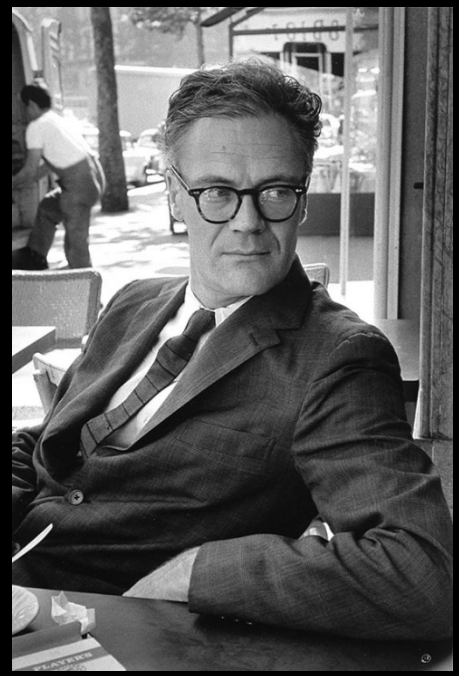
UNSW SYDNEY | Australia's Global University

Philip Mitchell

# Recent advances in bipolar disorder

*“This disease of the brain bears down on all the things that make us human: our moods, the way we see and experience the world, the way we think, our changing capacities of energy and will and imagination, our desires, the gift to create, our determination to live or die, our expectation of the future, our sanity.”*

Kay Redfield Jamison in “Robert Lowell, setting the river on fire: a study of genius, mania, and character” New York: Alfred A. Knopf, 2017



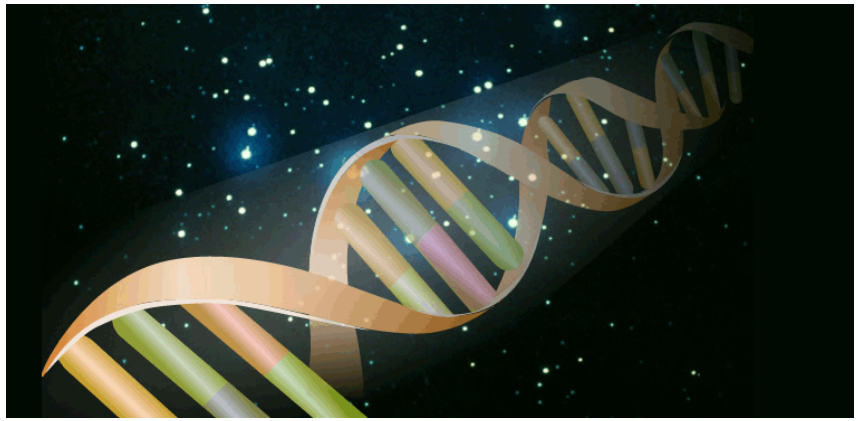
# Case history

- 25-year-old female university student
- Five years rapid-cycling bipolar II disorder
  - Alternation between depression and hypomania each 5-7 days
  - When depressed:
    - Sleeps at least 15 hours per day
    - Unable to concentrate
    - Frequent suicidal thoughts, leading to multiple attempts
  - When hypomanic:
    - Overactive, unfocussed, reduced need for sleep
- Poor response to wide range of appropriate therapies
- This case highlights the need to improve our understanding of bipolar disorder and thereby improve treatments


# Genetics of bipolar disorder

# Genetics

- Genetic factors account for up to 80 - 90% of the cause of bipolar disorder (McGuffin et al, 2003)
- Individuals with a first-degree relative (parent, child or sibling) with bipolar disorder are 10-14 times more likely to develop bipolar disorder than someone without such a family history (Mortensen et al, 2003)

