

The Neurobiology of Affective Disorders in Adolescents

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- The dilemma of the behavioural phenotype
- Genetics and treatment response
- Neural systems and mechanisms



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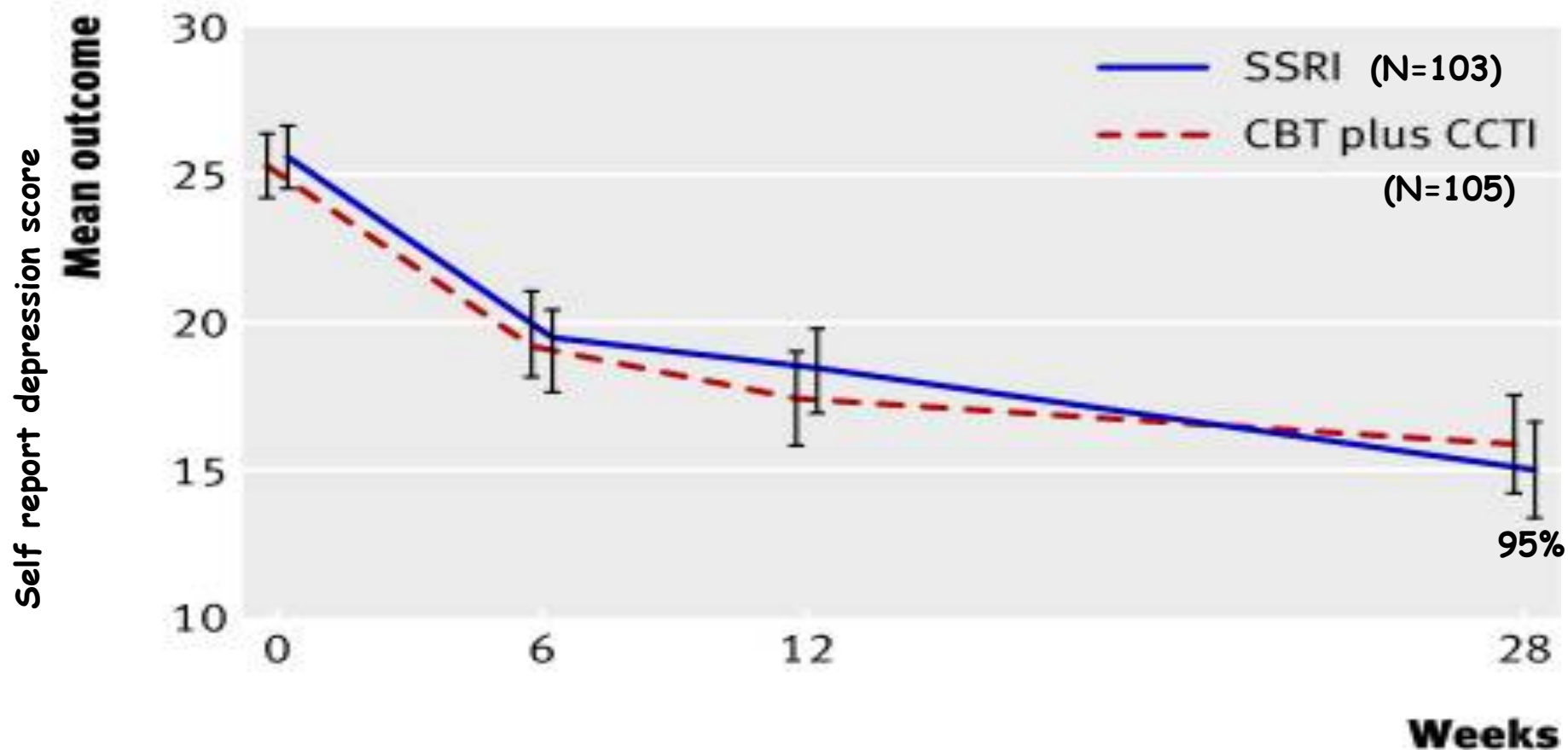
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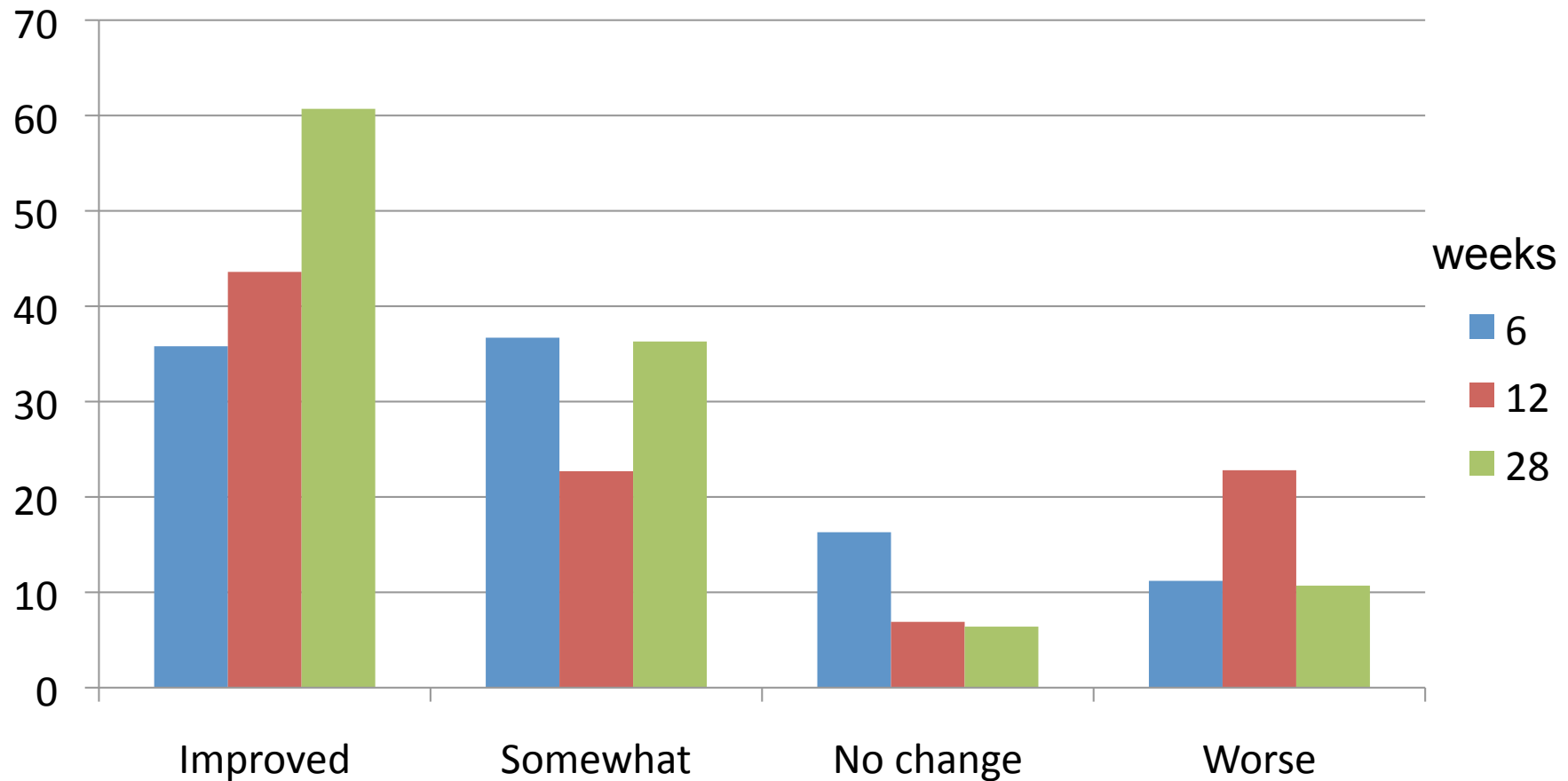
SSRIs and specialist care with and without cognitive behaviour therapy



Goodyer IM et al BMJ. (2007)335(7611):142.



