Background: In ongoing studies, using multimodal neuroimaging, we are examining prefrontal cortical-striatal-amygdala emotional regulation circuitry in infants, and youth at familial risk for mood disorders, to identify neural predictors of future risk for these disorders from infancy to adolescence.
Methods: Using tractography, quantitative anisotropy (QA), laboratory tasks and penalized regression, we measured in 3-month infants predictive relationships among white matter structural integrity in the cingulum, uncinate fasciculus and forceps minor and 9s-month emotional regulation capacity. Using penalized and Poisson regression, we examined associations among prefrontal-cortical-striatal-amygdala emotional regulation circuitry activity during a 2-back-working memory-emotional face distracter task in familial at-risk 9-17-year-olds and mood and anxiety changes over 4 years post scan.
Results: To date, in n=13, 3-month (65-126 days;3 female) infants, QA in a priori tracts, gender and maternal postnatal depression predicted 9-month (253-331 days) negative emotionality. Lower cingulum QA especially (non-zero coefficient:-0.097;beta=0.532;p=0.004) was associated with greater 9-month negative emotionality. Infant gender and maternal postnatal depression accounted for 59.1%, and neural measures 26.2%, of 9-month negative emotionality variance. In n=15(n=6 females)-parent with Bipolar Disorder and n=20(n=11 females)-parent with another psychiatric disorder at-risk youth, greater left dorsolateral prefrontal cortical activity to 2-back-happy-face-distracters vs. baseline (0-back-no-face-distracters) predicted greater depression severity 4 years(+/- I year) post scan(pseudo R2=0.28;p<0.001), accounting for baseline depression.
Conclusions: Lower infant prefrontal-cortical-amygdala circuitry white matter structural integrity, and greater prefrontal cortical activity in this circuitry in at-risk youth, are associated, respectively, with greater negative emotional reactivity later in infancy and greater depression in adolescence/early adulthood, and are objective markers of future mood disorder vulnerability in youth.
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Keywords: Infancy, At-Risk Youth, Brain Imaging, fMRI, Diffusion Imaging, Emotional Regulation

Variable Neurobehavioral Outcomes in Youth at Familial Risk for Mood Disorders

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Background: Youth at familial risk for mood disorders have aberrant emotion regulation networks. However, the formation of these networks that lead to variability in resilient or emergent mood symptom outcomes is poorly understood.
Methods: Rest and emotion task-based fMRI data was compared among healthy offspring of parents with bipolar disorder (BD-risk, n=43), parents with major depressive disorder (MDD-risk, n=46), and healthy controls (HCLs, n=50). Logistic regression was used to examine whether connectivity predicted psychopathology. Baseline connectivity among 24 HCLs, 23 high-risk who developed psychopathology (CVT), and 27 high-risk who remained resilient (RES) at 3-year follow-up were also compared.
Results: Intrinsic connectivity between amygdala, striatum and medial frontal cortex distinguished BD-Risk from MDD-Risk and HCLs ($p<0.001$ voxel-level and $p<0.05$ cluster-level FDR-correction) and predicted mood/anxiety disorders at follow-up (p=0.026, ß=-11.01). BD-risk youth had reduced putamen activation and decreased left putamen connectivity with the left anterior cingulate cortex while processing positive emotions compared to MDD-risk and HCLs. RES youth had reduced activation in the right supramarginal gyrus during happy versus calm conditions, and in the right precuneus and inferior frontal gyrus during fear versus calm conditions compared to CVTs. In RES youth, stronger baseline IPL-precuneus connectivity correlated with more prosocial behaviors (p=.004) and improved global functioning (p=.005) at follow-up.
Conclusions: Striatolimbic intrinsic connectivity may be an early and specific predictor of future mood/anxiety disorders in high-risk youth. In contrast, inferior parietal, caudate, and precuneus activation and connectivity during emotion processing may represent resilience markers. These regions may be useful targets for novel preventive approaches for at-risk youth.
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Keywords: Resilience, Functional Imaging, Risk For Mood Disorder, Longitudinal Study

SYMPOSIUM
Using Electronic Health Records for Large Scale Genomic and Environmental Psychiatric Outcomes Research
Chair: J. John Mann
Co-Chair: Ardesheer Talati

Using Electronic Health Records and Machine Learning to Predict Incident Psychiatric Hospitalization

