Full Abstracts for Poster Session

Wednesday, January 17, 2018

de Marneffe Building, 1st floor
Posters Displayed [9am-5pm]
- Staffed Poster Session 1 [1:00-1:50pm]
- Staffed Poster Session 2 [1:50-2:45pm]
Exhibitors [1:00-2:45pm]

Pierce Hall
Brief Communications [3:00-4:30pm]
Reception [4:30pm]
Title: Prevalence and Predictors of Anxiety Disorder Comorbidity in Affective and Non-Affective Psychotic Disorders

Key words: psychotic disorders, anxiety disorders, comorbidity, schizoaffective, bipolar

Background: Anxiety disorders are serious and common conditions. Although anxiety diagnoses are highly comorbid with mood disorders, their comorbidity with psychotic illnesses has not been widely established. Addressing anxiety disorders in psychotic illness has important clinical implications as anxiety may cause significant impairment. We previously found a high prevalence of anxiety disorders across psychotic disorders, with a significantly higher prevalence of anxiety in, especially panic disorder (PD), in schizoaffective disorder (SZA), compared to bipolar I disorder (BPI) and schizophrenia (SZ). In this study, we aimed to examine the prevalence and change in prevalence over time of anxiety disorders in a well-characterized sample of patients with first-episode and chronic affective and non-affective psychotic disorders. We also aimed to identify predictors of anxiety disorders across psychotic disorders.

Method: We used the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorder-IV-TR to examine rates of comorbid anxiety disorders in 1016 patients with bipolar I disorder (n=506), schizophrenia (n=260), and schizoaffective disorder (n=250). We included PD, agoraphobia without panic disorder (AWOPD), generalized anxiety disorder (GAD) and social phobia (SP) in our definition of “all anxiety disorders” (AAD). To inspect the changes in anxiety diagnosis trends over the years, we looked at the difference between the rates of anxiety diagnoses for participants pre-2012 (n=919) and post-2012 (n=97). Participants were also evaluated using the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS), and the Montgomery-Asperg Depression Rating Scale (MADRS).

Results: The rate of AAD was significantly higher in patients with SZA (26.8%) and BPI (19.6%), compared to SZ (13.5%) \( \chi^2(2) = 14.319, p=0.001 \). The rate of PD in SZA (20.0%) was significantly higher than BPI (9.3%), and SZ (8.5%) \( \chi^2(2) = 22.137, p<0.001 \). Additionally, GAD comorbidity was significantly higher in BPI (10.1%) and SZA (7.3%), compared to SZ (3.1%) \( \chi^2(2) = 11.884, p=0.003 \). We observed a significant increase in rates of anxiety comorbidity in our sample post-2012 (30.9%), compared to pre-2012 (18.6%) \( \chi^2(1) = 8.393, p=0.004 \). Patients with anxiety diagnoses were also significantly younger than patients without anxiety \( t=1.395, p=0.002 \). We will examine the association between anxiety disorders and clinical characteristics, including symptom severity, positive and negative symptoms, mood symptoms, and medication use across SZA, SZ and BPI.

Discussion: Our findings suggest that anxiety comorbidity is higher in affective psychotic disorders, including both SZA and BPI, compared to non-affective psychoses. We also found that since 2012, the rates of anxiety diagnoses have increased. A better understanding of anxiety in psychotic disorders has implications for clinical practice to improve identification and treatment of anxiety symptoms.

Topic areas:
Anxiety
Bipolar
Psychotic disorders
Schizophrenia
McLean Research Day 2018

Original Research - Clinical

Poster # 2
Time: 1:50-2:45pm

Presenting Author: Alexandra Hernandez-Vallant, Clinical Research Assistant; BS


Title: Validating a nine-item version of the Obsessive Beliefs Questionnaire (OBQ)

Key words: Obsessive-Compulsive Disorder, Intensive/Residential Treatment, Cognitive-Behavioral Therapy

Background: Changes in beliefs during cognitive-behavioral therapy (CBT) for obsessive-compulsive disorder (OCD) appear to be a critical aspect of recovery. Accordingly, authors often recommend the use of the 44-item version of the Obsessive Beliefs Questionnaire (OBQ) at several time points during treatment to monitor progress. However, for many individuals with OCD, completing multiple lengthy questionnaires presents a challenge which suggests a need for brief assessment methods. The current study aimed to develop and validate an abbreviated, nine-item version of the OBQ (OBQ-9) in a sample of individuals with OCD. We hypothesized that the original factor structure of the 44-item version of the OBQ (OCCWG, 2005) would be replicated: 1) responsibility and threat overestimation; 2) perfectionism and intolerance for uncertainty; and 3) importance of and control over thoughts.

Method: The sample consisted of 311 participants seeking intensive/residential treatment (IRT) for OCD. Participants completed the Yale-Brown Obsessive Compulsive Scale-Self Report (Y-BOCS-SR), the Dimensional Obsessive-Compulsive Scale (DOCS), the Obsessive Beliefs Questionnaire-44 (OBQ-44), the Hamilton Depression Scale (HAMD-6), and the Obsessive Beliefs Questionnaire-9 (OBQ-9)—the measure being validated in this study. To develop the OBQ-9, the three items with the highest factor loadings from each of the OBQ-44 subscale were included. Participants completed measures weekly, at admission, and discharge.

Results: An exploratory factor analysis utilizing Principle Axis Factoring with a Promax rotation revealed a three-factor solution accounting for 62% of the variance. These results replicate the factor structure from the OBQ-44 validation. Further, the OBQ-9 demonstrated good internal consistency, $\alpha = .85$, and test-retest reliability, $r(255) = .86$, $p < .001$. OBQ-9 scores decreased significantly from week 1 to week 6, $t(143) = 6.19$, $p < .001$.

Conclusion: The factor structure and psychometric properties of the OBQ-9 are consistent with a previous validation of the measure (i.e., OBQ-44; OCCWG, 2005). It was found to be a valid and reliable measure, meeting the need for brief assessments in clinical settings. As predicted, OBQ-9 total and subscale scores decreased significantly after six weeks of IRT, providing further support for the clinical utility of the tool and for its capacity to monitor ongoing changes in dysfunctional beliefs.

Topic areas:
OCD
Feasibility and acceptability of a smart-phone self-monitoring intervention for patients after discharge from a partial hospital program

Background: Patients are at high risk for re-hospitalization and suicide during the 30-day period following acute psychiatric treatment (Vigod et al., 2013). Currently, there are not many interventions offered to individuals during the period of transition from hospital care to outpatient treatment, and the need for a scalable intervention is urgent. We tested the feasibility and acceptability of a pilot smart-phone intervention that used Ecological Momentary Intervention to prompt participants to respond to daily self-monitoring questions about symptoms and use of CBT and DBT skills during the two weeks following discharge from a partial hospitalization program.

Methods: Adult patients attending a CBT and DBT skills-based partial hospital were randomized into either the smart-phone intervention group that included questions about the use of CBT and DBT-based skills, or a control symptom tracking only condition (both delivered via MetricWire). Participants were prompted to complete self-monitoring questions at five semi-random times each day for two weeks beginning the day after discharge.

Results: For purposes of examining feasibility and acceptability, the intervention and symptom tracking only conditions were combined for analyses. Of the 134 patients who were invited to participate in the study, 116 (87%) enrolled. 84 participants (72%) completed at least 70% of the daily symptom surveys, and 75% completed the final two-week follow-up assessment. Using 5-point scales, participants reported that the smart-phone app was “somewhat helpful” (M = 3.19, SD = .96), “very convenient” to use (M = 3.83, SD = .96), and that they were “very likely” to recommend this app to others (M = 4.00, SD = .91). No demographic variables predicted adherence to the survey prompts. Participants with more residual symptoms at discharge from the program completed more surveys during the intervention period (rs ranging from .18 to .22, ps ranging from .06 to .04).

Conclusion: This pilot post-acute intervention demonstrated excellent feasibility and acceptability. Furthermore, this intervention appears to be feasible and acceptable across gender, age, ethnoracial background, and student status. Future trials using a similar smart-phone intervention should lengthen the duration of the intervention, and test the effectiveness of the intervention at 3-months, 6-months, and 9-months post-discharge.

Topic areas:
Technology
**Title:** Exploring adherence to psychotropic medications compared to cardiovascular medications in patients with serious mental illness

Medication non-adherence is one of the biggest obstacles in treating patients with serious mental illness, with up to 74% of patients considered non-adherent to psychotropic medications (Beebe, Smith, & Phillips, 2016). In addition, patients within this population face a higher risk of cardiac events and metabolic syndrome, whose management require prescription of non-psychotropic medications. (Druss, Bradford, Rosenheck, Radford, & Krumholz, 2001). While adherence to psychotropic medication and factors influencing adherence to these medications have been studied, there is little information about adherence to non-psychotropic medications within the population. FITNESS [Fixed Dose Intervention Trial of New England: Enhancing Survival in SMI Patients] is an NIH-funded clinical trial to improve the risk of cardiac events that patients in this population face (NCT02188121). The present study uses baseline data to compare self-report of medication adherence to psychotropic medication and cholesterol and blood pressure medications. Participants enrolled in this study are taking a second-generation antipsychotic medication, and are receiving care at one of four study sites: McLean Hospital, Massachusetts General Hospital Bipolar Clinic, Massachusetts Mental Health Center, and the Michael J. Gill Clinic. At the baseline visit, participants complete the applicable VOILS medication adherence surveys customized based on the medications they are currently taking: VOILS Mental Health Medication, VOILS Antihypertensive Medication, and VOILS Cholesterol Medication. Of the 152 participants, 29 were on a cardiac medication (an antihypertensive or cholesterol-lowering agent). We found higher self-reported adherence to cardiac medication, 89.66% (n = 29), than to psychotropic medications 71.71% (n = 152). Further, psychotropic medication adherence was higher among the 29 participants who were taking cardiac medications 79.31%, compared to those who were not, 70.4% (n = 125) although still not at the adherence level for cardiac medications. These data align with published studies on non-psychotropic medication adherence within this population, which also found a higher adherence to non-psychotropic medication (Beebe, Smith, & Phillips, 2016; Pratt, Mueser, Driscoll, Wolfe, & Bartels 2006). These published studies have very small sample sizes and measure adherence using different tools. The final dataset from this clinical trial will measure adherence using multiple instruments and will have a larger sample size. It should therefore provide a better picture of psychotropic versus non-psychotropic medication adherence among patients with serious mental illness.

**Key words:** Psychosis, Medication, Adherence, Cardiovascular Risk, Antipsychotic
Title: Mindfulness Training for Substance Use Clinical Staff

Key words: Mindfulness, Burnout, Substance Use Disorders

Introduction: Mindfulness Based Relapse Prevention (MBRP) is an evidence-based, manualized intervention for substance use disorder that has been under-utilized primarily due to dissemination barriers (1). Furthermore, substance use treatment can be challenging for clinicians, and is associated with significant burnout. Mindfulness interventions have been useful in reducing clinician burnout (2). This study aimed to test the feasibility and acceptability of training substance use disorder clinicians in individual mindfulness based practice to reduce burnout and equip them to teach mindfulness more effectively to patients.

Methods: A mindfulness training seminar for interdisciplinary clinical staff was held at three residential substance use treatment facilities. The training included 5 components personal mindfulness practice, reviewing clinical evidence for mindfulness interventions, reviewing scientific research on the neurophysiological mechanisms of mindfulness, an introduction to Eastern theory of meditation, and training to improve implementation of mindfulness in clinical settings. Training was delivered over four hour-long sessions. Pre and post seminar knowledge assessments were performed. Pre seminar preferences and experience level were assessed. CSQ-8s were administered after the seminar to assess satisfaction.

Results (Data Collection Ongoing): A total of 42 clinical staff participated across three residential addiction treatment facilities, 34 completed pre-seminar surveys, while 26 completed post-seminar surveys. Participants answered 60% (n=34) of pre-seminar knowledge questions correctly. Participants rated learning a personal meditation practice and being able to teach meditation in clinical settings as the most important goals of the seminar (3.6/4 point scale). Learning neurophysiology mechanisms and Eastern theory were deemed the least important. 64% of participants had taught mindfulness to patients before. Most clinicians had learned mindfulness through reading and power-point based lectures (61%). Few participants (8%) had formal training in meditation practice. Most participants (88%) felt unsatisfied with their training in mindfulness, and most (91%) felt inadequately prepared to use it with patients. Participants answered 72% of the post-seminar knowledge questions correctly. Post seminar, 82% (n=26) of participants felt "comfortable" or "very comfortable" teaching mindfulness in a clinical setting. 92% participants were "very satisfied" with the training. 98% of participants would "definitely" repeat the training or recommend the training to a colleague. 96% of participants were able to adopt a more mindful state "sometimes" or "most of the time" after the training.

Discussion: Mindfulness practice is becoming an increasingly important part of substance use treatment. This study contributes to the evidence for a feasible and acceptable training module that confers demonstrated improvement in fund of knowledge and confidence in practice of mindfulness as applied to relapse prevention strategy. Replication of these results would suggest an effective method for enhancing dissemination of mindfulness practice as applied to relapse prevention.

Topic areas:

Addiction
Quality/Outcomes
**Presenting Author:** Amy Higgins, Student Visitor

**Co-Authors:** Sophie Brickman, Caitlin Monaghan, Mei-Hua Hall

**Title:** P50 Event Related Brain Potential, Smoking, and Clinical Features in Patients with First Episode and Chronic Psychosis

**Key words:** Psychosis, Sensory gating, Event related potential, Community functioning

**Introduction:** The P50 event related brain potential (ERP), a positive wave occurring 50 ms in response to identical paired clicks, is used to measure sensory gating: the brain’s ability to filter out redundant or unnecessary information. A deficiency in P50 inhibition has been identified as a possible biomarker of psychosis (Hall et al 2007, 2008). Studies have examined the associations between P50 inhibition deficit and clinical features, but the results have been inconsistent. In addition, evidence suggests that nicotine modulates sensory gating and that deficit of P50 inhibition is linked to the alpha-7-nicotinic receptor gene (Freedman et al., 2003). Due to the relationship between sensory gating and the nicotinic receptor gene, there is a particular interest in examining the effects of smoking on P50 inhibition. The present study examined (1) sensory gating deficit in first episode of psychosis (FEP) and chronic psychosis patients compared with controls, (2) the relationships between P50 ERP response, smoking, medication, clinical symptom severity, and (3) the relationship between P50 ERP response and real-life community functioning.

**Methods:** FEP patients (n=30), chronic patients (n=112), and controls (n=133) completed a 160 paired-click stimuli (5-ms duration; 2-ms rise/fall period; 500-ms interclick interval; 10-s intertrial interval) presented in 4 blocks (40 paired-click stimuli/block). Each block was separated by a 1-minute break. The average Cz electrode p50 ratio was used to assess sensory gating ([stimulus 2 amplitude/stimulus 1 amplitude]x100). Lower ratios indicated better sensory gating. To assess functioning, patients completed the Multnomah Community Ability Scale (MCAS). To assess symptom severity, patients completed the Positive and Negative Syndrome Scale (PANSS). Data analysis included ANOVAs and Pearson partial correlations to evaluate group differences and covariates (age and sex).

**Results:** Controls had significantly lower P50 ratios than both FEP patients (p=0.002) and chronic patients (p<0.001). Patients did not differ from each other. Lifetime smoking status was significantly correlated to increased P50 ratio (partial correlation=0.25, p=0.0003). The PANSS positive subscale had a significant effect on P50 ratio (correlation=−0.28 p=0.02), specifically in those diagnosed with bipolar disorder (correlation=−0.37 and p=0.03).

**Discussion:** The preliminary results of this study suggest that sensory gating deficits are present at first episode, supporting this deficit as a biomarker for psychosis. Consistent with the literature, smoking has an effect on P50 ratio ERP. Specifically, lifetime smokers seem to have worse sensory gating responses. This result strengthens the molecular link of sensory gating deficits with the alpha-7-nicotinic receptor. Also, the PANSS positive subscale is associated with lower P50 ratios in patients with bipolar disorder. We are currently examining the underlying mechanism contributing to this relationship.

**Topic areas:**
- Bipolar
- Psychotic disorders
- Schizophrenia
Presenting Author: Anna Seraikas, Clinical Research Assistant II; Bachelor of Science, Psychology

Co-Authors: Julia Cohen-Gilbert, Emily Oot, Derek A. Hamilton, Carolyn Caine, Maya Rieselbach, Lisa D. Nickerson, Sion K. Harris, Marisa M. Silveri, Jennifer T. Sneider

Title: Depression and Anxiety Symptoms Influence Hippocampal Brain Activation during a Spatial Memory Task in Healthy Adolescents

Key words: Adolescence, Anxiety, Depression, Memory, fMRI

Adolescence is characterized by significant structural and functional remodeling, particularly in brain regions influenced by symptoms of anxiety and depression. Accordingly, the objective of this study was to evaluate relationships between hippocampal activation, non-clinical levels of depression and anxiety, and memory in healthy adolescents. Functional magnetic resonance imaging data were acquired at 3Tesla during performance of a virtual water maze task in 32 (15 female) healthy adolescents. Participants were alcohol and drug naïve and recruited locally to participate in a three-year longitudinal study of adolescent brain development. Adolescents completed the Multidimensional Anxiety Scale for Children (MASC) and the State-Trait Anxiety Inventory for Children (STAI-C) to assess clinical symptoms of anxiety, and the Center for Epidemiological Studies Depression Scale for Children (CES-DC) to assess clinical symptoms of depression. Data at baseline demonstrate significant hippocampal activation during memory retrieval relative to motor control. Notably, greater hippocampal activation was significantly associated with higher anxiety scores from the MASC (p=.001) and the STAI-state (p=.020), and higher depression scores on the CES-DC (p=.006). Elevated hippocampal activation in adolescents with higher symptoms of anxiety and depression may reflect later maturation and/or differential inefficiency of this brain region when performing a memory task, which will be examined in the longitudinal component of the study. Given that symptoms of depression and anxiety typically manifest during this pivotal stage of brain development, these findings may shed important light on normative interactions between brain regions involved in memory and mood regulation.

Topic areas:
Anxiety
Child/Adolescent
Depression
Imaging
Relations between Fear-Potentiated Startle and Parasympathetic Activation

Background: Fear-potentiated startle (FPS) paradigms have provided a translational and experimental way to examine the processes of fear learning and inhibition. Previous research suggests that respiratory sinus arrhythmia (RSA) is a self-regulatory process linked to these mechanisms. The current study examined relations between the startle response and RSA among two samples that underwent an FPS paradigm. It was hypothesized that lower RSA (i.e., worse regulation) would be related to greater FPS response.

Method: Participants in the primary sample were 54 undergraduate students (M age = 18.97) enrolled at a large Midwestern university. Data collection for the secondary sample is ongoing and currently consists of 9 women with trauma exposure and symptoms of posttraumatic stress and dissociation (i.e., a clinical sample; M age = 40.59). The FPS response was measured via electromyography of the right orbicularis oculi muscle. The startle probe (noise burst) was a 108-decibel 40-millisecond burst of noise with near instantaneous rise, delivered through headphones. The unconditioned stimulus (UCS) was a 250-millisecond airblast directed at the larynx. Conditioned stimuli (CS) consisted of different colored shapes presented on a computer monitor (CS+ was paired with the airblast, while the CS- was not). FPS was calculated by subtracting the startle response to the startle probe alone (baseline) from that of the CS+/CS-.

Results: Among the primary sample, FPS to the CS- was significantly negatively related to RSA (r = -.31, p = .03), suggesting that worse self-regulation was related to higher startle response. For the clinical sample, FPS to the CS+ was significantly negatively related to RSA (r = -.94, p = .02), mirroring the effect observed in the primary sample.

Conclusion: Overall, our results suggest that decreased parasympathetic nervous system activity (i.e., worse self-regulation) is related to higher fear responding in both undergraduate and clinical samples. This supports previous research implicating both sympathetic (FPS) and parasympathetic (RSA) contributions to fear learning, which has implications for fear-related disorders such as PTSD and phobias. Future research is needed to determine how these mechanisms affect treatment response, and if they change over the course of treatment.

Topic areas:
PTSD
Presenting Author: Arkadiy Maksimovskiy, Post-Doctoral Research Fellow

Co-Authors: Anna Seraikas, Emily Oot, Maya Rieselbach, Carolyn Caine, Julia Cohen-Gilbert, Jennifer T. Sneider, Sion K. Harris, Lisa Nickerson, Marisa M. Silveri.