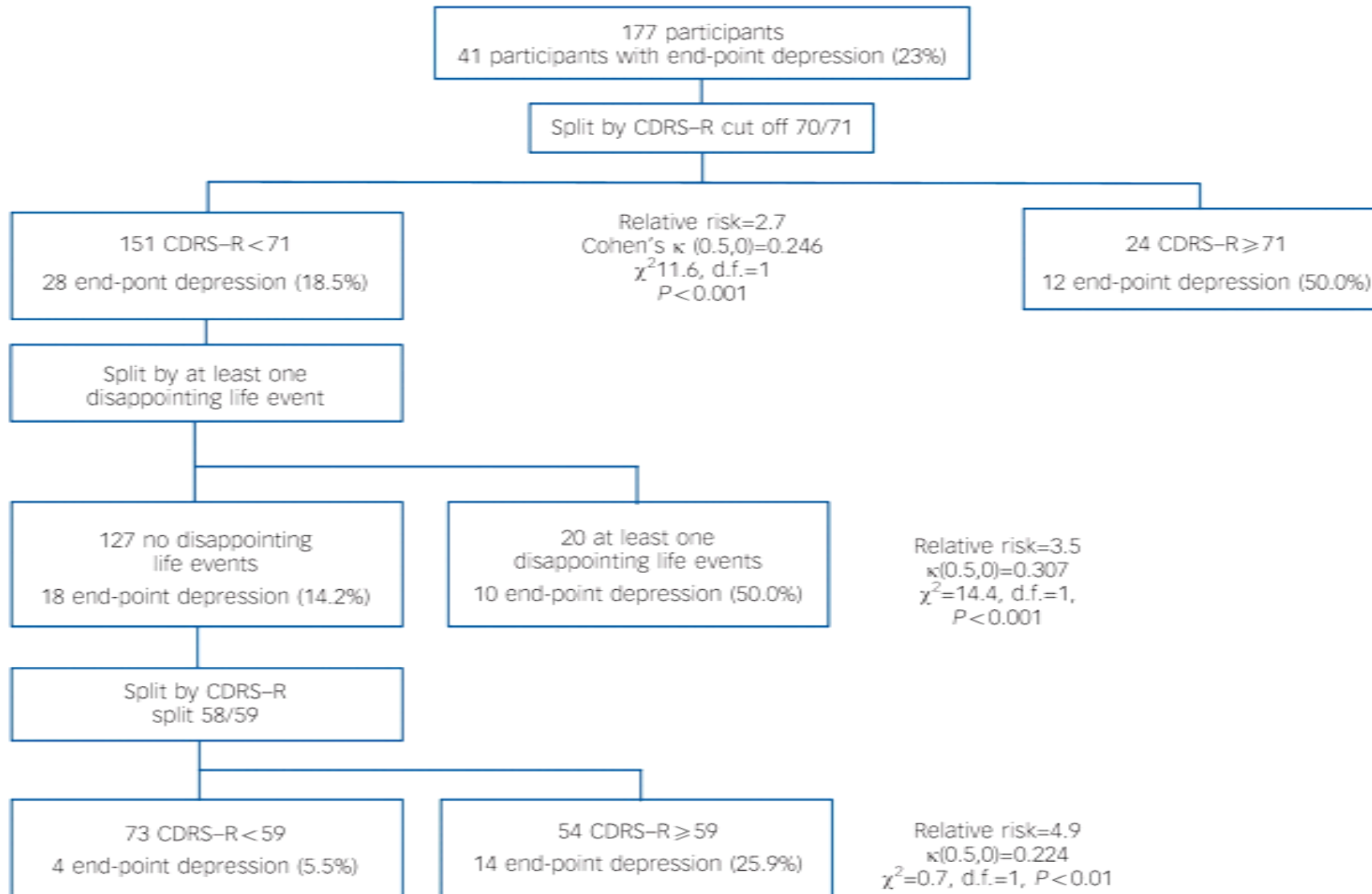
Clinical Global Impression Over The Study Period



Maximum clinical benefits may not be seen until 28 weeks after treatment begins



The Best Predictors Of End-point Depression.





Clinical Heterogeneity As A Conceptual Problem



The Psychopathology of Violence

- Anger and irritability are common features of mood disorders
- Expressed as violent acts: Suicidality ; Non suicidal self harm
- Aggression toward others
- Destruction of property (can lead away from diagnosis if a presenting feature)



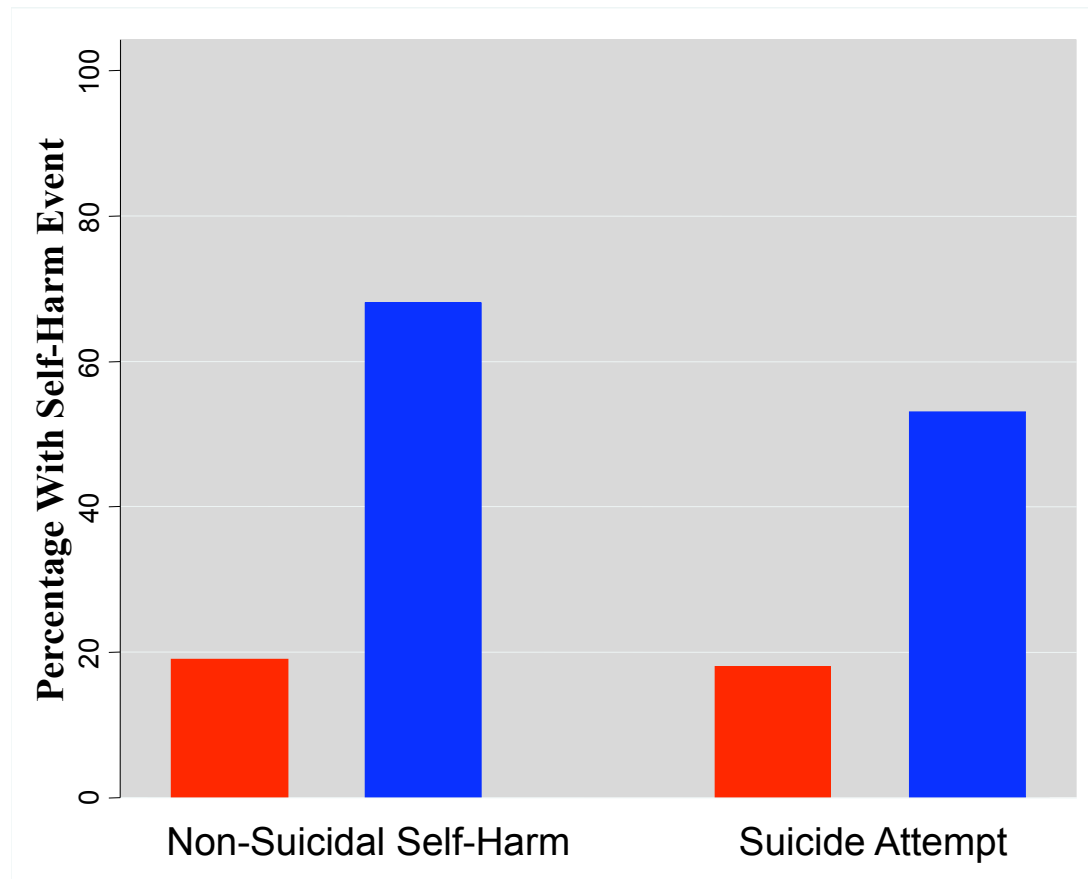
The Psychopathology Of Violence

- A great deal about suicidality
- Very little about non suicidal self harm
- NSSI not in DSM IV or ICD 10 : disorder or component (will be in DSM V).
- NSSI is an attempt to relieve immediate low mood: F>M , 50% not associated with depression



Non-Suicidal Self-Injury and Suicidality Events Over 28 Weeks' Follow-Up

- No NSSI month pre-baseline (N=105)
- NSSI in month pre-baseline (N=58)



Depressed Adolescents with pre-baseline NSSI had a 10-fold greater risk of suicide attempt during treatment than those with no self-injury

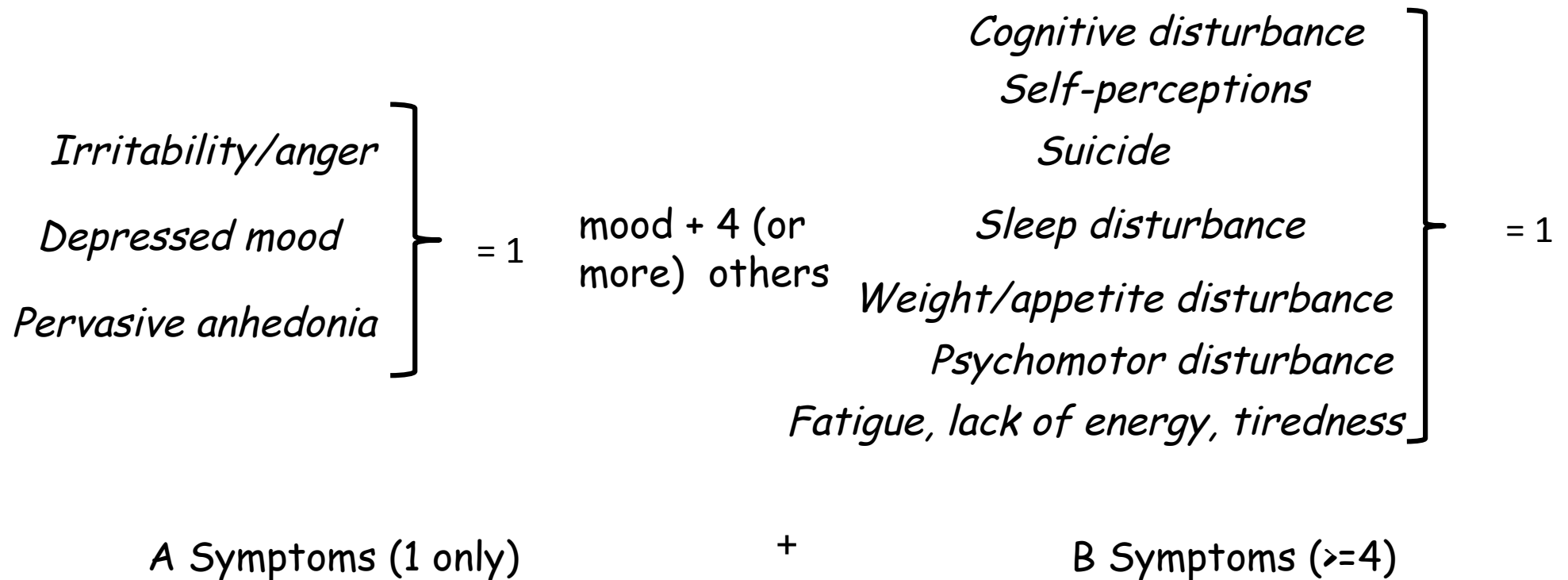
For NSSI, $\chi^2=39$, $df=1$, $p<0.0005$;
for suicide attempt, $\chi^2=22$, $df=1$, $p<0.0005$



Clinical Heterogeneity Viewed As A Methodological Problem



DSM Hierarchical Additivity: Unipolar Major Depression



No discrimination on the basis of location within depression syndromes.
No discrimination within population.
No accounting for chance



