Identifying young people at high risk for bipolar disorder: Laying the groundwork for prevention and early intervention

Philip Mitchell
Collaborators

- UNSW / Black Dog Institute, Sydney
  - G Roberts, W Wen, M Green, A Frankland, T Perich, P Lau, C Joslyn, F Levy, R Lenroot, E Holmes-Preston, C Sinbandhit

- QIMR Berghofer, Brisbane (neuroimaging)
  - M Breakspear, A Lord, A Perry

- Neuroscience Research Australia, Sydney (genetics)
  - J Fullerton, P Schofield

- US Multi-site Bipolar Disorder High-risk Study
  - JI Nurnberger, M McInnis, H Wilcox, A Glowinsky, H Edenberg
Bipolar disorder is strongly genetic (explains 70-80% of aetiological variance)

What factors determine which children or siblings of those with bipolar disorder will develop this condition and who will be resilient to this?

Elucidation of such factors would enable development of rational preventive or early intervention programs
CATCH THEM BEFORE THEY FALL.

Five hundred Australians are required for a world-first study to pinpoint the causes of bipolar disorder.

The focus is on 12 to 30 year-olds who have at least one relative with bipolar disorder but are not sufferers of the illness themselves.

One in 50 Australians suffers bipolar disorder yet there is still no way of identifying a person in the very early stages, or, who is at high risk.

Researchers from the Black Dog Institute and the University of NSW (UNSW) are undertaking the study in collaboration with major universities in the USA. They will look at all the factors that may contribute to the illness, including a patient’s DNA, brain imaging and psychological testing.

Early prevention for better results.

To participate: Please phone 1800-352-292 or email: bipolar-kidsandsibs@unsw.edu.au
Bipolar Disorder Kids & Sibs Study: Design

“Catch them before they fall – early prevention for better results”

- Baseline assessment:
  - Structured diagnostic interviews
  - Self-report questionnaires
  - Blood sample for SNPs, epigenetics
  - Brain imaging: structural MRI, functional MRI & DTI
  - Neuropsychological testing

- Annual follow-up
  - Briefer assessments

Diagram:
- Screening for Eligibility (N= ~ 1250)
- Total Baseline assessment: (N=373)
  - At-Risk (n=173)
  - Controls (n=131)
  - Bipolar (n=69)
- Follow up 1: (N= 253; ongoing)
  - At-Risk (n=136)
  - Controls (n=117)
- Follow up 2: (N= 208; ongoing)
  - At-Risk (n=106)
  - Controls (n=102)
- Follow up 3: (N= 169; ongoing)
  - At-Risk (n=89)
  - Controls (n=80)
- Follow up 4: (N= 109; ongoing)
  - At-Risk (n=64)
  - Controls (n=45)
- Follow up 5: (N= 19; ongoing)
  - At-Risk (n=19)
  - Controls (n=0)
Clinical findings
What clinical features precede the onset of bipolar disorder?

Tania Perich, Phoebe Lau, Dusan Hadzi-Pavlovic, Gloria Roberts, Andrew Frankland, Adam Wright, Melissa Green, Michael Breakspear, Justine Corry, Basia Radlinska, Clare McCormack, Cassandra Joslyn, Florence Levy, Rhoshel Lenroot, John I. Nurnberger Jnr, Philip B. Mitchell

School of Psychiatry, University of New South Wales, Australia
Black Dog Institute, Prince of Wales Hospital, Australia
Neuroscience Research Australia, Randwick, New South Wales, Australia
Division of Mental Health Research, Queensland Institute of Medical Research, Australia
Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
Prince of Wales Hospital, Randwick, New South Wales, Australia
Department of Psychiatry, Institute of Psychiatric Research, Indiana University School of Medicine, Indianapolis, USA
Table 3
Odds ratios and 95% confidence intervals for psychiatric disorders between at-risk, control and bipolar groups.

<table>
<thead>
<tr>
<th>Disorders</th>
<th>At-risk v control</th>
<th>Bipolar disorder v control</th>
<th>Bipolar disorder v at-risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any affective disorder</td>
<td>2.6 (1.2–5.6)*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>2.7 (1.2–6.3)*</td>
<td>9.7 (3.9–24.2)***</td>
<td>3.6 (1.6–8.1)**</td>
</tr>
<tr>
<td>Any behavioural disorder(^a)</td>
<td>3.9 (0.9–17.0)(^b)</td>
<td>7.9 (1.8–35.0)**</td>
<td>2 (0.6–6.7)</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>1.3 (0.5–3.9)</td>
<td>6.2 (2.1–18.3)**</td>
<td>4.7 (1.7–13)**</td>
</tr>
<tr>
<td>At least two lifetime diagnoses</td>
<td>3.2 (1.2–8.5)*</td>
<td>27.9 (9.7–79.8)*****</td>
<td>8.8 (3.7–21)*****</td>
</tr>
</tbody>
</table>

