The NNDC and Genetics of ECT (GenECT) Study

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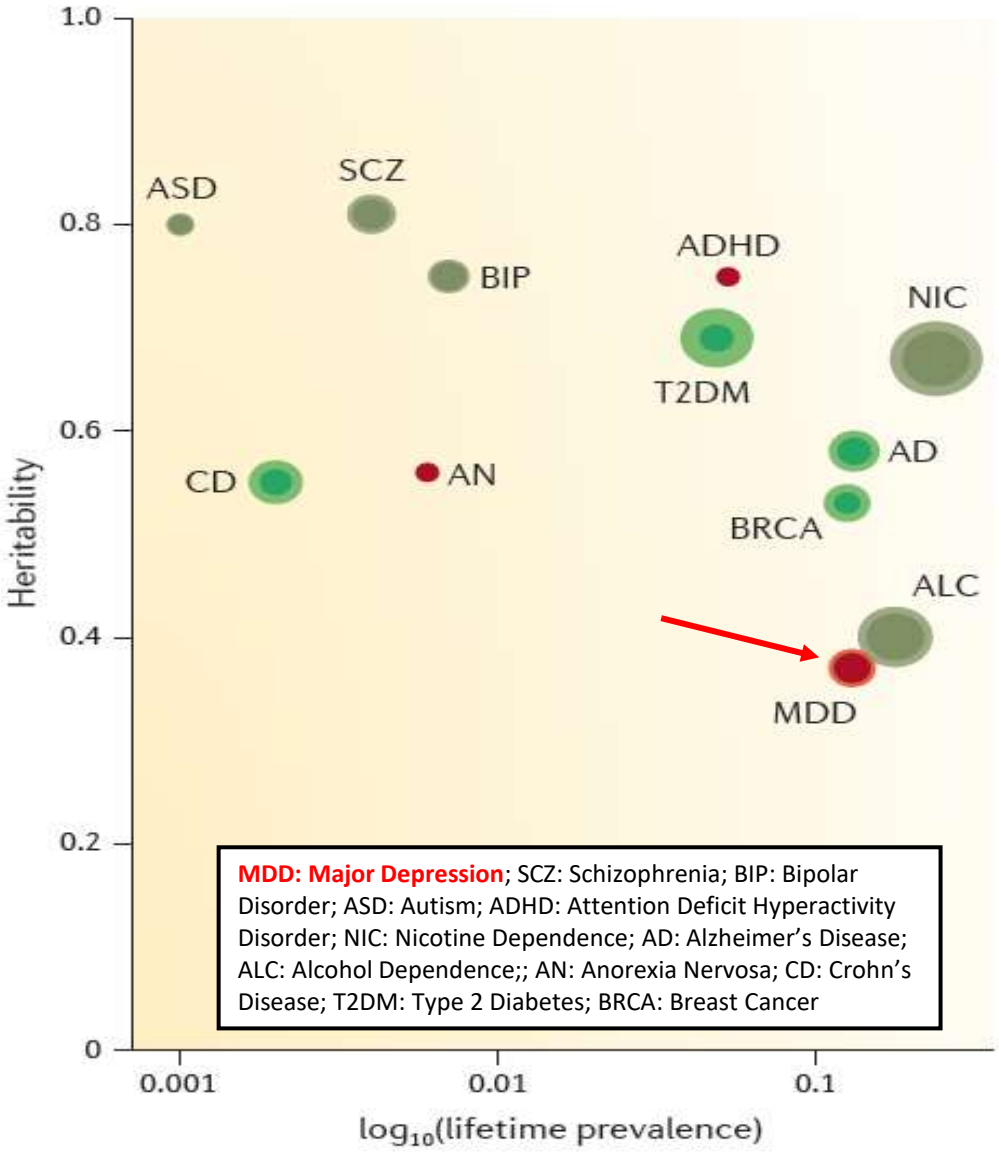
Major Depressive Disorder

- MDD affects ~15% of the population and is a leading cause of disability worldwide
- Effective treatments are available, but up to 1/3 of patients fail to respond to multiple trials with first line therapies
- Family, twin and adoption studies show that genetic factors contribute to 30-40% of risk for MDD



Sullivan et al., Nat Rev Gen, 2012

MDD – GWAS

nature neuroscience

ARTICLES

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Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions