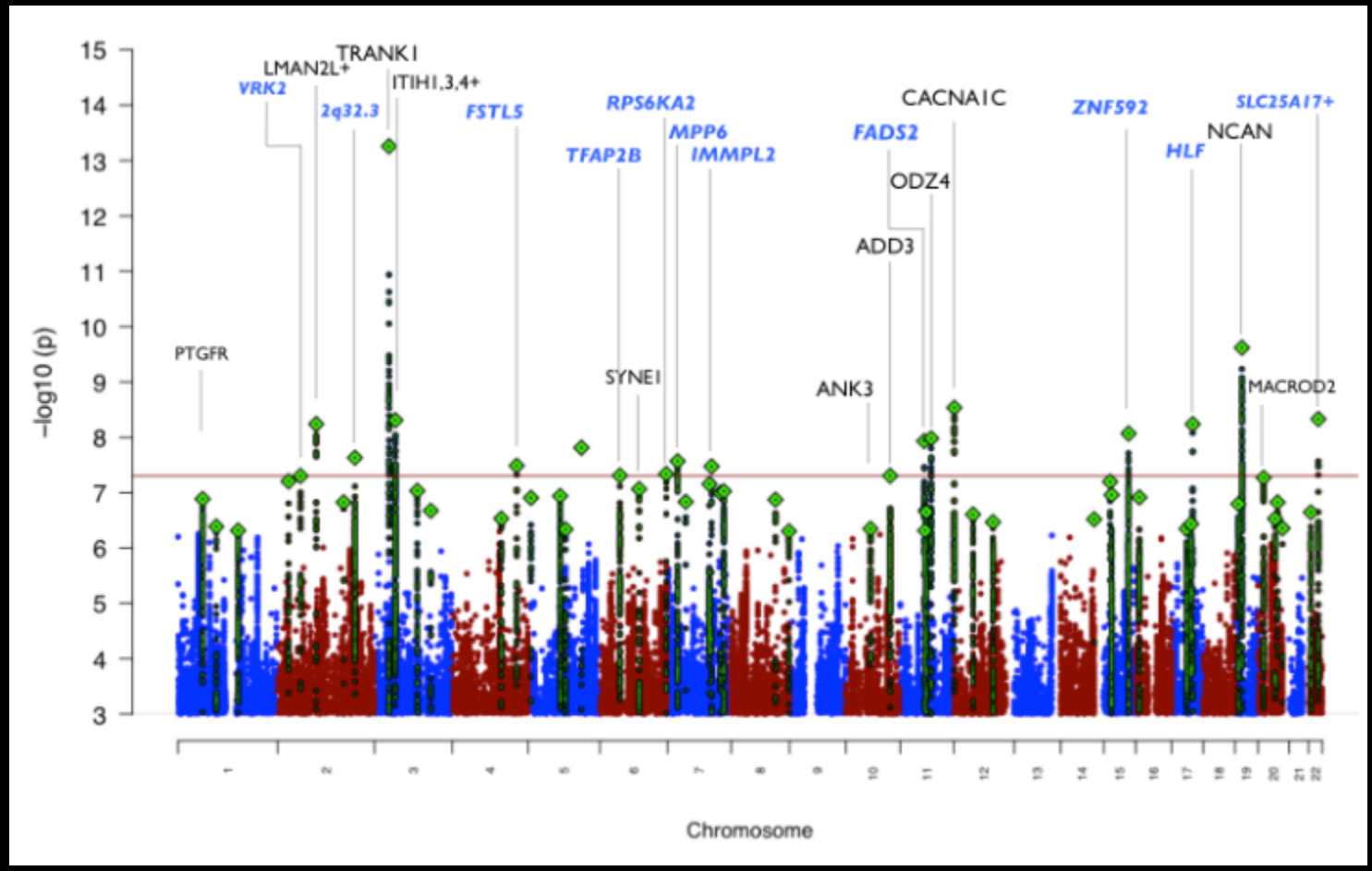


nature genetics

ARTICLES

https://doi.org/10.1038/s41588-019-0397-8

# Genome-wide association study identifies 30 loci associated with bipolar disorder




Stahl … Mitchell … et al (2019)

# Latest bipolar disorder GWAS results (Mullins … Mitchell et al; *Nature Genetics*, in press)

- Presented at World Congress on Psychiatric Genetics, Anaheim 2019
- Findings of Psychiatric Genomics Consortium (PGC3) Bipolar Disorders Group
- 64 genome-wide susceptibility loci
- 35 novel regions
  - 15 overlap with major depression
  - 35 overlap with schizophrenia
- Many expressed in dorsolateral prefrontal cortex
- Many relate to calcium channel receptors and pathways

JAMA Network | Open

Research Letter | Psychiatry

# De Novo Gene Variants and Familial Bipolar Disorder

Claudio Toma, PhD; Alex D. Shaw, PhD; Bronwyn J. Overs, BPsych; Philip B. Mitchell, MBBS, MD; Peter R. Schofield, PhD; Antony A. Cooper, PhD; Janice M. Fullerton, PhD

## Discussion

Examination of DNVs in psychiatric disorders has traditionally focused on singleton families. These findings suggest that DNVs may also contribute to mutational load in multiplex BD families, as previously observed for multiplex autism families.[6] Although this study is limited by the small sample size, the overall de novo mutation rate was comparable in cases and unaffected offspring, whereas deleterious DNVs were observed more frequently in participants with BD, which is consistent with previous reports in autism and schizophrenia.[2] This study highlighted *HP*, *PC*, *MAP4*, and *WDHD1* as potential susceptibility genes for BD. Additional sequencing studies in larger cohorts are needed to further delineate the impact of DNVs in BD.

ARTICLE INFORMATION

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**Published:** May 8, 2020. doi:10.1001/jamanetworkopen.2020.3382

# Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study

*Liping Hou*, Urs Heilbronner*, Franziska Degenhardt*, Mazda Adli, Kazufumi Akiyama, Nirmala Akula, Raffaella Ardau, Bárbara Arias, Lena Backlund, Claudio E M Banzato, Antoni Benabarre, Susanne Bengesser, Abesh Kumar Bhattacharjee, Joanna M Biernacka, Armin Birner, Clara Brichant-Petitjean, Elise T Bui, Pablo Cervantes, Guo-Bo Chen, Hsi-Chung Chen, Caterina Chillotti, Sven Cichon, Scott R Clark, Francesc Colom, David A Cousins, Cristiana Cruceanu, Piotr M Czerski, Clarissa R Dantas, Alexandre Dayer, Bruno Étain, Peter Falkai, Andreas J Forstner, Louise Frisén, Janice M Fullerton, Sébastien Gard, Julie S Garnham, Fernando S Goes, Paul Grof, Oliver Gruber, Ryota Hashimoto, Joanna Hauser, Stefan Herms, Per Hoffmann, Andrea Hofmann, Stephane Jamain, Esther Jiménez, Jean-Pierre Kahn, Layla Kassem, Sarah Kittel-Schneider, Sebastian Kliwicki, Barbara König, Ichiro Kusumi, Nina Lackner, Gonzalo Laje, Mikael Landén, Catharina Lavebratt, Marion Leboyer, Susan G Leckband, Carlos A López Jaramillo, Glenda MacQueen, Mirko Manchia, Lina Martinsson, Manuel Mattheisen, Michael J McCarthy, Susan L McElroy, Marina Mitjans, Francis M Mondimore, Palmiero Monteleone, Caroline M Nievergelt, Markus M Nöthen, Urban Ösby, Norio Ozaki, Roy H Perlis, Andrea Pfennig, Daniela Reich-Erkelenz, Guy A Rouleau, Peter R Schofield, K Oliver Schubert, Barbara W Schweizer, Florian Seemüller, Giovanni Severino, Tatyana Shekhtman, Paul D Shilling, Kazutaka Shimoda, Christian Simhandl, Claire M Slaney, Jordan W Smoller, Alessio Squassina, Thomas Stamm, Pavla Stopkova, Sarah K Tighe, Alfonso Tortorella, Gustavo Turecki, Julia Volkert, Stephanie Witt, Adam Wright, L Trevor Young, Peter P Zandi, James B Potash, J Raymond DePaulo, Michael Bauer, Eva Z Reininghaus, Tomas Novák, Jean-Michel Aubry, Mario Maj, Bernhard T Baune, Philip B Mitchell, Eduard Vieta, Mark A Frye, Janusz K Rybakowski, Po-Hsiu Kuo, Tadafumi Kato, Maria Grigoroiu-Serbanescu, Andreas Reif, Maria Del Zompo, Frank Bellivier, Martin Schalling, Naomi R Wray, John R Kelsoe*, Martin Alda*, Marcella Rietschel*, Francis J McMahon*, Thomas G Schulze**

*Lancet* 2016; 387: 1085–93

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January 21, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00143-4

## Summary

**Background** Lithium is a first-line treatment in bipolar disorder, but individual response is variable. Previous studies have suggested that lithium response is a heritable trait. However, no genetic markers of treatment response have been reproducibly identified.

**Methods** Here, we report the results of a genome-wide association study of lithium response in 2563 patients collected


# Studies of youth at high genetic risk: Towards early intervention

# 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.**

BLACK DOG INSTITUTE

UNSW
THE UNIVERSITY OF NEW SOUTH WALES

To participate: Please phone 1800-352-292
or email: bipolar-kidsandsibs@unsw.edu.au

Doing fine ... Jamie Tancred with his daughters. Photo: Chris Elfes

# Bipolar Disorder Kids & Sibs Study: Design

*"Catch them before they fall – early prevention for better results"*

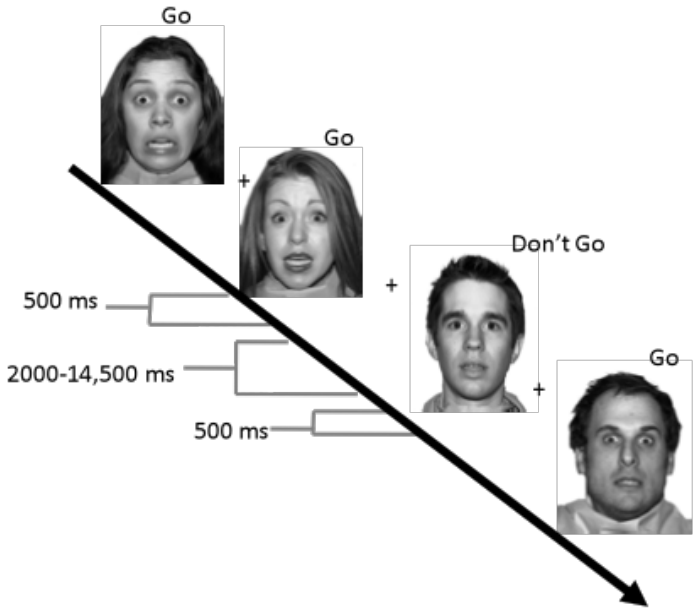
- **Three groups (all 12-30 years at baseline; recruitment ongoing)**
  - High-risk (first-degree BD relative; no current BD): 181
  - Controls (no family history of any mental illness): 133
  - Bipolar disorder: 70
- **Baseline assessment:**
  - Structured diagnostic interviews
  - Self-report questionnaires
  - Neuropsychological testing
  - Blood sample for SNPs, epigenetics
  - Brain imaging: structural MRI, MRS, functional MRI & DTI
- **Follow-ups:**
  - Clinical reviews annually
  - Scans and neuropsychological testing repeated at 2 years
  - Planning for 10-year scanning follow-up

