RDoC Distribution Study Descriptions

Contents

Study 70 – Consortium for Neuropsychiatric Phenomics

Summary

- **Grant Number:** 1UL1RR024911
- **PI:** Robert Builder, Ph.D. (rbilder@mednet.ucla.edu)
- **Study Design & Aims:**
    - The Consortium for Neuropsychiatric Phenomics (CNP) was one of 9 Interdisciplinary Research Consortia supported by the NIH Roadmap Initiative from 2007-2012. The CNP comprised 8 linked awards, including a Coordinating Center (UL1DE019580), five linked R01 awards (RL1MH083268, RL1MH083269, RL1DA024853, RL1MH083270, and RL1LM009833) and two center grant awards (PL1MH083271 and PL1NS062410).
    - The CNP was established on the principle that discovery of genetic mechanisms for complex mental disorders will ultimately demand integration of research on large numbers of phenotypes spanning multiple biological and behavioral scales, from genome to syndrome, and will require both novel informatics and data analytic strategies.
    - The CNP focused on two phenotype domains – memory/working memory and response inhibition – based on the facts that these neurocognitive domains have been examined across multiple levels of analysis and are relevant to multiple neuropsychiatric syndromes. To examine these domains the CNP collected interviews and rating scales, self-report measures, neurocognitive exams using both paper-pencil and computerized tests, and neuroimaging data comprising structural MRI (sMRI), high angular resolution diffusing imaging (HARDI), and functional MRI (fMRI) both at rest (rsfMRI) and during five different cognitive activation paradigms.
    - The CNP was committed to the perspective that most phenotypes should be considered dimensional until evidence of categorical structure was clear, and for this reason focused most on assessing phenotypes across a broad range of healthy people rather than specific groups representing individuals with neuropsychiatric syndromes. The CNP additionally did study smaller groups of people who had diagnoses of Schizophrenia, Bipolar Disorder, and Attention-Deficit/Hyperactivity Disorder (following DSM-IV), to determine where these individuals would fall within the healthy distributions.
    - There were two primary human studies: the LA2K study and the LA5C study. The LA2K study focused on recruitment, behavioral and cognitive phenotyping, and genotyping of healthy individuals. The LA5C study recruited patients with Schizophrenia, Bipolar Disorder, and ADHD for similar genotyping and behavioral and cognitive phenotyping, along with neuroimaging studies. Healthy people who participated in the LA2K study were also offered the opportunity to participate in the LA5C study to complete the additional neuroimaging procedures.

Acknowledgement

- Data and biomaterials for NIMH Study 70 were collected as part of the Consortium for Neuropsychiatric Phenomics (NIH Roadmap for Medical Research grants/Principal Investigators: UL1DE019580/Robert Bilder; RL1MH083268/Nelson Freimer; RL1MH083269/Tyrone Cannon; RL1DA024853/Edythe London; RL1MH083270/David Jentsch, RL1LM009833/D. Stott Parker; PL1MH083271/Robert Bilder; and PL1NS062410/Chris Evans). The project was completed at UCLA.

Publications

- 221 reported publications; See study-specific document "study70_publications.pdf"

Study 120 – RDoC Constructs: Neural Substrates, Heritability, and Relation to Psychopathology

Summary

- **Grant Number**: R01MH098098
- **PI:** David Zald, Ph.D. (david.zald@Vanderbilt.edu)
- **Study Design & Aims:**
  - The Tennessee Twin Study (TTS) Wave 2 was conducted by co-PIs David H. Zald, Ph.D. and Benjamin B. Lahey, Ph.D. at Vanderbilt University and the University of Chicago respectively. Additional co-investigators include Bennett Landman and Neil Woodward at Vanderbilt University, David Herda at NORC at the University of Chicago, and Paul Rathouz at the University of Wisconsin. The study was funded by the National Institute of Mental Health grant 5 R01 MH098098 RDoC Constructs: Neural Substrates, Heritability and Relation to Psychopathology.
  - The TTS-Wave 2 aimed to examine the relation between broad transdiagnostic dimensions of psychopathology and Research Domain Criteria (RDoC) functional constructs, and to identify the neural correlates of these constructs and dimensions. The first wave of the TTS included 3,990 representative child and adolescent twins who were assessed for psychopathology using the Child and Adolescent Psychopathology Scale. A subsample of participants was recruited for follow-up assessments as young adults. Twin pairs in which one of the subjects had evidence of internalizing or externalizing psychopathology in their youth were oversampled for recruitment in Wave 2. Wave 2 assessments included a dimensional assessment of psychopathology (externalizing, internalizing and general factors) based on the Young Adult-Diagnostics Interview Schedule for Children (YA-DISC), behavioral and self-report measures capturing RDoC constructs, fMRI of reward, aversive processing and response inhibition, structural T1 and diffusion weighted MRI and DNA genotyping. A total of 448 subjects completed scanning, while 499 completed the YA-DISC interview.