David M. Howard[1*], Mark J. Adams[1], Toni-Kim Clarke[1], Jonathan D. Hafferty[1], Jude Gibson[1], Masoud Shirali[1], Jonathan R. I. Coleman[2,3], Saskia P. Hagenaars[2,3], Joey Ward[4], Eleanor M. Wigmore[1], Clara Alloza[1], Xueyi Shen[1], Miruna C. Barbu[1], Eileen Y. Xu[1], Heather C. Whalley[1], Riccardo E. Marioni[5,6], David J. Porteous[5,6], Gail Davies[5,7], Ian J. Deary[5,7], Gibran Hemani[8], Klaus Berger[9], Henning Teismann[9], Rajesh Rawal[9], Volker Arolt[10], Bernhard T. Baune[11], Udo Dannlowski[10], Katharina Domschke[12], Chao Tian[13], David A. Hinds[13], 23andMe Research Team[14], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium[14], Maciej Trzaskowski[15], Enda M. Byrne[15], Stephan Ripke[16,17,18], Daniel J. Smith[4], Patrick F. Sullivan[19,20,21], Naomi R. Wray[15], Gerome Breen[2,3], Cathryn M. Lewis[2,3] and Andrew M. McIntosh[1,7]

Major depression is a debilitating psychiatric illness that is typically associated with low mood and anhedonia. Depression has a heritable component that has remained difficult to elucidate with current sample sizes due to the polygenic nature of the disorder. To maximize sample size, we meta-analyzed data on 807,553 individuals (246,363 cases and 561,190 controls) from the three largest genome-wide association studies of depression. We identified 102 independent variants, 269 genes, and 15 genesets associated with depression, including both genes and gene pathways associated with synaptic structure and neurotransmission. An enrichment analysis provided further evidence of the importance of prefrontal brain regions. In an independent replication sample of 1,306,354 individuals (414,055 cases and 892,299 controls), 87 of the 102 associated variants were significant after multiple testing correction. These findings advance our understanding of the complex genetic architecture of depression and provide several future avenues for understanding etiology and developing new treatment approaches.

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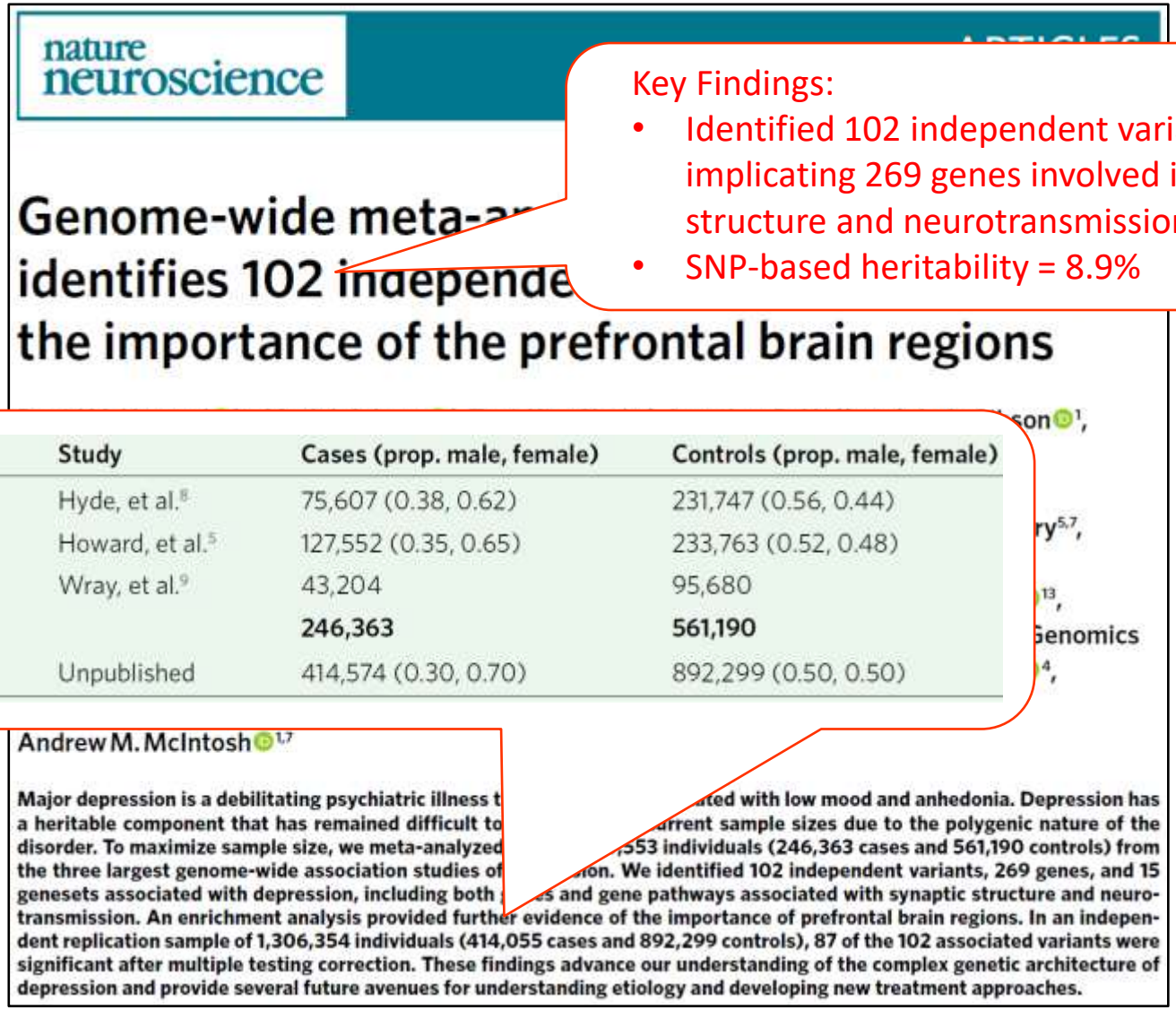
Key Findings:

- Identified 102 independent variants implicating 269 genes involved in synaptic structure and neurotransmission pathways
- SNP-based heritability = 8.9%

MDD – GWAS



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[4],

Cohort	Study	Cases (prop. male, female)	Controls (prop. male, female)
23andMe_307k	Hyde, et al.[8]	75,607 (0.38, 0.62)	231,747 (0.56, 0.44)
UK Biobank	Howard, et al.[5]	127,552 (0.35, 0.65)	233,763 (0.52, 0.48)
PGC_139k[a]	Wray, et al.[9]	43,204	95,680
Meta-analysis		**246,363**	**561,190**
Replication	Unpublished	414,574 (0.30, 0.70)	892,299 (0.50, 0.50)

Andrew M. McIntosh[1,7]

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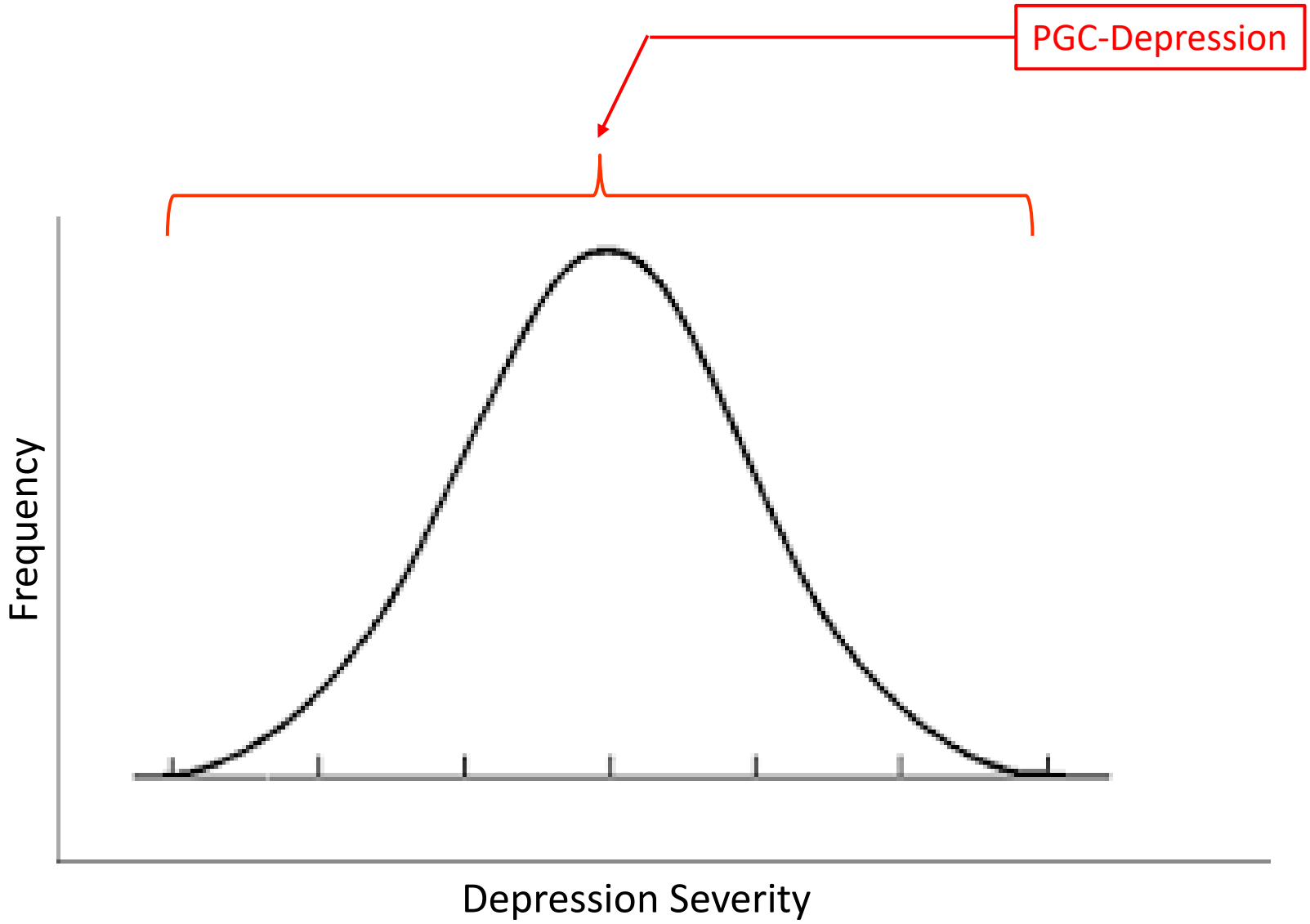
MDD – Heterogeneity