Title: Susceptibility to Boredom Predicted by Cortical Grey Matter Volume in Adolescents with Familial Risk for Alcoholism

Key words: Adolescence, Alcohol, Grey Matter, Boredom, Risk

Developmental reductions in grey matter volume (GMV) coincident with adolescence have been associated with age-related maturation of behavioral and cognitive control. Adolescents with a family history of alcoholism (FH+) exhibit alterations in grey matter structure that may confer neurobiological vulnerability for future hazardous drinking. To date, only focal regions have been examined in FH studies of brain structure. Thus, this study examined the influence of FH status on whole-brain morphology, and associations with sensation seeking and impulsiveness, two traits known to predict hazardous drinking. Thirty-three adolescents, ages 13-14 years old, were stratified into FH+ (n=17) and FH- (n=15) groups. Participants underwent magnetic resonance imaging (MRI) at 3T and completed the Brief Sensation Seeking Scale (BSSS) and the Barratt Impulsiveness Scale (BIS). Volumetric brain data were extracted using the Freesurfer pipeline and all FH comparisons were analyzed using regression models that included age and sex as covariates, which accounted for head size. FH+ status was associated with larger total GMV (p<0.03), relative to the FH- group, which appeared to be driven by larger cortical (p<0.001) rather than subcortical GMV. Although behavioral measures did not differ significantly between groups, the boredom susceptibility component of sensation-seeking was negatively correlated with larger cortical GMV (p<0.003), only in the FH+ group. The relationship between higher GMV and susceptibility for boredom in the FH+ group suggests that FH status may moderate the trajectory of grey matter sculpting that is developmentally adaptive, which may provide one possible pathway to a predisposition for risk-taking behavior.

Topic areas: Addiction
Presenting Author: Arthur Grayson III, Thesis Student/Master’s Candidate

Co-Authors: Pantazopoulos, Harry Pilobello, Kanoelani T., Chelini, Gabriele, Berretta, Sabina

Title: Morphological Categorization of Novel Extracellular Matrix Structures in Schizophrenia and Bipolar Disorder

Key words: cluster, mediodorsal, schizophrenia, bipolar disorder

Previous investigations from our lab have found novel ECM structures called 6-sulfated chondroitin (CS-6) glial clusters, which consist of 6-sulfated structures associated with glial cells. Findings from these investigations indicate glial clusters may be involved in synaptic regulation (see Chelini et al.’s poster). We previously reported marked reductions of these clusters in the amygdalae of persons diagnosed with Schizophrenia (SZ) or Bipolar Disorder (BD) compared to healthy people. Taken together, glial clusters may be involved in the cognitive and emotional processing deficits suffered by people with psychotic disorders. An investigation currently underway in our lab seeks to extend findings in the amygdala to the mediodorsal thalamic nucleus (MDTN). The MDTN was chosen due to its numerous, heavily myelinated axonal connections to the prefrontal cortex, where imaging studies have shown marked reductions in functional activity and connectivity of diseased persons with SZ and BD. During the current investigation, high resolution microscopic imaging of the clusters stained by immunoreaction to CS56 (a CS-6 specific antibody) staining led us to find distinctions in morphology indicating heterogeneity not previously seen. We hypothesize that these morphological differences, if confirmed, may correspond to different maturation states of glial clusters, and be differentially affected in people with SZ or BD. Tissue blocks containing the whole thalamus from 15 control, 15 SZ, and 15 BD subjects were sliced into coronal, serial sections, and processed for immunohistochemistry for CS-6. Stereological sampling methods include using brightfield on a Zeiss light-microscope at 40X magnification for the purpose of morphological characterization. On the basis of the typical morphological characteristics observed, we developed a set of criteria including size, shape and staining intensity to divide these structures into distinct categories. Sizes ranged from 50µm – 220µm in diameter. Shapes including circular, oval, and amorphous were counted only if the structures could be circumscribed within the diameter of size criteria. CS-6-stained intensity of a cluster must have been at least twice the intensity of background tissue. The most prominent characteristic of a cluster was then used to classify its category: fibrous, diffuse, densely diffuse, and type-4. Fibrous-types must include at least three sharply stained tendrils, and may exhibit a hollow center with diffuse staining throughout. Diffuse-types must be diffusely stained, may or may not exhibit a hollow center, and may have at most two tendrils. Densely diffuse-types must be quadruple the intensity of background, and exhibit the same shape as normal fuzz. Type-4s must have minimum three densely stained patched of CS-6 labeling not connected by fibrous tendrils. Ongoing quantification will establish the distribution of each category in the human MDTN, and will allow us to test for potential differences in numbers of clusters in people with SZ or BD compared to controls. Further investigations in rodents will examine a temporal aspect of the cluster morphology. We may determine if categories are indicative of cluster development during behavioral learning and memory consolidation. This will allow us to compare morphological cluster categories to functional regulation of synaptic plasticity following fear learning.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia
Title: Deaths by Suicide and Other Causes among Borderline Patients and Axis II Comparison Subjects over 24 Years of Prospective Follow-up

Objective: This study has two aims. The first is to determine rates of mortality due to suicide and other causes of borderline patients and axis II comparison subjects over 24 years of partially completed prospective follow-up. A second aim is to describe the timing and cause of observed mortality and to characterize decedents based on initial diagnosis, recovery status (i.e., symptomatic remission and good psychosocial functioning), age, and sex.

Method: A total of 290 adult inpatients meeting rigorous criteria for BPD and 72 axis II comparison subjects (OPD) were recruited and assessed during inpatient admission at McLean Hospital. These participants were subsequently followed and assessed every two years, with data collection now entering its 25th year. Over the course of follow-up, participant deaths were recorded, and death certificates were obtained when possible.

Results: Over 24 years of follow-up, a total of 45 (12.4%) participants died. Of these, 40 were BPD subjects (i.e., 13.8% of BPD subjects) and five were Axis II comparisons (i.e., 6.9% of comparison subjects). Borderline patients were significantly younger at the time of death than axis II comparison subjects (39.2 vs. 55 years-old). Seventeen (37.7%) deaths were due to suicide (5.5% of BPD subjects vs. 1.4% of OPD). Twenty-eight (62.2%) deaths were due to other causes (8.3% of BPD subjects vs. 5.6% of OPD). The clear majority of those in both groups who died either by suicide (87.5% BPD; 100% OPD) or non-suicide related causes (87.5% BPD; 75% OPD) did not achieve recovery before death.

Conclusions: Taken together, these findings suggest that individuals with BPD are at elevated risk of premature death. A disproportionate number of premature deaths occurred in borderline patients (and axis II comparison subjects) who did not achieve recovery.
Presenting Author: Christopher King, Research Data Analyst

Co-Authors: Christopher King, Victoria Joyce, Carol Nash, Anthony Sossong, and Ralph Buonopane

Title: Readmission Rates and Symptomological Profiles of Patients Admitted to a Pediatric Psychiatric Hospital

Key words: Readmission, Trauma, SITB

Background: Pediatric psychiatric hospitalizations increased 24 percent from 2007 to 2010, representing 10 percent of all U.S. pediatric hospitalizations, and 33 to 50 percent of these patients are readmitted within a year. The Centers for Disease Control estimates the cost of pediatric psychiatric care at $247 billion annually. Despite using significant medical resources, the population of children and adolescents admitted to psychiatric hospitals remains under-described in the research literature. This descriptive study sought to better understand this population by examining the medical records of all patients admitted to the McLean Franciscan Child and Adolescent Inpatient Program at Franciscan Children’s between January 1, 2011 and December 31, 2012.

Methods: Patients’ medical records were retrospectively queried for demographic information, reason for admission, symptomatology at admission, risk to self and others at admission, trauma exposure, and readmission rates and rehospitalization. Patients were divided into four discrete age groups to determine the symptomological and readmission profiles of these developmentally distinct groups.

Results: Younger children presented with high rates of externalizing symptoms and behaviors, whereas older children presented with higher rates of internalizing symptoms and behaviors. All age groups presented with high levels of self-injurious thoughts and behaviors. Trauma was reported at higher rates in younger children across most trauma types, and the youngest age group had the highest readmission rates.

Conclusions: On admission to an inpatient psychiatric unit, children and adolescents present with different reasons for admission, psychiatric symptomatology and trauma exposure, and have distinct rates of readmission. To improve clinical outcomes, more research is required to understand the systemic and developmental conditions that cause these different acuity and symptomological profiles, and to identify predictors of pediatric psychiatric readmission.

Topic areas:
Child/Adolescent
Quality/Outcomes
Objective: The factors that contribute to relapse to marijuana (MJ) use are not well understood, but cognitive, mood, sleep and craving play a key role. The profile of these changes led us to postulate that changes in brain chemistry might be a biomarker that heralded relapse. The present study was conducted to non-invasively quantify GABA and glutamate (glu) concentration using proton MRS within the dorsal anterior cingulate cortex (dACC) and caudate/putamen/striatal (CPS) regions during the first three weeks of MJ abstinence. These measures were acquired in conjunction with a comprehensive battery that assessed clinical state, craving, withdrawal signs, sleep/wake activity and cognitive performance. We hypothesized that GABA and glu in these brain regions fluctuate during the transition between active exposure, early and prolonged abstinence from MJ, and an imbalance of GABA and glu during abstinence may be the underlying source of withdrawal and related clinical symptoms that hinder efforts to maintain abstinence.

Methods: Recreational MJ users who met criteria for cannabis use disorder and remained abstinent from MJ use for three weeks under a McLean IRB approved protocol were included in this ongoing study. Thus far, four subjects have completed study measures. In vivo brain metabolites were measured using proton MRS at 3T at baseline, and at days 7 and 21 of abstinence. MRS data were processed offline using LC Model for quantitative analysis. Quantitative urine screens were used to confirm abstinence, while clinical state and withdrawal related scales included the PANAS, POMS, HAM-A, HAM-D, Cannabis Withdrawal Scale (CWS) and the Marijuana Craving Questionnaire (MCQ); sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) and fitbit. Group averages of GABA and glu were calculated for each time point and correlations between the metabolites and clinical measures were examined.

Results: Within the ACC, group averages of GABA and glu were reduced (-22% vs baseline for GABA, -14% for glu) on day 7, followed by a recovery towards baseline concentrations. At baseline, a strong negative correlation (R²=0.94) was noted between ACC GABA and urinary THC. THC was also negatively correlated with CWS (R²=0.70), POMS tension subscore (R²=0.70), and PANAS total negative scores (R² = 0.61). However, these correlations were weakened at days 7 and 21. Within the CPS region, group averages of GABA and glu were modestly increased during abstinence (GABA +3.2%, Glu +6.3%). When comparing baseline to day 7, no correlations existed between GABA and glu concentrations and either urinary THC or clinical measures. Nonetheless, across three weeks of abstinence, glu/GABA ratios in this region were significantly correlated with changes in the POMS tension subscore (R²=0.80). At Day 21, significant correlations appeared between glutamate and clinical measures as well as residual urinary THC.

Conclusion: Initial results suggest that THC may impact ACC function at baseline and CPS function after 21 days of abstinence from MJ. Data also indicate differential time course of changes in GABA and glu concentrations within dACC and CPS during abstinence. The present study supports the notion that brain neurochemicals correlate with behaviors that parallel MJ withdrawal.

Topic areas:
Addiction
McLean Research Day 2018

Program Description

Presenting Author: Claire Peterson, Research Assistant

Co-Authors: Claire Peterson, Alvaro Pascual-Leone MD PhD, Laura Germine PhD.

Title: Characterizing Cognitive Function in former NFL Players: the McLean Brain Health Study

Keywords: Cognition, Depression, Anxiety, Technology, TestMyBrain.org

The purpose of this abstract is to briefly describe the Brain Health Study of former NFL players, a substudy set to launch at McLean that is part of the larger NFL Players' Association funded Harvard Football Players Health Study (FPHS). The issue of health in former NFL players has been a subject of considerable public interest, and many studies are currently underway to understand the impact of concussion on the brain and the prevalence of conditions like Chronic Traumatic Encephalopathy (CTE). The Harvard FPHS differs from these other studies, however, as its goals are to understand the whole player, particularly those aspects of health (including brain health) that differ between players, and how understanding those differences may help us improve player health and well-being. The Brain Health Study is a substudy of the broader FPHS that uses modern technology for remote cognitive assessment and return of research results to engage and understand variations in cognitive health and cognitive style between players. The study takes advantage of the infrastructure of TestMyBrain.org, a cognitive assessment and participant engagement research platform supported by the Laboratory for Brain and Cognitive Health Technology here at McLean Hospital, where over 1.9 million people have already been tested. The aim is to recruit 2,000 former NFL players to complete a 45 minute battery of cognitive assessments, with specific measures selected to provide reliable scores across multiple cognitive and psychological domains. These measures will test short-term memory and attention, verbal IQ, verbal and visual episodic memory, processing speed, executive function and visuospatial attention. All tests were adapted from widely accepted measures in clinical neuropsychology and cognitive neuroscience to measure individual differences. In addition, to assess psychological functioning, former players will also complete the PHQ-9 (depression symptoms), the GAD-7 (anxiety symptoms) and a measure of personality factors. Upon completion of testing, participants will be shown their relative strengths based on test scores across the entire battery. Overall, this study uses modern technology to understand and measure the cognitive ability and mental wellbeing of former NFL players with a user-friendly scalable approach.

Topic areas:
Anxiety
Depression
Quality/Outcomes
Technology
Major Depressive Disorder (MDD) is associated with enhanced memory for negative stimuli and poor memory for positive stimuli. Previously, we have emphasized that dysfunction in brain reward networks may disrupt the encoding and consolidation of positive memories. A complementary hypothesis is that MDD influences retrieval, such that depressed adults find it easier to recall negative vs. positive memories. This could occur via mood congruency: low mood in MDD may be associated with tonic activation of semantic networks that represent negative information, which could facilitate retrieval of negative material. If so, then exposing depressed adults to stress might increase the bias towards negative material by eliciting an especially aversive emotional state. To test this hypothesis and gain insight into underlying neural mechanisms, we are recording the electroencephalogram (EEG) as adults with MDD and healthy controls complete a two-day study. On Day 1, negative and positive words are encoded using two tasks. In the “Describe” task, participants indicate whether words are self-descriptive. In the “Emotion” task, participants indicate whether words are positive. Immediately after encoding, free recall is tested. On Day 2, participants complete an “old/new” recognition memory test for half the encoded words. Following each “old” decision, source memory for the encoding task is probed. Next, participants undergo a brief acute stress procedure. Finally, recognition and source memory for the remaining encoded words is tested. This experiment is in early stages (MDD: n = 6; controls: n = 6), but the initial behavioral results are interesting. Free recall was characterized by a Group x Valence interaction, Z = 2.40, p < 0.02 (Poisson regression)—there was no group difference for negative words, but controls recalled more positive words than did depressed adults, Z = 1.92, p = 0.055. Moreover, controls showed better recall for positive vs. negative words (p = 0.006), but depressed adults did not (p = 0.83). If these results are due to biased retrieval in MDD, then the positive memory deficit should be reduced for recognition memory. Indeed, a Group x Stress (pre, post) x Encoding Task x Word Valence ANOVA on corrected recognition scores revealed effects of Word Valence (p = 0.007) and Encoding Task (p = 0.03), but no effects involving Group (ps > 0.36). In stark contrast to free recall, the Valence effect reflected better recognition memory for positive vs. negative words in both groups (the Task effect reflected better memory for words from the “Describe” task). Similarly, a Group x Stress x Word Valence ANOVA on d’ scores revealed only a main effect of Word Valence due to higher d’ for positive vs. negative words. No group differences emerged for response bias or source memory, and recognition confidence was lower post-stress for both groups (p = 0.05). These results may change substantially with increased samples. Currently, however, the fact that depressed adults showed a positive memory deficit for recall but a positive memory advantage for recognition strongly is striking, as it strongly suggests that disrupted retrieval processes contribute to emotional memory biases in MDD.

**Key words:** depression, memory, emotion, stress, EEG

**Topic areas:**

- Depression
- Imaging
Associations Between CBT and DBT Skills use in Daily Life and Symptom Improvement Following Partial Hospitalization

Background: In order to benefit from Cognitive Behavioral Therapy (CBT) and Dialectical Behavior Therapy (DBT) skills based treatments, it is crucial for individuals to actually practice such skills and apply them to their day-to-day life. The first month following psychiatric hospitalization is a critical period in which patients are at greater risk for hospital readmission and relapse. While patients receive intensive CBT and DBT skills training during partial hospitalization, it is unclear whether these skills are utilized following discharge or whether using skills is associated with maintenance of treatment gains. Thus, we investigated the frequency with which patients self-reported using CBT and DBT skills after partial hospitalization. We used Ecological Momentary Assessment (EMA) sampling via smartphone technology to investigate skill-use in participants' natural environment and daily life. We hypothesized that use of different CBT and DBT skills after discharge might result in different symptom outcomes.

Methods: 26 adults suffering from acute psychiatric symptoms received CBT and DBT-based treatment focusing on various skills including cognitive restructuring, behavioral activation, mindfulness and exposure during partial hospitalization. During the acute phase of treatment, patients completed a battery of assessments, on a daily basis, measuring various symptoms including stress, mood/anxiety, and positive/negative affect (M days = 10). In the 2 weeks following discharge, participants were notified 5 times per day to complete a survey, assessing symptoms and skill use including Negative Automatic Thoughts (NAT), behavioral activation, mindfulness, exposure, and self-assessment on their smartphones. At discharge and on day 14 of the EMA sampling, patients completed the Patient Health Questionnaire (PHQ-9 depression measure) and Generalized Anxiety Disorder Assessment (GAD-7).

Results: To date, 26 participants have completed the study (recruitment is ongoing, projected n = 58). Preliminary analyses conducted on skill use showed that participants on average reported using 55.73 (SD = 31.932) skills over the course of two weeks. During the two weeks, behavioral activation (M=8.73) and mindfulness (M=8.00) skills were used most frequently. Analysis of the correlation between skill use during the 2 weeks following discharge and symptom severity measured by the GAD-7 and PHQ-9 scores revealed trends towards several associations. Although not statistically significant, use of a number of skills correlated with outcomes. The most noteworthy correlation was found between self-assessment and reduction in anxiety (p = 0.053).

Conclusion: Practicing CBT and DBT skills in the immediate period following discharge from partial hospitalization led to better treatment outcomes. Patients most frequently reported using behavioral activation and mindfulness after discharge. This pilot study suggests that self-reported skill use correlates with improved symptom outcome. Technology use allowed in the moment assessment of skill use in patients' daily lives and may be helpful in reminding patients of potential skills they can use to maintain wellness. Results from this study will help inform how utilizing skills following discharge can best be used to maximize durability of treatment gains. Larger studies with greater power are needed to further support our findings.
Presenting Author: Dawn Sugarman, Assistant Professor, Department of Psychiatry, Harvard Medical School Division of Alcohol and Drug Abuse, McLean Hospital

Co-Authors: Meghan E. Reilly, BA, Shelly F. Greenfield, MD, MPH

Title: Web-based Intervention for Women Receiving Care in Mixed-Gender Treatment Programs for Substance Use Disorders

Key words: substance use disorders, technology, women

The majority of women receive treatment for substance use disorders (SUDs) in mixed-gender settings. However, few mixed-gender SUD treatment programs contain women-specific components. Treatment programs that incorporate women-specific components have been shown to lead to enhanced treatment outcomes for women with SUDs. In a pre-pilot study, we developed a gender-responsive, web-based intervention delivered via iPad for women with SUDs as an addition to treatment as usual in a mixed-gender, inpatient SUD treatment program. The intervention was developed by adapting psychoeducational material from three modules of the Women’s Recovery Group, an evidence-based, women-focused, single-gender group therapy for women with SUDs. Three topics of key relevance to women with SUDs were selected: (1) The Effect of Drugs and Alcohol on Women’s Health, (2) Managing Mood, Anxiety, and Eating Problems without Using Substances, and (3) Women and their Partners. Results showed a high level of satisfaction with the intervention but that modifications to expand the content and enhance the interactivity of the intervention could further enhance satisfaction. The lack of and need for gender-responsive care in acute and sub-acute levels of mixed-gender SUD treatment called for expanded examination of the intervention beyond the inpatient setting. For this pilot study, women enrolled in three levels of mixed-gender SUD treatment (inpatient, partial hospitalization, and outpatient) were included if they were (a) 18 years of age or older, and (b) able to read and provide informed consent. Two additional modules were added to the modified intervention: (1) Violence and Abuse, and (2) Women as Caretakers. Patient satisfaction with the intervention and attitudes about the relevance of the gender-responsive components of the intervention to SUD treatment were measured post-intervention. Forty-four women (mean age=39.4, SD=14.9; 93% white; 25% married) completed the study. Similar to the pre-pilot results, participants indicated a high level of satisfaction with the intervention (M=35.3, SD=4.5; maximum possible score=40). Satisfaction did not significantly differ by level of care (F=0.15, df=2, p=0.86) and was not associated with number of previous treatment episodes (r=-.04, p=0.78). The elements of the intervention that were rated as the most relevant to recovery (Likert scale 0-4; 4=extremely relevant) were: the link between substance use and other mental health problems (M=3.7, SD=0.7), how to manage feelings without using substances to cope (M=3.5, SD=0.9), and the effects of substance use on self-care (M=3.5, SD=0.8). These results suggest that the intervention is applicable to women regardless of their previous experience in treatment and has the potential to be a highly sustainable strategy for increasing gender-responsivity across multiple levels of care.