Creating Mathematical Models of Psychopathology Takes Into Account Location, Discrimination and Chance

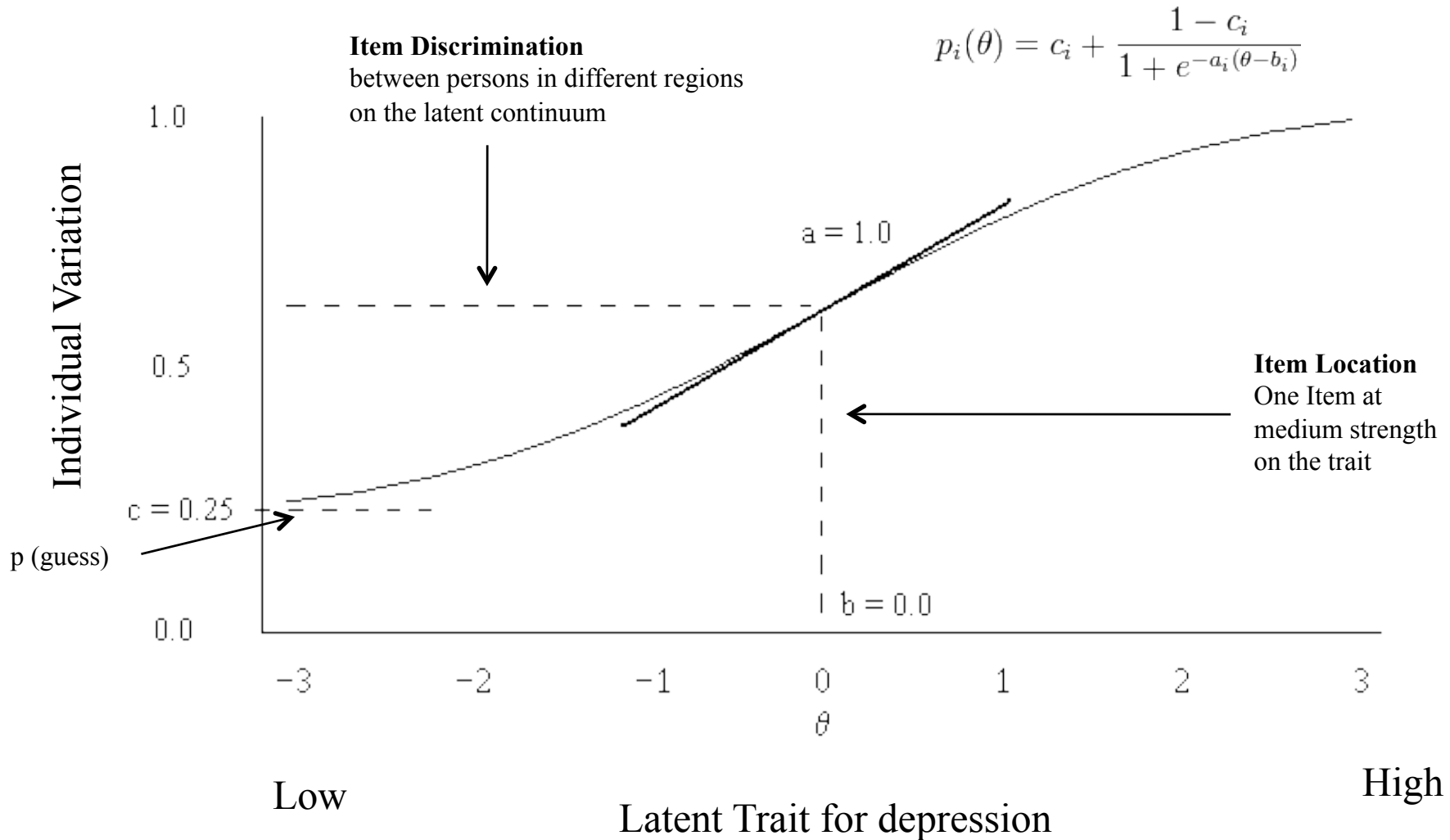


The Item Response Theory (IRT) Approach

- IRT provides a framework for evaluating how well assessments work, and how well individual items on assessments work
- IRT models scale the difficulty of items and the ability of people on the same metric.
- IRT models are generally not sample- or test-dependent.

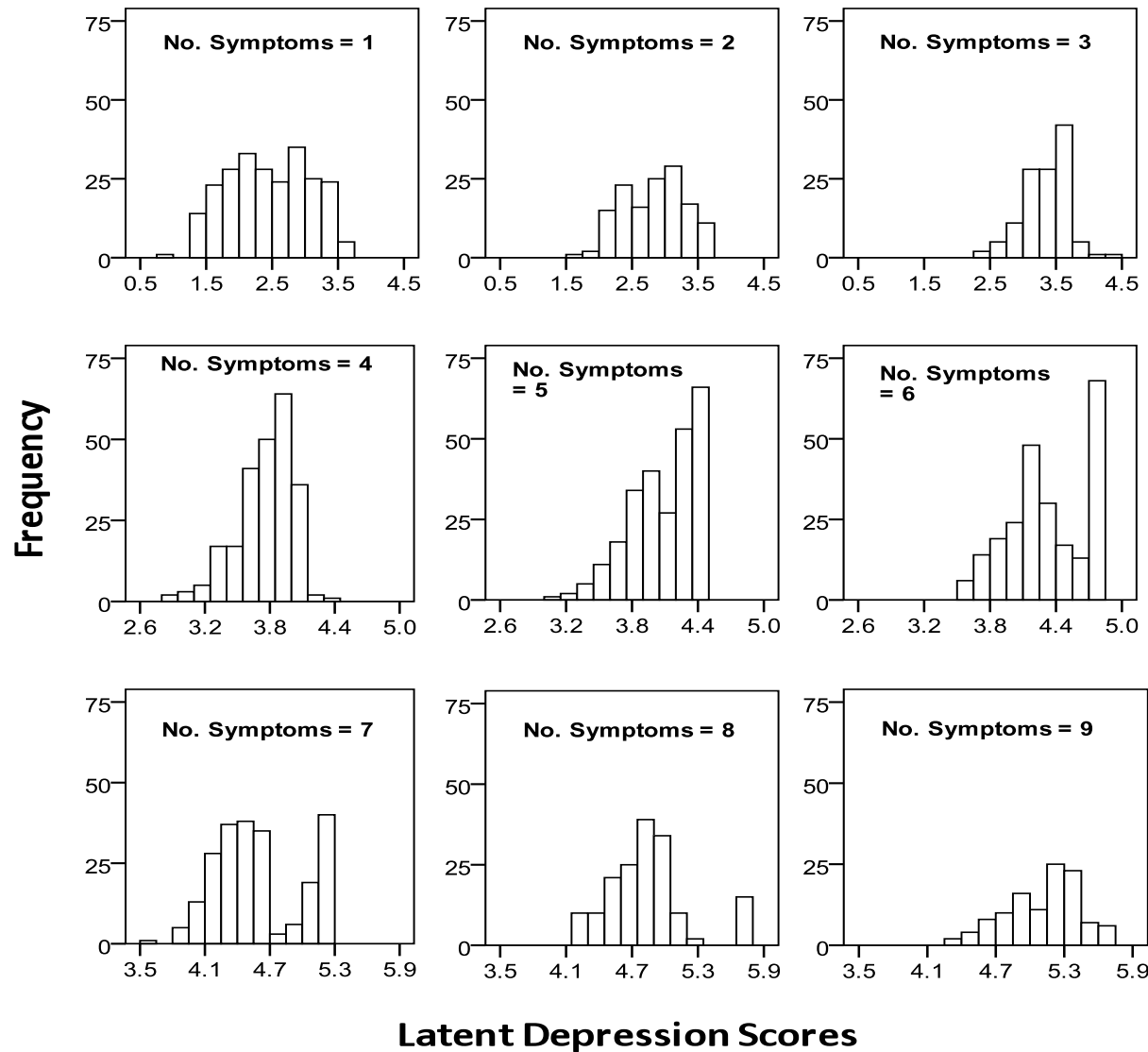


A computational approach accounts for location, discrimination and chance





Information Loss : Symptom Count Against The Latent Trait: K-Sads Network



The raw count of depression symptoms from 3,400 K-Sads gives identical scores to people with highly discrepant levels of latent depression - a process that results in a substantial loss of information.



Estimates of Symptom Discrimination Parameters and Factor Loadings

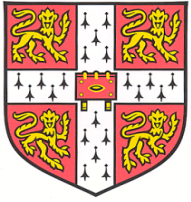
Symptom	Discrimination ^a	<i>SE</i>	factor loading	<i>SE</i>	Odds ratio	
Depressed Mood	2.71 _a	0.15	0.94	0.05	15.03	} Best Discrimination From Non Depressed
Anhedonia	2.33 _a	0.13	0.89	0.05	10.28	
Fatigue	1.83 _b	0.10	0.79	0.05	6.23	
Irritability	1.80 _b	0.09	0.78	0.05	6.05	
Concentration	1.77 _b	0.10	0.78	0.05	5.87	
Sleep	1.39 _c	0.08	0.67	0.05	4.01	} Worst Discrimination From Non Depressed
Worthlessness/guilt	1.24 _{cd}	0.07	0.62	0.05	3.46	
Psychomotor	1.23 _{cd}	0.07	0.61	0.05	3.42	
Weight/appetite	1.03 _{de}	0.06	0.54	0.05	2.80	
Suicide	0.86 _e	0.05	0.46	0.04	2.36	

Data from IRT analysis of 3,400 K-Sads interviews in adolescents ranging from community through to specialist depression clinic for severe cases



Are some depressive symptoms reflective of more severe depression than others?