Acknowledgement

- Papers, book chapters, books, posters, oral presentations, and all other printed and digital presentations of results derived from TTS-Wave 2 data should contain the following wording in the acknowledgments section: "Data were provided by the Tennessee Twin Study (Principal Investigators: David Zald and Benjamin Lahey), which was funded by the National Institute of Mental Health (5 R01 MH098098)."

Publications

- None reported

Study 142 – Psychosis and Affective Research Domains and Intermediate Phenotypes (PARDIP)

Summary

- **Grant Number:** R01MH096913-01A1
- **PIs:**
  - Godfrey Pearlson, M.D. (Godfrey.Pearlson@HHChealth.org)
  - Matcheri Keshavan, M.D. (mkeshava@bidmc.harvard.edu)
  - Carol Tamminga, M.D. (carol.tamminga@utsouthwestern.edu)
- **Study Design & Aims:**
  - Psychotic symptoms are present in a significant subset of individuals with Bipolar Disorder (BD) and carry devastating personal and clinical implications. Most biomedical research on BD has ignored the variable presentation of psychosis possibly overlooking biologically significant heterogeneity in BD; such heterogeneity may cause inconsistencies in the literature by treating BD as a homogenous category 7,18. The expression of psychosis in some BD patients (BD-P) and absence in others (BD-NP) may indicate divergent disease processes of critical nosological and clinical relevance. PARDIP leverages a large sample of BD, a comprehensive battery, and sophisticated analytic tools to establish whether BD-P and BD-NP represent a difference in degree or a difference in kind. Long-term goals: This work will critically impact how BD is classified and studied, provide robust targets for effective future etiological studies, and clarify the utility of available biomarkers o major psychiatric disturbance. PARDIP represents a step toward mechanistically based classification of psychiatric disorders. Specific Aims: PARDIP will (i) identify the patterns of bo-cognitive disruptions which mark psychosis (BD-P`BD-NP) or mood instability in general (BD`healthy comparisons), (ii) explore how these biomarkers relate to one another and to other dimensions of psychopathology present in BD, and (iii) utilize latent class and cluster analyses of the multivariate dataset to verify taxonicity within BD with regard to psychosis and uncover latent psychiatric subgroups of interest for future genotyping and etiological research. Methods: The three-year PARDIP project will recruit 135 psychotic BD, 135 non-psychotic BD, and 135 psychiatrically healthy comparison subjects (all new recruits), administering a comprehensive battery focused on the psychosis and mania

domains of psychopathology. We will obtain measures of neurophysiology, (smooth pursuit eye movements, antisaccades, auditory ERPs), cognition (cognitive battery, response inhibition, spatial working memory), neuroanatomy (structural magnetic resonance imaging [MRI]), emotional processing (ERPs to emotional pictures), intrinsic brain state (resting functional MRI connectivity), and circadian function (Actigraphy). We will compare biomarkers between BD-P, BD-NP, and H groups to determine which track with psychosis and which track with affective disturbance. We will identify common sources of variance among measures with joint-ICA and PCA approaches, and examine how biomarkers and biomarker composites relate to other aspects of clinical heterogeneity. Taxometric procedures (MAXCOV- HITMAX and its multivariate extension MAXEIG-HITMAX and k-means clustering) will be carried out with the multivariate dataset to empirically identify distinct subgroups of subjects. PARDIP will be conducted by 4 experienced research groups (across 3 collection sites) with a long history of close and productive collaboration.

Acknowledgement

- Data and biomaterials for NIMH Study 142 were collected as part of Psychosis and Affective Research Domains and Intermediate Phenotypes (PARDIP), supported by NIMH grant R01MH096913-01A1. The principal investigators are Dr. Godfrey Pearlson (Yale University), Dr. Carol Tamminga (University of Texas Southwestern), and Dr. Matcheri Keshavan (Harvard University). The ClinicalTrials.gov identifier is NCT02218853.