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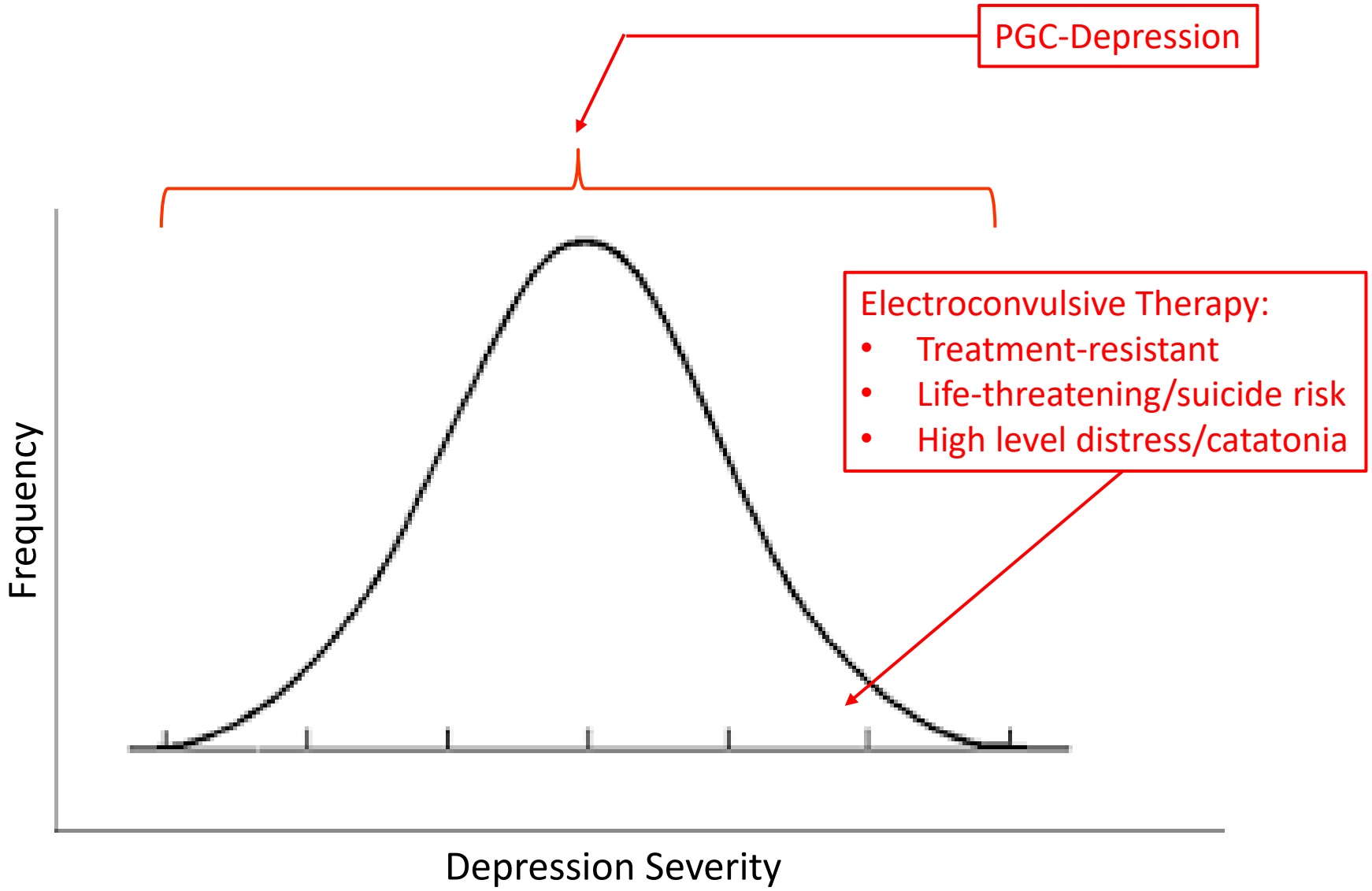
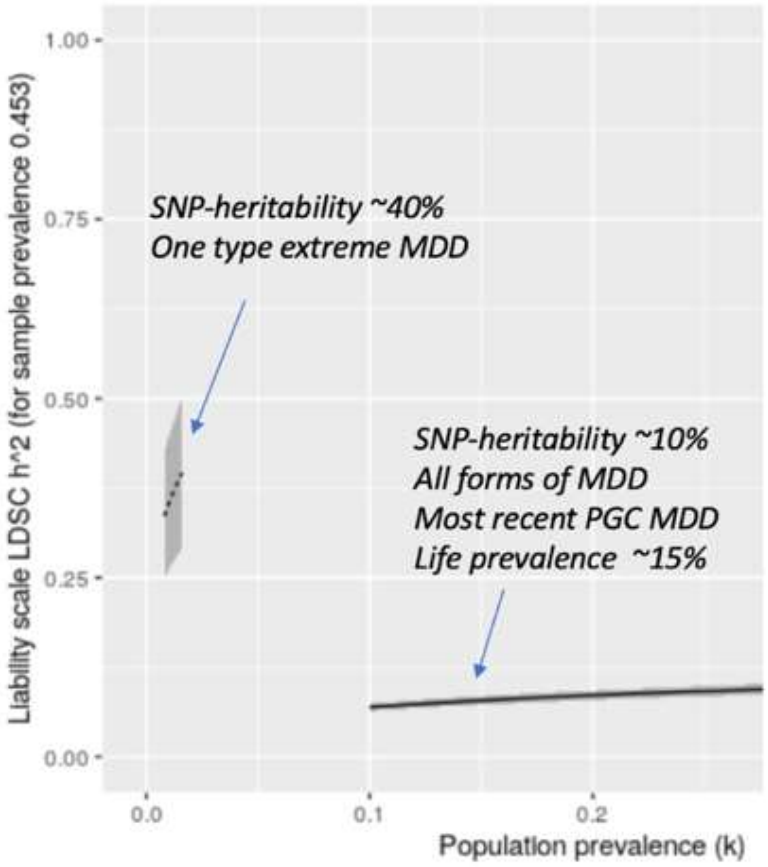