Adjusting for participant gender, age, ethnicity and home environment (parents).  
*\(p < 0.05\); **\(p < 0.01\); ***\(p < 0.001\).  
\(^a\) Behavioural disorders included: Attention Deficit Hyperactivity Disorder, Conduct Disorder and Antisocial Personality Disorder.  
\(^b\) \(p = 0.073\).
Fig. 1. Onset of disorders in at-risk, control and bipolar disorder groups. (A) Affective disorders; (B) Anxiety disorders.
High risk studies:  
Risk ratio for any depressive disorder

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bella et al. (2011)</td>
<td>12.469</td>
<td>1.734</td>
<td>89.680</td>
<td>2.507</td>
<td>0.012</td>
</tr>
<tr>
<td>Birmaher et al. (2010)</td>
<td>2.533</td>
<td>0.104</td>
<td>61.508</td>
<td>0.571</td>
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<tr>
<td>Duffy et al. (2007)</td>
<td>14.409</td>
<td>2.012</td>
<td>103.205</td>
<td>2.656</td>
<td>0.008</td>
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<tr>
<td>Garcia-Amsador et al. (2013)</td>
<td>1.500</td>
<td>0.164</td>
<td>13.696</td>
<td>0.359</td>
<td>0.719</td>
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<tr>
<td>Grigoroiu-Serbanescu et al. (1989)</td>
<td>6.000</td>
<td>0.741</td>
<td>48.590</td>
<td>1.679</td>
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<tr>
<td>Hammen et al. (1990)</td>
<td>2.111</td>
<td>0.594</td>
<td>7.498</td>
<td>1.156</td>
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<td>Numberger et al. (2011)</td>
<td>3.711</td>
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<td>10.380</td>
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<td>Perich et al. (2015)</td>
<td>2.331</td>
<td>1.328</td>
<td>4.091</td>
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<td>Petresco et al. (2009)</td>
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<td>0.181</td>
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<tr>
<td>Singh et al. (2007)</td>
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<td>Vandeleur et al. (2012)</td>
<td>2.455</td>
<td>1.458</td>
<td>4.135</td>
<td>3.379</td>
<td>0.001</td>
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</table>

*
High risk studies:
Risk ratio for any anxiety disorder

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bella et al. (2011)</td>
<td>3.379</td>
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<td>Bird et al. (2010)</td>
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<td>Garcia-Amador et al. (2013)</td>
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<td>26.905</td>
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<td>5.641</td>
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<td>Petresco et al. (2009)</td>
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<td>Radke-Yarrow et al. (1992)</td>
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<td>Singh et al. (2007)</td>
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<td>Vandeleur et al. (2012)</td>
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<td>1.279</td>
<td>2.701</td>
<td>3.251</td>
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</table>

* indicates a significant finding.
High risk studies: Risk ratio for any behavioural disorder

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td>Bella et al. (2011)</td>
<td>3.751</td>
<td>1.675</td>
<td>8.398</td>
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<td>Birmaher et al. (2010)</td>
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<td>6.720</td>
<td>1.861</td>
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<td>35.161</td>
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<td>113.139</td>
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<td>Grigoriou-Serbanescu et al. (1989)</td>
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<td>0.719</td>
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<td>Nurnberger et al. (2011)</td>
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<td>3.260</td>
<td>0.741</td>
<td>0.459</td>
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<td>Petresco et al. (2009)</td>
<td>7.395</td>
<td>0.925</td>
<td>59.103</td>
<td>1.887</td>
<td>0.059</td>
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<tr>
<td>Singh et al. (2007)</td>
<td>15.543</td>
<td>0.906</td>
<td>266.581</td>
<td>1.892</td>
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<td>Vandelever et al. (2012)</td>
<td>1.005</td>
<td>0.442</td>
<td>2.286</td>
<td>0.012</td>
<td>0.990</td>
</tr>
</tbody>
</table>

* Denotes significantly different from the baseline
Do prior anxiety or behavioural disorders increase risk to later onset of affective disorders?

- In Dunedin long-term prospective study (Kim-Cohen et al, 2003) adult mania was more likely to have been preceded by conduct and/or oppositional defiant disorder (aOR 2.5) and juvenile depression (aOR 3.3).

- Prior anxiety disorders (Duffy et al, 2012; Nurnberger et al, 2011) and behavioural disorders (Nurnberger et al, 2011) predicted increased risk of later onset of affective disorders in high risk samples.

- In our high risk sample, anxiety and behavioural disorders did not increase later risk to affective disorders.

