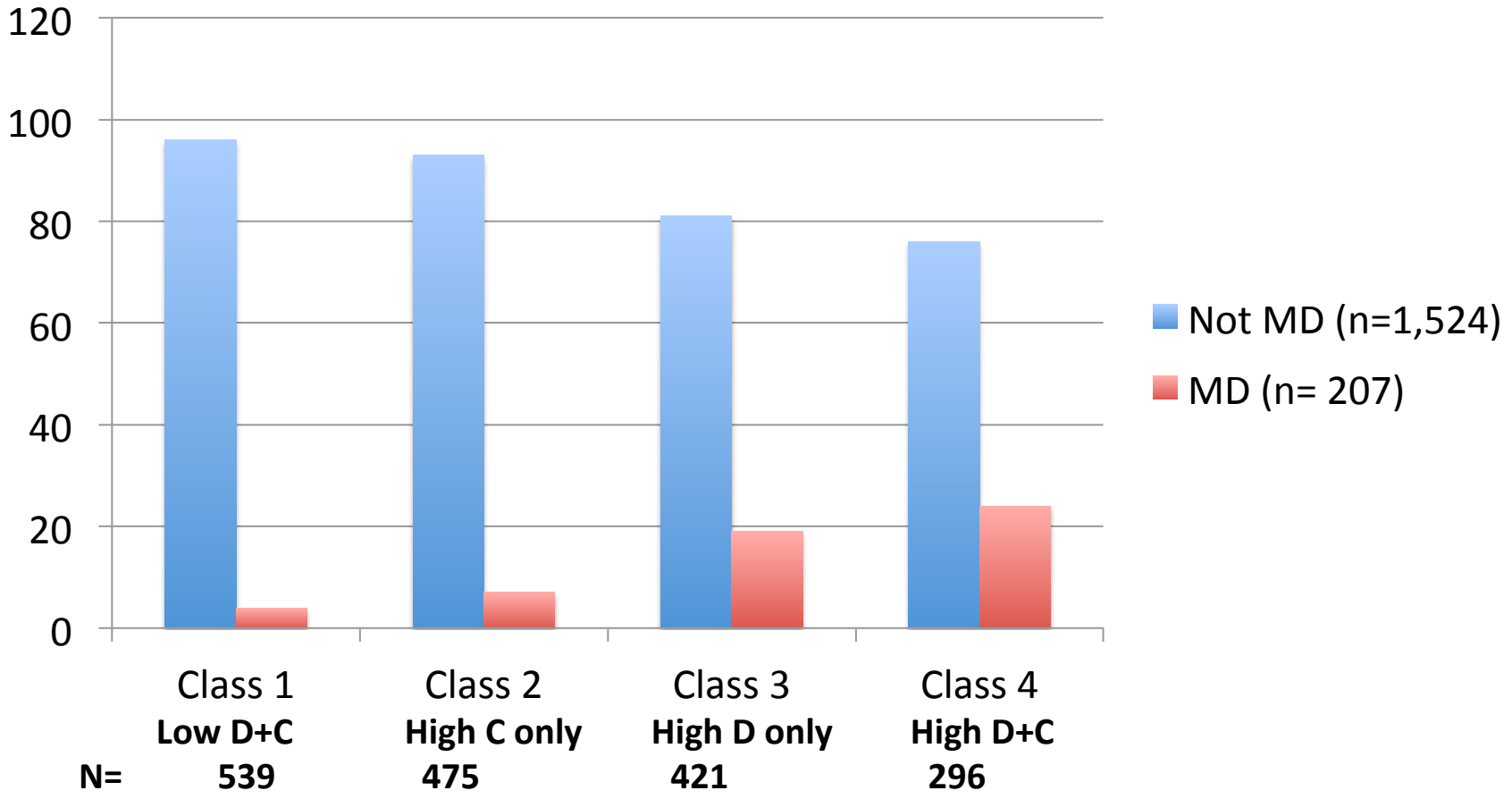
Psychoendocrine Population Markers Depressive Cognitions and Clinical Disorders