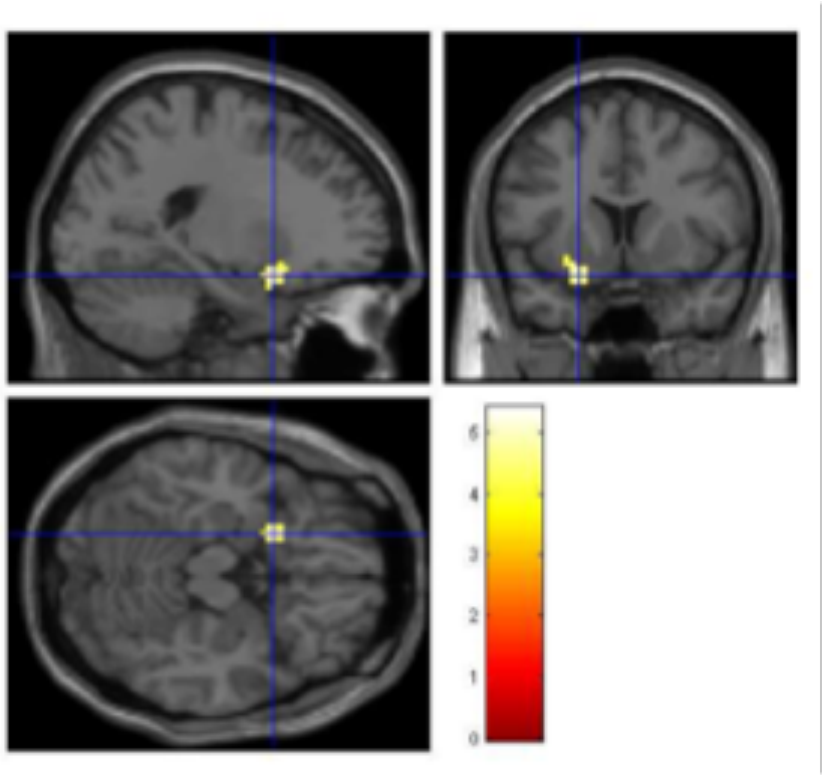
# Traumatic Stress Interacts With Bipolar Disorder Genetic Risk to Increase Risk for Suicide Attempts

Holly C. Wilcox, PhD, Janice M. Fullerton, PhD, Anne L. Glowinski, MD, Kelly Benke, PhD, Masoud Kamali, MD, Leslie A. Hulvershorn, MD, Emma K. Stapp, PhD, Howard J. Edenberg, PhD, Gloria M.P. Roberts, PhD, Neera Ghaziuddin, MD, Carrie Fisher, BSN, RN, Christine Brucksch, BSN, RN, Andrew Frankland, PhD, Claudio Toma, PhD, Alex D. Shaw, PhD, Elizabeth Kastelic, MD, Leslie Miller, MD, Melvin G. McInnis, MD, Philip B. Mitchell, MD, John I. Nurnberger, Jr., MD, PhD

Journal of the American Academy of Child & Adolescent Psychiatry
VOLUME 56 NUMBER 12 DECEMBER 2017

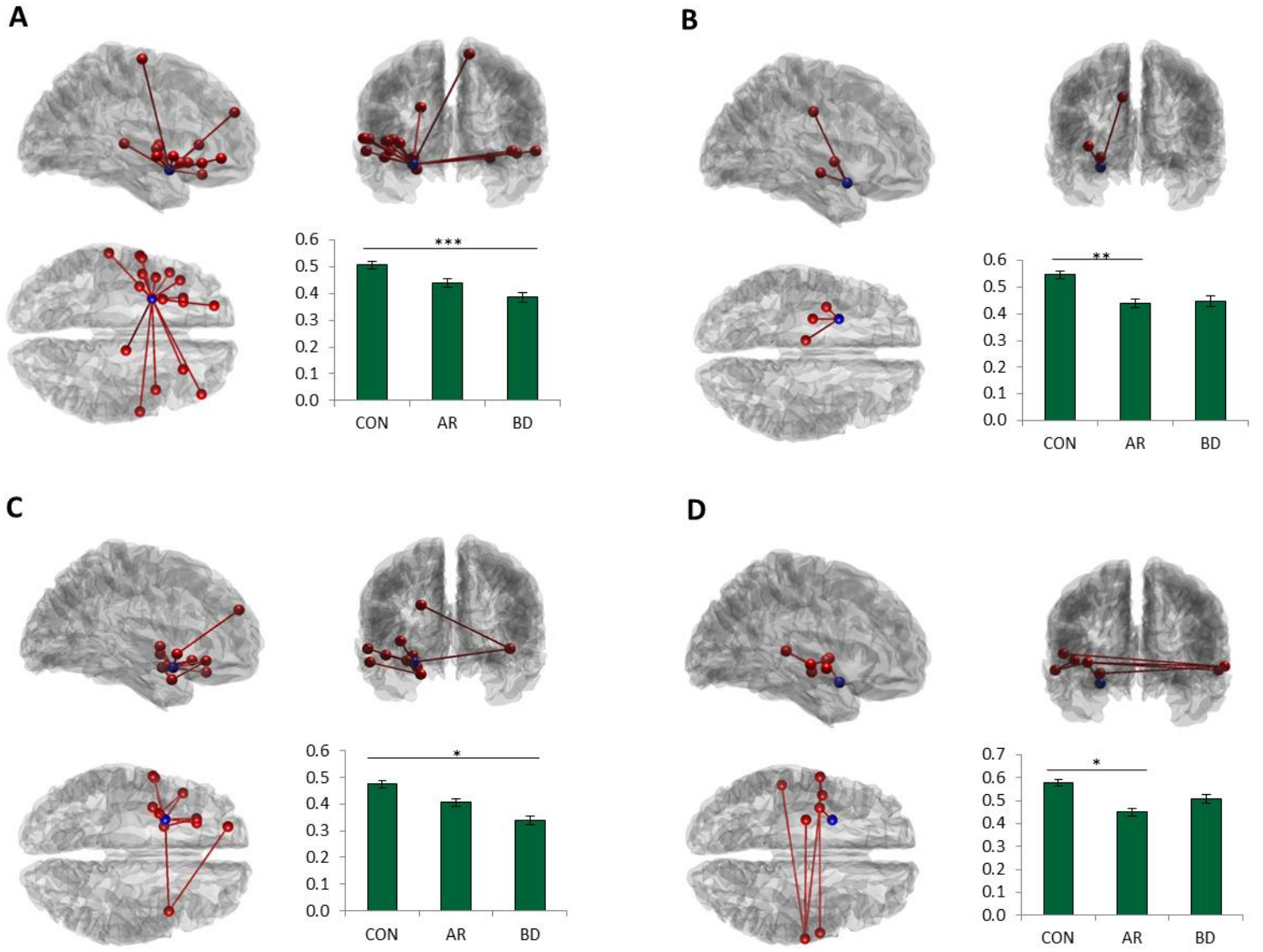
Participants were required to view streams of emotionally salient faces and inhibit their motor response (“no-go”) to a number of target emotions