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Background: Addressing mental health conditions in the context of hospitalization prediction provides novel opportunities to mitigate admission rates, lower psychiatric healthcare costs, optimize healthcare delivery models and inspire a fresh impetus in improving outpatient services tasked with managing patients with mental health needs.
Methods: This study applied a retrospective case-control study design using electronic health record (EHR) data on patients across New York City who were aged 18 years or older between 2010-2017, with histories of depression diagnosis or

antidepressant therapy (n=470,242); and those with no history of antidepressant therapy or diagnoses of depression, bipolar disorder, schizophrenia, or psychosis (n=1,000,000). The outcome was defined as 1-year risk of incident psychiatric hospitalization. For each patient we collected >600 features including demographics, diagnoses, healthcare utilization, outpatient medications, and procedures, and developed multiple machine learning models to predict the risk of a psychiatric hospitalization.
Results: Our preliminary results indicate that the prediction performance in terms of Area Under the Receiver Operating Curve (ROC) is highest for XGBoost (0.77), followed by Random Forest (0.76), Logistic Regression (0.75) and Multi-Layer Perceptron (MLP; 0.73). Comparing across features, patient diagnoses and encounter information derived from the EHRs are more useful to the hospitalization risk prediction task, while the procedures are not very informative. Also, the deep learning model (MLP) did not achieve higher performance, contradicting our initial assumption.
Conclusions: This study demonstrates that compared to traditional machine learning algorithms, deep learning models do not significantly improve our ability to predict incident psychiatric hospitalizations using EHR data.
Keywords: Machine Learning, Psychiatric Hospitalization Prediction, Electronic Health Record (EHR)

Multiple Polygenic Risk Score Analysis Reveals Genetic Contributions to Psychiatric Traits in Research and Electronic Health Records Data

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Background: Recent studies demonstrate polygenic risk score (PRS) associations with psychiatric disorders in large research datasets. We investigated the contributions of multiple PRSs to sub-phenotypes of bipolar disorder (BD) in a research sample, and to psychiatric diagnoses from electronic health records (EHRs).
Methods: We tested the association of PRSs with BD sub-phenotypes including BD type, rapid cycling, psychosis, and suicidality in >800 BD cases from Mayo Clinic. We then tested the association of PRSs with EHR-derived diagnoses including BD, depression, and anxiety, as well as suicide attempt in ~10,000 participants from the Mount Sinai BioMe biobank. In each sample, we computed PRSs for psychiatric phenotypes and related traits, and tested the association of each PRS with each phenotype of interest, computing the improvement in Nagelkerke's R2 for each PRS, and for all PRSs combined.
Results: The BD data analysis replicated prior findings and revealed novel associations. For example, BD without rapid cycling was predicted primarily by BD-PRS (p=7.6E-09), while BD with rapid cycling was predicted by PRSs for several psychiatric disorders. Suicide attempts in BD cases were associated with neuroticism (p=0.0076) and major depressive disorder (MDD; p=0.027) PRSs. Analysis of EHR-derived phenotypes in BioMe revealed associations consistent with research-cohort findings (e.g. association with BD diagnosis with schizophrenia-PRS (p=1.3E-05), anxiety diagnosis with MDD (p=9.4E-04) and neuroticism (p=1.9E-03) PRSs, and suicide attempt with MDD-PRS (p=0.014)].
Conclusions: This study highlights the utility of PRSs in dissecting genetic differences between clinical subgroups and demonstrates that PRSs can predict EHR-derived psychiatric traits.
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Keywords: Electronic Health Record (EHR), Polygenic Risk Score, Bipolar Disorder, Biobank

Natural Language Processing of Clinical Notes in Biome Identifies Relationship Between Psychiatric Phenotype and Polygenic Risk Scores

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Background: Our group has found evidence that rare and common variants influence different symptom classes in psychotic illness, but these studies were limited by a lack of high-dimensional clinical data from the large case/control cohorts typically available for such efforts. Large biobank cohorts with genetic data tied to electronic medical records (EMR) present a unique opportunity to overcome this limitation through the application of natural-language processing (NLP) to clinician notes.
Methods: We define a set of symptoms for each of the 4 psychiatric clinical domains (psychotic, manic, depressive and cognitive) using terminology from standard rating scales in psychiatric research for psychosis (PANSS), mania (YMRS), depression (MADRS) and cognition (MOCA). The output of this analysis step is 4 individual-level PheRS. Polygenic risk scores for SCZ and rare variant burden are calculated for each individual. We assess the association between the the 4 PheRS variables (psychotic, manic, depressive, cognitive) and the 3 genetic risk metrics (PRS, CNV burden, rSNV burden).
Results: The PANSS and YMRS were selected as the starting point for identifying a comprehensive list of 118 psychotic phenomena for the psychosis PRS, which were then manually mapped to SNOMED-CT and filtered to result in a set of 34 high-confidence psychosis terms. Positive association was observed between PheRS and PRS.
Conclusions: In general, this preliminary analysis found that the CLiX NLP pipeline already established and supported by our institution is a powerful tool for creating high-dimensional, structured psychiatric clinical profiles from BioMe EHR notes.
Keywords: Genetics, Psychiatry, Psychosis

Adding Personal and Social Determinants of Health to Electronic Health Records

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