Psychoendocrine Subgroups In 2 Distinct Adolescent Community Populations in Cambridge



Classes created from a discovery sample n=666 with both measures at0,8 and 12 months
Replicated in a 2nd sample , n=1198 with D measures at 0, 18,36 months but Cort at only

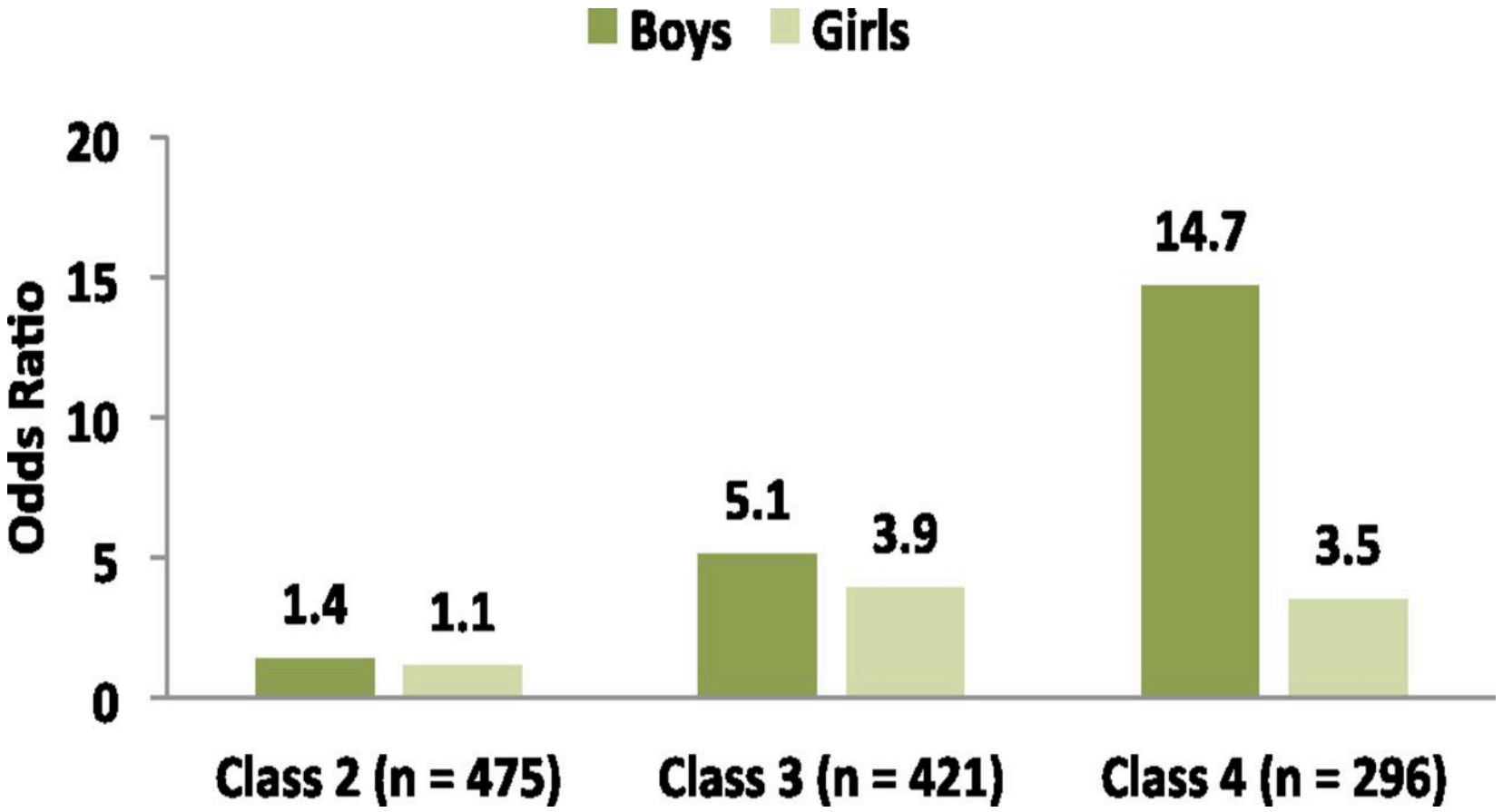
Clinical Depression Cases By Class