Topic areas:
Addiction
Technology
Women
McLean Research Day 2018

Original Research - Pre-Clinical

Poster # 18
Time: 1:50-2:45pm

Presenting Author: Debkanya Datta, Instructor in Psychiatry, Assistant Neuroscientist
Co-Authors: Sivan Subburaju, Weiji Wang, Anju Vasudevan

Title: Novel therapeutic roles of human stem cell derived-endothelial cells in psychiatric disorders

Key words: endothelial cells, interneurons, cell therapy, pluripotent stem cells

Abnormalities in GABAergic interneurons are implicated in the pathology of severe neurological conditions like schizophrenia, autism and epilepsy, for which no effective cure is available to date. Transplantation of interneurons in diseased brain is a promising cell-based approach for treatment of these disorders. Human pluripotent stem cells have emerged as an important source of interneurons for cell therapy. In mouse xenograft studies, human stem cell derived-interneuron precursors could differentiate in vivo, but required a prolonged time (up to seven months) to migrate from the graft site and integrate with the host tissue. This is a serious obstacle for clinical feasibility of this approach. For transplantation to be effective, especially for very sick or severe patients, grafted neurons should migrate to the affected areas and integrate with the host brain at a faster rate. Recent novel findings from our group, linking vascular cells to interneuron migration, is significant in addressing this problem. Our group has discovered that endothelial cells lining the periventricular vascular network of the forebrain, function as physical substrates for migrating interneurons, and provide navigational cues for correct neuronal distribution in the developing brain. In this study, we aim to translate this discovery into a novel co-grafting strategy to increase the efficiency of interneuron transplantation. Co-transplantation of human periventricular endothelial cells with human GABAergic interneurons will accelerate the migration of grafted neurons in the diseased brain, leading to faster and longer-lasting therapeutic effect. To obtain renewable source of cells for co-grafting, we generated human periventricular endothelial cells in vitro by differentiating human pluripotent stem cells towards periventricular lineage, using a protocol that we established in the lab. The derived cells showed endothelial specific (CD31, vWF), and periventricular specific (GABRB3, GABA, NNX2.1, DLX1/2) protein expression, and displayed pro-angiogenic properties of tube formation, sprouting, and long-distance migration. Furthermore, human periventricular endothelial cells enhanced the migration of human GABAergic interneurons in vitro. Taken together, we have generated pure population of human periventricular endothelial cells, and set the stage for testing the effect of the co-transplantation in vivo. Our ongoing study involves co-transplantation of endothelial cells and interneurons in striatum and hippocampus of NOD SCID mouse. We expect to demonstrate that transplanted periventricular endothelial cells will form a migration promoting corridor that will help interneurons travel long distances in shorter periods of time and integrate robustly within the adult brain. We expect that our co-delivery strategy will lead to faster, longer lasting effect of interneuron transplants in diseased brains, and facilitate the advancement of interneuron-based therapy into a clinical setting.

Topic areas:
Neurology
Schizophrenia
McLean Research Day 2018

Original Research - Clinical

Poster # 19
Time: 1:00-1:50pm

Presenting Author: Deborah Levy, Director, Psychology Research Lab; Associate Professor

Co-Authors: Charity J. Morgan, Mark F. Lenzenweger, Deborah L. Levy

Title: A Tale of Two Endophenotypes in Clinically Unaffected Relatives of Schizophrenia Patients

Key words: Schizophrenia, thought disorder, genetics, antisaccades, endophenotype

Background: A number of traits associated with schizophrenia aggregate in relatives of schizophrenia patients at rates much higher than that of the clinical disorder. These traits, considered candidate endophenotypes, may be alternative, more penetrant manifestations of schizophrenia risk genes than schizophrenia itself. In order for an endophenotype to potentially increase the power of genetic analyses, not only should the distribution of the quantitative trait be heterogeneous in unaffected relatives, but the trait must also be found in unaffected relatives at a higher rate than in the general population.

Methods: Here we evaluate the suitability of two provisionally identified endophenotypes: thought disorder with schizophrenic features and antisaccade error rate.

Results: We demonstrate that thought disorder with schizophrenic features meets both of the criteria for an endophenotype. In contrast, we show that, while there is significant heterogeneity in performance on the antisaccade task in unaffected relatives, we do not find evidence of a higher rate of antisaccade errors in unaffected relatives compared to normal controls.

Conclusion: These findings provide further support for the utility of this approach for evaluating the suitability of a given trait as a candidate endophenotype and suggest that thought disorder with schizophrenic features may be more useful as a schizophrenia endophenotype than antisaccade error rate.

Topic areas:
Psychotic disorders
Schizophrenia
Presentation Title: Magnetic Resonance Spectroscopy detects transient brain temperature increase in rhesus macaques with Simian Immunodeficiency Virus infection

Key words: MRS, Animal models, SIV, Thermometry, Translational research

Background: Human Immunodeficiency Virus (HIV) infection induces a cascade of deleterious processes resulting in neuronal injury and apoptosis, which can lead to neurological disorders known as neuroAIDS and HIV-Associated Neurocognitive Disorders (HAND). The rhesus macaque Simian Immunodeficiency Virus (SIV) model is well-established and facilitates studies of disease progression, as well as efficacy assessments of novel interventions. In vivo Magnetic Resonance Spectroscopy (MRS) permits noninvasive, longitudinal measurements of brain chemistry and physiology, including changes induced by SIV. Previously, we used MRS in SIV-infected macaques to detect complex temporal and regional changes of choline (Cho) concentrations, which increased two weeks post infection (wpi), then decreased to near-normal levels at 4 wpi, followed by elevations at later time points. Cho elevations have been associated with increased levels of inflammation biomarkers in SIV and HIV studies. As inflammation has been linked to cerebral hyperthermia, we hypothesized that SIV could also induce brain hyperthermia. We performed a retrospective MRS thermometry analysis to determine whether SIV also induces brain hyperthermia.

Methods: The present analysis included sixteen adult rhesus macaques. After baseline MRS scans, animals were inoculated with SIV-mac251 virus (10 ng SIVp27, i.v.) and their CD8 lymphocytes were depleted with an antibody (cM-T807) administered, 6, 8, and 12 days post-inoculation. Proton (1H) MRS PRESS (point-resolved spectroscopy) traces (TR/TE=2.5s/30ms, 192 averages) and associated unsuppressed water reference traces were acquired on a 3T MR scanner (Siemens Magnetom TIM Trio). Spectra were obtained from four brain voxels placed in the Basal Ganglia (BG), Parietal Cortex (PC), Frontal Cortex (FC), and White Matter (WM). LCModel was used to estimate metabolite concentrations. Temperatures were estimated from the 1H frequency difference between N-acetylaspartate (NAA) and the unsuppressed water (H2O) peak according to the equation $T_{\text{brain}}(\text{oC}) = 36.0 - 103.80 \times (\delta_{\text{H2O}} - \delta_{\text{NAA}} - 2.6759)$. 

Results: In all four brain regions, temperature was significantly elevated 2 weeks post inoculation (wpi) relative both to 0 wpi (baseline) and 4 wpi. P-values for the 2 wpi to baseline comparisons were, FC: $p=0.0005$, PC: $p=0.0032$, BG: $p=0.0258$, WM: $p=0.0061$ (repeated-measures ANOVA, post-hoc comparisons). Additionally, choline levels correlated with temperature in all four regions, FC: $p=0.005$, Pearson $R=0.4044$, PC: $p=0.005$, $R=0.4029$, WM: $p=0.0012$, $R=0.4579$, and BG: $p=0.046$, $R=0.2921$.

Conclusion: We detected transient temperature increases in SIV-infected rhesus macaques in four brain regions at 2 wpi relative to baseline. In all regions, brain temperature correlated with brain Cho changes, suggesting that SIV transiently increases brain temperature by increasing brain inflammation. We previously found frontal cortex temperature increases with MRS thermometry in mice that were conditionally induced to express HIV-Tat protein. Taken together, these results indicate that MRS thermometry is informative in HIV models, and may be useful for assessing effects of novel treatments that reduce inflammation.

Topic areas:
- Imaging
- Neurology
Presenting Author: Gabriele Chelini, Post Doctoral Fellow

Co-Authors: Kanoelani Pilobello Cristina Berciu Durning Peter Teniel S. Ramikie Siva Subramanian Rachel Jenkins Moazzzam Kahn Kerry Ressler Sabina Berretta

Title: Chondrotin-6 sulfate clusters: Association of synaptic domains and regulation of synaptic plasticity during fear learning.

Key words: plasticity, fear conditioning, learning and memory, translational research, Schizophrenia

Growing evidence indicates that the brain extracellular matrix (ECM) is critically involved in the regulation of synaptic plasticity, both during critical periods of postnatal development and in adulthood. Chondroitin sulfate proteoglycans (CSPGs), critical ECM components composed by a core proteins and long sugar chains, have been extensively investigate for their synaptic function. Recent findings, from Sabina Berretta’s lab, showed CSPGs affected in people with schizophrenia (SZ) and Bipolar Disorder (BD). Interestingly, novel dandelion-shaped structures, enriched in chondroitin-6-sulfated CSPG (CS-6 clusters), were reported decreased in people with SZ and BD, but their biological function is currently not understood. Here we first report the ultrastructural composition of a CS-6 cluster microenvironment, showing CS-6 accumulation in astrocytes end-feet and dendritic spines postsynaptic density. Furthermore, we first provide evidence for a biological function of these structures, showing marked increased of CS-6 clusters following fear learning. These findings suggest that CS-6 CSPG is dynamically regulated during learning and contributes to synaptogenesis machinery by accumulating into the post-synaptic terminal, upon secretion from astrocytes.

Topic areas:
Anxiety
Bipolar
PTSD
Schizophrenia
Technology
Presenting Author: Gabriella Ponzini, Student

Co-Authors: Nathaniel Van Kirk, Meghan Schreck, Jacob Nota, Casey Schofield, Jason Krompinger, Brian Brennan, Christina Gironda, Jason Elias

Title: Does Motivation Impact OCD Symptom Severity? An Exploration of Longitudinal Effects

Key words: Obsessive Compulsive Disorder, Motivation, Structural equation modeling, Exposure and response prevention

Background: Understanding the role of motivation in OCD treatment is of clinical import given the requisite autonomous role of patients in exposure and response prevention (ERP). The present study assessed readiness to change (RTC) and committed action (CA) derived from the University of Rhode Island Change Assessment (URICA), in relation to OCD symptom severity as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Methods: Participants were 496 patients (50% female) with a mean age of 34 (SD = 13.81) from an intensive/residential treatment (IRT) center for OCD and related disorders. Utilizing a cross-lagged panel design within the structural equation modeling framework, we assessed first-lag directed arrows within constructs, within-time cross-sectional construct correlations, and diagonal-directed arrows of RTC, CA, and Y-BOCS scores at admission, 1 month, and discharge.

Results: Preliminary findings suggested a stability of variables across time (all p’s < .001). Within time cross-sectional relations between Y-BOCS and CA were negative and present at admission (β = -.17, p < .001), 1 month (β = -.28, p < .001), and discharge (β = -.33, p < .001), suggesting that patients who reported more severe OCD symptoms endorsed less commitment to behavioral change during that time. Additionally, Y-BOCS at 1 month negatively predicted CA at discharge (β = -.15, p = .04), suggesting that patients had a lower commitment to behavior change at the end of treatment. Alternatively, Y-BOCS positively predicted RTC at discharge (β = .17, p = .01), and post-hoc analyses revealed that patients with more severe OCD symptoms at 1 month had more recognition of their OCD at the end of treatment (β = -.20, p = .01).

Conclusions: Our data provide initial evidence for the importance of longitudinal evaluation of motivation as a dynamic construct (specifically CA) during OCD treatment. Notably, this study highlights a potential for supplementing ERPs with motivation-enhancement techniques throughout treatment to augment treatment effectiveness.

Topic areas: OCD
Title: Targeting Activated Microglia in the Brain by Delivering Antibodies via Nanoparticles for MRI/PET

Key words: clathrin nanotechnology, CD11b antibody, activated microglia, inflammation, imaging

Background: Positron emission tomography (PET) has provided important evidence for microglial activation in neuropsychiatric disorders. Antibodies (Abs) have been developed that can suppress inflammation and prevent neurodegeneration. However, antibodies cannot easily cross an intact blood-brain-barrier (BBB) or diffuse within brain tissue. Only 0.1% of plasma Abs enter the central nervous system (CNS) naturally via diffusion through a compromised BBB, or BBB saturation, but CNS concentrations are not sufficient for diagnostic PET or Magnetic Resonance Imaging (MRI), or therapeutic efficacy. Our goal was to develop a novel theranostic method for noninvasive high-efficiency targeted delivery of antibodies to activated microglia cells in the CNS.

Methods: Monoclonal CD11bAbs for labeling activated microglia were PEGylated and conjugated to clathrin triskelia (CTs) through cysteine residues. The size and uniformity of the nanoparticle (NP) was determined by dynamic light scattering. An animal model of CNS inflammation in schizophrenia was used for in vivo studies. Sprague Dawley rats received intraperitoneally 10 mg/kg of MK-801 that induces microglia activation. Control animals received saline. CD11bAb-CT nanoprobes, or CD11b-Abs without CTs, were delivered intranasally in rats 3 days after MK-801 administration to target activated microglia. Animals were sacrificed 3 hours after intranasal administration, and immunohistochemistry and stereological analyses were performed. For molecular MRI/PET imaging, brain distribution of iron oxides or C14 labeled CD11b-Ab-nanoprobes were assessed in rats 3 hours after intranasal administration. Radioactivity was measured in different brain regions with scintillation counting methods.

Results: One molecule of CD11bAb was attached per clathrin triskelion, and low doses (64 µg/kg) of these small (42 nm) nanoparticles were delivered intranasally in rats. Three hours later CD11bAb-nanoprobes were found only in the rat brain regions with activated microglia: retrosplenial cortex, hippocampus, entorhinal and piriform cortex. CD11b-Abs that were delivered without clathrin did not enter the brain. Fluorescent and light microscopic examination of these brain regions confirmed specific targeting of microglia with CD11bAb-nanoprobes. Statistical analyses with repeated measures ANOVA showed that densities of activated microglia in hippocampus (e.g., dentate gyrus $F(1,4)=110.85, p<0.0005$) and retrosplenial cortex ($F(1,4)=75.58, p<0.001$) were markedly higher in animals that received MK801 compared to controls. The highest concentrations of new PET nanoprobes were detected in hippocampus (5±0.5 fmol/mg or 4.7% ID/g) and retrosplenial cortex (4.8±1.8 fmol/mg) of MK801 treated animals. Nanoprobes were not detected in regions lacking activated microglial cells (e.g., cerebellum). Light microscopy also confirmed integrity of the new MRI nanoprobes in the rat brain, as iron and CD11bAb staining co-localized in the rat brain.

Discussion: Our results demonstrate that engineered clathrin nanoparticles enabled CD11b-Abs to effectively bypass a BBB intranasally, and to target MK-801 activated microglial cells within specific brain regions, using ~300 times lower doses than reported in previous BBB technologies studies. Hence, clathrin appears to provide a highly efficient nanoplatform for targeted delivery of antibodies to the CNS. This nanotechnology strategy may lead to development of new CNS theranostics for MRI/PET imaging of inflammation in neuropsychiatric disorders, for monitoring disease progression and recovery, and for efficiently treating CNS disorders through targeted delivery of specific anti-inflammatory antibodies.

Topic areas:
Imaging, Technology
Presenting Author: Gwenievere Birster, Clinical Research Assistant

Co-Authors: Elizabeth Olson, Gwenievere Birster, Isabelle Rosso

Title: Anterior insula-nucleus accumbens connectivity in PTSD: clinical and decision-making correlates

Key words: posttraumatic stress disorder, neuroimaging, cognition, functional connectivity

Introduction: Hyper-responsivity of fear- and extinction-related regions including the anterior insula (AI) is well-documented in posttraumatic stress disorder (PTSD). Dysregulation in reward-related circuitry in PTSD has received increasing attention, with reduced activity in regions including the nucleus accumbens (NAcc). Recently, a white matter pathway connecting the right AI to the right NAcc was identified in the human brain; this pathway likely involves inhibitory control of the right AI over NAcc activity. We hypothesized that increased right AI-NAcc coherence would be associated with greater symptom severity in PTSD.

Methods: 20 participants (13 female) with current DSM-IV PTSD were included. Probabilistic tractography was performed using FSL’s bedpostx and probtrackx, from a seed in the right NAcc to the right AI. Tracts were masked and used to extract fractional anisotropy (FA) values. Age and gender were included as nuisance covariates.

Results: Higher FA was associated with higher lifetime PTSD severity (CAPS scores, partial r (16) = 0.542, p = 0.020), driven by significant associations with avoidance and re-experiencing (but not hyperarousal) symptom clusters. In 11 participants who also had delay discounting data, higher FA was associated with steeper delay discounting, r (9) = -0.635, p = 0.036, but not with anhedonia, r (16) = 0.084.

Discussion: Increased FA between the right AI and right NAcc was associated with greater lifetime symptom severity. While hyperactivity in the AI and hypoactivity in the NAcc have been previously demonstrated, this finding suggests that altered white matter microstructure in the pathway connecting these regions may also be relevant to PTSD severity.

Topic areas:
PTSD
Presenting Author: Hadley Heinrich, Clinical Research Assistant


Title: ‘Finding the sweet spot’ for insight: investigating the relationship between insight and sociability and effects on symptom severity in patients with serious mental illness.

Key words: psychotic disorders, insight, sociability, serious mental illness, symptom severity

Insight functions as a complex factor in recovery from mental illness, with some studies citing high or “good” insight as a risk factor for poor self-esteem, hopelessness, depression, and suicidality in patients struggling with heavily stigmatized illnesses (Stoklosa et al. 2017; Mutsatsa et al. 2006; Hasson-Ohayon et al. 2006), and others citing high insight as correlated with higher medication adherence and better post-discharge adjustment (Mohamed et al. 2009; McEvoy et al. 2004; Frese et al. 2000). In the case of serious mental illness, in which both chronicity and severity are incorporated into the diagnosis of a mental disorder, factors such as social isolation, level of social interest, and social effectiveness may also inform level of insight and symptom severity (Lysaker et al. 1998). This analysis aimed to explore whether insight makes an impact on symptom severity in patients with serious mental illness and whether social functioning has additional effects on symptom severity, independently or in conjunction with insight. We used data collected from an ongoing randomized clinical trial on cardiovascular disease prevention in patients with severe mental illness, based out of McLean Hospital. The data were collected from research interviews conducted at the baseline visit, and comprise clinician-rated items from multiple instruments measuring symptoms of mania, depression, positive and negative symptoms, and community functioning. An insight index and a sociability index were constructed using items from separate instruments (YMRS, MCAS, SUMD; SANS, PANSS, MCAS), with an insight score and sociability score assigned to each participant. Multiple regression analyses were conducted examining symptom severity, insight scores, and sociability scores. A moderately strong correlation was identified between symptom severity and insight level ($r = .000203$), with higher insight scores (lower clinical insight) significantly associated with higher PANSS Total scores ($F (9, 28.127) = 3.315, p = .007$), confirming the hypothesis that patients with higher insight levels have lower symptom severity. A strong correlation was also identified between symptom severity and sociability ($r = 6.6182 \times 10^{-11}$), with higher sociability scores (higher sociability) significantly associated with higher PANSS Total scores ($F (12, 19.259) = 2.815, p = .021$). There was no significant interaction between insight and sociability in predicting symptom severity. The sociability result suggests that patients with higher sociability also display higher symptom severity, perhaps as a result of greater social involvement due to symptoms, an unexpected association that warrants further investigation.

Topic areas:
Psychotic disorders
Title: Sex Differences in Non-Suicidal Self-Injury in a Partial Hospital Program

Key words: NSSI, Sex Differences, Partial Hospital

Introduction: Non-suicidal self-injury (NSSI) has been widely researched as a predictor of adverse outcomes, including suicidal ideation and actions. Much of the research to date has focused on NSSI among females, although more recent studies have documented sex differences in characteristics of NSSI. Research suggests that sex differences may be present in specific NSSI methods, motivations to engage in NSSI, and age of NSSI onset. Sex differences may be more pronounced in studies conducted in clinical samples, in which females are more likely than males to report NSSI. Given these potential differences, there is a need to understand characteristics of NSSI in acute treatment settings, which report high rates of NSSI. The present study aims to characterize sex differences among patients in a partial hospital program in regards to NSSI rates, age of onset, methods, and latency to engage in NSSI. We hypothesized that females would have higher rates of NSSI than males, and that females would be more likely to endorse cutting, biting, scratching, hair pulling, and interfering with wound healing, while males would be more likely to endorse burning and hitting/head banging. We hypothesized that the age of onset for NSSI among females will be younger than males, and that the latency between urge to self-injure and NSSI action will not differ between males and females.

Methods: Data were collected from 1,460 patients (Mean age = 33.48 [SD = 13.5], 54.2% female) attending McLean Hospital's Behavioral Health Partial Hospital Program (BHP). Upon admission to the program, patients completed self-report questionnaires, which included the Inventory of Statements About Self Injury (ISAS), a well-validated self-report measure assessing NSSI.