Symptom	Threshold 1		Threshold 2		Rank order of Threshold 2 estimates ^b	
	estimate	<i>SE</i>	estimate ^a	<i>SE</i>		
Concentration	3.91	0.16	4.48 _a	0.17	1	} Best screening symptoms for severe depression
Worthlessness/guilt	3.66	0.15	4.55 _{ab}	0.17	2	
Sleep disturbance	3.93	0.16	4.59 _{ab}	0.17	3	
Depressed mood	3.76	0.15	4.65 _{bc}	0.17	4	} Less good but frequently used
Fatigue/energy	4.12	0.16	4.68 _{bcd}	0.17	5	
Irritability	3.80	0.15	4.79 _{cd}	0.18	6	
Anhedonia	4.27	0.17	4.84 _d	0.18	7	
Psychomotor	4.12	0.17	5.03 _e	0.18	8	
Weight/Appetite	4.65	0.18	5.33 _f	0.20	9	
Suicide	5.08	0.19	6.24 _g	0.23	10	



Dimension Approach Using Computational Modelling

- Provides greater precision for depressive features
- Illustrates the level of difficulty of a symptom
- Discriminates individual ability within a population
- Provides new and additional information for rct's
- Can be implemented in clinical practice through IT devices

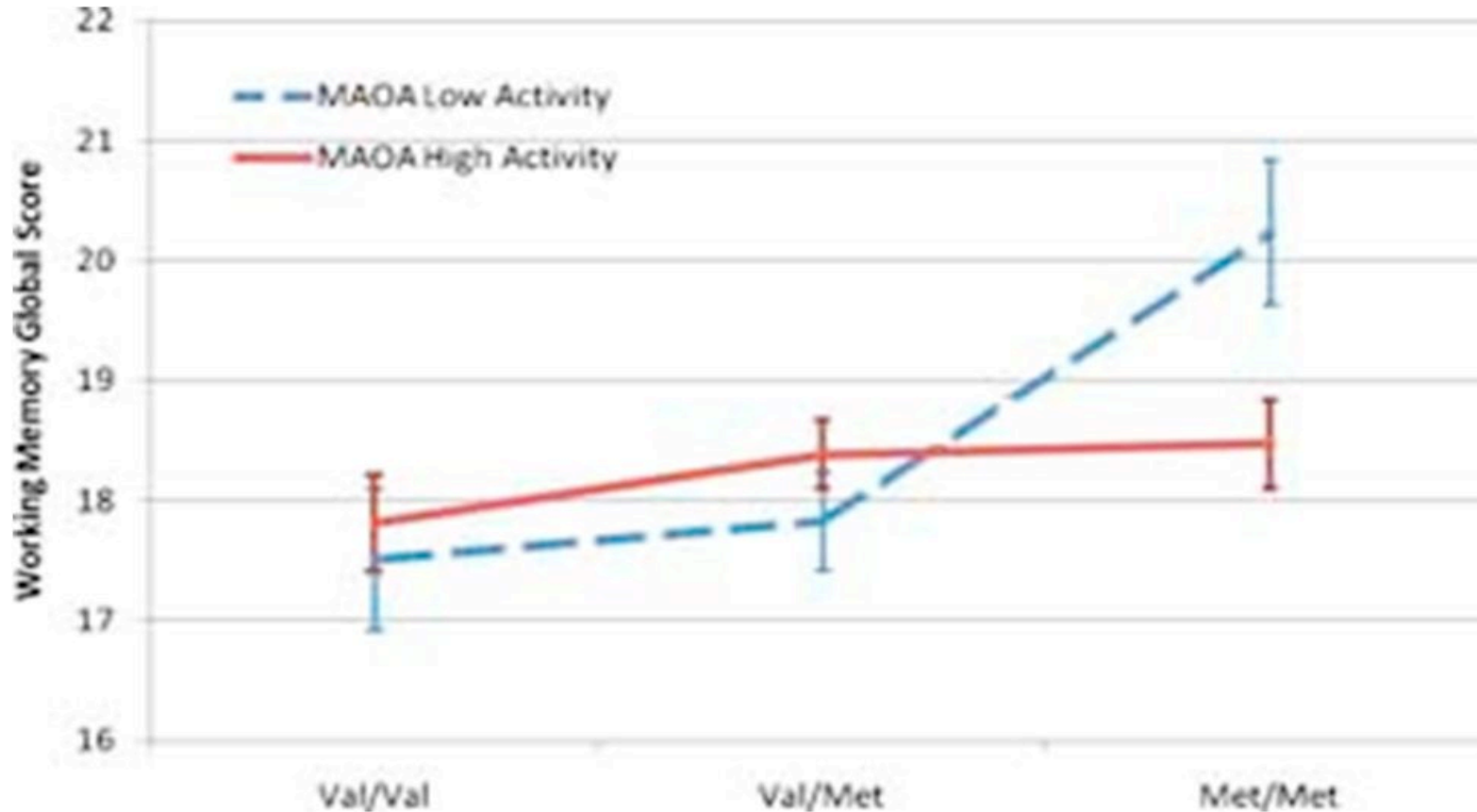


Genetic factors and affective disorders

- Biologically driven hypotheses and gene hunting principles can both apply (GWAS). May be synergistic.
- Genetic moderation of cognition and/or physiological processes related to psychopathology may denote an intermediate phenotype.
- Assume that most variables are surrogates as we have yet to reveal causal pathways within individuals.



Gene-gene relations and working memory



COMT × MAOA
interaction term: $F = 4.17$; DF 2,2324,
 $P = 0.016$.

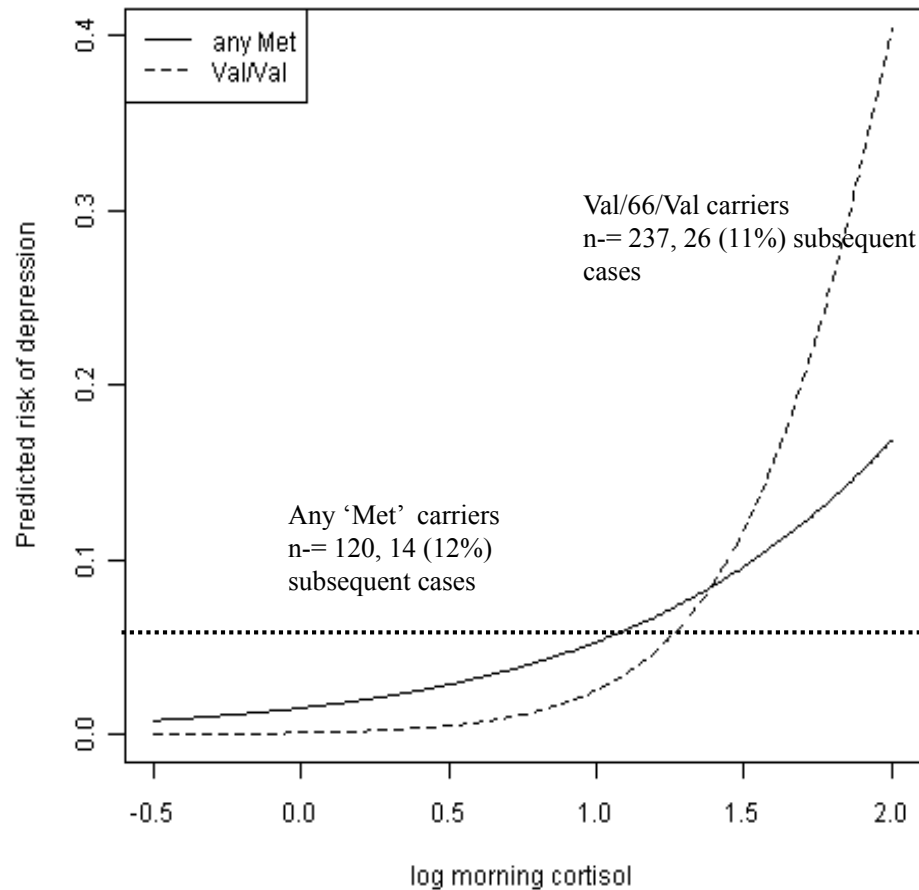
COMT Variants

Working memory global score (mean, SE) by COMT and MAOA in 2,324 boys at age 10 years.