- **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

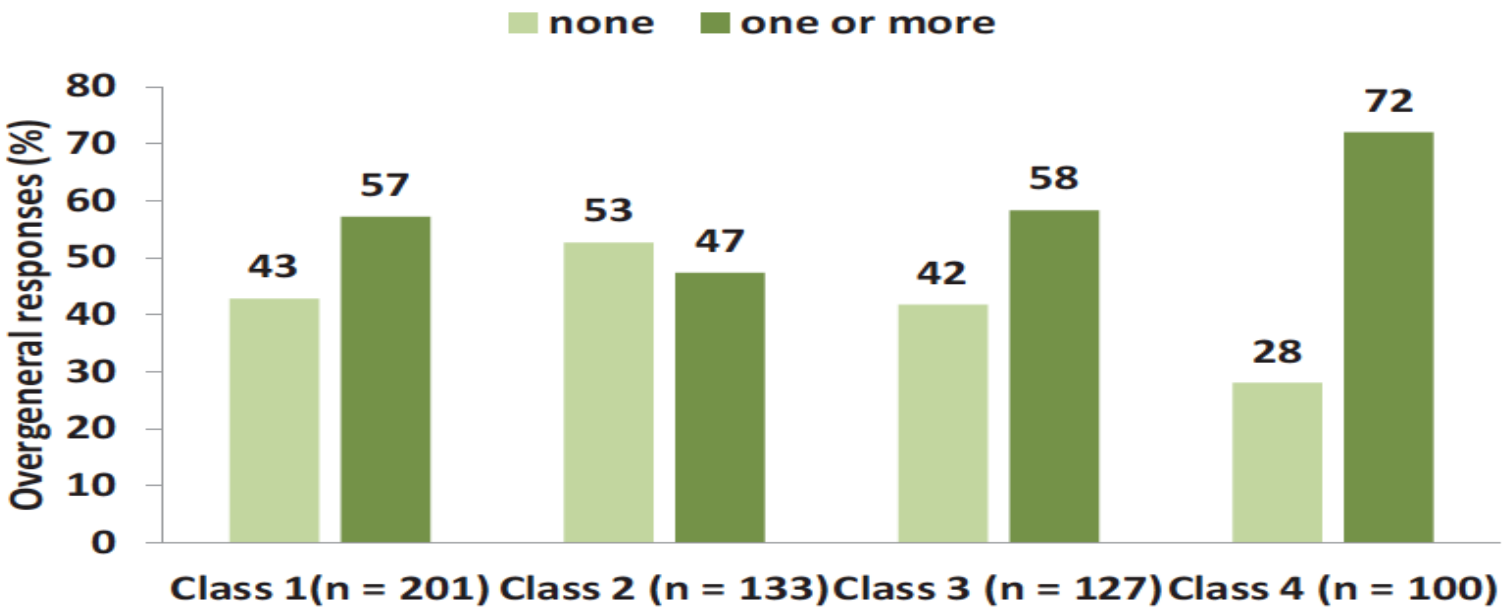


The odds ratios for MD in each class by sex. The reference group is class 1 (*n* = 539). Adjusted for cohort, age, and pubertal status.

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

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 × classes interaction (P = 0.83).