Participants “at risk” of bipolar showed a lack of engagement of left inferior frontal gyrus during inhibition of response to fearful faces

Roberts et al. (2013) *Biol. Psychiatry*




A, B - Seeded to left IFG

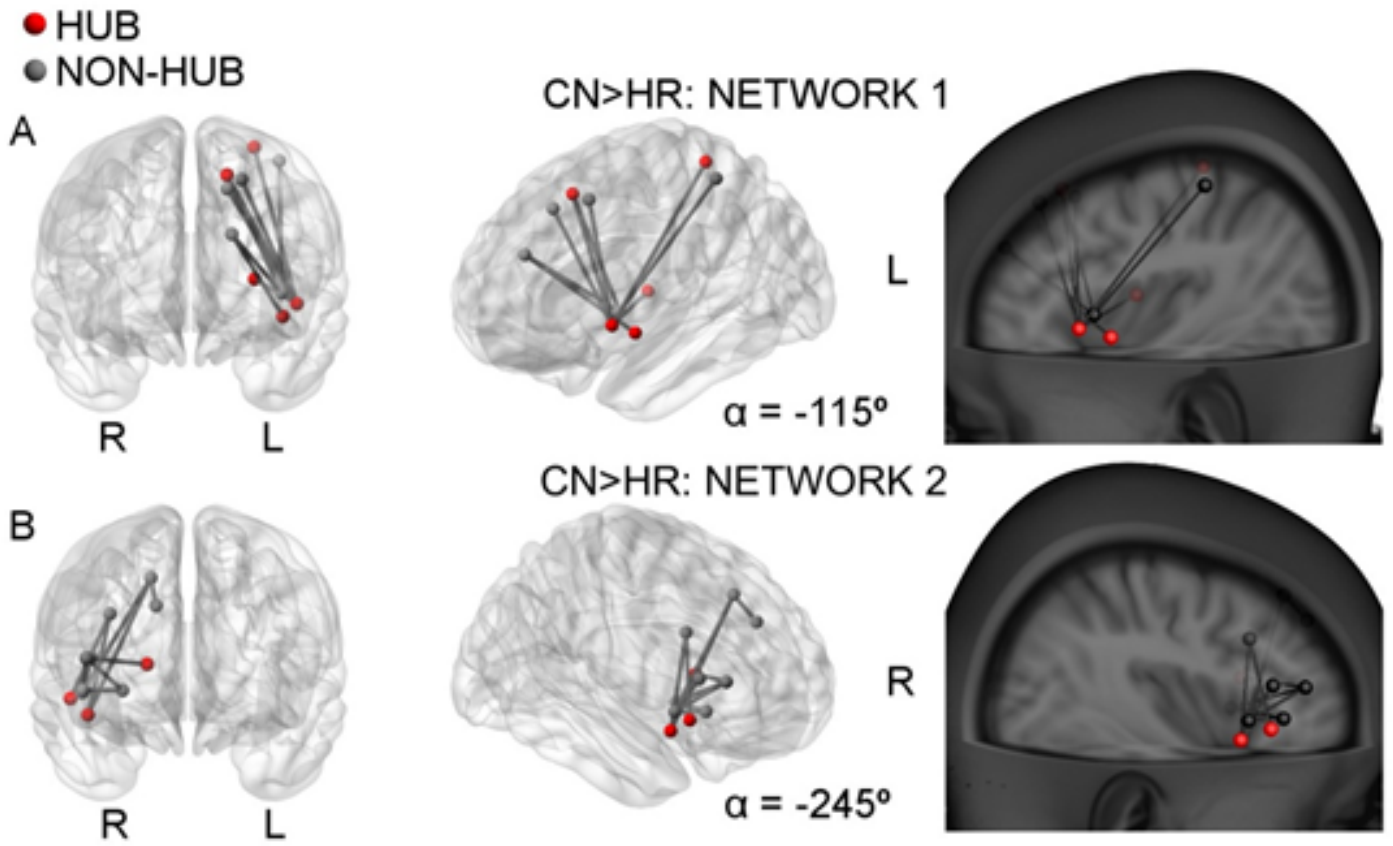
C, D - Whole brain

In bipolar subjects, the left IFG was functionally disconnected from a constellation of regions including bilateral insula, anterior temporal pole and dorsal anterior cingulate (F=3.75, $p$<0.001, FWE corrected). At risk (AR) subjects showed a trend level disconnection of the same network.