Results: 48.6% of BHP patients endorsed a history of NSSI. Consistent with previous research, females were significantly more likely than males to report NSSI, X² (1, N=1460) = 23.17, p < .001, with 54.5% of females and 41.7% of males reporting NSSI. Females also endorsed more total NSSI methods, t(657.80)=2.92, p < .01. The most common method among females who engage in NSSI was cutting (31.6%), while males most frequently endorsed head banging/hitting (19.9%). Overall, females showed significantly higher rates of cutting, scratching, and interfering with wound healing than did males (p < .001). No sex differences emerged for burning, hair pulling, or biting (ps > .11). In addition, no sex differences emerged for age of onset of NSSI, t(664) = .18, p = .86. However, males reported engaging in NSSI in response to NSSI urges significantly faster than females, Mann-Whitney U = 39571.5, p < .01.

Discussion: These results demonstrate that there are considerable sex differences among those who engage in NSSI. The present research provides insight into where those differences exist, and to what degree, in the partial hospital setting. Given findings that males report significantly less time between NSSI urges and action than do females, future research may need to consider interactions between impulsivity and sex differences in NSSI outcomes. In addition, findings support the need for continued treatment development to address high rates of NSSI observed among females.

Topic areas:
Anxiety
Depression
Gender Differences
The Geriatric Psychiatric Research Program (GPRP) participates in multi-site research aimed at identifying and investigating treatments for the behavioral symptoms of Alzheimer’s Disease (AD). Our research collaborates closely with and complements the Geriatric Psychiatry Division’s clinical programs, as our studies address behavioral symptoms of AD encountered frequently among our inpatient and outpatient populations—namely, agitation, aggression, and sleep disturbances. Due to a lack of efficacious treatments, these symptoms remain leading causes of institutionalization and hospitalization of AD patients. While agitation and aggression are common symptoms of mild to severe AD, there are currently no treatments approved by the FDA for this indication. To date, a small number of placebo-controlled trials have assessed the efficacy of antipsychotics and anticonvulsants, with results suggesting potential efficacy of the former class when compared to placebo. However, due to a higher mortality rate of elderly patients taking antipsychotics, the FDA issued a ‘black-box’ warning for use of these medications in elderly patients with dementia. Identifying an effective and tolerable pharmacological treatment for agitation and aggression in AD is imperative, as these symptoms can increase patient distress as well as place immense burden on both caregivers and healthcare providers. The GPRP is one of multiple sites participating in a randomized, double-blind, placebo-controlled trial of low-dose Lithium as a treatment for agitation and aggression, with or without psychosis, in outpatients with AD. Lithium is a well-established treatment for bipolar mania, having been used for this indication for over 50 years. However, this is the first controlled trial of Lithium intended to determine its efficacy and safety in elderly AD patients with these behavioral symptoms. To date, we have enrolled 3 subjects at our site. Although often less apparent than agitation and aggression, sleep disturbances are a harmful behavioral symptom of AD. As the disease progresses, one’s circadian rhythms become increasingly disturbed. These disruptions commonly manifest as Irregular Sleep-Wake Rhythm Disorder (ISWRD)—a condition characterized by irregular sleep patterns across the whole 24-hour cycle. Patients experience multiple and inconsistent bouts of sleep throughout the day and night, rather than one continuous stretch of sleep at night. Decreases in the quality and duration of sleep in turn contribute to the further cognitive decline of AD patients. Additionally, irregular sleep creates stress for caregivers, as they too lose sleep and may worry about the safety of their loved ones during the middle of the night. However, due to side effects such as confusion and increased risk of falls associated with common sleeping drugs, there are currently no drugs approved for sleep disturbances in dementia patients. Our site is participating in a Phase II, double-blind, placebo-controlled, randomized trial of Lemborexant to treat ISWRD in Alzheimer’s patients. Developed by Eisai co., Lemborexant is a dual orexin receptor antagonist currently being tested in Phase III trials for insomnia. It is believed that the drug can help normalize sleep patterns without the harmful side-effects characteristic of other sleep medications currently available. We are working on recruiting our first subject.
Altered sleep architecture and circadian rhythms are associated with various stress sensitive psychiatric illnesses. Unpublished data has shown that altered signaling within the PACAP (pituitary adenylate cyclase activating polypeptide) system is associated with increased night awakenings and altered sleep patterns in clinical populations with post-traumatic stress disorder (PTSD). Importantly, our lab has recently demonstrated that stress exposure caused long-duration increases in paradoxical (PS; rodent form of REM sleep) and slow wave sleep (SWS) in susceptible male mice. Furthermore, this stress paradigm also altered PACAP receptor expression in the brain, suggesting that these changes may contribute to altered sleep architecture. The current set of studies used both male and female mice to determine if central PACAP administration causes long-duration changes in sleep architecture and circadian rhythms. Mice were implanted with wireless telemetry devices and cannula aimed at the ventricular system. We found that administration of a behaviorally relevant dose of PACAP into the ventricular system immediately decreased activity levels in male and female mice, and returned to baseline a week following treatment. In males, but not females, PACAP infusion caused an acute increase in time spent in SWS and PS. Importantly, PS time remained elevated a week following treatment in males only. PACAP infusion altered frequency band power a week following treatment in both male and female mice. Therefore, PACAP infusion alters sleep architecture in a sex-dependent manner, and may be a mechanism through which stress causes long-duration changes in sleep architecture. Similarities between our data and that of clinical literature will be discussed.
The use of nicotine products such as cigarettes and smokeless (chewing) tobacco in the military is highly prevalent, but it is not known how nicotine affects vulnerability to stress and stress-related conditions including post-traumatic stress disorder (PTSD). Previous work has demonstrated that nicotine can facilitate learning while also relieving stress. These two actions may have opposing effects on vulnerability to stress-related illness such as PTSD, which is thought to involve learning and memory components. Pilot studies in our lab suggest that voluntary intravenous self-administration (IVSA) of nicotine in rats can reduce the impact of a traumatic event, as reflected by decrease responsivity to a context previously associated with footshock in the fear-potentiated startle (FPS) paradigm. These findings suggest that nicotine use in soldiers might reduce pathological responses that occur in contexts that have broad similarities with those in which a trauma was experienced, whether in combat settings or after returning home. The present research was conducted to determine if the putative beneficial effects of nicotine on contextual fear learning are retained when the drug is given by a different (safer) route of administration, using a model of the nicotine patch. Male Long-Evans rats were implanted with a subcutaneous iPRECIO™ programmable minipump for a period of 44 days. After 7 days of recovery, animals received 21, 10, or 1-day exposure to 0.3 mg/kg of nicotine or saline for a 12-hr on/12-hr off period. At the end of the exposure period, rats were trained in the FPS paradigm, which provides an index trauma and enables quantification of exaggerated startle response and extinction deficits, two characteristics observed in humans with PTSD. Next, nicotine exposure was discontinued for a period of 10 days and context-potentiated startle (CPS) and FPS were determined in each subject in three test sessions 48-hrs apart. Initial results suggest that chronic exposure to a low dose of nicotine administered through the “patch” leads to decreased responsiveness to trauma (footshock)-associated contexts, similar to findings after voluntary self-administration of the drug. Experiments to assess the effects of a higher dose of nicotine (1.0 mg/kg/day) are currently underway. These findings suggest that passive administration of nicotine alone can impact physiological responses to trauma in a context, raising the possibility that nicotine could be used medically to reduce the psychological impact of trauma.
Title: Targeted Treatment of a Genetic Mutation in Glycine Decarboxylase with D-cycloserine in Psychotic Disorders

Key words: D-cycloserine, D-serine, NMDAR, glycine, copy number variant

Background. The identification of mutations in specific genes could enable personalized, “medically actionable” treatment interventions. We identified a potentially informative mutation, a rare structural rearrangement that includes a triplication of the glycine decarboxylase gene (GLDC). GLDC is the enzyme that catabolizes glycine, a precursor of D-serine, both of which are co-agonists at the NMDA receptor (NMDAR). Four copies of GLDC would be expected to increase the degradation of glycine, resulting in low levels of brain glycine and NMDAR-mediated hypofunction, which has been strongly implicated in the pathophysiology of psychotic disorders. Carriers of this mutation may especially benefit from augmentation of psychotropic drug treatment with NMDAR co-agonists.

Method. We carried out a double-blind placebo-controlled clinical trial (six weeks per arm) of D-cycloserine (DCS), a partial agonist at the NMDAR glycine site, followed by 24 weeks of open-label DCS, in two related individuals who are carriers of the GLDC mutation, one with a diagnosis of bipolar disorder with psychotic features and the other with a diagnosis of schizo-affective disorder. Clinical assessments were carried out every two weeks using the PANSS, BPRS, YMRS, HAM-D, and CGI. The same individuals previously completed trials of acute and chronic glycine augmentation, which produced significant symptom improvement but caused problematic GI side effects.

Results. DCS produced a significant reduction in severity of psychotic symptoms in both the blinded and open-label conditions. Conclusion. DCS is an effective augmentation in psychotic individuals selected for being carriers of duplications or triplications of GLDC, and may also have therapeutic actions in carriers of other genetic variants resulting in NMDAR hypofunction. DCS is a preferable alternative to glycine as a targeted treatment in light of its clinical efficacy, ease of administration and favorable side effect profile.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia

Substantial evidence from current neuroimaging research has reported deficits in circuit connectivity between the prefrontal cortex, amygdala, and thalamus in people with schizophrenia. These disturbances strongly correlate with cognitive dysfunction and learning and memory impairment, and growing evidence indicates that abnormal oligodendrocyte maturation may be associated with altered thalamocortical circuits found in schizophrenia. The cellular mechanisms underlying abnormal oligodendrocyte maturation are currently unknown, and further investigation may elucidate therapeutic targets for treatment. Current neuroimaging and human post-mortem findings support the hypothesis that cognitive impairment and sensory dysfunction in schizophrenia may be associated with structural alterations in the thalamus, and limitations in resolution at the cellular level highlight the necessity of quantifying neuronal and glial volumes in post-mortem studies. In addition, mouse models and stem cell models of schizophrenia pathology report altered oligodendrocyte stem cell maturation and migration, supporting the potential role of oligodendrocyte dysfunction in the axon-rich mediodorsal nucleus of the thalamus as a locus of schizophrenia pathophysiology. While much emphasis has naturally been placed on neuronal circuit deficits and regional neuronal volume reduction comparisons, non-volumetric diffusor tension imaging (DTI) indicates microstructural white matter abnormalities in the thalamus. Our research centers on the mediodorsal thalamic nucleus, a large sub nucleus containing numerous thalamic outputs to the cortex and amygdala, which has been implicated in sensory and cognitive output dysfunction in people with schizophrenia. Oligodendrocytes play a fundamental role in sustaining myelin integrity throughout adulthood, and losses in mature oligodendrocytes or an inability to mature from immature oligodendrocyte progenitor cells would critically impact thalamocortical connectivity in schizophrenia. We seek to determine whether mature oligodendrocytes are decreased in the mediodorsal thalamus in schizophrenia by means of quantifying myelin oligodendrocyte specific protein immunoreactive (MOSP-IR) oligodendrocytes in post-mortem human tissue using immunohistochemical staining and light microscopy. We collected whole thalamic specimens of control (n=15), subjects with schizophrenia (n=15), and bipolar disorder (n=15), and performed immunohistochemistry to quantify the number of MOSP-positive oligodendrocytes in the mediodorsal thalamic nucleus. We will employ quantitative stereological sampling to estimate total numbers and numerical densities of MOSP-IR oligodendrocytes in the human mediodorsal thalamus, analyzing longitudinal patient medical data, including exposure to medication, smoking and alcohol use history, post-mortem interval, age, sex, and brain weight to control for confounding factors. We expect that the numbers of MOSP-positive oligodendrocytes in the mediodorsal thalamus of people with schizophrenia will be significantly reduced. Our lab has identified abnormal expression of chondroitin sulfate proteoglycans (CSPGs) in post-mortem brain samples of subjects with schizophrenia. We recently identified novel CSPG structures consisting of coats of CSPGs, including NG2, around axons. Abnormal CSPG expression may thus affect axonal coats, potentially impacting axonal conductance and organization. Ongoing studies will examine the relationship of mature oligodendrocyte cell numbers with immature oligodendrocytes expressing NG2, and in turn with axonal coats, to determine if myelin deficits are associated with glial cell maturation and/or axonal coat abnormalities.
Presenting Author: Julia Cohen-Gilbert, Instructor

Co-Authors: Lisa D. Nickerson, Jennifer T. Sneider, Emily N. Oot, Anna M. Seraikas, Micheal L. Rohan, Marisa M. Silveri

Title: College binge drinking associated with decreased frontal activation to negative emotional distractors during inhibitory control

Key words: Alcohol, fMRI, Impulsivity, Emotion, Emerging adult

The transition to college is associated with an increase in heavy episodic alcohol use, or binge drinking, during a time when the prefrontal cortex and prefrontal-limbic circuitry continue to mature. Traits associated with this immaturity, including impulsivity in emotional contexts, may contribute to risky and heavy episodic alcohol consumption. The current study used blood oxygen level dependent (BOLD) multiband functional magnetic resonance imaging (fMRI) to assess brain activation during a task that required participants to ignore background images with positive, negative, or neutral emotional valence while performing an inhibitory control task (Go-NoGo). Subjects were 23 college freshmen (7 male, 18-20 years) who engaged in a range of drinking behavior (past three months’ binge episodes range = 0-19, mean = 4.6, total drinks consumed range = 0-104, mean = 32.0). Brain activation on inhibitory trials (NoGo) was contrasted between negative and neutral conditions and between positive and neutral conditions. Results showed that a higher recent incidence of binge drinking was significantly associated with decreased activation of dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), and anterior cingulate cortex (ACC), brain regions strongly implicated in executive functioning, during negative relative to neutral inhibitory trials. No significant associations between binge drinking and brain activation were observed for positive relative to neutral images. While task performance was not significantly associated with binge drinking in this sample, subjects with heavier recent binge drinking showed decreased recruitment of executive control regions under negative versus neutral distractor conditions. These findings suggest that in young adults with heavier recent binge drinking, processing of negative emotional images interferes more with inhibitory control neurocircuitry than in young adults who do not binge drink often. This pattern of altered frontal lobe activation associated with binge drinking may serve as an early marker of risk for future self-regulation deficits that could lead to problematic alcohol use. These findings underscore the importance of understanding the impact of emotion on cognitive control and associated brain functioning in binge drinking behaviors among young adults.

Topic areas:
Addiction
Imaging
Presenting Author: Julie M. McCarthy, Research Fellow

Co-Authors: Kelly M. Dumais, Ph.D. Maya Zegel, B.A. Amy C. Janes, Ph.D.

Title: Reduced Functional Connectivity Between Cognitive Control and Reward Regions in Women vs. Men with Chronic and Acute Nicotine Exposure

Key words: sex, nicotine, fMRI, executive control network

Relative to men, women experience greater difficulty quitting smoking. Such sex differences may be explained by disrupted communication between brain regions involved in cognitive control given the link between relapse and cognitive dysfunction. Within the executive control network (ECN), reduced interhemispheric coupling is associated with cognitive deficits and relapse. Poor coupling between key ECN hubs and regions promoting habit formation/maintenance (e.g., between dorsolateral prefrontal cortex (DLPFC) and dorsal striatum (DS)), could also underlie sex differences in ending the habit of smoking. We aimed to determine the nature of sex differences in interhemispheric ECN connectivity and connectivity between DLPFC and DS in the context of chronic and acute nicotine exposure to understand the extent to which sex differences exist and are modulated by nicotine. Thirty-six smokers (19 women) and 17 non-smokers (8 women) completed a resting state functional magnetic resonance imaging scan. Non-smokers were scanned after placebo and 2mg nicotine lozenge. Interhemispheric correlation values were calculated between the left/right ECN, while correlation values for DLPFC-DS coupling were calculated within hemisphere. In smokers, women had less interhemispheric ECN (p=0.009) and DLPFC-DS coupling (p=0.003) than men. In non-smokers, a sex x drug interaction was significant (p=0.032) for DLPFC-DS but not ECN coupling. Nicotine, but not placebo, administration elicited weaker DLPFC-DS coupling in women compared to men (p=0.036). Nicotine dependent women showed less interhemispheric ECN and DLPFC-DS coupling than men. In non-smokers, acute nicotine reduced DLPFC-DS coupling in women, mirroring the sex difference noted in chronic smokers. These findings suggest that sex differences in DLPFC-DS coupling is mediated by nicotine. Given that interhemispheric ECN coupling was not impacted by acute nicotine it is unclear whether women with such reduced coupling are more prone to smoke or if interhemispheric ECN coupling is reduced following more chronic use.

Topic areas:
Addiction
Gender Differences
Imaging
Alcohol use disorder (AUD) is one of the most co-occurring disorders among people seeking treatment for post-traumatic stress disorder (PTSD), a neuropsychiatric stress and anxiety-related disorder that often develops after experiencing traumatic or stressful life events. Many PTSD patients tend to use alcohol in an attempt to ameliorate the debilitating symptoms. However, repeated excessive alcohol consumption often leads to the development of an AUD that appears to worsen PTSD symptoms. Therefore, there is a critical need for systemic studies on the neurobiological underpinnings of the interactions between these disorders to tailor effective therapeutic strategies to reduce alcohol abuse and dependence in PTSD patients. The amygdala is a critical neural substrate of both aversive and appetitive behaviors. Recent studies in mice, including work from our own group, have indicated that distinct subpopulations of neurons within the amygdala are differentially responsible for the activation and inhibition of fear memory. In addition, divergent ensemble activity from these subpopulations seems to mediate positive or negative valence coding. The amygdala is also directly affected by a variety of acute and chronic stressors as well as addictive substances, which can lead to sensitization of its reactivity. Particularly, it has been shown that patients with comorbid AUD and PTSD exhibit hyper-reactivity of the amygdala upon presentations of both aversive/distressful stimuli and alcohol cues. These intriguing findings suggest that the amygdala is a key structure mediating the interactions between AUD and PTSD; however, molecular, cellular and neural circuit mechanisms underlying amygdala dysfunction in AUD and PTSD comorbidity are not well understood. We are employing a combination of a Thy1 Cre-driver mouse line, both optogenetic and chemogenetic neural circuit manipulation, and in vivo electrophysiological recording techniques to examine: 1) whether the experience of traumatic stress and subsequent alcohol consumption alter the neuronal ensemble code in a specific Fear-Off (Thy1+) neuronal subpopulation in the basolateral amygdala and 2) if stress-induced excessive alcohol intake is mediated by changes in the firing rate of Thy1+ neurons and functional interactions between the amygdala Thy1+ neuronal projections and the nucleus accumbens (NAcc) - a central structure of substance addiction - which can consequently lead to the escalated alcohol use. Preliminary results from ongoing experiments will be presented. The findings of these studies will provide the first insight into the crucial roles of distinct subpopulations of amygdala neurons in stress-induced excessive alcohol consumption. The results will also shed light on how the amygdala interacts with the NAcc to lead to the development of alcohol addiction. Ultimately, the findings of these studies may provide new ways for developing diagnostics and novel therapeutic interventions for AUD and PTSD patients.

**Topic areas:**
- Addiction
- Anxiety
- PTSD
- Technology
Objective: Marijuana (MJ) remains the most widely used recreational drug in the US. Attempts to quit MJ use often result in acute withdrawal effects, such as anxiety, physical discomfort, and sleep disruption, all of which contribute to high rates of relapse. The mechanism by which specific withdrawal symptoms contribute to an increased risk of relapse remain unknown. One potential explanation is that severity of certain withdrawal symptoms peak soon after an attempt at abstinence is made, suggesting there is a heightened vulnerability when a cluster of symptoms occur at the same time. Consequently, MJ users experiencing the symptom cluster during these first weeks of abstinence could be particularly vulnerable to relapse. The purpose of the present study is to determine if the severity of a specific mood state (e.g., anxiety) and withdrawal symptoms (e.g., irritability, physical discomfort, sleep disruption etc.) peak as a cluster in the first week of a 21-day abstinence period in heavy MJ users.

Method: To date, the study consists of four participants who met criteria for cannabis use disorder at baseline and initiated a 21-day abstinence period. Participants completed weekly mood measures (e.g., State-Trait Anxiety Inventory) and reported MJ-related withdrawal symptoms, such as physical discomfort symptoms (e.g., Cannabis Withdrawal Scale) and sleep disruption (e.g., Pittsburgh Sleep Quality Index (PSQI)) collected at four distinct time points: baseline, and abstinence days 7, 14, and 21. Repeated measures ANOVA was used to analyze changes in state anxiety, physical withdrawal symptoms, and sleep disruption during the different time points. Quantitative urine screens were used to confirm abstinence.

Results: A significant main effect for PSQI sleep disruption scores over time (p = 0.018) was observed. Post-hoc comparisons indicated that sleep disruption scores increased from baseline (4.75 ± 2.22) to Day 7 (6.00 ± 3.74) and then decreased from Day 7 to Day 21 (2.50 ± 2.38). Post-hoc analyses revealed no significant differences between time points. There were no significant differences in reported state anxiety or withdrawal scores. This preliminary suggests that poor sleep quality and disruption are particularly salient withdrawal symptoms that can occur during early MJ abstinence.