Publications

- None reported

Study 147 – Longitudinal Family/Molecular Genetic Study to Validate Research Domain Criteria

Summary

- **Grant Number:** 1R01MH101519-01A1
- **PIs:**
  - Stephen Faraone, Ph.D. (faraones@upstate.edu)
  - Stephen Glatt, Ph.D. (stephen.glatt@psychgenelab.com)
- **Study Design & Aims:**
  - The goal of this study, funded under the NIMH's Research Domain Criteria (RDoC) initiative, was to find more efficient and informative ways to characterize psychiatric symptoms and associated behaviors in children. In this case-control family/molecular genetic study, we used self-report questionnaires and computer-based tests to profile reward behavior, its mediators, and its associated dimensions of psychopathology in children (ages 6-12), their siblings, and their parents. We recruited approximately equal numbers of "typically developing" and "psychiatrically affected" children and their family members to represent a broad range of psychopathology and reward behaviors. In addition

to clinical and experimental data, we also generated genotypes by genome-wide association scanning of peripheral blood or saliva samples from all subjects, and RNA-abundance data from RNA-sequencing of peripheral blood samples of a subset of 96 participants. The acquired data allow for an evaluation of the construct, convergent, divergent, and genetic validation of the RDoC "Positive Valence Systems (reward)" domain, or possible revision to that framework as indicated.

Acknowledgement

- Data and biomaterials for NIMH Study 147 were collected as part of the Longitudinal Family/Molecular Genetic Study to Validate Research Domain Criteria, supported by NIMH grants: R01 MH 101519; R01 MH 101519-01A1S1; R01 MH 101519-02S1; R01 MH 101519-03S1. The principal investigators are Stephen Glatt and Stephen Faraone, Norton College of Medicine at SUNY Upstate Medical University. The ClinicalTrials.gov identifier is NCT02415647.

Publications

- Hess JL, Nguyen NH, Suben J, Meath RM, Albert AB, Van Orman S, Anders KM, Forken PJ, Roe CA, Schulze TG, Faraone SV, Glatt SJ. Gene co-expression networks in peripheral blood capture dimensional measures of emotional and behavioral problems from the Child Behavior Checklist (CBCL). Transl Psychiatry. 2020 Sep 23;10(1):328. doi: 10.1038/s41398-020-01007-w. PMID: 32968041; PMCID: PMC7511314.
- Albert AB, Wagner KE, Van Orman SE, Anders KM, Forken PJ, Blatt SD, Fremont WP, Faraone SV, Glatt SJ. Initial Responsiveness to Reward Attainment and Psychopathology in Children and Adults: An RDoC Study. Psychiatry Res. 2020 Jul;289:113021. doi: 10.1016/j.psychres.2020.113021. Epub 2020 Apr 18. PMID: 32447091; PMCID: PMC7572668.
- Nguyen NH, Albert AB, Van Orman S, Forken P, Blatt SD, Fremont WP, Faraone SV, Glatt SJ. Effort valuation and psychopathology in children and adults. Psychol Med. 2019 Dec;49(16):2801-2807. doi: 10.1017/S0033291718003884. Epub 2019 Jan 14. PMID: 30636648.
- Hess JL, Kawaguchi DM, Wagner KE, Faraone SV, Glatt SJ. The influence of genes on "positive valence systems" constructs: A systematic review. Am J Med Genet B Neuropsychiatr Genet. 2016 Jan;171B(1):92-110. doi: 10.1002/ajmg.b.32382. Epub 2015 Sep 14. PMID: 26365619.

Study 154 – FAST MAS KOR Phase 2a

Summary

- **Grant Number:** HHSN2712011000061

- **PIs:**
  - Gerard Sanacora, M.D., Ph.D. (gerard.sanacora@yale.edu)
  - John Nurnberger, M.D., Ph.D (jnurnber@iupui.edu)
  - Sarah Lisanby, M.D. (lisan001@win.duke.edu)