- However, within our bipolar disorder group (Perich et al, 2015), prior behavioural disorders were associated with later development of to bipolar disorder (p < 0.01).
Fig. 1. Proposed staging sequence.
Review Article

Diagnostic guidelines for bipolar depression: a probabilistic approach


The greater likelihood of the diagnosis of BIPOLAR I DEPRESSION should be considered if ≥ 5 of the following features are present

Symptomatology and mental state signs
- Hypersomnia and/or increased daytime napping
- Hyperphagia and/or increased weight
- Other ‘atypical’ depressive symptoms such as ‘leaden paralysis’
- Psychomotor retardation
- Psychotic features and/or pathological guilt
- Lability of mood/manic symptoms

Course of illness
- Early onset of first depression (< 25 years)
- Multiple prior episodes of depression (≥ 5 episodes)

Family history
- Positive family history of bipolar disorder

Comparing the Phenomenology of Depressive Episodes in Bipolar I and II Disorder and Major Depressive Disorder Within Bipolar Disorder Pedigrees

Andrew Frankland, PhD; Ester Cerrillo, MD; Dusan Hadzi-Pavlovic, MPsychol; Gloria Roberts, PhD; Adam Wright, M ClinPsych; Colleen K. Loo, MD, FRANZCP; Michael Breakspear, PhD, FRANZCP; and Philip B. Mitchell, AM, MD, FRANZCP, FRCPsych

Evidence from family pedigrees indicates that depressive episodes in bipolar disorder may differ from those in major depression. We examined this in pedigrees of bipolar patients with a family history of depression using a protocol based on ClinPsych software and computerized rating.

Comparison of depressive episodes in bipolar disorder and in major depressive disorder within bipolar disorder pedigrees

Philip B. Mitchell, Andrew Frankland, Dusan Hadzi-Pavlovic, Gloria Roberts, Justine Corry, Adam Wright, Colleen K. Loo and Michael Breakspear
Do at-risk subjects have a “bipolar depressive” profile?

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**DIGS Sample**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=73)</th>
<th>At-Risk (n=57)</th>
<th>Bipolar (n=47)</th>
<th>Proband (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSM-IV MDE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (15.1)</td>
<td>20 (35.1)</td>
<td>44 (93.6)</td>
<td>75 (82.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Control (n=11)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (36.4)</td>
<td>14 (70.0)</td>
<td>41 (93.2)</td>
<td>66 (88.0)</td>
<td></td>
</tr>
<tr>
<td>0 (0)</td>
<td>6 (30.0)</td>
<td>37 (84.1)</td>
<td>56 (74.7)</td>
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</tr>
<tr>
<td>0 (0)</td>
<td>2 (10.0)</td>
<td>19 (43.2)</td>
<td>28 (37.3)</td>
<td></td>
</tr>
<tr>
<td><strong>N=6 At-Risk with 4+ probabilistic features</strong></td>
<td></td>
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<tr>
<td>7541030001</td>
<td>Converter at FU 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7541085001</td>
<td>No sx</td>
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<td>7541196001</td>
<td>No sx</td>
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<tr>
<td>7541223001</td>
<td>At baseline: BPNOS; Converter at FU 3</td>
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<tr>
<td>7541478004</td>
<td>At baseline: Possible BP-II, No sx at FU 2</td>
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</tr>
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</table>
Neuropsychological testing
Neuropsychological functioning

- The at-risk (AR) participants showed impaired verbal intelligence and affective inhibition relative to healthy controls (HC).

- Unlike prior studies (of older healthy family members), AR subjects did not show impairments in general intellectual ability, working memory, visuospatial or language ability.

Mc Cormack ... Mitchell (Psychological Medicine; In Revision)
Assessment of First and Second Degree Relatives of Individuals With Bipolar Disorder Shows Increased Genetic Risk Scores in Both Affected Relatives and Young At-Risk Individuals


Fullerton et al, 2015
Brain imaging
Reduced Inferior Frontal Gyrus Activation During Response Inhibition to Emotional Stimuli in Youth at High Risk of Bipolar Disorder

Gloria Roberts, Melissa J. Green, Michael Breakspear, Clare McCormack, Andrew Frankland, Adam Wright, Florence Levy, Rhoshel Lenroot, Herng Nieng Chan, and Philip B. Mitchell

Results: Whole-brain corrected analyses revealed a highly specific and significant lack of recruitment of the inferior frontal gyrus when inhibiting responses to fearful faces in the high-risk participants compared with control subjects (p = .011, family-wise error, peak voxel).

