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
Co-Investigators

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Rosemary Abbott

John Suckling
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Joe Herbert
SSRIs and specialist care with and without cognitive behaviour therapy

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
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, χ²=39, df=1, p<0.0005; for suicide attempt, χ²=22, df=1, p<0.0005.
Clinical Heterogeneity Viewed As A Methodological Problem
DSM Hierarchical Additivity: Unipolar Major Depression

Irritability/anger
Depressed mood
Pervasive anhedonia

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

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

mood + 4 (or more) others

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

Item Discrimination
between persons in different regions on the latent continuum

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

Individual Variation

Low Latent Trait for depression

High

Item Location
One Item at medium strength on the trait
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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Discrimination</th>
<th>SE</th>
<th>factor loading</th>
<th>SE</th>
<th>Odds ratio</th>
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</thead>
<tbody>
<tr>
<td>Depressed Mood</td>
<td>2.71&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.15</td>
<td>0.94</td>
<td>0.05</td>
<td>15.03</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>2.33&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.13</td>
<td>0.89</td>
<td>0.05</td>
<td>10.28</td>
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<tr>
<td>Fatigue</td>
<td>1.83&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10</td>
<td>0.79</td>
<td>0.05</td>
<td>6.23</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.09</td>
<td>0.78</td>
<td>0.05</td>
<td>6.05</td>
</tr>
<tr>
<td>Concentration</td>
<td>1.77&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10</td>
<td>0.78</td>
<td>0.05</td>
<td>5.87</td>
</tr>
<tr>
<td>Sleep</td>
<td>1.39&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.08</td>
<td>0.67</td>
<td>0.05</td>
<td>4.01</td>
</tr>
<tr>
<td>Worthlessness/guilt</td>
<td>1.24&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>0.07</td>
<td>0.62</td>
<td>0.05</td>
<td>3.46</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>1.23&lt;sup&gt;cd&lt;/sup&gt;</td>
<td>0.07</td>
<td>0.61</td>
<td>0.05</td>
<td>3.42</td>
</tr>
<tr>
<td>Weight/appetite</td>
<td>1.03&lt;sup&gt;de&lt;/sup&gt;</td>
<td>0.06</td>
<td>0.54</td>
<td>0.05</td>
<td>2.80</td>
</tr>
<tr>
<td>Suicide</td>
<td>0.86&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.46</td>
<td>0.04</td>
<td>2.36</td>
</tr>
</tbody>
</table>

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

*Cole D et al (2011) Psychological Assessment, in press*
Are some depressive symptoms reflective of more severe depression than others?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Threshold 1</th>
<th>Threshold 2</th>
<th>Rank order of Threshold 2 estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>SE</td>
<td>estimate (^a)</td>
</tr>
<tr>
<td>Concentration</td>
<td>3.91</td>
<td>0.16</td>
<td>4.48 (_a)</td>
</tr>
<tr>
<td>Worthlessness/guilt</td>
<td>3.66</td>
<td>0.15</td>
<td>4.55 (_{ab})</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>3.93</td>
<td>0.16</td>
<td>4.59 (_{ab})</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3.76</td>
<td>0.15</td>
<td>4.65 (_{bc})</td>
</tr>
<tr>
<td>Fatigue/energy</td>
<td>4.12</td>
<td>0.16</td>
<td>4.68 (_{bcd})</td>
</tr>
<tr>
<td>Irritability</td>
<td>3.80</td>
<td>0.15</td>
<td>4.79 (_{cd})</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>4.27</td>
<td>0.17</td>
<td>4.84 (_d)</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>4.12</td>
<td>0.17</td>
<td>5.03 (_e)</td>
</tr>
<tr>
<td>Weight/Appetite</td>
<td>4.65</td>
<td>0.18</td>
<td>5.33 (_f)</td>
</tr>
<tr>
<td>Suicide</td>
<td>5.08</td>
<td>0.19</td>
<td>6.24 (_g)</td>
</tr>
</tbody>
</table>

Best screening symptoms for severe depression

Less good but frequently used
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

Val/66/Val carriers
n= 237, 26 (11%) subsequent cases

Any ‘Met’ carriers
n= 120, 14 (12%) subsequent cases

Risk by 5HTTLPR genotype

Any ‘s’ carriers
n=223,24 (11%) subsequent cases

l/l carriers
n=134,16 (12%) subsequent cases

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.

Velders FP Psychoneuroendocrinology. 2011 Feb 11. [Epub ahead of print]
FKBP5 and suicidality in adolescents with treatment resistant depression

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).

Brent D, AM J Psych 2010 167(2):190-7

N= 155 TRD cases from the TORDIA trial.
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

Vol decrease in rACC: patients
Corr abuse scales: patients

Vol decrease in rACC: controls
Corr abuse scales: controls

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

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.
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.

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.

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

Research Evaluations at 6, 12 and 36 weeks from treatment. End of treatment time recorded. Relapse risk assessed at 52 and 86 weeks.

540 DSM MDD (mod/severe)

Randomised to 3 treatment arms

MR-IMPACT
Genetic Assay
Cognitive Assay
Cortisol Assay

Short Term Psychotherapy
30 sessions/30 weeks

Cognitive Behaviour Therapy
20 sessions/20 weeks

Specialist Clinical Care
12 sessions /20 weeks
Thanks to Funding Agencies

Wellcome Trust
MRC
NIHR