Conclusions: Disrupted sleep quality and its critical role in MJ withdrawal has been well-established in the literature. Our findings confirm sleep status as an important factor, but we have also identified that individuals are particularly vulnerable to relapse during the first week of abstinence. A larger sample size will permit us to analyze the other signs and symptoms in order to identify a more comprehensive cluster of symptoms that contribute to MJ relapse. Once the more salient signs and symptoms are identified, better treatment programs can be developed to specifically target these items before they emerge; data collection is ongoing.

Topic areas:
Addiction
Assessments of behavioral symptoms (e.g. depression, anxiety, insomnia, agitation) in Alzheimer’s Disease trials have relied exclusively on self- or observer report scales whose limitations are well documented. Mobile and wireless sensors have been used to offset some of these limitations and can provide continuous, passive behavioral data. However, in dementia, these devices are not ideally suited because of the need to carry/wear and regularly recharge the devices. Such devices are also unable to provide spatial information such as location, or vital signs. Emerald is a device developed at MIT for in-home, non-intrusive patient monitoring. This device uses radio signals to passively collect data on sleep, motion, spatial location and respiratory rate without touching the patient. In this study, we describe (a) the process of developing behavioral biomarkers using data from this device, (b) how such data can be used for clinical decision making, and (c) how combining information on socio-environmental factors can identify triggers of behavioral symptoms. This work describes the device’s first use in a clinical setting to monitor dementia symptoms. We installed the device in the room of a 77-year old female with Alzheimer’s disease in an Assisted Living facility. Data collection began 05/17. In Phase 1, we measured her behavior continuously and identified four behavioral markers of clinical relevance to this patient: gait speed, spatial location, respiratory rate and sleep patterns. We developed a measure of pacing severity, which was the daily aggregation of number of episodes where the patient moved 6 feet or greater in the same direction without stopping. In Phase 2, the patient’s clinician utilized these markers to propose medication changes. Prior to implementing changes, the behavioral findings identified by the sensor were confirmed by Assisted Living staff who observed the patient daily. In Phase 3, we gathered collateral information about the patient’s social activity (e.g. number of visitors, trips outside the facility, group participation) and mapped it onto sensor data to assess temporal associations. Additionally, we qualitatively compared sensor data with staff-report information. While staff reported the patient’s behavior dichotomously as either ‘calm’ or ‘restless,’ the sensor was able to detect variations in behavior by time of day, variations over a week, escalation in pacing, and episodes of awakening late at night. This study establishes the safety and feasibility of using a radio-signal based non-wearable, non-mobile sensor in a residential care setting for dementia. Data collected by the device provided much more detailed information about behavior than staff report. Since most behavioral studies rely on staff report, a device such as this holds potential to exponentially improve the quality of clinical trial data. We demonstrated that device data could be used for early detection of behavioral changes and subsequent medication adjustment and to identify triggers for behavior symptoms, such as visits from family members. Our preliminary findings point to a large potential for contactless radio-signal based devices in clinical trials as well as patient care.
Yoga relieves stress-related and psychiatric illnesses (Kabat-Zinn, 2017) and depression and anxiety symptoms (e.g., Pilkington Kirkwood, Rampes & Richardson, 2005; Cramer, Lauche, Langhorst, & Dobos, 2013). Research shows yoga improves mental health in outpatient and community settings, but less is known about its value in more intensive treatment settings. The present study is an examination the effects of a single yoga session on outcomes in a transdiagnostic sample of psychiatric patients receiving CBT/DBT skills training in a partial hospital setting. The object of this investigation was to further study the effects of yoga as complementary treatment in a behavioral health partial hospital setting. One hundred and four partial-hospital attendees (39.8% male, 59.2% female, 1% other/non-binary gender) attended at least one yoga session between March 2016 – 2017. Weekly 50-minute yoga sessions included: physical movement, guided mindfulness, meditation, breathing exercises, and focus on the mental health healing process. A pre-post intervention design measured (a) short-term changes in positive and negative affect before and after a single adjunctive yoga session and (b) symptom change over the course of treatment. All participants completed comprehensive assessments including: a modified Positive and Negative Affect Schedule (PANAS; Watson et al., 1988); Patient Health Questionnaire-9 (PHQ-9; Kroenke & Spitzer, 2002); Generalized Anxiety Disorder-7 (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006); Five Facet Mindfulness Questionnaire – Short Form (FFMQ-SF; Bohlmeijer, ten Klooster, Fledderus, Veehof, & Baer, 2011); and the Mini International Neuropsychiatric Interview (MINI: Sheehan et al., 1998). A repeated-measures MANOVA was used to examine affective changes during the yoga session. Relationships between demographic variables and affect change were assessed with one-way ANOVAs and correlations. A multiple regression analysis examined the relationship of diagnoses to changes in affect. Our results were encouraging. We will present data supporting our first hypothesis: yoga session participants reported significant increases in positive affect and decreases in negative affect during the group. The data demonstrates both positive and negative affect changed significantly. We will also present data speaking to acceptability and perceived mechanisms of action. Participants in the yoga group rated the quality of their care significantly higher, indicating greater satisfaction with overall treatment. This study supports the value of a yoga session during treatment in intensive settings, and suggests that yoga increases participants’ overall satisfaction with treatment. Future research should explore optimal use of yoga interventions in intensive treatment setting.

**Key words:** Mood, CBT, Yoga, Acceptability, Affect
Presenting Author: Kim Cramer, Senior Admin Manager, Clinical Research Coordinator, Partners Biobank

Co-Authors: Chuda Rijal, J. Hunter Howie, Kerry Ressler

Title: Partners HealthCare Biobank at McLean Hospital: The Potential of Large Scale Research in a Psychiatric Inpatient Setting.

Key words: Biobank, genetics, depression, anxiety

Background: Establishing the genetics underlying human pathology is crucial to fully understand the mechanisms of disease and identify more effective treatments. Blood-based biomarkers are fundamental to research and therapy for a number of medical conditions. McLean Hospital participates in the Partners Healthcare Biobank (Biobank), a multi-institutional research initiative that provides researchers with necessary materials to investigate the genetic factors in disease.

Methods: Patients with diverse psychiatric diagnoses are recruited to participate in the Biobank from inpatient units specializing in: depression and anxiety, addiction and substance abuse, psychotic disorders, obsessive compulsive disorders, and geriatric psychiatry. Consenting to the project grants the Biobank access to patient health information. Genetic materials (DNA, plasma, and serum) are collected through blood draws, and patients complete a lifestyle and environment questionnaire. Current research intends to seek potential relationships between these self-report measures, psychometrics, and genomic data.

Results: Since January 2016, McLean Hospital has enrolled over 2200 patients. More than 73,000 patients have consented to participate in the greater Partners Biobank. The statistical analysis reveals that the psychiatric inpatient population (N= 3423) has a higher consent rate than overall Partners Biobank, X2 (1, N = 79256) = 240.25, p < .001. Data from depression and anxiety units (N= 1275) also follows this trend, X2 (1, N = 77981) = 82.73, p < .001. Consent status information from collaborating studies and online consents were not included in this analysis.

Conclusions: These preliminary data suggest that there is a higher willingness of McLean patients to participate in the Partners Biobank. This may have potential implications for the viability of large-scale research in an inpatient, psychiatric setting. Furthermore, the Partners Biobank is an important component to enable future genomic research in psychiatric and other disorders. To date, the Partners Biobank has provided samples or data to more than 120 research studies.

Topic areas:
Anxiety
Bipolar
Depression
GeriatricOCD
Psychotic disorders
The use of synthetic cathinones, or “bath salts,” has become more widespread in recent years. “Bath salts” share many chemical properties with psychostimulants like methamphetamine, or entactogens like 3,4-methylenedioxymethamphetamine (MDMA or “Ecstasy”), presumably reflecting structural differences that lead to differing neurochemical actions. Yet, currently available synthetic cathinones have not been well-characterized in primate species, and it is unclear which pharmacological activity mediates their abuse-related behavioral effects.

The present study was initiated to address this question, using drug discrimination procedures to evaluate several synthetic cathinones in two groups of squirrel monkeys. Each subject was trained to respond on either of two levers under a FR10 schedule of reinforcement and, during training sessions, responding on one lever was reinforced after pretreatment with vehicle whereas responding on the second lever was reinforced after pretreatment with the training drug. Under terminal conditions, one group of monkeys discriminated 0.1 mg/kg methamphetamine from saline; the other group discriminated 0.6 mg/kg MDMA from saline. Drug or saline lever assignments were counter balanced across the left and right levers within each group. Training sessions comprised multiple components, and a component consisted of a ten-minute timeout period, followed by ten presentations of the FR10 schedule, each followed by a brief 50-second timeout. After criterion performance was met (≥ 90% correct), test days interspersed training days, with at least two training days between each test day. The effects of five different synthetic cathinones (α-PVP, MDPV, mephedrone, methylone, and methcathinone) were tested in both groups. A full range of doses of each drug was administered using cumulative dosing procedures. Results show that doses of 0.1 mg/kg – 0.32 mg/kg of MDPV, α-PVP, and methcathinone were identified as methamphetamine in subjects trained to discriminate 0.1 mg/kg methamphetamine from vehicle, whereas doses of mephedrone and methylone up to those that decreased overall response rates did not generalize. Preliminary results suggest an opposite profile of substitution in MDMA--trained animals. Thus, mephedrone and methylone, but not MDPV, α-PVP, and methcathinone,-- did appear to generalize to MDMA. These results demonstrate that synthetic cathinones have differing substitution profiles in animals trained to discriminate methamphetamine or MDMA, which may reflect differing subjective effects and, perhaps, differing abuse liability in man.

**Topic areas:**
Pharmacology
Focusing on sex as a biological variable in cognitive neuroscience is essential for understanding the basic neural mechanisms contributing to sex differences in behavior, cognitive function, and psychiatric disease. For example, women have higher rates of internalizing disorders, such as depression and anxiety, while men have higher rates of externalizing disorders, such as anti-social personality disorder, yet the neural mechanisms underlying such sex differences are not well understood. Sex differences in large-scale brain networks that modulate internal and external attentional processes may predispose each sex to these categories of mental illness. Cognitive tasks requiring external focus engage the dorsal attention network (DAN) and suppress the default mode network (DMN, which is highly active during resting mentation), while the frontoparietal control network (FPN) flexibly couples with the DMN and/or DAN to support internal and external attention. Whether men and women engage these networks differently during tasks that require external attention is not well known, and may give insight into sex differences in attentional engagement that may impact a range of cognitive processes. Using functional magnetic resonance imaging (fMRI) data from a large sample (n=190) of healthy participants from the Human Connectome Project, we investigated sex differences in DMN, DAN, and FPN activation during an incentive processing task (exposure to reward and loss stimuli) and during a working memory task (0-back and 2-back task). We chose these tasks because the working memory task is known to reliably suppress the DMN and activate the DAN, while the incentive processing task also requires external attention but includes valenced stimuli. We defined the DMN, DAN, and FPN using independent component analysis via FSL’s MELODIC tool on an independent group of healthy participants’ resting state scans (n=16). Multivariate spatial regression of the resulting maps against each subject’s fMRI data was done to calculate the strength of activation of each network during each task condition (reward, loss, 0-back and 2-back versus baseline fixation). We found that, relative to men, women show increased suppression of the DMN (reward trials: $t = 3.16, p = 0.003$; loss trials: $t = 3.22, p = 0.002$) and greater activation of the DAN (reward trials: $t = 3.07, p = 0.004$; loss trials: $t = 2.80, p = 0.010$) during incentive processing, but not during working memory. There were no sex differences in FPN activation for either task. Our results suggest that, compared to men, women engage more attentional resources to valenced external stimuli by showing greater suppression of the DMN, which modulates internally-oriented mentation, and greater activation of the DAN, which modulates externally-oriented attention. Sex-specific neural processing of valenced stimuli may give insight into the neural mechanisms regulating sex biases in internalizing and externalizing psychiatric disorders.
The gold standard for measuring ethanol in the body is blood alcohol concentration (BAC). However, breath samples are far more practical in terms of speed of analysis, convenience and breath also avoids the risk of infection. Past research has identified a number of factors that may influence the accuracy of breath alcohol concentration (BrAC) and in turn, may affect the breath-blood alcohol partition coefficient (Hlastala, 1998; Norberg et al., 2003; Jones and Andersson, 1996; Reynolds 2001). The goal of the present study was to document and then quantify the differential effect of several real-world drinking scenarios on BrAC as compared to BAC. Six different scenarios were selected: exercise, consuming a “last call” drink after a priming dose, eating (social snacking and full meal), and two control groups (low and high dose). A secondary aim was to document the effects of speed of drinking and alcohol dose. Male and female social drinkers between 21-40 years of age signed an informed consent and passed a physical and psychiatric exam in order to participate in up to six different scenarios. Blood was sampled at 2- or 5-min intervals via an antecubital arm vein using an indwelling catheter. BAC was quantified by gas chromatography with flame ionization detection (GC/FID). Participants received a 0.3 or 0.9 g/kg dose of 40% vodka, either with or without a mixer. The dose was consumed in 2 minutes for the exercise, last call, and control scenarios or over 1.5 hours for the two eating scenarios. BrAC was also recorded every 2 or 5 minutes using a hand-held breathalyzer (Intoximeter Alco-Sensor FST). The study visit concluded once the BrAC was at or below 0.068% for three consecutive readings. To determine the accuracy of BrAC as compared to BAC across scenarios, we examined the R2 values of individual drinking scenarios as well as the overall R2 value for all of the data. R2 values are as follows: 0.9001, 0.8321, 0.7864, 0.7815, 0.7412, and 0.6022 for Last Call, Control – High Dose, Exercise, Social Snacking, Control- Low Dose, and Full Meal, respectively, with an overall R2 value of 0.8906. To correct for buccal alcohol contributing to erroneously high readings after consuming alcohol, the BrAC data for the first 20 minutes was removed from the exercise, last call, and control scenarios and the first 1.5 hours was removed from the eating scenarios. The results confirm the direct relationship between BrAC and BAC, and advance our knowledge by demonstrating that this strong correlation persists even after manipulating the alcohol dose, speed of consumption, and engagement in a variety of real world scenarios including exercise, last call, and social snacking. The one exception was the Full Meal scenario and the low correlation for this condition is most likely due to a restricted range of data comparison points; data collection for this scenario is ongoing.
Our objective for this study was to assess how best to engage Partners Biobank participants in further research opportunities, a critical step towards large-scale research efforts such as the All of Us research program (Precision Medicine Initiative). Specifically, we wanted to understand what recruitment messages were the most likely to attract participants to start and complete a brief research study. To answer this question, we contacted approximately 33,000 patients as part of a regularly scheduled Biobank newsletter. In the middle of the newsletter, there was a brief recruitment message and link to a pair of cognitive assessments administered by TestMyBrain.org. Participants were randomized to one of three recruitment messages emphasizing: (1) the opportunity to contribute to scientific research, (2) fun brain games, and (3) return of research results, specifically learning more about your cognitive style. Overall participation was low at 4.9% of opened emails. However, the rate of participation was significantly different across message formats (Chi-squared: 17.9; $p < 0.0001$), with the message emphasizing return of research results attracting 55% more participants than the brain games message and 18% more than contributions to science. Recruitment rates did not differ significantly across message formats based on race, gender, sex, or age. Overall, these data strongly indicate that return of research results is the best method for engaging Biobank participants, compared with more standard recruitment messages emphasizing gamification/entertainment or contributions to science.

**Topic areas:**
Technology
Presenting Author: Madeline Kuppe, Clinical Research Assistant

Co-Authors: Kelly A. Sagar, M. Kate Dahlgren, Rosemary T. Smith, Ashley M. Lambros, Staci A. Gruber

Title: The Cannabis Curve: Transient Decrements in Verbal Learning Among Medical Marijuana Patients

Key words: Medical Marijuana, Verbal Learning, Verbal Memory, RAVLT

Background: The relationship between chronic, heavy recreational marijuana (MJ) use and cognitive decrements has been well documented in the scientific literature, particularly with regard to poorer performance on measures of verbal learning and memory. However, few studies thus far have examined whether such decrements extend to medical MJ (MMJ) use. Given that 29 states and Washington, DC have fully legalized MMJ and an additional 18 states allow some MMJ products, it is imperative to assess cognitive outcomes related to MMJ use. Preliminary reports from our lab have demonstrated improvements in executive function in MMJ patients over initial phases of treatment, but it is unclear whether similar outcomes will be observed on measures of verbal learning and memory.

Methods: As part of a larger study, patients were recruited from local MMJ certification centers. Patients were assessed before beginning regular MMJ treatment, after 3 months of treatment, and after 6 months of treatment. At each visit, patients completed a series of clinical scales and a neurocognitive battery, which included the Rey Auditory Verbal Learning Task (RAVLT) to assess both initial learning and longer-term verbal memory. Patients also provided comprehensive details regarding their MMJ treatment regimens.

Results: After 3 months of MMJ treatment, patients achieved significantly fewer correct responses following the long delay condition of the RAVLT relative to their baseline performance. Additionally, patients exhibited trends for fewer correct responses at Trial 1 as well as across all trials (1-5) relative to baseline. Following 6 months of MMJ treatment, although patients continued to demonstrate fewer correct responses on the long delay condition of the RAVLT relative to baseline, performance was improved relative to the 3-month assessment. In fact, after 6 months of MMJ treatment, patients demonstrated improved performance on all initial learning trials and made significantly fewer intrusions at Trial 1 and across all trials (1-5). A trend was also observed after 6 months for fewer perseverations across all trials relative to baseline levels of performance.

Conclusions: Patients demonstrated significant but temporary impairments in verbal learning over the course of MMJ treatment; decrements observed after 3 months of MMJ treatment were no longer apparent after 6 months of treatment. Further, significant improvement in verbal learning, as indicated by fewer intrusions and perseverations, was observed after 6 months of treatment. Verbal memory decrements persisted after 6 months of MMJ treatment relative to baseline despite some improvement relative to assessments at 3 months of treatment. These results suggest that verbal learning decrements may be transient among patients using MMJ, resolving after patients habituate to MJ, but that decrements in verbal memory may persist for longer periods of time. Future studies should examine verbal memory changes over a longer course of MMJ treatment to assess whether these changes remain or eventually resolve.

Topic areas:
Quality/Outcomes
Depression is characterized by deficits in reward-based learning. In previous studies, depression was shown to be associated with dysfunctional processing of reward and punishment demonstrated by reduced reinforcement learning. Recent literature suggested that amisulpride, a presynaptic D2/D3 dopamine receptor antagonist, enhanced reinforcement learning signals in healthy individuals. However, little is known about its effect on learning signals in depressed individuals. In the current study, we hypothesized that amisulpride increased both reward and punishment learning in depressed individuals. To test our hypothesis, we followed a double-blind, placebo-controlled protocol, during which 32 participants with clinical depression (MDD) and 31 healthy controls (HC) were randomly assigned to receive either a placebo, or a low dosage of amisulpride (50 mg). Participants performed a social RL task during an MRI scan. During the task, subjects had to choose one of two stimuli presented on the screen in order to obtain a reward (cheer sound) or avoid a punishment (boo sound). Subjects had to learn, by trial and error, the changing stimulus–outcome associations. Participants also completed Snaith Hamilton Pleasure Scale (SHPS) and Beck Depression Inventory (BDI) to assess anhedonic and depressive symptoms respectively. For the behavioral analysis, learning rate was calculated by adding the deviation between the subjects' and pre-defined total choice across the task, and a Group x Condition (Drug/Placebo) x Valence (Reward/Punishment) ANOVA of learning rate was conducted. fMRI data were processed using SPM12 and onset times of reward and punishment feedbacks were convolved with hemodynamic response function. As nucleus accumbens (NAc) has been strongly implicated in reward learning and depression, we extracted parameter estimates from left and right NAc and analyzed them using SPSS. Results: Behavioral analyses revealed a main effect of Valence (reward vs. punishment; p< .001) on reinforcement learning rate across groups (HC vs. MDD) and conditions (drug vs. placebo). In addition, a trend towards significance for the Group x Condition interaction was observed. Exploratory post-hoc analyses revealed amisulpride enhanced learning in the clinical group, but not in controls, regardless of reward or punishment. Consistent with the literature, reward learning signals were observed in the striatum and punishment learning signals were observed in the insula and habenula across all subjects. However, no significant differences were observed between HC and MDD, either in the placebo or drug conditions in the nucleus accumbens. Conclusions: As hypothesized, our preliminary findings show that behaviorally, amisulpride increased reinforcement learning in depressed individuals, potentially revealing antidepressant-effects of amisulpride.
Presenting Author: Maria Mavrikaki, Instructor

Co-Authors: Mavrikaki Maria, Pantano Lorena, Potter David, Rogers-Grazado Maximilian A, Amr Sami S and Chartoff Elena

Title: *Sex-dependent changes in miRNA expression following stress*

Key words: sex differences, stress, microRNAs (miRNAs)

Anxiety disorders disproportionately affect women compared to men, and sex differences in stress response have been described. miRNAs are small non-coding RNAs regulated by factors such as stress and gonadal sex, and they have been implicated in the pathophysiology of multiple psychiatric disorders. The present study assessed putative sex differences in the effects of an ethologically relevant stressor, adolescent social isolation (SI), on miRNA expression in the bed nucleus of stria terminalis (BNST), a brain region implicated in anxiety. Male and female Sprague-Dawley rats underwent SI during adolescence or remained grouped housed (GH), and were tested for anxiety-like behavior in the elevated plus maze as adults. Small RNA sequencing was performed on tissue extracted from the BNST. We show that adolescent SI induced a more robust anxiogenic profile in females compared to males. Using differential expression analysis, we found that SI stress resulted in differential expression of 56 miRNAs unique for females, 25 miRNAs unique for males, and 12 miRNAs were differentially expressed in both sexes compared to GH controls. Our future studies aim to identify the mRNA targets of those stress- and sex-regulated miRNAs, and to assess the effects of specific stress-and sex-regulated miRNAs on anxiety-like behavior. These results suggest that stress- and sex-regulated miRNAs might underlie, in part, sex differences in the anxiogenic effects of SI.