Roberts/Lord, Mitchell, Breakspear. (2017) *Biological Psychiatry*

# Brain network disturbances in bipolar disorder

## High risk < Controls



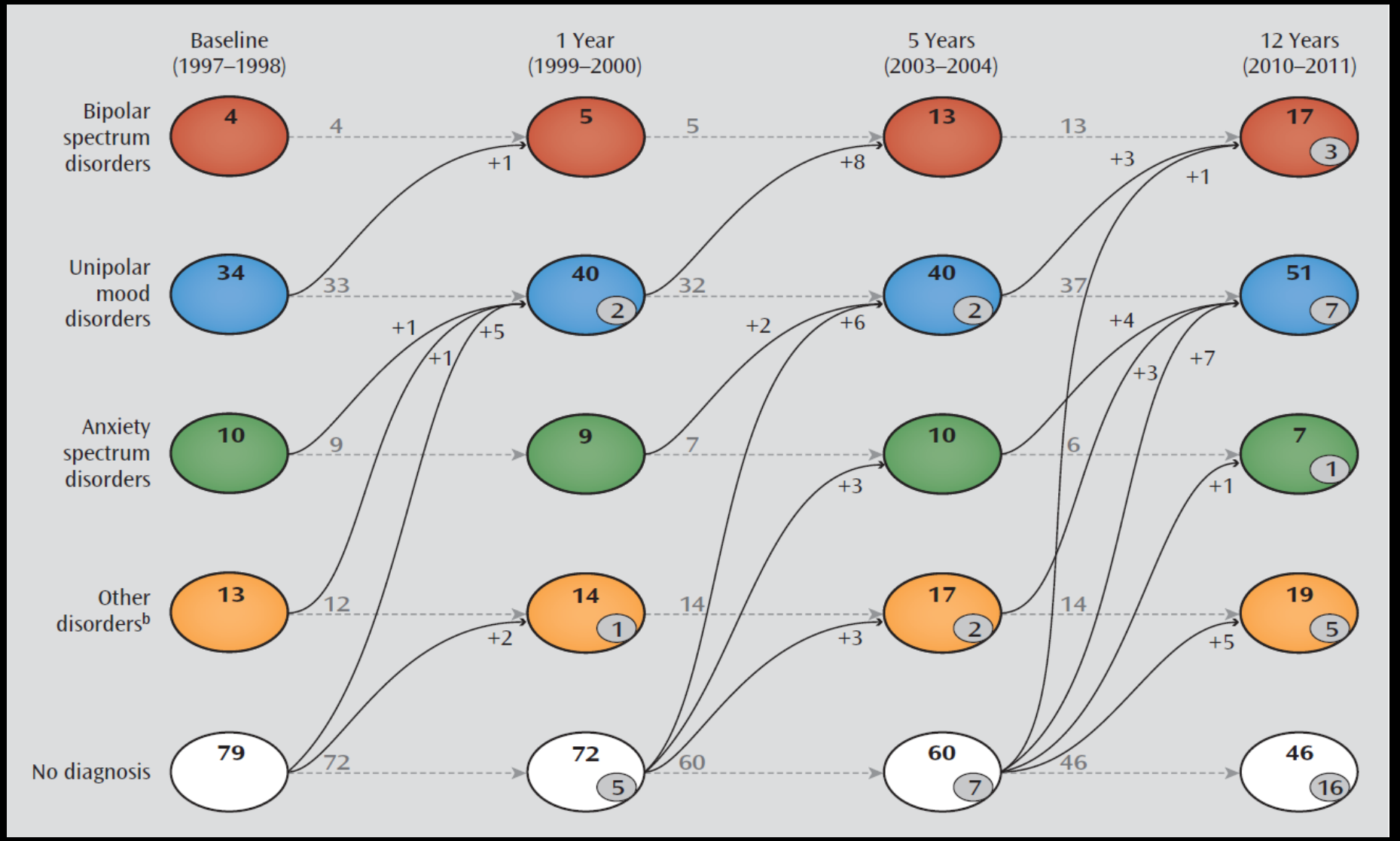

$p_{corrected}$<0.01
Hedges' g=0.86

$p_{corrected}$<0.005
Hedges' g=0.96

Structural brain networks integrating emotion and cognitive control - including hubs - are weaker in the "high risk" group