- **Study Design & Aims:**
  - The available treatment for patients with mood and anxiety disorders have significant limitations. There is a need to develop new treatments for people with these disorders. Many research studies carried out in animals and a few preliminary studies carried out in humans suggest that medications which block kappa opioid receptors (KOR) have potential for being effective new treatments for patients with mood and anxiety spectrum disorders. These medications have shown particular promise for improving one important type of difficulty experienced by many patients who suffer from mood and anxiety spectrum disorders referred to as anhedonia, which is an impairment in reward-related function.
  - This study tested the hypothesis that KOR antagonism is a promising means of improving anhedonia in patients with mood and anxiety spectrum disorders. We tested this hypothesis by evaluating whether we could establish Proof of Concept (POC) that a relatively selective KOR antagonist, JNJ-67953964 (formerly known as LY2456302 and CERC-501), engages neural circuits involved in mediating reward-related function in patients with mood and anxiety spectrum disorders with anhedonia. We attempted to establish POC in this study in order to determine whether there is a sufficient basis for pursuing future work evaluating whether KOR antagonism has therapeutic effects on clinical and behavioral measures of reward-related functioning.
  - The study was a 8-week, double-blind, placebo-controlled trial where subjects were randomized to JNJ-67953964 and placebo in a 1:1 ratio. The study was carried out in 6 academic centers. Key entry criteria included anhedonia (score of at least 20 on the Snaith Hamilton Pleasure Scale [SHAPS]) and the presence of a DSM-IV-TR mood or anxiety spectrum disorder based on the MINI Structured Diagnostic Interview. The primary outcome measure for the study was level of activation in the ventral striatum during anticipation of reward in the Monetary Incentive Delay Task. Key secondary measures were the SHAPS and a behavioral test, the Probabilistic Reward Task.

Acknowledgement

- Data and biomaterials for NIMH Study 154 were collected as part of FAST MAS KOR Phase 2a, supported by NIMH grant HHSN2712011000061. The principal investigators are Dr. Gerard Sanacora (Yale University), Dr. John Nurnberger (Northwestern University), and Dr. Sarah Lisanby (Duke University).

Publications

- None reported

Study 171 – Genetic Contributions of Negative Valence Systems to Internalizing Pathways

Summary

- **Grant Number:** R01MH101518

- **PI:** Roxann Roberson-Nay, Ph.D. (roxann.robersonnay@vcuhealth.org)
- **Study Design & Aims:**
    - Internalizing disorders (ID) represent the largest domain of emotional disturbances that affect the general population. In recent years, significant effort has been put into examining and defining basic dimensions of functioning (e.g., neural or physiologic) that cut across internalizing disorders as traditionally defined by current nosology. Thus, the goal of the current study is to examine relationships between measures constructed to probe negative valence system (NVS) expression (e.g., fear, anhedonia) in a genetically informative adolescent twin sample. This design allows for the examination of the interplay between genetic and environmental factors as a way of elucidating causal mechanisms involved in the NVS and the role the NVS plays in pathways to internalizing symptoms and syndromes. Within this design we will administer an informative suite of well-validated dimensional measures that tap into the NVS, focusing on five related constructs including anxiety, fear, stress, sadness/anhedonia, and irritability. The influence of genes on psychopathology changes such that different developmental stages are associated with a unique pattern of risk factors representing a dynamic interplay between development, genes, and environment. For this reason, we will target a critical developmental period, focusing on the transition that begins during the late teen years and proceeds into young adulthood. This transition will involve moving away from home/family and established peer networks for approximately half of the general population. For these individuals, a number of significant environmental changes will occur that will impact their emotional functioning and trajectory of internalizing symptom expression. Thus, measuring NVS before this unique developmental period from a genetically informed perspective is ideal for determining the shared and specific contributions of genes and environment to NVS expression and its influence on ID development.

Acknowledgement

- Data and biomaterials for NIMH Study 171 were collected as part of Genetic Contributions of Negative Valence Systems to Internalizing Pathways, supported by NIMH grant R01MH101518. The principal investigator is Roxann Roberson-Nay, Virginia Commonwealth University.

Publications

- Sawyers C, Sheerin C, Eastman M, Burchett J, Howell P, Neigh G, Amstadter AB, Hettema J, Roberson-Nay R. Genetic and environmental influences on cortisol reactivity to a psychosocial stressor in adolescents and young adults. Psychoneuroendocrinology. 2021 May;127:105195. doi: 10.1016/j.psyneuen.2021.105195. Epub 2021 Mar 8. PMID: 33714784; PMCID: PMC8186845.
- Qi J, Rappaport LM, Cecilione J, Hettema JM, Roberson-Nay R. Differential Associations of Distress Tolerance and Anxiety Sensitivity With Adolescent Internalizing Psychopathology. J Clin Child Adolesc Psychol. 2021 Jan-Feb;50(1):97-

104. doi: 10.1080/15374416.2019.1602838. Epub 2019 May 6. PMID: 31059291; PMCID: PMC6832780.