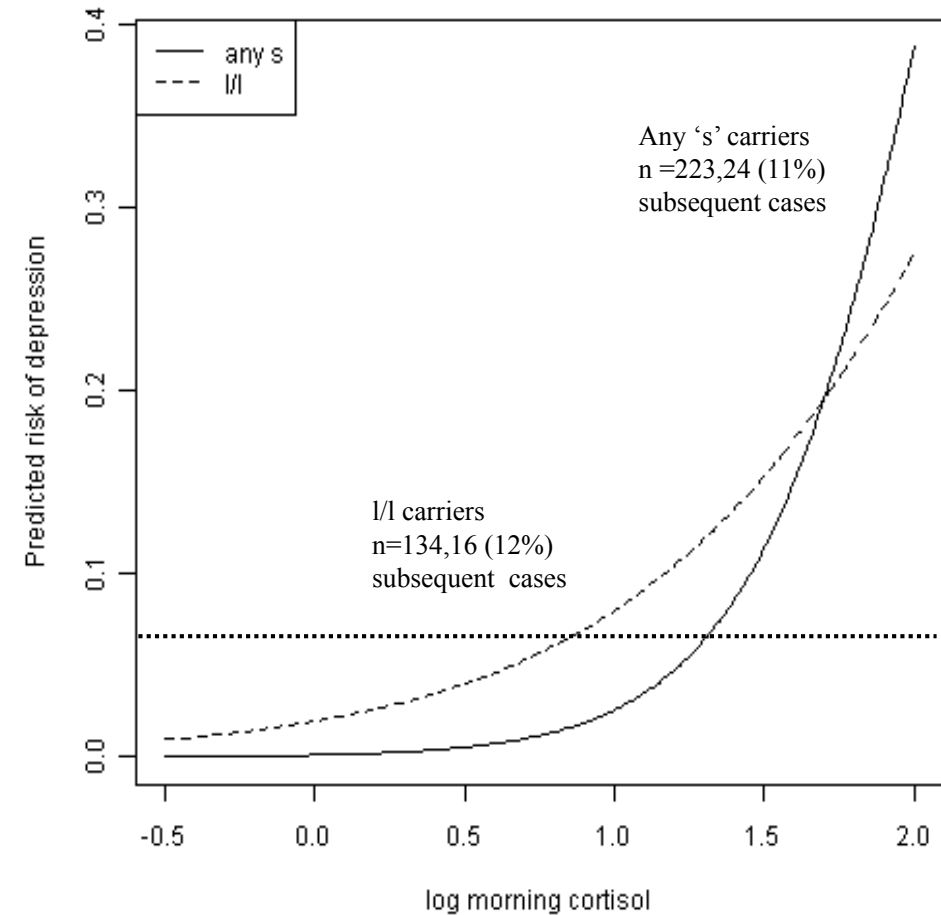
BDNF And 5HTTLPR Moderate Morning Cortisol Levels To Predict Subsequent Major Depression

Risk by BDNF genotype



Log morning cortisol (ng/ml)

Risk by 5HTTLPR genotype



Log morning cortisol (ng/ml)

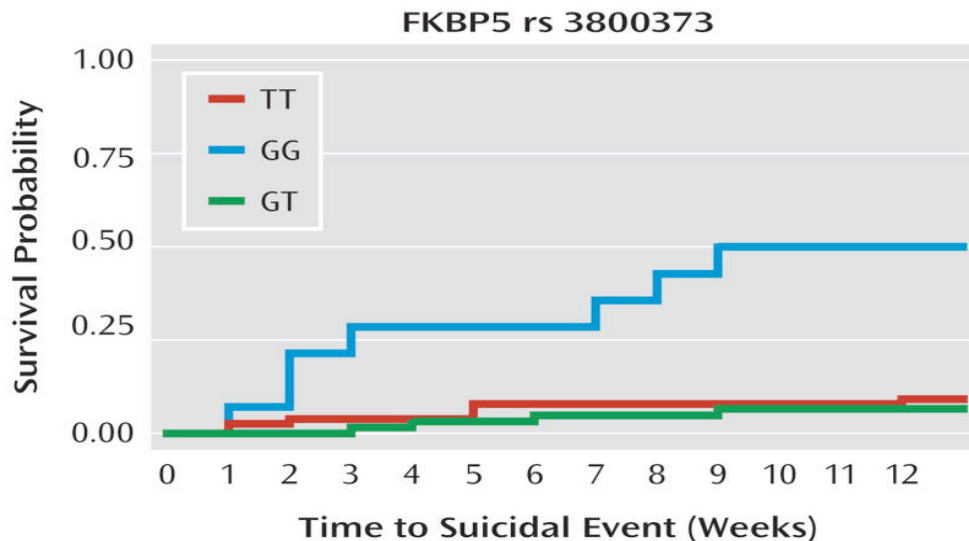
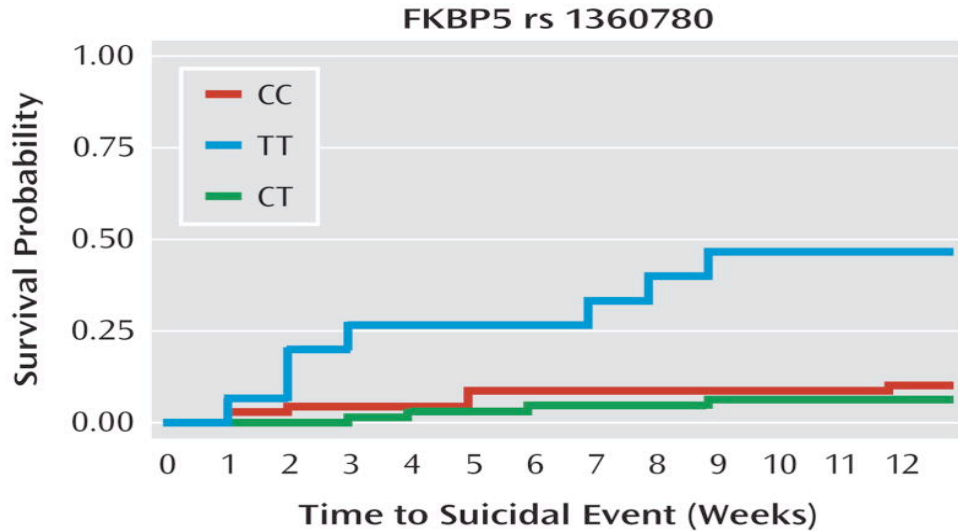


GWAS and the HPA System:

- Candidate SNPs moderating cortisol secretion. Replication studies (n=1711) ; (n=2928) ; (n=2836).
- 1456 SNPs in 33 candidate genes.
- 4 SNPs (rs9470080, rs9394309, rs7748266 and rs1360780) in the FKBP5 gene were associated with:
 - i) all 4 associated with decreased cortisol
 - ii) increased risk of depressive symptoms (rs9470080: OR 1.19 (95%CI 1.0; 1.4).
- FKBP5 codes for a protein causing subsensitivity of the glucocorticoid receptor.



FKBP5 and suicidality in adolescents with treatment resistant depression

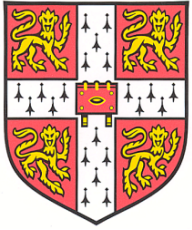


N= 155 TRD cases from the TORDIA trial .

No relationship was observed between any polymorphism and response to treatment.

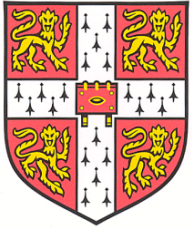
The FKBP5 rs1360780TT and rs3800373GG genotypes were associated with suicidal events (n=18).

These two SNPs were in significant linkage disequilibrium ($r=0.91$).



Gene Factors And Affective Disorders

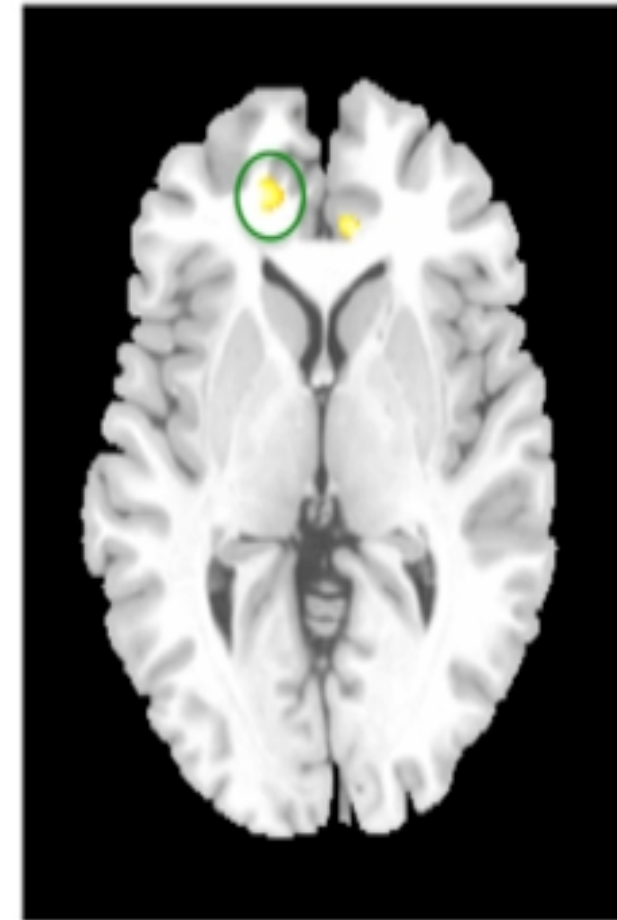
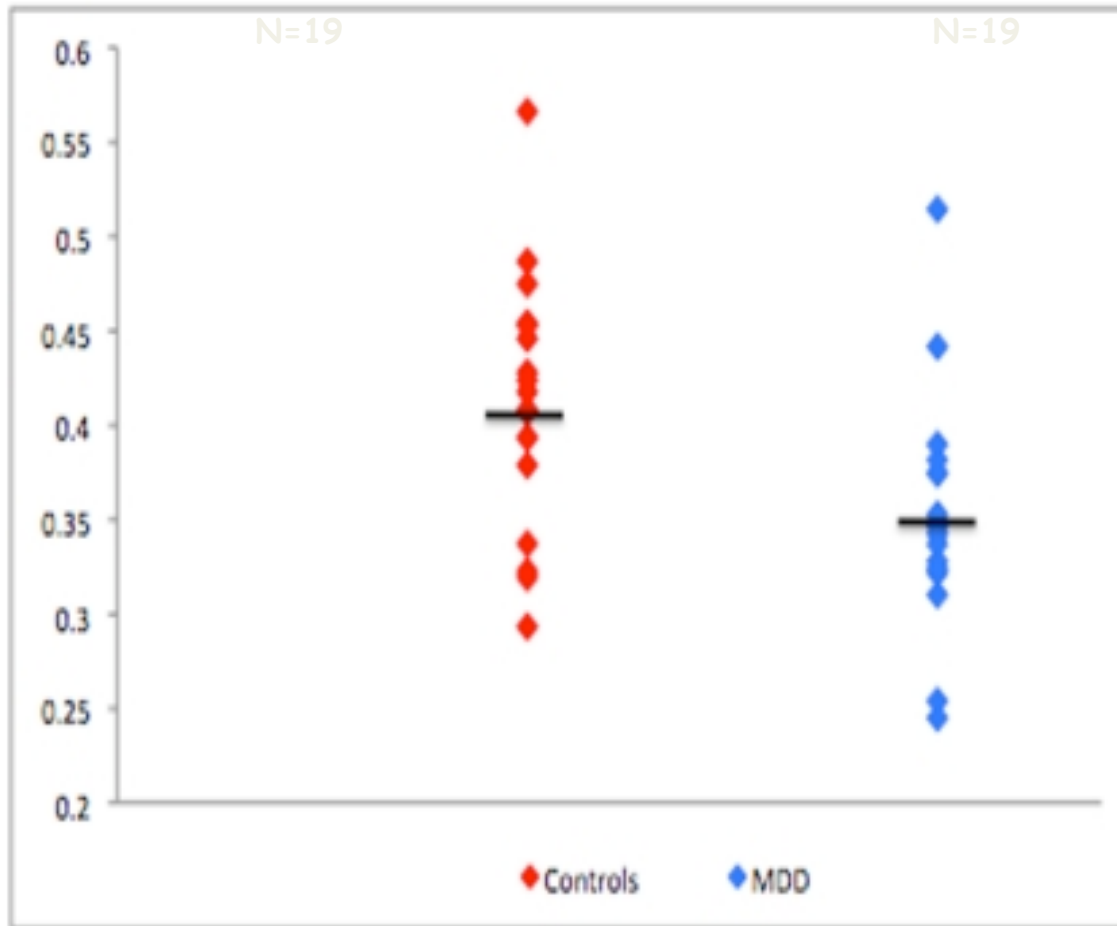
- Gene variants moderate circulating cortisol and memory functions but not yet both in the same sample.
- FKBP5 moderates the liability for suicidal behaviour.
- Need prospective studies of adolescence and mechanistic studies of corticoid-mediated effects on neurocognition.
- Proof of principle brain studies would be a first start.