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

Summary

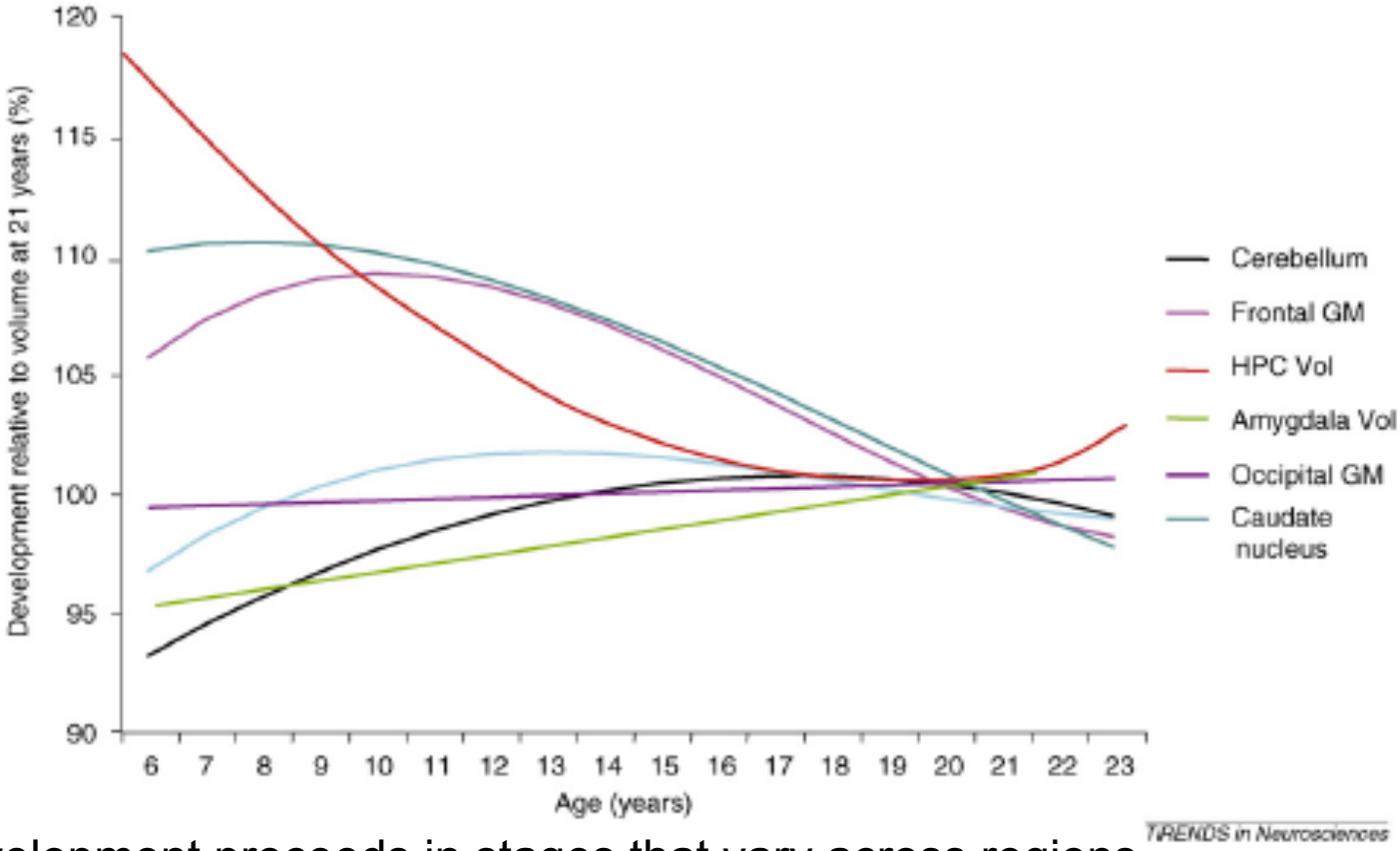
- 5HTTLPR ‘s’ carriers + child maltreatment at risk for high anxiety and depressive symptoms .
- Impaired bottom up emotion processing and/or difficulties in top down ‘learning through uncertainty’.
- Dual processing cognitive deficits hypothesis.
- High depression/distress traits + high morning trait 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