Topic areas:
Anxiety
Gender Differences
Exploring the Role of Doublecortin (DCX) in Fear

BACKGROUND: The majority of research on doublecortin (DCX)-expressing cells has occurred in the context of neurogenesis, but recent evidence supports an association between affect and DCX levels even in non-neurogenic regions, including the basolateral amygdala (BLA). However, the functional and behavioural role of BLA DCX expression has not yet been explored, and DCX’s contributions to local plasticity remain unclear. The goal of the current study is to ascertain what role, if any, BLA DCX may play in the acquisition and expression of fear. Here we present our preliminary data on this topic.

METHODS: C57BL/6 mice underwent associative fear conditioning during which tones (conditioned stimuli; CS) were paired with foot shock. Fear expression, extinction, and behavioural generalization were assessed in tandem with protein expression of DCX in the BLA. To explore the impact of stress on these measures, mice were exposed to early (5wks) or late (8wks) acute immobilization stress, followed by fear conditioning.

RESULTS: Although we found no evidence of group differences in DCX expression among either animals exposed to stress or fear conditioning, our results suggest that DCX may play a role in individual variation in response to threat. Exposure to shock or fear acquisition appeared to modulate DCX levels such that by 24hrs post-exposure high-freezing animals displayed elevated DCX as compared to low-freezing animals. High-DCX animals also displayed more rapid acquisition of fear and a greater tendency to associate unpaired tones with shocks, suggesting an enhancement in learning speed at the expense of discrimination. Similarly, higher DCX expression was associated with increased generalization of fear to tones that differed in frequency from the CS. Subsequent exposure to the CS during fear expression testing and extinction training likewise appeared to modulate DCX as a function of individual levels of freezing, and our early evidence suggests that the persistence of these associations may be strengthened by early immobilization stress.

CONCLUSION: DCX expression in the BLA is associated with individual differences in threat-induced freezing and generalization, and early stress may influence how robustly this association is maintained during adulthood. DCX may therefore prove an interesting candidate for future studies in resilience.

Topic areas:
Anxiety
PTSD
Presenting Author: Mary Kathryn Dahlgren, Senior Clinical Research Assistant

Co-Authors: Kelly A. Sagar, Rosemary T. Smith, Ashley M. Lambros, Madeline K. Kuppe, Staci A. Gruber

Title: Life is a Highway: Assessing the Residual Impact of Heavy Recreational Marijuana Use Without Acute Intoxication on Driving

Key words: marijuana, driving, non-intoxicated, residual impact

Background: Marijuana (MJ) is the most popular illicit substance in the US; the most recent national survey from the Substance Abuse and Mental Health Services Administration indicated that 118.5 million people aged 12 or older reported at least one lifetime use and 24.0 million reported at least one use in the past month (SAMHSA, 2017). As eight states and Washington DC have legalized recreational use of MJ for adults, it is critical to assess the potential impact MJ use has on complex skills such as driving. Evidence suggests that recent MJ use and higher levels of MJ metabolites are associated with impaired driving, but research thus far has primarily focused on the effects of acute intoxication. The objective of the current study was to assess the potential residual impact of MJ use in the absence of acute intoxication on driving.

Methods: Current, heavy, recreational MJ users, defined as those who use at least five of the last seven days, report at least 1,500 lifetime uses, and test positive for urinary cannabinoids, were compared to non MJ-using healthy control (HC) participants on a driving simulator program (STISIM Drive, Systems Technology Inc.), which includes both rural and urban driving conditions and takes approximately 10 minutes to complete. In order to assess the potential impact of age of MJ onset, MJ users with early onset (regular use prior to age 16) and those with late onset (regular use at 16 or older) were compared to HC participants. At the time of testing, MJ users were abstinent for a minimum of 12 hours and therefore not acutely intoxicated.

Results: Overall, MJ users demonstrated poorer performance on the driving simulator relative to HC participants. Specifically, MJ users had significantly more speed exceedances, more pedestrian collisions, and fewer stops at red lights relative to HC participants. Additionally, trends emerged for MJ users to miss more stop signs, make more centerline crossings, and spend greater percentage of time over the speed limit relative to HCs. Interestingly, when the MJ-using group was divided into those with early versus late age of MJ use onset, it became clear that the observed between-group differences were attributable to the early MJ onset group. For example, early onset users had hit significantly more pedestrians relative to HC participants, and no significant differences were detected between the HC and late onset groups. Further, correlation analyses revealed that earlier age of MJ onset was associated with increased number of collisions and increased number of missed stop signs.

Conclusions: The current data suggest that chronic, heavy MJ users, particularly early onset users, demonstrate impaired driving in the absence of acute intoxication. Interestingly, impairment occurring without acute intoxication differed slightly from reports of impaired driving associated with acute intoxication. For example, acute MJ intoxication is commonly associated with slower driving, while the current study observed faster driving in non-intoxicated MJ users; future studies should investigate the link between behaviors associated with MJ use, particularly early use, (e.g., impulsivity, risk-taking) and their impact on cognition.

Topic areas:
Addiction
Adolescence is a developmental period characterized by rapid changes in the brain, placing teens at high risk for initiation and escalation of substance use. Many adolescents seeking substance use treatment have co-occurring psychiatric diagnoses, including a high rate of anxiety disorders. Few studies have examined whether domains of anxiety differ between adolescents with and without substance use disorders, and whether treatment differentially affects these groups. This study examined adolescent patients (N=486, ages 13-19, mean age=17.0 ± 1.4 years) enrolled in a two-week residential treatment program. The Multidimensional Anxiety Scale for Children (MASC) was administered at intake and discharge and included physical symptoms, social anxiety, harm avoidance, and separation anxiety subscales. Psychiatric and substance use diagnoses were established at intake using the MINI-KID Structured Clinical Interview. Among this adolescent sample, 358 met criteria for a substance use disorder (SUD+), including cannabis (77%), alcohol (50%), hallucinogen (16%), opioid (15%), and benzodiazepines (12%). Anxiety diagnoses included social phobia (40%), generalized anxiety disorder (38%), posttraumatic stress disorder (18%), panic disorder (17%), agoraphobia (12%), obsessive-compulsive disorder (5%), and separation anxiety disorder (3%). Significant reductions in total anxiety, physical symptoms, social anxiety, and separation anxiety were evident at discharge (p<.001), however, harm avoidance increased (p<.005). Total and separation anxiety decreased significantly in the SUD- group (p<.005), while all MASC subscales were lower at discharge in the SUD+ group, with the exception of harm avoidance (p<.001), which increased significantly (p<.005). Substance users also exhibited greater reductions in social and total and greater increases in harm avoidance after treatment (p<.005). Lower harm avoidance correlated with greater emotion regulation difficulties, higher impulsivity, and more frequent risky behaviors (substance use and rule breaking). These results indicate that residential treatment for co-occurring disorders differentially influences anxiety symptoms in adolescents with and without SUD. A significant increase in harm avoidance after treatment may be adaptive, serving as a protective factor against subsequent risk-taking, including relapse. Future research should investigate whether increased harm avoidance after treatment is predictive of lower rates of relapse in substance-using adolescents, and potentially, interventions that target and enhance recovery on this domain of anxiety should be explored.
The prevalence of tobacco cigarette smoking is twice as high among individuals with major depressive disorder (MDD) compared to the general population, suggesting a link between MDD and nicotine use. One hypothesis suggests that individuals with MDD use nicotine as a form of self-medication. Such a hypothesis is plausible given nicotine’s ability to enhance reward function and induce plastic changes in cortico-striatal pathways, which is disrupted in those with MDD. Specifically, individuals with MDD show reduced connectivity between the nucleus accumbens (NAc) and the rostral anterior cingulate cortex (rACC) while also showing enhanced connectivity between the dorsolateral prefrontal cortex (DLPFC) and the dorsal striatum (DS). Such disrupted functional connectivity patterns have been related to blunted positive affect and disease severity, suggesting that normalizing these connections may ultimately mitigate depressive symptoms. To determine the impact of acute nicotine on cortico-striatal connectivity, we administered nicotine to non-smoking individuals with (n = 18) and without MDD (n = 17) prior to collecting resting state functional magnetic resonance imaging (rsfMRI) data. All participants tested negative for alcohol and illicit drug use, were medication-free at the time of the study, and groups were matched on age and sex. Nicotine or placebo was administered in a double-blind, randomized, cross-over design such that peak nicotine levels were reached during fMRI scanning. Following standard fMRI pre-processing, a seed-based analysis was used to evaluate cortico-striatal connectivity. Results showed a significant drug by group interaction for NAc-rACC connectivity (F = 5.54, p = 0.025). On the placebo visit, post-hoc analysis confirmed prior findings that individuals with MDD have reduced NAc-rACC connectivity relative to healthy controls (p < 0.001). While nicotine significantly increased NAc-rACC coupling in those with MDD (p < 0.001), nicotine did not influence coupling in controls. There also was a significant drug by group interaction for DLPFC-DS connectivity (F = 5.87, p = 0.021). Relative to healthy controls, individuals with MDD had significantly greater DLPFC-DS coupling on the placebo day. This enhanced DLPFC-DS coupling in those with MDD was reduced by nicotine (p = 0.007). Nicotine had no impact on DLPFC-DS coupling in healthy controls. These findings show that acute nicotine normalizes cortico-striatal connectivity in non-smokers with MDD, suggesting a mechanism underlying the link between MDD and nicotine dependence. This work has implications not only for understanding the co-morbidity between these disorders, but also suggests the need to revisit using nicotinic medications to treat aspects of MDD.
Title: Ensuring quality and compliance using a gas delivery system in cerebrovascular imaging analysis

Key words: Cerebrovascular reactivity, BOLD analysis, Imaging analysis, Quality assurance

Our laboratory has designed and tested a portable MRI-compatible gas delivery system to be used during functional magnetic resonance imaging (fMRI) experiments for performing calibrated cerebrovascular reactivity (CVR). We will describe the construction of the device and present methods of validation from an ongoing R01 protocol. CVR provides a measure of brain blood vessels’ capacity for vasodilation and corresponding changes in cerebral blood flow. The brain depends on the vasculature to maintain constant cerebral blood flow and to flexibly respond to changes in oxygen demand. CVR measures can provide critical information on cerebrovascular integrity, which has implications for individuals who are at risk for stroke and is also considered a potential mechanism that may contribute to observed cognitive problems. For example, individuals who are at an increased risk for stroke will display a delay in vasodilation compared to individuals who are not at risk for stroke due to compromised cerebrovascular integrity; these changes in CVR can be quantified using fMRI. The blood-oxygen-level-dependent (BOLD) signal measured with fMRI is sensitive to changes in cerebral blood flow and volume. Manipulating the vasodilation of blood vessels and obtaining information on CVR can be achieved through administration of gases or a breath hold challenge, which can be detected as changes in the BOLD signal. Accurate monitoring of administered gases and compliance to the breath hold challenge is needed to properly manipulate vasodilation and ensure data quality.

The gas delivery system administers medical air, oxygen, and carbogen (a combination of oxygen and carbon dioxide) to participants in the MRI scanner to capture changes in CVR. The system contains gas tanks, tubes connecting from the tanks to a mouthpiece, and switches to turn gas administration on and off. The mouthpiece has an additional small tube attached at its base that hooks up to the BIOPAC capnography system. The BIOPAC records gas concentration in the exhaled breath of the participant and displays the results in real time on a computer display, allowing adjustments in gas delivery to be made instantaneously. Participant compliance can be checked via associated changes in the signal and the amount of CO2 that participants exhale, as observed via the BIOPAC. For example, the breath hold challenge requires that participants hold their breath after expiration instead of after inspiration, as the former elicits a BOLD response that goes above baseline which allows meaningful changes in CVR to be observed. A participant who correctly exhaled before the breath hold task will show an immediate increase of CO2 before the breath hold due to the expelled air. By obtaining this information, CVR can be quantified in both clinical and research settings. As CVR can provide critical information in understanding cerebrovascular dysfunction, this system can be translated into a medical setting to aid physicians in better predicting stroke in at risk patients, or into a research setting to better understand the etiology behind observed cognitive problems. Within these manual manipulations of CVR, monitoring of quantity of delivered gases is critical in ensuring data quality and participant compliance.

Topic areas:
Imaging
McLean Research Day 2018

Original Research - Clinical

Poster # 51
Time: 1:00-1:50pm

Presenting Author: Nikolaos Daskalakis, Associate Neuroscientist & Member of the Faculty


Title: Genetically Predicted Gene Expression in the Brain and Peripheral Tissues Associates With PTSD

Key words: gene expression, brain, periphery, PTSD, imputation

Background: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder occurring in a subset of individuals exposed to trauma. To date, little is known about the genetic etiology of the disorder, although the latest GWAS demonstrates that genetic heritability is at a comparable level to that of other psychiatric disorders. PTSD development involves multi-systemic dysregulation in multiple brain and peripheral tissues, and epidemiologic evidence suggests that PTSD patients commonly have psychiatric, cardiovascular, metabolic and immune comorbidities.

Methods: The transcriptomic imputation framework using expression quantitative trait loci (eQTL) reference panels and machine-learning methods can predict gene expression from large genotype data, offering the opportunity to conduct tissue-dependent PTSD-gene associations. Here, we apply CommonMind Consortium (CMC) and Genotype-Tissue Expression (GTEx) derived gene expression prediction (GReX) models to the PGC-PTSD genotype data (9,245 cases/ 24,285 controls). GReX models corresponded to multiple tissues (11 brain regions, 5 cardiovascular tissues, 2 endocrine tissues, 1 peripheral nerve, 1 adipose tissue and whole blood). We stratified analyses according to trauma type (civilian vs. combat trauma), sex, and self-defined ancestry.

Results: We identified 15 significant PTSD-gene associations, corresponding to 12 unique genes and 11 unique tissues, of which 3 were in periphery (heart atrial appendage, tibial artery, tibial nerve). Identified genes were in pathways previously associated with PTSD. Results also indicated that there was a substantial genetic heterogeneity between civilian and combat PTSD risk. Using PsychENCODE reference map, we demonstrated that brain-based PTSD-association statistics correlated with the probability for neuronal histone marks of open chromatin. Furthermore, in a blood gene expression dataset (n=175), we confirmed a more significant correlation of observed PTSD differences in the blood with the GReX PTSD differences in the blood compared to the other tissues. In the CMC dataset, we compared microarray-based gene expression in DPLFC between 10 PTSD cases and 51 controls (matched for age, sex, and ancestry) and observed a high degree of replication of observed PTSD differences in the brain-based GReX PTSD differences, and vice versa. Finally, reduced GReX of a microglia-related gene, SNRNP35, in BA9 brain region had the strongest association with PTSD. In a traumatized inner city cohort (n=96), fMRI activity was analyzed in relation to performance in a response inhibition task. There was a significant effect of a SNRNP35 eQTL on brain activity only in interaction with PTSD, where the minor allele associated with reduced GReX of SNRNP35, was also associated with low BA9 activity.

Conclusions: Our transcriptomic imputation analyses identified novel genes for PTSD risk, with a tissue resolution. SNRNP35 is the most promising gene for further functional investigation of its role in stress vulnerability and resilience.

Topic areas:

PTSD
Presenting Author: Oeystein Brekk, Postdoctoral research fellow (PhD)

Co-Authors: O. R. BREKK1, M. HUEBECKER2, E. B. MOLONEY1, A. MOSKITES1, D. A. PRIESTMAN2, F. M. PLATT2, *P. HALLETT1, O. ISACSON1;  1Neuroregeneration Res. Inst., Harvard Med. Sch. / McLean Hos., Belmont, MA; 2Dept. of Pharmacol., Univ. of Oxford, Oxford, United Kingdom

Title: **Glycosphingolipid accumulation in the brain in aging is associated with alpha-synuclein dimerization**

Key words: Aging, Glycosphingolipids, Alpha-synuclein

Aging is the most significant risk factor for developing several neurodegenerative disorders, including Parkinson’s disease (PD) and Alzheimer’s disease (AD), and the vast majority of cases are non-familial. The connections between aging and disease-associated genes, for example GBA1, alpha-synuclein, or Tau, are not fully understood. We have previously observed an age-dependent reduction in glucocerebrosidase (GCase) activity (encoded by GBA1) in normal aging in the human brain (Rocha et al., 2015, Ann. Clin. Trans. Neurol.2(4):433-8). Our recent lipidomic analysis in the brains of wildtype mice between 1.5 and 24 months of age, indicates that aging reduces GCase activity also in mouse brain, and induces accumulation of glycosphingolipids (GSLs), including an elevation of glucosylceramide and glucosylsphingosine. Pharmacological inhibition of glucocerebrosidase in mice, which elevates these same GSLs in the brain, promotes alpha-synuclein aggregation (Rocha et al., 2015, Antiox. Redox Sig.23(6):550-64), and gene delivery of GBA reduces alpha-synucleinopathy in animal models (Rocha et al., 2015, Neurobiol. Dis. 82:495-503). In the current study, we have tested whether GSL accumulation in the normal aging brain of FVB wildtype mice, is associated with disturbances in the conformational and phosphorylation states of alpha-synuclein and Tau, and markers of intracellular protein degradation pathways. When comparing detergent soluble- and insoluble fractions of whole brain homogenates from 6 weeks old mice versus >2 years aged mice, we identified a dimeric alpha-synuclein band in aged animals in both fractions that was completely absent in the young animals. Furthermore, we observed hyperphosphorylation of soluble and insoluble tau protein within the aged cohort, and a strong accumulation of polyubiquitinated proteins in older animals in the detergent insoluble fraction. Ongoing studies will test region specificity of these protein changes in the aging brain, and whether pharmacologically induced increased GSL levels in young mice phenocopies the specific alpha-synuclein and Tau changes we have observed in aging. Overall, we hypothesize that perturbation of GSL metabolism in aging may precede or be part of abnormal protein handling, and accelerate degenerative processes in vulnerable neurons in PD and other neurodegenerative disorders.

Topic areas: Alzheimer's/Dementia
**Presenting Author:** Paris Singleton, Clinical Research Assistant II

**Co-Authors:** Erin Bondy, Jeremy G. Stewart, Christian A. Webb, Blaise Aguirre, Cynthia Kaplan, Diego Pizzagalli, Randy P. Auerbach

**Title:** Electrocortical Reward-Related Markers Among Healthy and Borderline Personality Disorder Youth

**Key words:** BPD, ERP, RewP

**Background.** Borderline personality disorder (BPD) is a debilitating condition characterized by reward processing deficits (Andreou et al., 2015). Presently, it is unclear how event-related potentials can differentiate BPD and healthy youth. The current study tested reward processing differences in healthy and BPD youth in response to rewarding and non-rewarding feedback.

**Method.** The study included two groups of adolescents aged 13-23 years: (a) healthy controls (HC = 35) and (b) borderline personality disorder (BPD = 33). Participants completed diagnostic interviews and a guessing task in which participants were rewarded or penalized on each trial while electroencephalography data were acquired. The reward positivity (RewP) was probed 230-330 ms post-feedback, and we hypothesized that BPD youth would have a smaller RewP difference wave (losses regressed onto wins) relative to HC adolescents.

**Results.** A significant Group (HC, BPD) x Condition (Win, Loss) interaction emerged, $F(1, 66) = 4.42, p = 0.04, \eta^2 = 0.06$, and post-hoc analyses revealed a significant difference in wins and losses in the HC group, $F(1,66) = 32.04, p = 0.001, \eta^2 = 0.327$, and the BPD group, $F(1, 66) = 6.590, p = 0.013, \eta^2 = 0.091$. Also, the HC group had a significantly greater difference score compared to the BPD group ($t(66) = 2.05, p = 0.04$).

**Conclusions.** BPD youth showed a more blunted response to rewards, suggesting that abnormal reward processing may be a core etiological mechanism that contributes to the onset of BPD in youth.


**Topic areas:**
BPD
Child/Adolescent
Presenting Author: Poopak Hafezi, Psychiatry research fellow

Co-Authors: Poopak Hafezi, Elizabeth Bolger, Kyoko Ohashi, Laura Hernandez Garcia, Cynthia McGreenery, Leslie Weiser, Alaptagin Khan, Martin Teicher.