Neural Systems And Affective Disorders

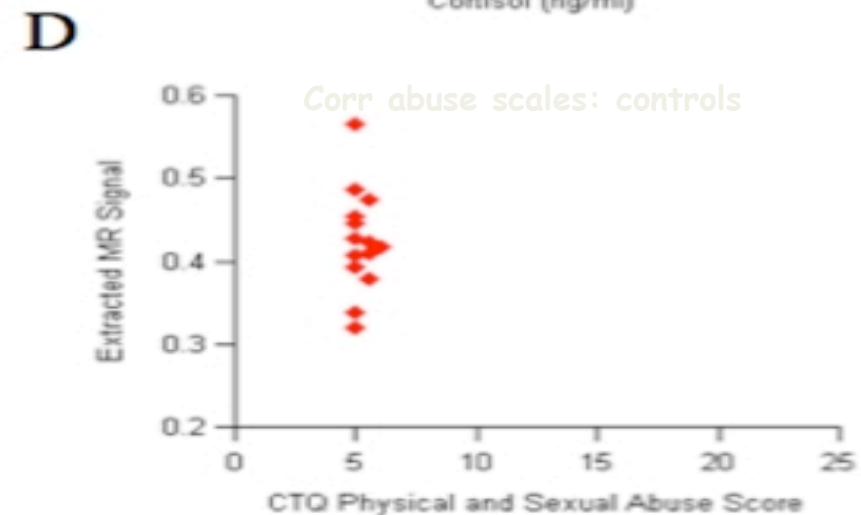
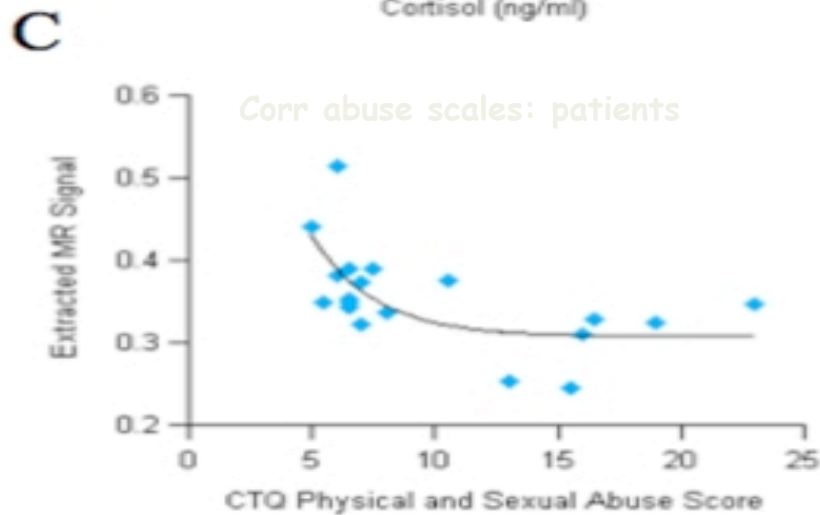
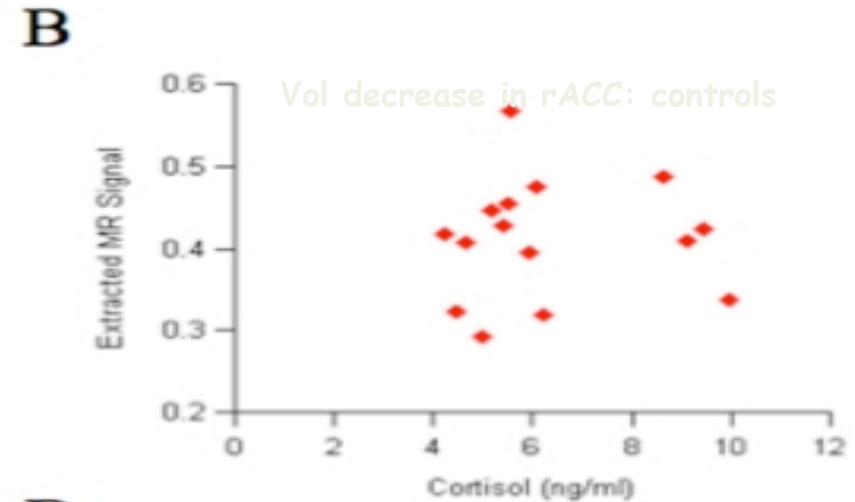
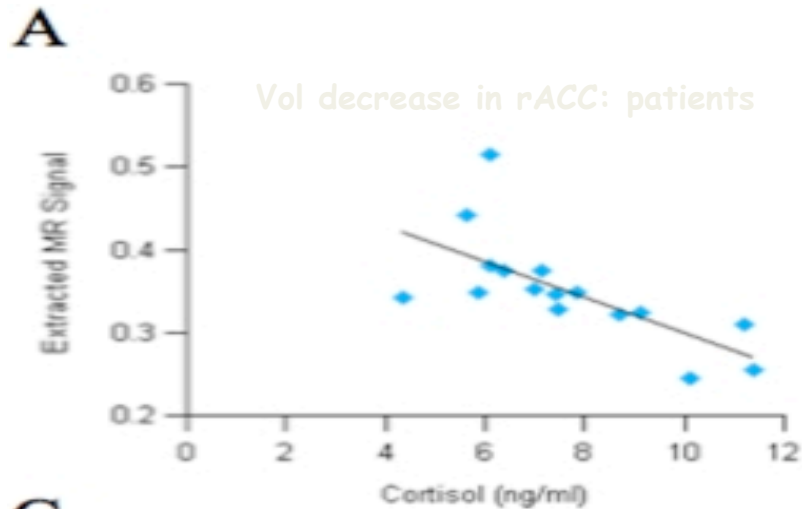


Differences in volume of rACC among controls (n=19) and MD adolescent patients (n=19)