Roberts*/Perry*, Mitchell, Breakspear (2018) *Molecular Psychiatry*

# Transition to Mood Disorders in the Dutch Bipolar Offspring Cohort (N=140)




*(Am J Psychiatry 2013; 170:542–549)*

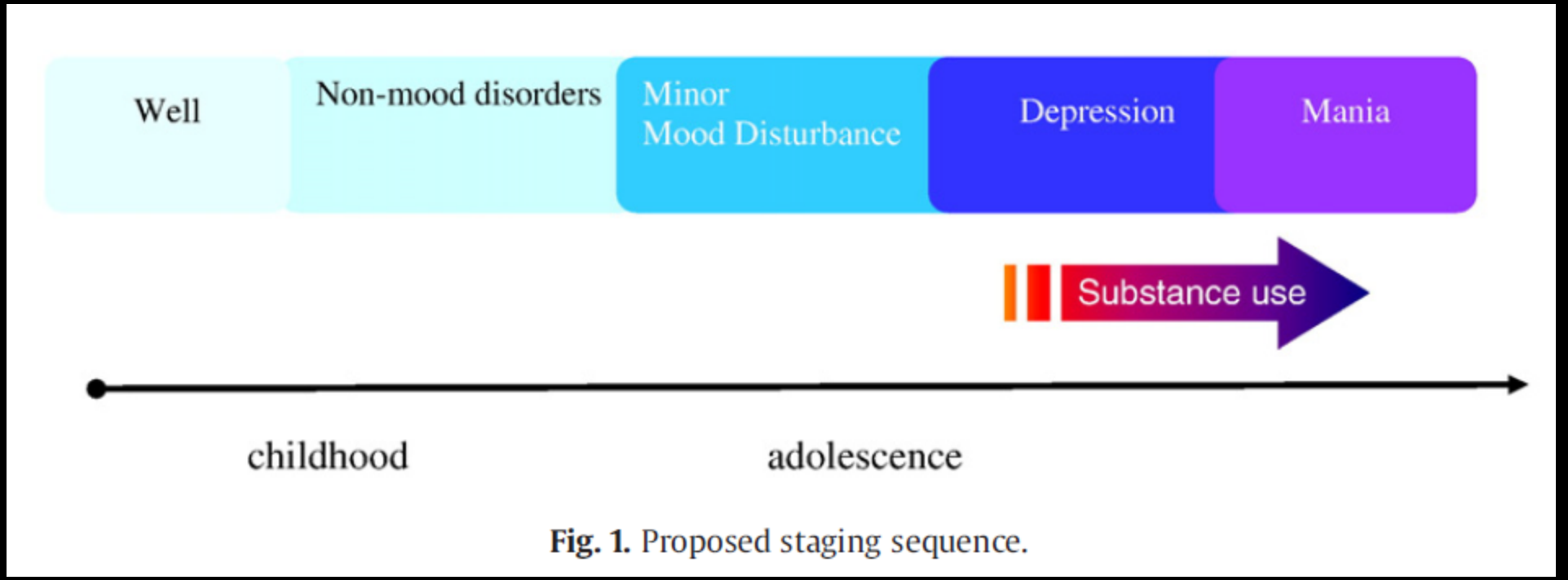



**Fig. 1.** Proposed staging sequence.

Duffy et al, *J Affect Disord*, 2012

# Clinical outcomes – 2021 update

- Cohort now followed for up to 10 years
- 75% retention rate for at least clinical assessment
- 14 of the high risk group have now developed threshold BD-I (4) or BD-II (10) (i.e., 7.7%)
- 29 subthreshold BD since baseline (16%)
- 12 others: the first onset of a major depressive episode (6.6%)