Title: Effectiveness of Phototherapy on Early Morning Attention, EEG and Functional Brain Activity in School Children

Key words: Electroencephalography, Lite Book, Circadian Phase, Adolescence

Introduction: Adolescence is characterized by a number of important biological changes, alterations in brain metabolism, sleep quality and circadian phase. Circadian acrophase shifts resulting in a strong urge to stay up and awaken late. Hence, a large percentage of normal adolescents arrive at school with an insufficient amount of sleep, which can take a substantial toll on their academic performance. In this study, we sought to test the hypothesis whether consistent morning use of a portable phototherapy device by healthy adolescents would shift the circadian phase of their normal rest-activity rhythm and enable to fall asleep earlier, receive increased amount of sleep and perform better on tests of attention and academic performance.

Methods: 26 un-medicated adolescents (8M/18F, ages 13-18, mean 17.1 ± 1.4 years), with no psychiatric symptoms were recruited at a local school. Subjects were instructed to use the Litebook Elite™ for 30 mins each morning. Assessments included pre-post phototherapy activity monitoring to determine bedtime, rise time and total sleep time, in addition to attention, academic performance and processing speed and IQ, as well as behavioral and emotional screening. EEG was used to assess alertness, drowsiness and sleep as well as functional brain imaging. Pre and post LiteBook actigraph data on bed time, rise time, total sleep time and sleep efficiency were analyzed using linear mixed effects models.

Results: There was a significant interactive effect between degree of LiteBook use (percent use) and school day classification on rise time (F1,308 = 6.76, p = 0.0098), with greater LiteBook use leading, in particular, to earlier rise times on non-school days. Further, LiteBook use was associated with reduced day-to-day variability in rise times (Likelihood ratio (LR) test = 18.51, p < 0.0002). There were significant effects of percent LiteBook use on measures of improved attention of the Quotient ADHD System vigilance task. Greater LiteBook use was associated with greater post-test improvement in accuracy and reduction in errors of omission. Additionally, the degree of LiteBook use was significantly associated with increase in eyes-opened beta1 spectral power, particularly in leads F8 (p = 0.026), T5 (p = 0.0029), P3 (p = 0.020) and O2 (p = 0.0036). Structural MRI findings revealed a significant quadratic effect of phototherapy use on the right dentate gyrus (F1,7 = 6.13, p = 0.0425), which showed a trend level interaction with age (F1,7 = 3.57, p = 0.100).

Conclusions: There is compelling scientific evidence that school children, particularly adolescents are chronically sleep deprived and this degree of sleep restriction exerts demonstrable effects on memory encoding, consolidation and processing speed. We also know that the primary reason that adolescents are sleep deprived is due to a naturally occurring phase delay in their biological clock. Through this small pilot study, we provide convincing evidence that light treatments, through even low cost portable devices can phase advance the biological clock, thus reversing this problem.

Topic areas:
Child/Adolescent
Imaging
Quality/Outcomes
Effects of Chronic Cocaine Self-Administration on Cognition-Related Behavior in Nonhuman Primates

Cocaine addiction is a longstanding public health concern. Long-term cocaine use is associated with cognitive deficits such as impulsivity which may reduce the effectiveness of behavioral interventions. However, there is surprisingly little known about long term effects of chronic cocaine exposure on cognitive performance. Therefore, the current study aimed to evaluate the effects of chronic cocaine self-administration on performance in two touchscreen-based cognitive tasks over the course of nine months. These touchscreen cognitive tasks, repeated acquisition and discrimination reversal, serve as animal models of learning and cognitive flexibility, respectively. Six male squirrel monkeys were trained in a touchscreen chamber to discriminate between two simultaneously-presented stimuli (acquisition). Once this task was mastered, subjects then re-learned the discrimination with the contingencies switched (reversal). Subjects were trained to discriminate and reverse numerous stimuli across sessions. After performance on both touchscreen tasks became stable, subjects were implanted with intravenous catheters and trained to self-administer cocaine. A wide range of doses were tested in each subject, and the dose which yielded the highest daily intake was chosen for subsequent daily self-administration. Subjects self-administered high dosages of cocaine daily during 1-hr sessions for 9 months, followed by 1 month of abstinence. Performance in touchscreen tasks were examined every 30 sessions of cocaine self-administration and after a 30 day abstinence period. Each touchscreen probe examined the acquisition and reversal rate for 5 novel discriminations, and was conducted 22 hours after the previous self-administration session. Results indicate that after 30 sessions of cocaine self-administration, subjects required significantly more trials to master both acquisition and reversal compared to baseline performance. Reversal was much more adversely affected compared to acquisition. We observed a positive correlation between dosages of self-administered cocaine and trials required to master acquisition tasks across individual subjects. Touchscreen performance steadily improved across sessions and after 120 sessions of cocaine self-administration, performance did not differ significantly from baseline. Touchscreen performance following 1 month of cocaine abstinence most closely approximated baseline levels. These data indicate that self-administered cocaine can markedly impair discrimination learning and cognitive flexibility processes, but that these cognitive deficits may decrease in severity over time. Future studies will examine effects of potential treatment drugs on cocaine-induced cognitive deficits.
Presenting Author: Rachel Geyer, Clinical Research Assistant; B.A.

Co-Authors: Roger D. Weiss, Monika Kolodziej, R. Kathryn McHugh

Title: Sleep Disruption and Pain-Related Craving in Chronic Pain: The Role of Opioid Misuse

Key words: chronic pain, opioid misuse, sleep disruption

Introduction: Sleep disruption is common among those experiencing chronic pain and is associated with an array of negative outcomes. Among the negative consequences of sleep disruption is increased reactivity to stressors, such as pain and psychosocial stress. However, it is unknown whether sleep disruption increases stressor-induced opioid craving, a risk factor for opioid analgesic misuse. Indeed, opioid-dependent individuals report greater craving on days when sleep quality the previous night is lower than usual. The present study aims to extend prior research by testing the association between sleep disruption and pain-induced craving among those with chronic pain who were prescribed opioids.

Methods: A sample of 51 participants (24 women; mean age = 54.6 years) who were prescribed opioid analgesics for chronic neck or back pain was recruited from a pain management clinic of a large, urban hospital. Participants completed a variety of self-report measures, including the Pittsburgh Sleep Quality Index, the Opioid Craving Scale, the Positive and Negative Affect Schedule, the Current Opioid Misuse Measure, and the Brief Pain Inventory. Participants also completed a series of experimental tasks designed to test responding to pain. A linear regression analysis was used to test whether sleep disruption was associated with greater craving in response to pain induction in adults with chronic pain, both with (n = 31) and without (n = 20) opioid misuse.

Results: Results indicated that greater sleep disruption was associated with greater opioid craving in response to pain induction, controlling for age, gender, pain severity, and negative affect. This result was qualified by a significant interaction between opioid misuse and sleep disruption, in which the association between sleep disruption and craving was stronger among those with more severe medication misuse.

Conclusion: Among those with chronic pain, sleep disruption was associated with greater pain-related craving. This effect was driven by those who misused their medications, for whom the association between sleep disruption and craving was robust. This finding is consistent with negative reinforcement models of substance misuse, in which opioids are used to relieve distress, even despite negative consequences. Sleep disruption may be an important marker of risk for opioid misuse among those with chronic pain. Adequate treatment of sleep disruption may be a promising target for mitigating negative outcomes (including opioid craving) in this population.

Topic areas:
Addiction
Presenting Author: Ravi Shah, Research Fellow

Co-Authors: Christina M. Temes, Frances R. Frankenburg, Garrett M. Fitzmaurice, Mary C. Zanarini

Title: Time-varying comorbid disorders as predictors of recovery from borderline personality disorder over the course of 20 years of prospective follow-up.

Key words: Borderline personality disorder, Longitudinal course, Recovery

Objective: The aim of this study was to determine the impact of axis I disorders on recovery status of borderline patients over the course of 20 years of prospective follow-up.

Method: A semi-structured interview for DSM-III-R axis I disorders (SCID-I) was administered at baseline to assess the presence or absence of comorbid axis I disorders in 290 inpatients who met rigorous criteria for borderline personality disorder (BPD). Ten follow-up interviews, including the SCID I, separated by 24 months were conducted over 20 years. Time-varying predictors (absence of mood, substance, PTSD, anxiety, and eating disorders) were used to predict recovery status—which is defined as concurrent symptomatic remission and good social and good full-time vocational functioning.

Results: Sixty percent of those with BPD obtained a two-year recovery over the two decades of follow-up. When the absence of current comorbid axis I disorders was used in a multivariate logistic regression to predict recovery from borderline personality disorder, absence of substance use disorders (OR=4.91) was the strongest predictor of recovery, followed by absence of eating disorders (OR=2.84), PTSD (OR=2.81), mood disorders (OR=2.21), and anxiety disorders (OR=1.73).

Conclusions: The findings from this study suggest that the absence of comorbid substance use disorders is most closely associated with the achievement of recovery from borderline personality disorder.

Topic areas:
BPD
Title: Association between mutual-help groups & opioid abstinence among prescription opioid dependent patients with and without agonist treatment during 42-month post-treatment follow-up?

Key words: addiction, treatment, prescription opioids, buprenorphine

Background: In the multi-site CTN Prescription Opioid Addiction Treatment Study (POATS), participants receiving agonist treatment had significantly better opioid use outcomes during the main trial and at 18-, 30-, and 42-month follow-up. However, many participants abstained from opioids during the month prior to the month 18 (37%) and 42 (50%) assessments, respectively, far higher than in the main trial (<10%); 80% of those in agonist treatment abstained at months 18 and 42. This exploratory analysis examined factors related to successful outcomes in those not receiving agonist treatment.

Methods: A total of 338 of 653 original POATS participants also participated in the Long-term Follow-up Study, which consisted of 45-60 minute telephone interviews by McLean Hospital staff at months 18, 30, and 42 post-randomization.

Results: At each follow-up assessment, at least half of the study participants self-reported opioid abstinence (50-64%) in the past month, regardless of whether or not they were currently in treatment for opioid use disorder. Most (61-66%) reported treatment for opioid use disorder in the past month; for example, at month 18, 32% were in opioid agonist treatment, 23% were attending mutual-help groups, and 13% were in outpatient counseling. The association between mutual-help attendance and opioid abstinence varied by opioid agonist treatment: among those not in opioid agonist treatment, mutual-help attendance was significantly associated with opioid abstinence ($\chi^2(1)=4.98-5.78$, p values=.02-.03 at the 3 follow-up assessments); however, among those in opioid agonist treatment, mutual-help attendance was not associated with opioid abstinence ($\chi^2(1)=0.28-1.75$, p values=.18-.59 at the 3 follow-up assessments).

Conclusions: It was common for patients to seek agonist treatment at the conclusion of the treatment trial, and those in agonist treatment were more likely to be opioid-abstinent at long-term follow-up. Mutual-help attendance appeared to be associated with opioid abstinence, but that association was statistically significant only in the absence of opioid agonist treatment.

Topic areas:
Addiction
Quality/Outcomes
Background: Marijuana (MJ) contains over 100 phytocannabinoids that modulate activity of the body’s endocannabinoid system, involved in regulating various physiological and cognitive processes. The two most common phytocannabinoids are Δ9-tetrahydrocannabinol (THC), the main psychoactive constituent in MJ, and cannabidiol (CBD), the primary non-intoxicating constituent that has recently been touted for its potential medicinal benefits. Interest in medical applications for MJ have increased over the past several decades, and currently medical marijuana (MMJ) is legal in 29 states plus Washington, D.C. However, thus far, no studies have evaluated the differential impact of THC and CBD on clinical state and cognition in MMJ patients over the course of treatment.

Methods: As part of a larger longitudinal study, patients were recruited from local MMJ certification centers and were assessed before beginning MMJ and after three months of MMJ treatment on measures of clinical state, including the Profile of Mood States (POMS), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). In order to assess potential changes in cognition, patients also completed a battery of neurocognitive assessments, which included the Multi-Source Interference Task (MSIT), a robust measure of executive function and cognitive control processing, which a subset of patients completed during concurrent functional magnetic resonance imaging (fMRI). Variables related to MMJ treatment regimens, including specific product information (via laboratory testing) were also collected. Using this information, patients were divided into those who primarily used THC-dominant (THC-Dom) or CBD-dominant (CBD-Dom) MMJ products and strains in order to analyze the differential impact of THC versus CBD on clinical state and cognition.

Results: Following three months of treatment, the CBD-Dom group reported improvements in self-reported ratings of depression and anxiety, as evidenced by significant reductions in BDI, BAI, and POMS Total Mood Disturbance (TMD) scores and a trend for reduced POMS Depression scores. Interestingly, after three months of treatment, the THC-Dom group reported trends for increased POMS Depression and TMD scores, whereas BDI and BAI ratings did not change significantly. In terms of cognitive performance, after three months of treatment, CBD-Dom patients performed significantly better on both the control and interference conditions of the MSIT, while THC-Dom patients only demonstrated trends for improved performance on the interference condition. Further, fMRI activation in the cingulate cortex (CC) and frontal regions of interest during the MSIT increased in the CBD-Dom group after three months of treatment, approaching levels of activation in healthy controls observed in previous studies, while increased CC and frontal activation was not significant in the THC-Dom group.

Conclusions: After three months of MMJ treatment, patients reported differential changes in clinical state and executive function, with CBD-Dom patients demonstrating greater improvement in self-reported depression and anxiety symptoms, executive function, and a larger magnitude of increased brain activation during the MSIT compared to THC-Dom patients. These preliminary data suggest that “what’s in your weed” may be of critical importance in determining the effects of MMJ on variables such as clinical state, cognition, and brain function.

Topic areas: Anxiety, Depression, Imaging, Quality/Outcomes
Disorders with combined or rapidly altering features of depression and excitement have long been recognized. As described by his associate Weygandt in 1895, mixed states (Die Mischzustände) may have encouraged Kraepelin to consider all recurring major mood disorders as a single entity (manic-depressive illness). DSM included mixed-states of bipolar disorder in 1994, and currently (2013) recognizes mixed features in depression or mania. Such conditions are clinically complex and challenging to treat, but little is known about their epidemiology or prognostic implications, based on currently accepted definitions. Accordingly, we conducted a systematic review of reports of the prevalence of mixed features in primarily depressive, hypomaniac, or manic states. Systematic searching identified 17 reports from 13 world regions involving over 19,000 mood-disorder subjects. Prevalence of cases with ≥3 features of opposite polarity averaged 27.8% [CI: 27.2–28.5] overall, and differed significantly among bipolar and major depressive disorders, ranking: bipolar-depressed (35.2% [33.8–36.5]) = bipolar-manic or hypomaniac (35.1% [32.9–37.3]) > major depressive disorder-depressed (23.8% [23.0–24.5]). We also evaluated characteristics of 1582 mood-disorder patient-subjects at mood disorder centers in Sardinia and Rome, of whom 387 (24.5%) had depression with ≥3 hypomanic features, or dysphoric [hypo]mania at an index episode near intake. Prevalence of mixed features ranked: bipolar-II (30.4%) > bipolar-I (19.8%) = unipolar major depression (19.8%); women (26.2%) > men (21.9%); and with depression (21.0%) > mania or hypomania (10.1%). Subjects with mixed features were significantly more likely to: [a] be women, [b] have earlier illness-onset, [c] have more irritable temperament, [d] abuse substances, [e] attempt suicide, [f] be more ill and respond less well to treatment during long-term follow-up, and [g] be treated more with antipsychotics and less with antidepressants. In conclusion, mixed features in depression and mania were quite prevalent, especially in bipolar-II disorder, and were associated with clinically less favorable illness, substance abuse, and suicide attempts.
Characterizing antidepressant combinations and implications for treatment in a psychiatric hospital sample

Depression, Polypharmacy, Antidepressant, Demographics, Treatment Outcomes

Background: Antidepressant use increased by 5% in the general population from 1999 to 2014, according to the CDC. For individuals with treatment-resistant depression, antidepressants are often combined with additional medications. However, there is a dearth of research characterizing polypharmacy in real-world psychiatric hospital settings and even less data regarding the use of multiple antidepressants. Answering previous studies’ calls for an understanding of the use of multiple antidepressants, the current study examined (1) rates of antidepressant polypharmacy; (2) demographics and clinical characteristics of patients prescribed multiple antidepressants; and (3) the impact of antidepressant polypharmacy on treatment outcome in a partial hospital program.

Methods: 1307 patients seeking treatment at a partial hospital program from September 2015 to June 2017 completed a self-report measure of depressive symptoms (Patient Health Questionnaire (PHQ-9)) and the clinical global improvement scale (CGIS). Patients received pharmacotherapy management and cognitive behavioral therapy for typically 3-10 treatment days. Medication prescribed upon admission and primary diagnosis were obtained from patient medical records. We created groups according to antidepressant polypharmacy (no antidepressants, 1 antidepressant, 2 or more antidepressants).

Results: Upon admission to the partial hospital, 68% of patients were prescribed at least one antidepressant. Of the patients prescribed an antidepressant, 33% were prescribed more than one. Of the patients prescribed multiple antidepressants, 97% were prescribed antidepressants from multiple subclasses. The most common antidepressant combination was an SSRI and a tetracyclic. Compared to individuals not prescribed antidepressants, individuals prescribed one or more antidepressants were significantly older, female, white, had less formal education, and working full time. Individuals prescribed an antidepressant were also reported significantly more symptoms of depression, anxiety, self-injury and less symptoms of psychosis. Individuals prescribed one versus multiple anti-depressants did not differ on any of the demographic or clinical characteristics. Antidepressant use did not predict treatment outcome, controlling for baseline severity.

Conclusions: Most individuals entered the psychiatric partial hospital program with an antidepressant prescription, and many were prescribed multiple antidepressants and a variety of combinations of classes. We will discuss the prescription patterns and associations with treatment response in the context of current guidelines for treatment-resistant depression. Limitations of this study include the naturalistic treatment setting and lack of control group. Additional results regarding how primary diagnosis affects the pattern of results will be presented.
**Presenting Author:** Shelly Greenfield, Chief Academic Officer, McLean Hospital, Professor of Psychiatry

**Co-Authors:** R. Kathryn McHugh, PhD, Dawn Sugarman, PhD, Meghan Reilly, BA, Garrett Fitzmaurice, ScD

**Title:** Perceived Stress and Depression in Substance Use Disorder Treatment

**Key words:** depression, stress, group therapy, co-occurring disorders, behavioral therapy

**Aims:** Depression is highly prevalent among those with substance use disorders, and is negatively associated with treatment outcome. Studies have found evidence for the reduction of depressive symptoms during substance use disorder treatment; however, it is unclear whether factors other than reductions in substance use affect this change. The aim of this study was to examine whether reductions in perceived stress were associated with changes in depression over the course of substance use treatment, above and beyond the effect of substance use.

**Methods:** This is a secondary analysis of a randomized clinical trial (N=138) testing two group therapies for substance use disorders: the Women's Recovery Group and Group Drug Counseling. Participants completed self-report measures of stress and depressive symptoms at 4 assessment points, each 3 months apart. We conducted a linear mixed model examining whether perceived stress predicted depressive symptoms at the next assessment, controlling for depressive symptoms at the prior assessment, and concurrent days of substance use. This lagged model also controlled for demographic variables, treatment condition, and major depression.

**Results:** Preliminary analyses found that both perceived stress and depression significantly decreased over the course of treatment. The results of the lagged mixed model found that perceived stress was associated with later depressive symptoms, even when controlling for previous depressive symptoms and days of substance use (Est.=0.58, SE=0.05, t=2.58, p = .01).

**Conclusions:** These results support the observation that depressive symptoms decline significantly in substance use disorder treatment. In this study, perceived stress was significantly associated with subsequent depressive symptoms, even controlling for substance use. These results may reflect a shared mechanism for the reduction of stress and depressive symptoms, or could reflect that reductions in stress yield reductions in depressive symptoms. Further understanding of these changes will help to refine treatments to target co-occurring depression.

**Topic areas:**
Addiction
Depression
Women
Presenting Author: Sina Azimi, Technical Research Assistant
Co-Authors: Nima Azimi, Ryan O’Conner, John-Paul Argenti, Miles G. Cunningham
Title: Optimizing Intracerebral Delivery of Therapeutics within the Central Nervous System (CNS)
Key words: Agarose Phantom Brain, Intracerebral Microinjection Instrument, Microcannula, Stroke

Introduction: Restorative neurological therapeutics such as stem cells and viral vectors, are being developed and utilized as neurosurgical interventions for diseases in the central nervous system. To take full advantage of the benefits of these new therapeutics, delivery methodology must be precise and minimally invasive. Designs for delivery cannulas were engineered to determine the specifications that minimized or eliminated reflux of therapeutic retrogradely around the delivery cannula. One such design has been incorporated in a novel delivery instrument, the Intracerebral Microinjection Instrument (IMI). The IMI has proven to be highly accurate, to minimize trauma, and to permit three-dimensional dissemination of therapeutic in complex arrays within the human brain.