- Roberson-Nay R, Lapato DM, Wolen AR, Lancaster EE, Webb BT, Verhulst B, Hettema JM, York TP. An epigenome-wide association study of early-onset major depression in monozygotic twins. Transl Psychiatry. 2020 Aug 25;10(1):301. doi: 10.1038/s41398-020-00984-2. PMID: 32843619; PMCID: PMC7447798.
- Rappaport LM, Carney DM, Brotman MA, Leibenluft E, Pine DS, Roberson-Nay R, Hettema JM. A Population-Based Twin Study of Childhood Irritability and Internalizing Syndromes. J Clin Child Adolesc Psychol. 2020 Jul-Aug;49(4):524-534. doi: 10.1080/15374416.2018.1514612. Epub 2018 Oct 30. PMID: 30376640; PMCID: PMC6491264.
- Moore AA, Rappaport LM, Blair RJ, Pine DS, Leibenluft E, Brotman MA, Hettema JM, Roberson-Nay R. Genetic underpinnings of callous-unemotional traits and emotion recognition in children, adolescents, and emerging adults. J Child Psychol Psychiatry. 2019 Jun;60(6):638-645. doi: 10.1111/jcpp.13018. Epub 2019 Feb 18. PMID: 30779145; PMCID: PMC6520193.
- Eastman ML, Moore AA, Cecilione J, Hettema JM, Roberson-Nay R. Confirmatory factor structure and psychometric properties of the Multidimensional Peer Victimization Scale. J Psychopathol Behav Assess. 2018 Dec;40(4):725-735. doi: 10.1007/s10862-018-9678-2. Epub 2018 Apr 14. PMID: 30416254; PMCID: PMC6221199.
- Eastman ML, Verhulst B, Rappaport LM, Dirks M, Sawyers C, Pine DS, Leibenluft E, Brotman MA, Hettema JM, Roberson-Nay R. Age-Related Differences in the Structure of Genetic and Environmental Contributions to Types of Peer Victimization. Behav Genet. 2018 Nov;48(6):421-431. doi: 10.1007/s10519-018-9923-1. Epub 2018 Sep 21. PMID: 30242573; PMCID: PMC6233884.
- Cecilione JL, Rappaport LM, Hahn SE, Anderson AE, Hazlett LE, Burchett JR, Moore AA, Savage JE, Hettema JM, Roberson-Nay R. Genetic and Environmental Contributions of Negative Valence Systems to Internalizing Pathways. Twin Res Hum Genet. 2018 Feb;21(1):12-23. doi: 10.1017/thg.2017.72. PMID: 29369039; PMCID: PMC5884079.
- Cecilione JL, Rappaport LM, Verhulst B, Carney DM, Blair RJR, Brotman MA, Leibenluft E, Pine DS, Roberson-Nay R, Hettema JM. Test-retest reliability of the facial expression labeling task. Psychol Assess. 2017 Dec;29(12):1537-1542. doi: 10.1037/pas0000439. Epub 2017 Feb 23. PMID: 28230406; PMCID: PMC5568997.
- Rappaport LM, Sheerin C, Savage JE, Hettema JM, Roberson-Nay R. Clinical characteristics of latent classes of CO2 hypersensitivity in adolescents and young adults. Behav Res Ther. 2017 Jun;93:95-103. doi: 10.1016/j.brat.2017.03.015. Epub 2017 Mar 30. PMID: 28395158; PMCID: PMC5502686.
- Moore AA, Carney D, Moroney E, Machlin L, Towbin KE, Brotman MA, Pine DS, Leibenluft E, Roberson-Nay R, Hettema JM. The Inventory of Callous-Unemotional Traits (ICU) in Children: Reliability and Heritability. Behav Genet. 2017 Mar;47(2):141-151. doi: 10.1007/s10519-016-9831-1. Epub 2016 Dec 1. PMID: 27909830; PMCID: PMC5305430.

- Savage JE, Sawyers C, Roberson-Nay R, Hettema JM. The genetics of anxiety-related negative valence system traits. Am J Med Genet B Neuropsychiatr Genet. 2017 Mar;174(2):156-177. doi: 10.1002/ajmg.b.32459. Epub 2016 May 19. PMID: 27196537; PMCID: PMC5349709.