Conclusions: Impaired inhibitory function of the inferior frontal cortex may represent a trait marker of vulnerability to bipolar disorder. That this finding was revealed during inhibition of emotional material further implicates dysregulated frontolimbic brain networks as a potential neurocognitive endophenotype for bipolar disorder and provides evidence for pre-existing functional disturbances in those at high genetic risk for bipolar disorder.
We used a **FACIAL EMOTION GO/NO-GO TASK** to elicit emotion regulatory systems:
- heightened emotional reactivity and/or impaired inhibition are implicated neurocognitive endophenotypes for bipolar disorder
- no previous fMRI study had examined emotional inhibition in offspring of bipolar disorder probands

**Conditions:** (alternating targets)
- Male-female
- Fear-calm (neutral)
- Happy-calm (neutral)

**Instruction:**
Respond to all fearful facial expressions by making a button press, but do not to respond to any other expressions

Roberts et al, 2013
Figure 2. Between-group whole brain analysis: fear distractors minus fear targets. The left inferior frontal gyrus showed a smaller effect of this contrast in the bipolar at-risk (AR-BD) group compared with control subjects (Brodman area 47; cluster size = 34 voxels; Montreal Neurological Institute peak voxel coordinates: $x = -21, y = 11; z = -17$). (A) Statistical Parametric Mapping output image. (B) Peak-voxel beta signal plot.
Network dysfunction of emotional and cognitive processes in those at genetic risk of bipolar disorder

Michael Breakspear,1,2,3,* Gloria Roberts,3,4,* Melissa J. Green,3,4,5,6 Vinh T. Nguyen,1 Andrew Frankland,3,4 Florence Levy,3 Rhoshel Lenroot3,6 and Philip B. Mitchell3,4
Effective Connectivity

inhibition (DLPFC)
fear X inh (IFG)
faces (FFA)

fear (AC)

Breakspear, Roberts, ..., Mitchell (2015) *Brain*
Functional Connectivity

Structural Connectivity

Controls > Bipolar at-risk

Breakspear, Perry, Roberts, Mitchell (In preparation)
Early intervention / prevention
Therapeutic interventions for those at high risk to bipolar disorder

- No ‘preventive’ intervention studies
- Only one RCT of short-term efficacy of family-focused therapy for AR subjects with BD-NOS, MDD or cyclothymia (Miklowitz et al, 2013)
Objective: Depression and brief periods of (hypo)mania are linked to an increased risk of progression to bipolar I or II disorder (BD) in children of bipolar parents. This randomized trial examined the effects of a 4-month family-focused therapy (FFT) program on the 1-year course of mood symptoms in youth at high familial risk for BD, and explored its comparative benefits among youth in families with high versus low expressed emotion (EE).  

Method: Participants were 40 youth (mean 12.3 ± 2.8 years, range 9–17) with BD not otherwise specified, major depressive disorder, or cyclothymic disorder who had a first-degree relative with BD I or II and active mood symptoms (Young Mania Rating Scale [YMRS] > 11 or Child Depression Rating Scale > 29). Participants were randomly allocated to FFT–High Risk version (FFT-HR; 12 sessions of psychoeducation and training in communication and problem-solving skills) or an education control (EC; 1–2 family sessions).  

Results: Youth in FFT-HR had more rapid recovery from their initial mood symptoms (hazard ratio = 2.69, \( p = .047 \)), more weeks in remission, and a more favorable trajectory of YMRS scores over 1 year than youth in EC. The magnitude of treatment effect was greater among youth in high-EE (versus low-EE) families.  

Conclusions: FFT-HR may hasten and help sustain recovery from mood symptoms among youth at high risk for BD. Longer follow-up will be necessary to determine whether early family intervention has downstream effects that contribute to the delay or prevention of full manic episodes in vulnerable youth.  


Key Words: expressed emotion, high risk, early warning signs, psychoeducation, psychosocial intervention.
Conclusions I

- Current findings cross-sectional only
- ‘At-risk’ (AR) group demonstrates:
  - Higher rates and earlier onset of depressive, anxiety and behavioural disorders compared to controls
  - Impaired verbal intelligence and affective inhibition relative to controls
  - Higher bipolar disorder polygenic risk scores
  - Impaired IFG function and connections (fMRI, resting state connectivity; effective connectivity; and structural connectivity)
- In coming years, will be able to identify any potential predictors of risk to “conversion” to bipolar disorder and/or MDD
Conclusions II

- Clinical, neuropsychological, genetic and neuroimaging studies are all suggesting potential ‘more nuanced’ targets for early intervention studies among first-degree relatives of those with bipolar disorder.
  - Either as single targets (e.g. depressive, anxiety, behavioural disorders) or some algorithm of multiple modalities (e.g. clinical, genetic and neuroimaging).

- What would be the most appropriate interventions?
  - Targeted psychological interventions?
  - Medications? – but raises major ethical concerns of risk re benefit.