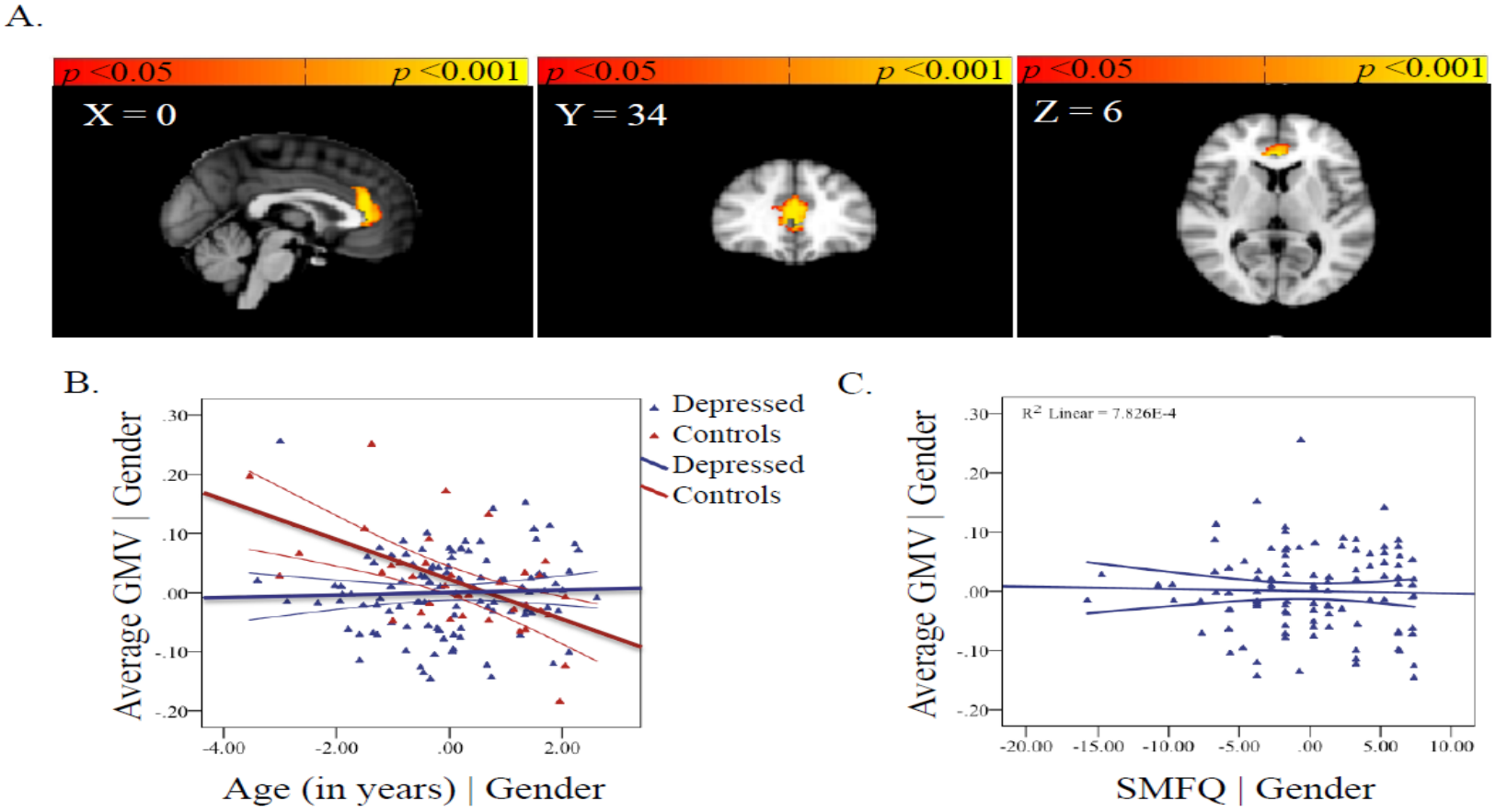
Grey Matter Reduction And Affective Disorders Meta-Analysis Findings

- 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.