ECT-MDD – Preliminary Data



- ECT-MDD GWAS of N=3,200 identified through Sweden registries
- SNP-based heritability is ~40% for ECT-MDD vs ~10% for PGC-MDD on the liability scale over range of population prevalence estimates

With permission from Clemens, Landen and Sullivan, Manuscript in Preparation

GenECT-IC

US Sites (NNDC):
Johns Hopkins University
Emory University
McLean Hospital
Pine Rest Christian
Stanford University
Ohio State University
University of Florida
University of Massachusetts
University of Pennsylvania
University of Iowa
Louisville University
Indiana University
UT Houston
University of North Carolina
University of Utah
UT Southwestern
Northwell/Hofstra
Cleveland Clinic
Yale University
Mount Sinai
Kaiser Permanente
Vanderbilt University
MGH Partners

International Sites:
University of Munster
University of Adelaide
Central Institute of Manheim
University of Barcelona
Autonomous University of Barcelona
University of Marburg
University of Bielefeld
University of Brescia
Poznan University of Medical Sciences
Gothenburg University
Karolinska Institutet
University of New South Wales
Trinity College
University of Glasgow
CNTW NHS Foundation Trust
Cardiff University
King's College of London
University of Worcester
University of Bergen
University of Calgary
University of British Columbia
Queen's University
Keio University School of Medicine
Black Dog Institute
University of Melbourne