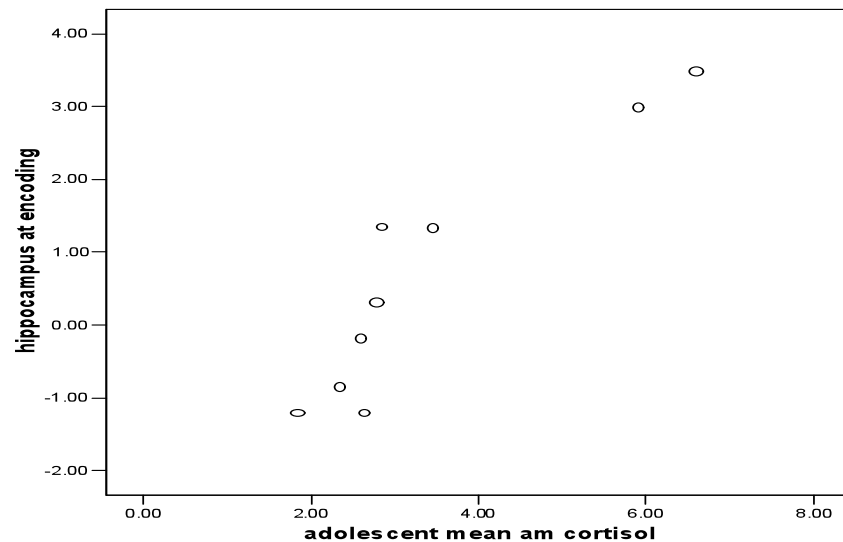
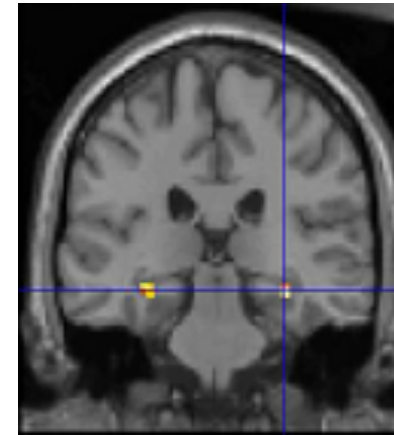
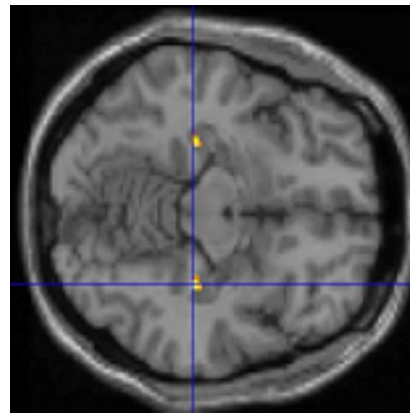
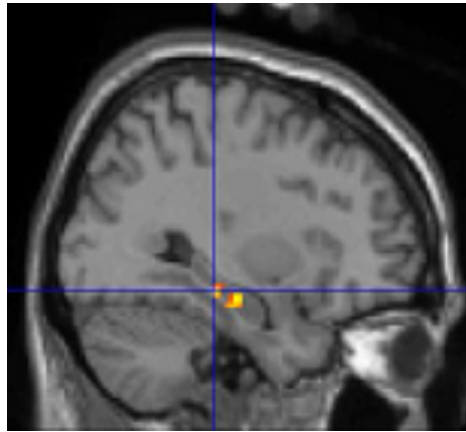


Morning cortisol, child maltreatment decreased grey matter volume in the rACC





Memory activity now and morning cortisol levels when depressed 7-12 years previously



Positive correlation between first episode MD (n=9, 23 yrs old) morning cortisol levels during adolescence and present day activity during encoding in the hippocampus as a well adult (~ 9 years later). ROI hippocampal mask $p < 0.001$ uncorrected FDR, corrected $p = 0.016$

$Rho = 0.883, p = 0.002, n = 9$

Ruth Hewson- Barry : Ph.D. thesis 2006 University of Cambridge

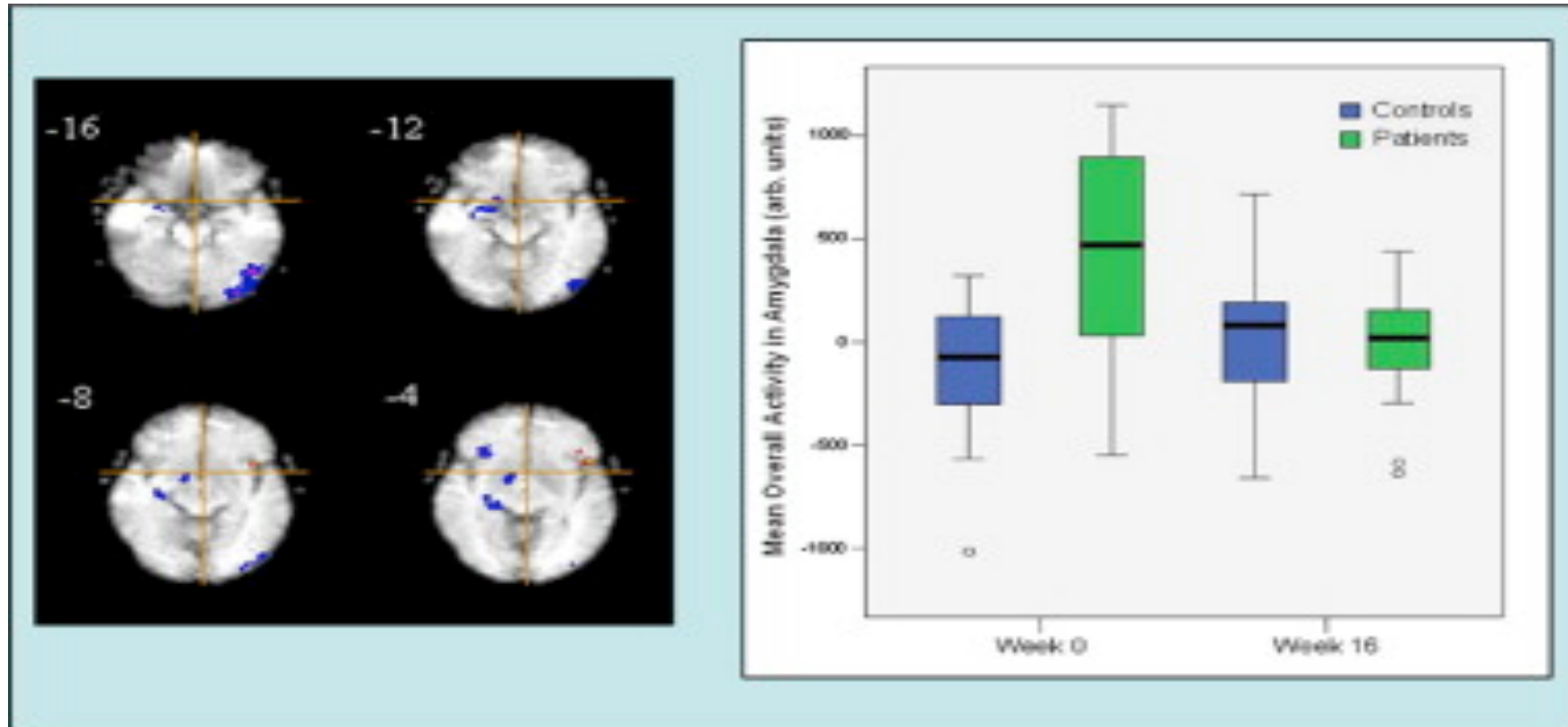


Neural systems, and the treatment of affective disorder

- No published MRI studies within RCT designs for depressed adolescents.
- Naturalistic longitudinal studies of depressed adults strongly support restitution of limbic-frontostriatal structures.
- Less clear if all functional impairments resolve.
- One study of adult structure and function in depressed patients within an RCT design.



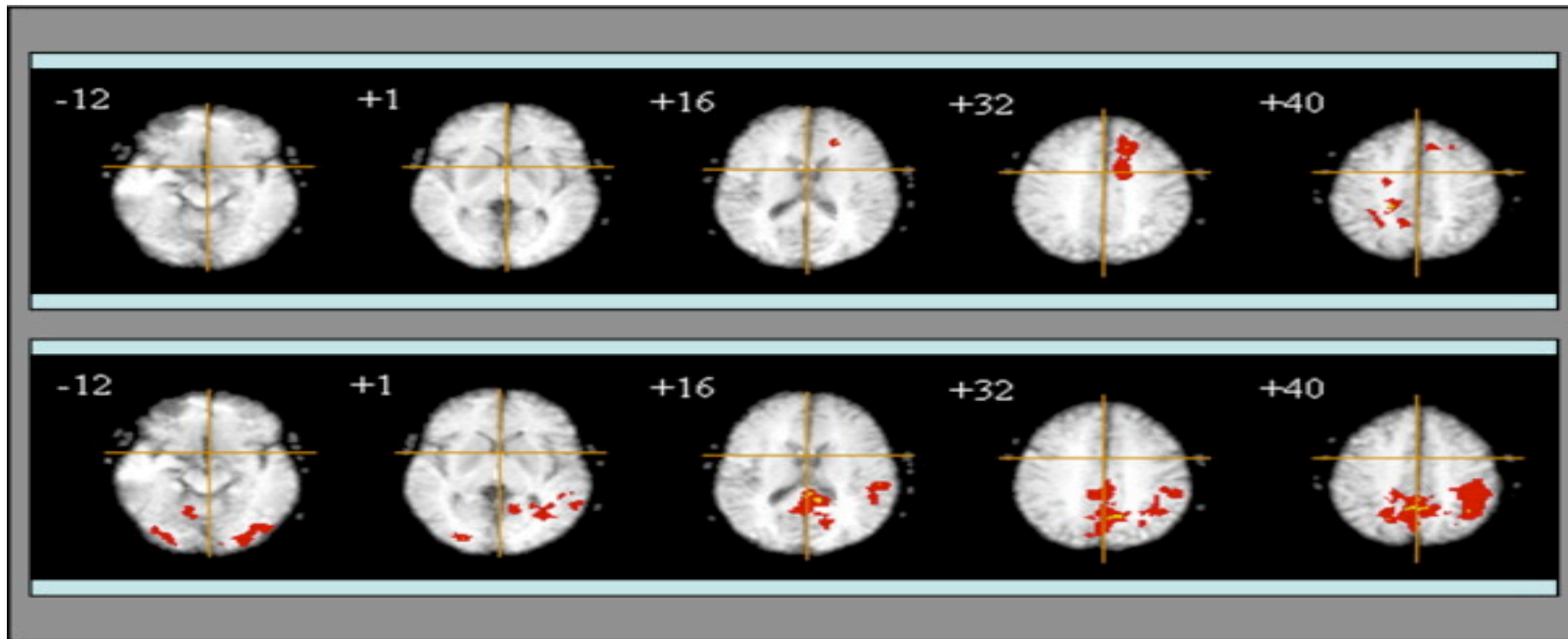
Longitudinal change in amygdala activity in depressed adults (n=17)



Greater right amygdala activity in patients (n=17) relative to control subjects before treatment. No significant difference between groups at the week 16 scan after treatment.