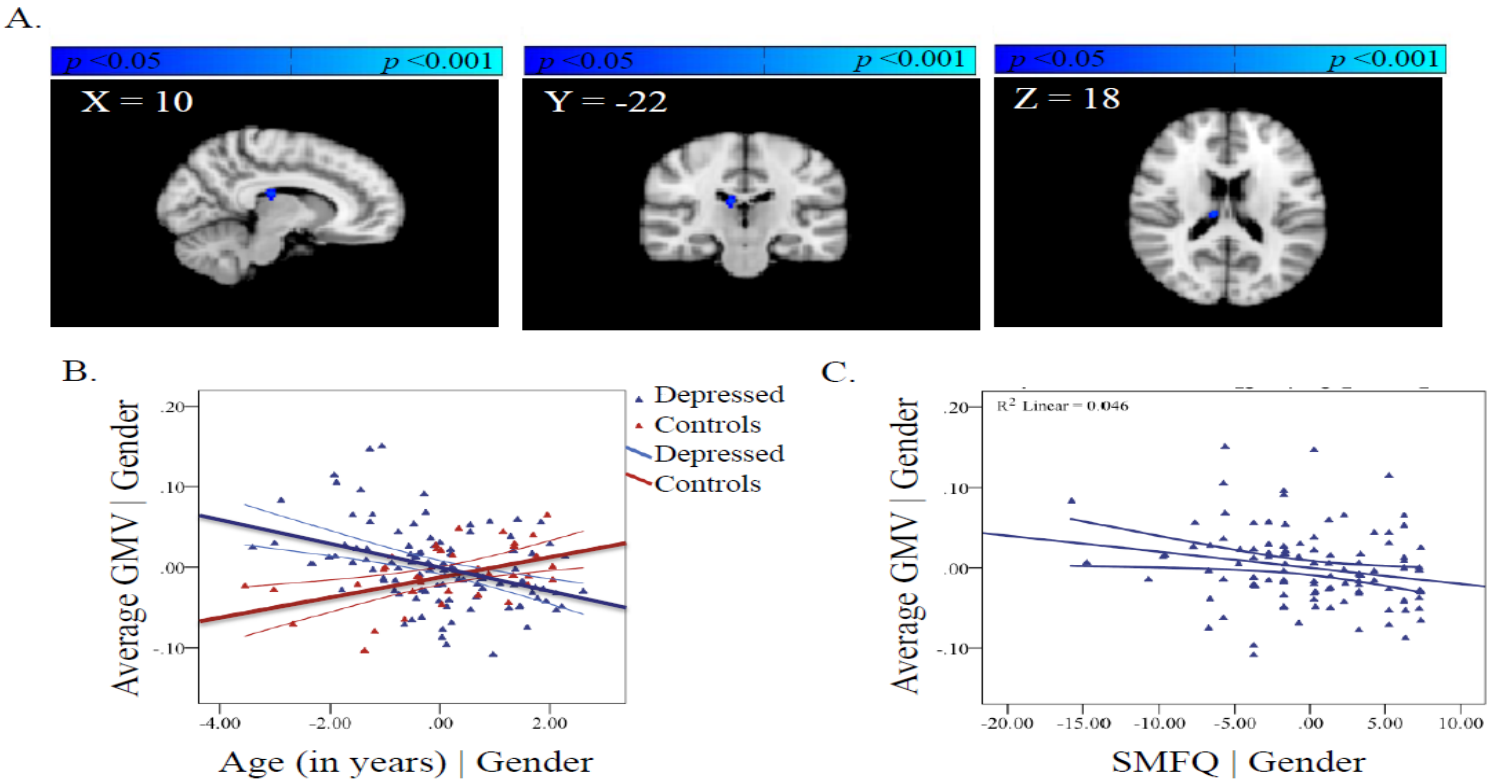
Age & Symptom Correlates of GMV in the ACC.