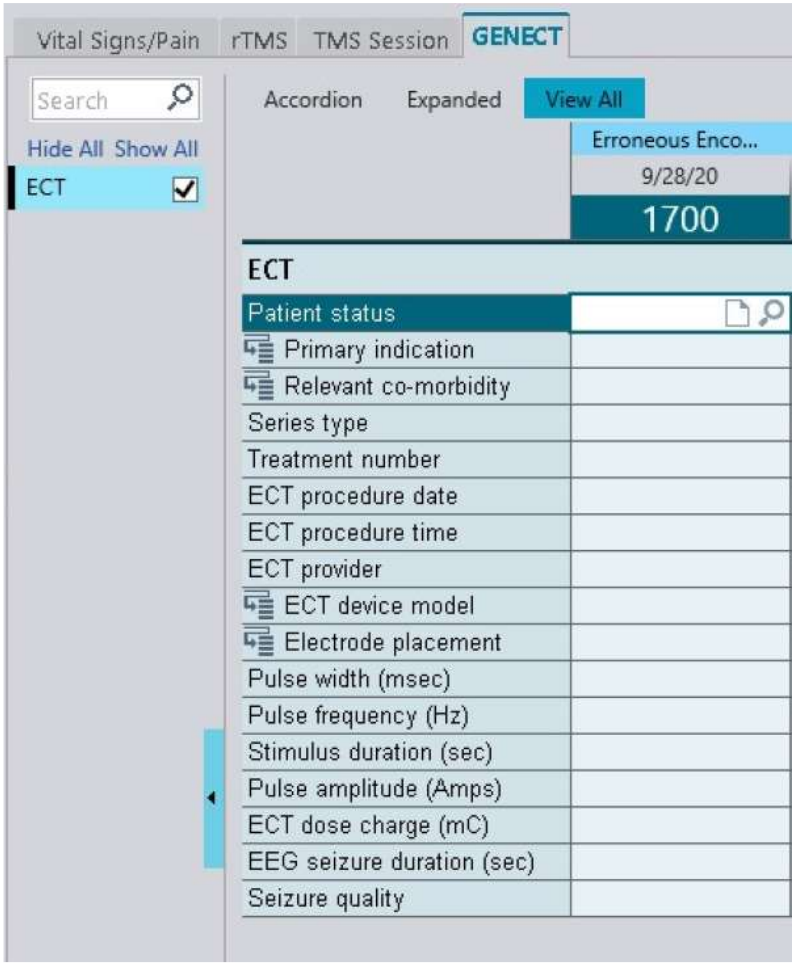
NIMH R01 – GenECT

SPECIFIC AIMS:

1. Ascertain, consent, phenotype, and biosample 15,000 patients receiving ECT for severe/treatment-resistant depression in the U.S.
2. Conduct genome-wide association study of MDD cases versus controls to examine the genetic architecture of severe/treatment-resistant depression
3. Conduct genome-wide association study of response to ECT in MDD cases with longitudinal outcome data
   - Over 1/3 of patients fail to achieve remission for acute treatment; and over 1/3 may experience relapse
   - ECT associated with cognitive impairments, that limit further use and focus of controversy

NNDC ECT – Harmonization

- Harmonize clinical documentation of ECT across NNDC centers – flowsheet template:



- Implement the Mood Outcomes Program in ECT centers to standardized outcome measures (PHQ9, GAD7, CSSRS)

NNDC – ECT/rTMS/Ketamine

- **NNDC ECT Harmonization**
  - Manuscript on ECT harmonization recommendations (in process)
  - GenECT R01 first of many grants that leverage the NNDC ECT Task Force and its harmonization work (future)
- **NNDC rTMS Harmonization**
  - Developed similar rTMS flowsheet template for harmonizing clinical documentation of rTMS across NNDC centers (done)
  - Pilot implementation of rTMS flowsheet at JHU/Sibley (in process)
- **NNDC Ketamine Harmonization**
  - Developed SmartForm for esketamine clinic that generates a procedure note and the required REMS forms for upload (done)
  - Harmonize of IN and IV Ketamine (future)
- **Multi-site studies across NNDC centers of fact-acting treatments for severe and/or treatment-resistant depression (future)**

Acknowledgements

NNDC

ECT Task Force
Irving Reti
Dan Maixner
Paresh Patel
William McDonald
Mustafa Husain
Richard Weiner
Holly Lisanby

rTMS Task Force
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