# Specific depressive features predict onset of hypo/mania

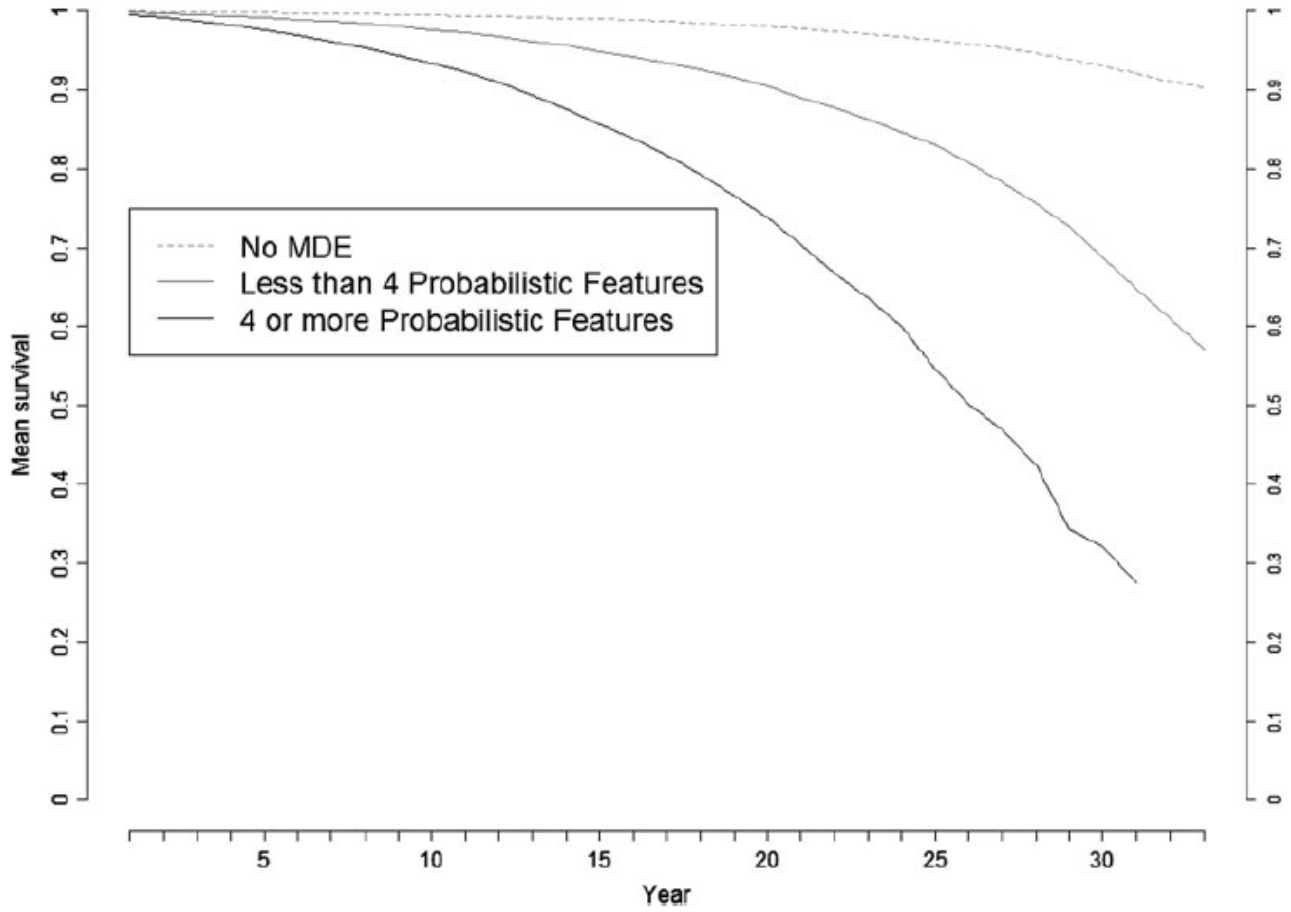


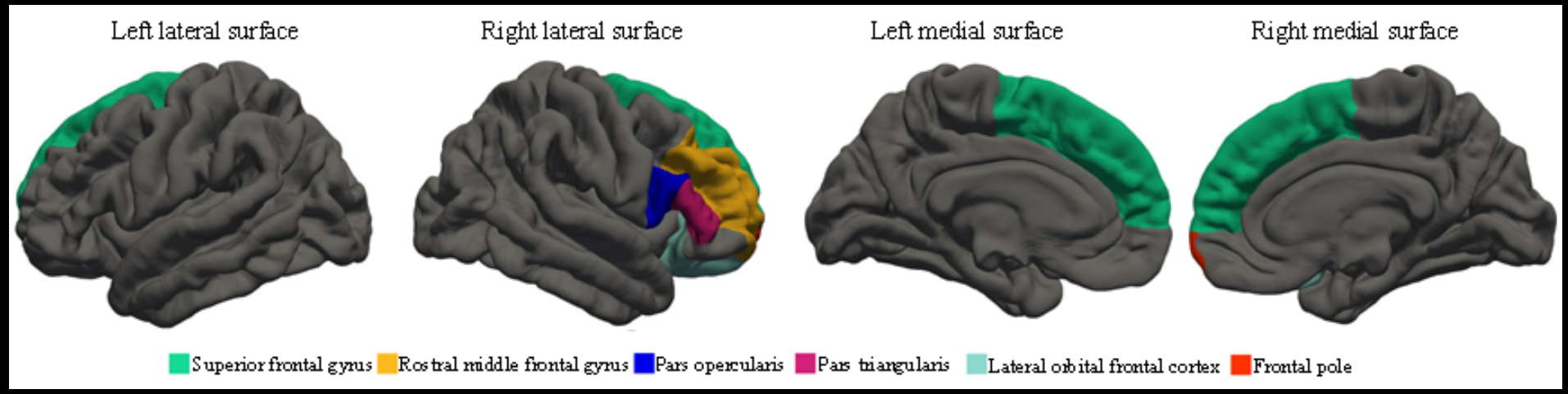

**Fig. 1.** Risk of conversion to threshold bipolar disorder over time among all high-risk participants, comparing those with no MDE, those with MDE and <4 Probabilistic features, and those with MDE and ⩾4 Probabilistic features.

**Frankland … Mitchell**
***Psychol Med* (2018)**

# Neuroimaging – 2021 update

- 170 HR, 126 CON and 68 BD subjects (n=364) have had a baseline 3T MRI scan (average age = 21.1±5.0 years).
- 222 individuals (127 HR; 95 CON) have completed a second scan ~2.1 years later (i.e., 75% of HR subjects)

# Significant group by time interactions for gray matter thickness




**Roberts … Mitchell,**
***Psychological Medicine* (2020)**

# Conclusion

- Findings indicate that brain structural changes are occurring early – even before illness develops
- Emphasises need for early intervention

The American Journal of
Psychiatry
175th Year of Publication

REVIEWS AND OVERVIEWS
Evidence-Based Psychiatric Treatment

# Early Intervention in Bipolar Disorder

Eduard Vieta, M.D., Ph.D., Estela Salagre, M.D., Iria Grande, M.D., Ph.D., André F. Carvalho, M.D., Ph.D., Brisa S. Fernandes, M.D., Ph.D., Michael Berk, M.D., Ph.D., Boris Birmaher, M.D., Mauricio Tohen, M.D., Dr.P.H., Trisha Suppes, M.D., Ph.D.

*Am J Psychiatry 2018; 175:411–426; doi: 10.1176/appi.ajp.2017.17090972*

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Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jad

Review article

# Psychological interventions for young people at risk for bipolar disorder: A systematic review

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frontiers in Psychiatry

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Check for updates

# What Would Digital Early Intervention for Bipolar Disorder Look Like? Theoretical and Translational Considerations for Future Therapies

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