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.

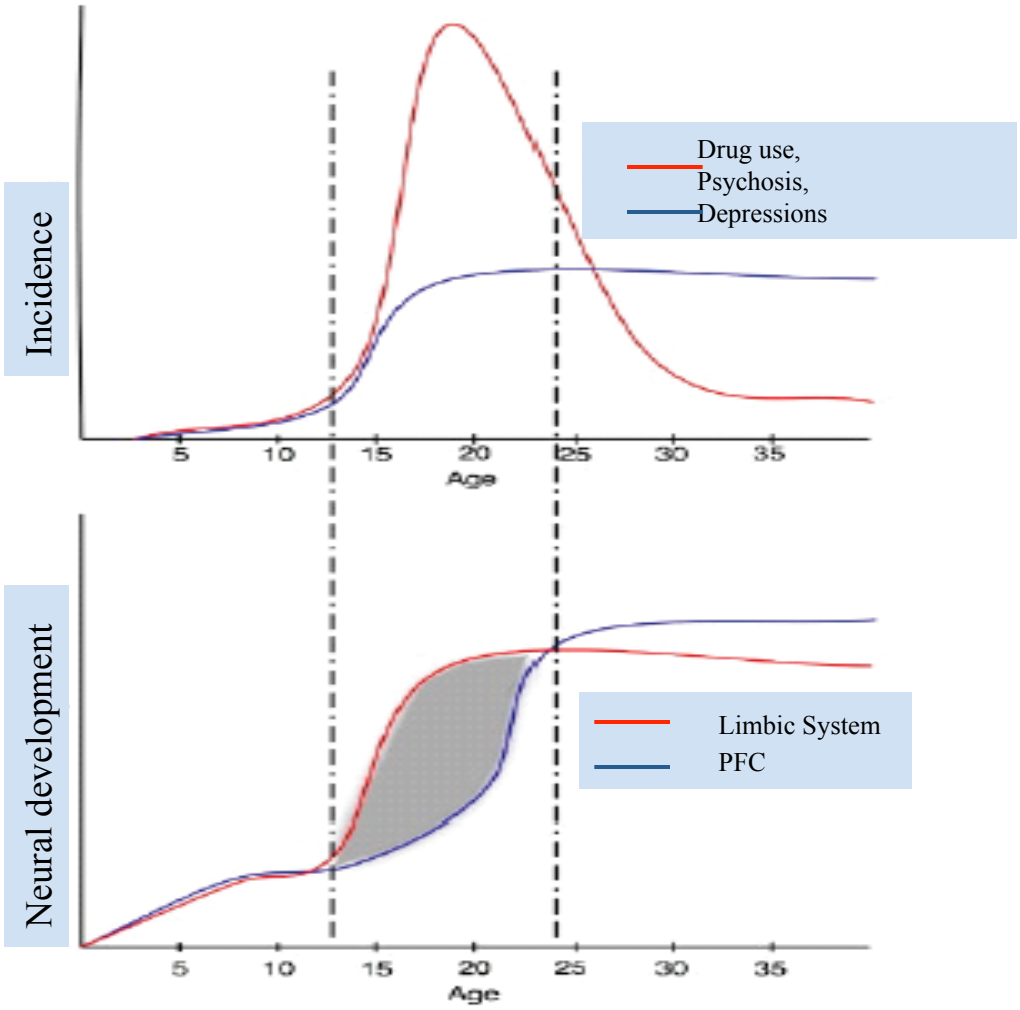
MDD only: GMV in thalamus (not ACC) 1/symptoms.

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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