Longitudinal change

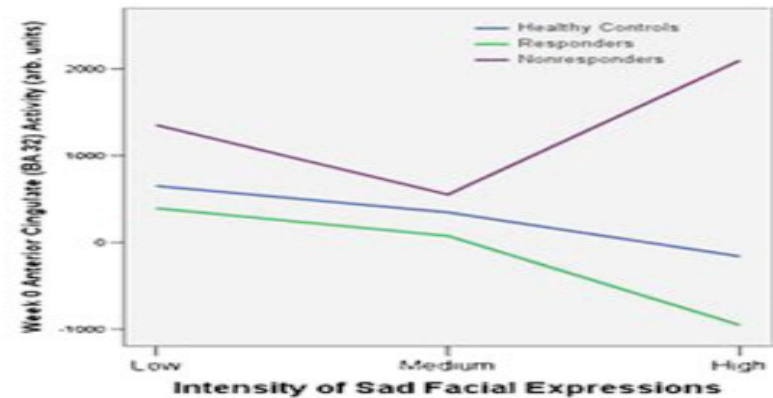
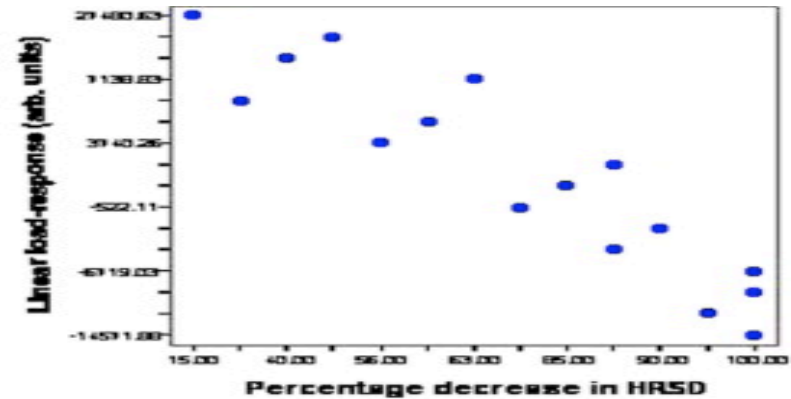
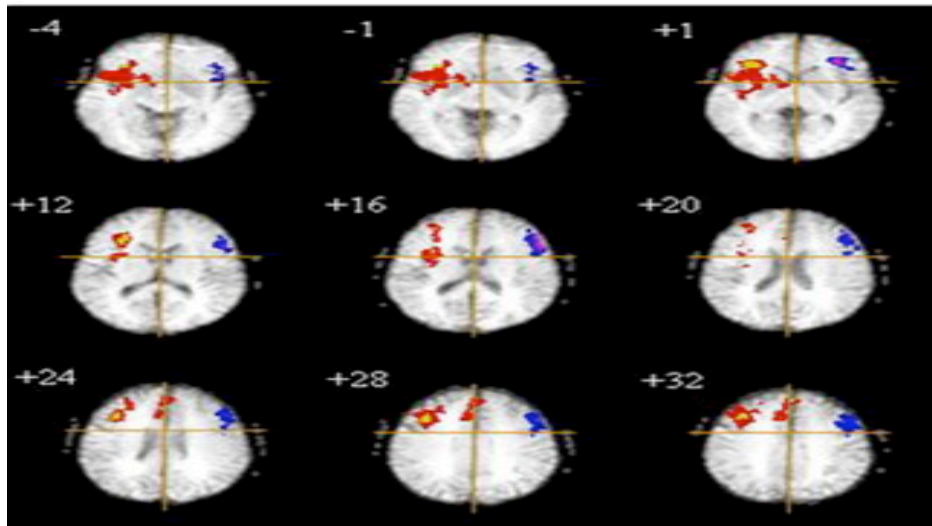


Anterior cingulate extending to the superior frontal gyrus, posterior cingulate gyrus, inferior parietal cortex and precuneus with a significant increase at the follow-up scan.

Fusiform and lingual gyri left lateral temporal and inferior parietal cortices, posterior cingulate cortex precuneus and cerebellum showed a greater response in patients relative to control subjects at baseline, which decreased following CBT.

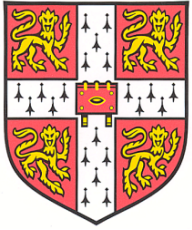


Predicting clinical response at week 16



Faster symptom improvement strongly associated with greater grey matter volume in anterior cingulate cortex, insula, and right temporo-parietal cortex.

Faster improvement was also predicted by greater functional activation of anterior cingulate cortex.



Neural Systems and Depression

- Modular rather than specific brain regions.
- Some regions may be more sensitive than others.
- Adolescence sensitive memory deficits (HPA mediated)?
- Dopamine and serotonin mediation of reward and behavioural inhibition deficits in adolescence ?
- Both *G* and *E* influences remain poorly defined.



A Way Forward

Reveal structural and functional neural trajectory in healthy and in mentally unwell adolescents.

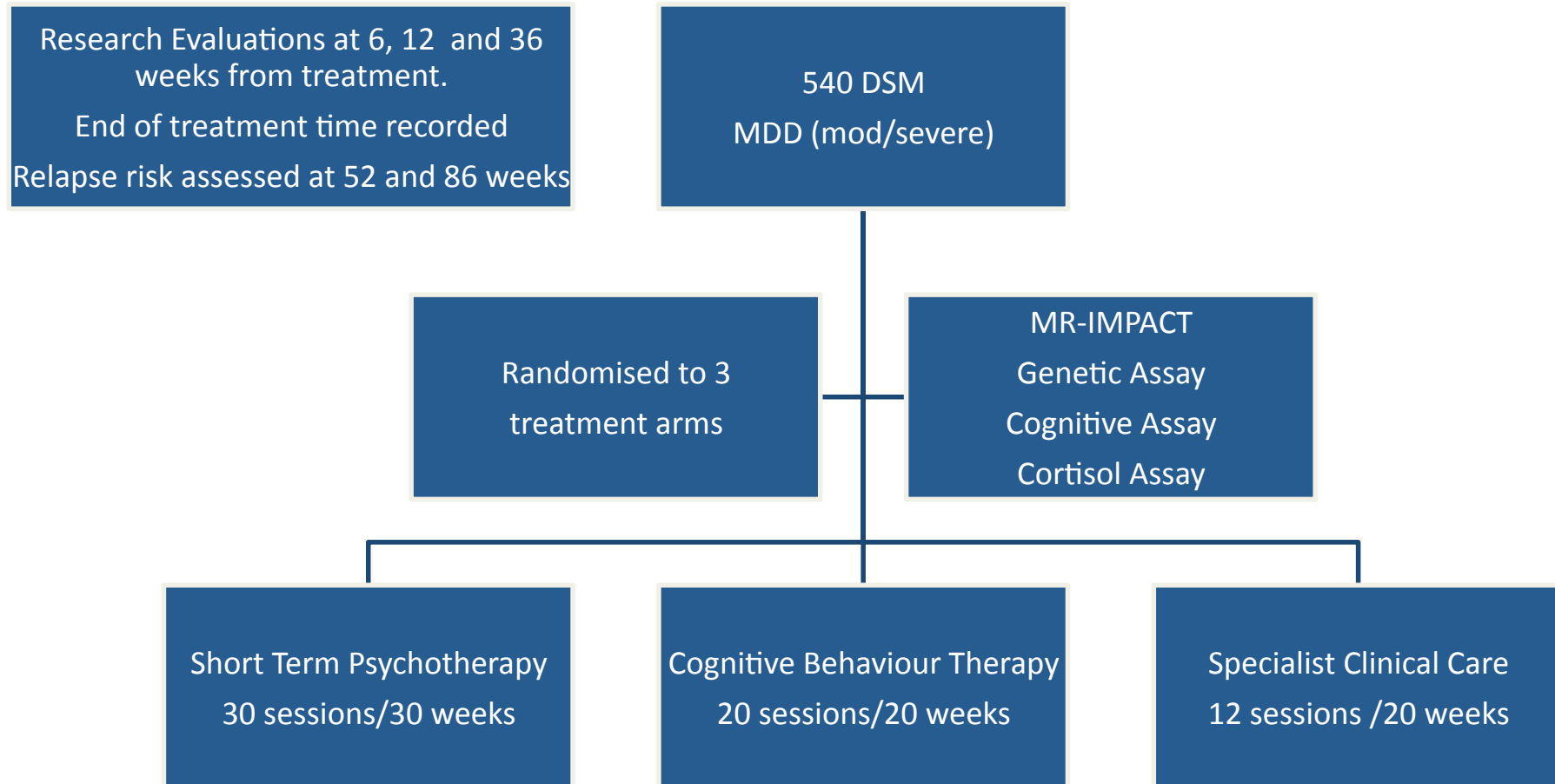
Reveal the *G* and *E* influences on individual differences in normal and non-normal development.

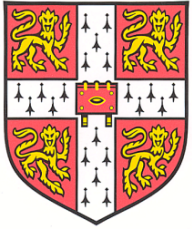
Improve precision in behavioural analysis of clinical symptoms using computational modelling.

Ensure treatment studies include moderating and mediating variables in their designs.



Improving Mood With Psychoanalytic Psychotherapy And Cognitive Behaviour Therapy: THE IMPACT STUDY





Thanks to Funding Agencies

Wellcome Trust

MRC

NIHR