Materials/Methods: Microcannulas with variable specifications were tested for the delivery of blue latex microsphere suspension into a phantom brain model made with 0.6% agarose. The design variables included differences in internal and external diameter and variations on step design as well as flow rate. All simulated injections were documented with a video monitor.

Results: A cannula design that shows reduced reflux was engineered into the IMI which was then tested using an agarose phantom brain the actual size of a human brain. A simulated tumor was placed within the phantom brain and was successfully targeted with the IMI. The three-dimensional volume of the agarose tumor was completely filled with blue latex microspheres the size of viral particles using a single overlying penetration of the IMI.

Conclusion/Discussion: With further development of stem cell biology in recent years, an interest in utilizing neural transplantation as a therapeutic intervention has reemerged. The same cannot be said regarding the advancement of delivery technology as it has not changed in nearly 100 years. With the sophistication of new novel therapeutics, delivery methodology should follow suit enabling accurate, reproducible placement of precise volumes of therapeutic in strategic locations of the brain. The IMI has met this challenge and is presently being used to deliver therapeutic stem cells in patients having suffered basal ganglia strokes. IMI technology enabled an unprecedented number of grafts to be placed tactically surrounding ischemic lesions. The procedure was well-tolerated by all patients and post-surgical recovery was without any subsequent complications. The IMI has repeatedly shown functionality and safety in complex human neural transplantation procedures and is appropriate for other restorative neurosurgical applications.

Topic areas:
Neurology
Technology
Presenting Author: Sriramya Potluri, Research Coordinator; BA


Title: Marginalized identities in intensive/residential treatment (IRT) for obsessive-compulsive disorder (OCD)

Key words: Marginalized Identities, OCD, IRT

Background: Research indicates that those who hold one or more marginalized identities (MIs) may experience treatment barriers to engage in evidence-based treatment compared to their non-marginalized counterparts (e.g., disparity in the access, quality and outcome of mental health care; Williams et al, 2016; Fuchs et al, 2013). This study aimed to investigate differences in symptom severity and treatment response among individuals who do and do not hold MIs, engaged in treatment for OCD.

Methods: 406 residents receiving IRT for OCD completed the Yale-Brown Obsessive-Compulsive Scale (YBOCS), Dimensional Obsessive-Compulsive Scale (DOCS) and Obsessive Beliefs Questionnaire-9 (OBQ-9) at admission/discharge. A “marginalization score” was created by summing MIs in the categories of age, gender, race, ethnicity, education, religion, and incidence of homelessness.

Results: The majority of our sample were 98.8% non-Hispanic, 92.1% White, 54.4% male, 97.5% below the age of 65 (M=30.96), 98.3% with at least high school education and 96.6% no history of homelessness. In line with previous OCD literature (Williams et al, 2015), our sample was not representative of the general population. Linear regression analyses indicated that higher marginalization is associated with increased overall symptom severity ($\beta=.873$, t(402)=2.035, p=.042) and severity of compulsions ($\beta=.756$, t(402)=3.031, p=.003) at admission. Among individuals who endorsed concerns about Symmetry, Completeness, and the Need for Things to be “Just Right” (NJRE; measured by DOCS-4), those with MI reported higher severity of symptoms at both admission (marginalized:M=7.08, SD=6.05; non-marginalized:M=5.72, SD=5.77; p=.02, d=0.23) and discharge (marginalized:M=4.14, SD=4.22; non-marginalized:M=3.08, SD=3.76; p=.028, d=0.27). A t-test indicated higher obsessional beliefs in individuals with MIs, at admission (marginalized:M=35.46, SD=12.5; non-marginalized:M=31.48, SD=11.327; p=.002, d=0.33) and at discharge (marginalized:M=27.218, SD=11.48; non-marginalized:M=24.606, SD=11.04; p=.042, d=0.23).

Conclusion: Results provide preliminary evidence of associations between MIs and higher symptom severity, compulsions and obsessional beliefs. Findings suggest that individuals with MIs endorsed higher symptoms on the DOCS-4 throughout treatment. Results support the importance of considering the role of marginalization in symptom severity/presentation for individuals with OCD. Further investigation is warranted to address how treatment may be augmented to ameliorate these differences.

Topic areas:
OCD
McLean Research Day 2018

Original Research - Pre-Clinical

Poster # 65
Time: 1:00-1:50pm

Presenting Author: Suyan Li, Research Fellow
Co-Authors: Yota Uno, Uwe Rudolph, Thea Anderson, Joseph Coyle

Title: D-Serine and Astrocytes: Characteristics of Primary Astrocyte Cultures

Key words: astrocyte, D-serine, Serine racemase, N-Methyl-D-Aspartate Receptor, Glycine Decarboxylase

Background: Serine racemase (SR) is an enzyme which can generates D-serine from L-serine. D-serine acting as co-agonist of N-methyl-D-aspartate receptors (NMDAR) plays a critical role in normal brain function. SR and D-serine were first discovered in cultured astrocyte cells. Recent studies showed SR and D-serine only present exclusively in neuron in mouse brain. However in pathologic condition, reactive astrocytes can also express SR and D-serine. Since cultured astrocytes exhibit features of reactive astrocytes, here we characterized D-serine and the expression of enzymes involved in its disposition in primary glial cultures.

Methods: Primary astrocyte cells were isolated from mouse cortices. We use HPLC measure the concentration of D-serine in cell culture medium and western blot for protein expression level of involved enzymes in primary astrocyte cells. RT-PCR and RNA-scope were used to check the expression level of SR in mRNA level.

Results: SR and D-serine expressed in cultured astrocytes from wild type mouse (n=6) cortices but not in cultured astrocytes from SR knockout mice (n=6). When astrocytes just isolated from the brain (day 3), SR expression can barely detected. But SR expression level increase significantly with the duration in culture (day 5 and day 7), so does the concentration of D-serine in cell-cultured medium. However SR mRNA expression was observed from the earliest time (day 1) in culture and increased significantly in day 5 and day 7 primary astrocyte cells. Astrocytes derived mice over-expressing glycine decarboxylase (TRIP, n=5) exhibited a more rapid clearance of glycine and accumulation of D-serine from the medium than astrocytes obtained from wild-type (WT) mice whereas astrocytes from SRKO mice showed slow clearance of glycine and no accumulation of D-serine. We checked the expression of Lipocalin2 (LCN2), the marker of reactive astrocyte in primary astrocytes and found its expression increased with the duration in culture. The expression of LCN2 in astrocytes from TRIP mice was significantly higher than astrocytes from wild type or SRKO mice.

Conclusion: In this study, astrocytes transform to reactive state in vitro and express SR and D-serine. These results provide additional support for the conclusion that reactive astrocytes express SR and release D-serine.

Topic areas:
Schizophrenia
McLean Research Day 2018

Original Research - Clinical

Poster # 66
Time: 1:50-2:45pm

Presenting Author: Talia Cohen, Clinical Research Assistant II

Co-Authors: Dost Ongur, M.D., PhD, Justin Baker, M.D., PhD, Eve Lewandowski, PhD

Title: Relationships between symptom presentation and resting state functional connectivity in first episode psychosis

Key words: first episode psychosis, functional connectivity, psychotic disorders, mania

Psychotic disorders (including schizophrenia, schizoaffective disorder, and psychotic bipolar disorder) are debilitating illnesses that affect around 1% of the population. Abnormalities in resting state functional connectivity (rsFC) in patients with psychotic disorders are well documented in literature; however, little research has investigated the relationship between network connectivity and symptom presentation. This study aimed to identify relationships between clinical domains and rsFC in a first episode psychosis (FEP) population. Data were collected from a sample of 37 FEP patients recruited from the McLean OnTrack Clinic. We conducted a covariance matrix between measures of symptom domains (including the YMRS, MADRS, and PANSS) and Yeo et al.’s (2011) 17 networks of functional connectivity. Results showed a strong positive Pearson correlation between YMRS scores and Ventral Attention Network connectivity ($r = .553, p <.01$). We believe these results are a step towards understanding which cortical networks are most closely associated with the pathological symptom presentation in FEP patients.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia
McLean Research Day 2018

Original Research - Pre-Clinical  

Presenting Author: Tania Lintz, Research Assistant II  
Co-Authors: Maria Mavrikaki, Sarah Page, Elena H. Chartoff  

Title: Effects of morphine abstinence on oxycodone self-administration in male and female rats  

Key words: addiction, rat, distress intolerance, sex difference, self-administration  

Prescription opioid abuse is a major public health concern. Opioid abuse is associated with heightened levels of distress intolerance—defined as the perceived inability to tolerate negative physical (e.g. pain) and emotional states. This raises the possibility that distress intolerance measures can be used to predict the likelihood of initiating prescription opioid abuse. Chronic opioid administration leads to dependence, characterized by a withdrawal syndrome comprising intense, short-lived physical symptoms and protracted stress-like psychological symptoms. It is thought that the intense desire to avoid withdrawal-induced negative states contributes to continued drug use and the transition to addiction. Accumulating evidence indicates that women are more likely than men to abuse opioids to self-treat negative affect and pain, suggesting that the predictive power of withdrawal-induced negative affective states would be greater in women. Here we used acoustic startle, warm water tail flick latency, and somatic withdrawal signs as proxies for distress intolerance in adult male and female Sprague Dawley rats after a non-contingent regimen of escalating dose chronic morphine (or vehicle). However, although somatic withdrawal signs were increased in morphine-treated male and female rats, we did not observe evidence of withdrawal-induced hyperalgesia, increased acoustic startle, or decreased open arm time in the EPM during morphine withdrawal. After 2-weeks abstinence from morphine (or vehicle), rats were implanted with jugular vein catheters and allowed to self-administer oxycodone (0.06 mg/kg/inf). We found that male rats self-administered more oxycodone than females during the 5-day acquisition period. Although prior morphine treatment tended to increase oxycodone intake in males and females, there was not a significant effect. Distress intolerance measures were correlated with oxycodone self-administration behavior (N=21 rats/sex). We found that some measures of distress intolerance (e.g., tail flick latency, acoustic startle amplitude, and time in the open arms in the elevated plus maze) taken at baseline (pre-morphine) and during morphine withdrawal significantly correlated with the total amount of oxycodone taken during acquisition. These data support our hypothesis that both distress intolerance measures taken either before or after a regimen of painkiller treatment can be used to predict vulnerability to oxycodone abuse.

Topic areas:  
Addiction  
Gender Differences
McLean Research Day 2018

Program Description

Poster # 68
Time: 1:50-2:45pm

Presenting Author: Teresa Henderson, Staff Nurse, BSN

Co-Authors: Paula Bolton, NP

Title: The Use of ECT Group Programming to Foster Recovery

Key words: Support group, ECT, Recovery

Electroconvulsive therapy (ECT) is used to treat a number of treatment resistant psychiatric conditions. By the time patients seek ECT treatment they have often failed a number of other treatment modalities. Stigma associated with mental illness and especially with treatment resistance often leaves patients feeling isolated and fearful of disclosure to others. This adds to the burden of doubt that often accompanies the decision to seek ECT treatment. Fear of the side effects of ECT (including cognitive and memory side effects) is often cited by those considering ECT and is the primary concern of patients undergoing ECT treatment. Peer support has been a powerful tool in recovery for patients with serious mental illness. The development of peer support groups co-led by ECT nurses and persons with lived experience has helped patients and significant others gain emotional, informational and social support. The main goals of the ECT support groups has been to instill hope, to share information and experiences, to promote caring and support among the group members, to dispel misconceptions and stigma, to identify and strengthen social networking and affiliation and to empower members in their recovery process. The process of developing and refining the ECT support group programming for both inpatients and outpatients and the ongoing development of cognitive retraining groups for members will be discussed. The use of ECT nurses along with peer specialists has added to the richness of the programming.

Topic areas:
- Anxiety
- Bipolar
- Depression
- Geriatric
- Schizophrenia
McLean Research Day 2018

Original Research - Pre-Clinical

Poster # 69
Time: 1:00-1:50pm

Presenting Author: Teresia Osborn, PhD, Assistant Neuroscientist, Instructor

Co-Authors: Ria Thomas, Deepika Dinesh, Eliza Ferrari, Joanna Korecka, Ole Isacson, Penny Hallett

Title: Optimization of factors in protocols to differentiate iPSCs into midbrain dopamine neurons for Parkinson’s disease

Key words: Parkinson’s disease, Dopaminergic, iPSC

Parkinson’s disease (PD) is a chronic progressive neurodegenerative disease in which dopaminergic neurons originating in the substantia nigra degenerate, resulting in loss of motor control. Treatment with L-DOPA can initially restore dopaminergic (DA) levels and motor function, but does not treat the disease. At the onset of symptoms and diagnosis about 70% of the midbrain DA neurons have degenerated, at which stage treatment with therapeutics to prevent cell loss is too late. Instead, neural transplantation with midbrain dopamine neurons can specifically replace the DA cell population and provide functional motor benefits in patients with PD. The use of pluripotent stem cell derived neurons provides the opportunity to overcome current limitations posed by fetal donor tissue in PD. For this approach, robust and reproducible protocols for differentiation of pluripotent stem cells toward ventral midbrain dopaminergic fates are essential. We have previously published two differentiation protocols that generate midbrain dopaminergic neurons (Cooper O. et al., Mol Cell Neurosci. 2010 Nov;45(3):258-66 and Sundberg M., et al., Stem Cells. 2013 Aug;31(8):1548-62). Our recent efforts have led to an efficient xeno-free and feeder-free protocol that we have successfully 1) transplanted into 6-OHDA lesioned rats using both a fresh and frozen-thawed cell preparation, with successful graft survival and behavioral recovery, 2) used for autologous transplants in parkinsonian primates and 3) used in vitro in cell vulnerability and drug-discovery studies. Here we have compared factors commonly used in protocols for differentiation of iPSCs into midbrain dopaminergic neurons and show that the ideal concentrations, timing of addition, as well as protein isoforms (FGF8a vs. FGF8b) differ depending on the underlying protocol and procedure. As the reality of using midbrain dopaminergic neurons derived from pluripotent stem cells for transplantation is getting closer to the clinic, an understanding and clarification of the differences in the protocols proposed for such use is essential.

Topic areas:
Neurology
Neuroinflammation is common in many psychiatric disorders, contributing to the selective neuronal degeneration of Alzheimer's disease and Parkinson's disease. Recent research suggests that inflammation may also contribute to the pathophysiology of schizophrenia. This study aims to clarify how schizophrenic symptoms arising from glutamatergic dysfunction may make patients more vulnerable to systemically induced neuroinflammation. We model schizophrenia using mice with impaired N-methyl-D-aspartate receptor (NMDAR) activity caused by genetically silencing serine racemase (SR), which synthesizes the forebrain NMDAR co-agonist D-serine. SR is a risk gene for schizophrenia, and our SR-knockout mice (SRKO's) replicate schizophrenic pathology with impaired NMDAR signaling, reduced long-term potentiation, and decreased dendritic branching and spine density. Their reduced activation of NMDARs on interneurons leads to decreased inhibitory signaling and excessive subcortical dopamine release associated with psychosis. To determine the neurological consequences of bodily infection in schizophrenia, we intraperitoneally injected adult SRKO mice and age-matched wild-type (WT) littermates with 1mg/kg of lipopolysaccharide, a bacterial toxin that produces a systemic immune response as well as neuroinflammation. Several hours after injection all the mice looked ill, as expected. However, 22h after injection the SRKO mice began showing seizure-like activity and dying while the WT's remained unaffected. Although clinicians observe that systemic inflammation can be associated with schizophrenic relapse in their patients, research into how and why this occurs is still quite new. Our pilot study suggests that NMDAR hypofunction directly sensitizes our schizophrenia model mice to neuroinflammation, either by decreasing their resilience or amplifying neurotoxicity. This study is ongoing, with completion expected before January 2018.

Topic areas:
Schizophrenia
Title: Anterior cingulate glutamate levels are linked to abnormal high-frequency resting-state functional connectivity in bipolar disorder

Key words: Depression, Bipolar, Imaging, Electroencephalography, MRS

Background: Abnormal activity in large-scale functional networks is a consistent finding in mood disorders. Among these networks, functional magnetic resonance imaging (fMRI) studies indicate that deficits in cognitive control and emotion regulation may be linked to aberrant resting-state functional connectivity (rsFC) within the central executive network (CEN). However, since fMRI has limited temporal resolution, much remains unknown about how neuronal synchronization at higher frequencies contributes to these disturbances. Furthermore, despite evidence suggesting that rsFC is impacted by glutamatergic transmission, and concurrent evidence of abnormal anterior cingulate glutamatergic function in mood disorders, no study to date has examined whether rsFC disturbances and glutamatergic disturbance are linked in mood disordered individuals. The current study aimed to address this gap in the literature.

Method: We capitalized on the high temporal resolution of electroencephalography (EEG) to investigate the temporal dynamics of rsFC in individuals with unipolar (n=44) and bipolar (n=17) mood disorders, and healthy controls (n=24). Ratios of glutamate to glutamine (Glu/Gln) in the rostral anterior cingulate cortex (rACC) was measured using MRS. rsFC within the DMN and CEN was computed in the delta, theta, alpha and beta frequencies using a measure of lagged phase synchronization in conjunction with a distributed source localization technique. This method avoids the effects of volume conduction as it represents the connectivity of computed intra-cortical, as opposed to scalp-based, signals after the potentially artifactual zero-lag contribution has been excluded.

Results: A main effect of Group emerged for CEN connectivity in the Beta-3 frequency band, F(2,82)=4.08, p=.02, where the bipolar group had significantly higher connectivity compared to the control group (p=.02), and marginally stronger connectivity relative to the unipolar group (p=.095). Although groups did not differ in rACC Glu/Gln (p>.05), within the bipolar group, stronger Beta-3 band CEN connectivity correlated with levels of rACC Glu/Gln (r=.55, p=.03) as well as manic symptomatology (r=-.53, p=.04). No group differences emerged for DMN connectivity (p>.05).

Conclusions: These findings extend our understanding of the temporal dynamics of rsFC by showing that high-frequency rsFC in the CEN – a network critically implicated in emotion regulation – is associated with bipolar mood symptomatology. Furthermore, the findings build on prior work pointing to glutamatergic abnormalities in mood disorders by showing that disruptions in rACC glutamatergic transmission may drive aberrant high-frequency communication within the CEN. These results point to a potential mechanism linking glutamate abnormalities to emotion dysregulation in bipolar disorder.

Topic areas:
Bipolar
Depression
Imaging
McLean Research Day 2018

Original Research - Clinical

Poster # 72
Time: 1:50-2:45pm

Presenting Author: Ashley Lambros, Clinical Research Assistant II

Co-Authors: Kelly A. Sagar, M. Kathryn Dahlgren, Atilla Gonenc, Rosemary T. Smith, Madeline K. Kuppe, Scott E. Lukas, Staci A. Gruber

Title: Improved Stroop Performance and Increased Cortical Activation Following Three Months of Medical Marijuana Treatment

Key words: medical marijuana, executive function, fMRI, Stroop

Background: Currently, 29 states and the District of Columbia have fully legalized medical marijuana (MMJ) programs and an additional 18 states offer limited access to MMJ. In the U.S. alone it is estimated that over 1.2 million individuals are certified for MMJ treatment, not including those who elect to use products derived from industrial hemp and therefore do not require certification. While significant efforts have been made to understand the impact of recreational marijuana use, little research has focused on the cognitive impact of MMJ treatment. Accordingly, the current study was designed to assess the impact of MMJ treatment on cognitive performance and associated patterns of brain activation, specifically during tasks of executive function and inhibitory processing.

Methods: As part of a larger ongoing longitudinal study, patients were recruited from local MMJ certification centers, and were assessed before beginning MMJ and again after three months of MMJ treatment on measures of clinical state and cognition. A subset of participants also underwent functional magnetic resonance imaging (fMRI) while completing a modified version of the Stroop Color Word Test, a measure of inhibitory control and executive function that reliably and consistently activates regions of interest in the cingulate (CC) and frontal cortex. The Stroop has three conditions: color naming, word reading and interference. During the interference condition, participants are presented with words printed in an incongruent color (i.e. “blue” printed in green ink), and must name the color of the ink, thereby inhibiting the overlearned response of reading.

Results: Following three months of MMJ treatment, patients demonstrated significantly improved performance during the Stroop interference condition with significantly fewer errors of commission and omission, relative to their baseline performance. Further, during this condition, fMRI analyses revealed that within the CC, although no significant activation was observed at baseline, MMJ patients demonstrated significant activation following three months of MMJ treatment. Activation within the frontal cortex was localized to the left frontal gyrus at baseline, and increased to include bilateral frontal regions following three months of treatment. Additionally, improved performance and brain activation changes occurred within the context of improvements in mood, quality of life and sleep quality.

Conclusions: Results, which represent preliminary data from the first MMJ study to assess measures of cognition and brain function, suggest improved Stroop task performance and alterations in patterns of brain activation following three months of MMJ treatment. This is in contrast to previous studies of young recreational MJ users, which have reported an association between MJ use, poorer task performance and changes in brain function. Interestingly, following treatment, the observed patterns of activation particularly within the CC, more closely resembled healthy control activation patterns from previous studies than patients’ baseline state, suggesting potential “normalization” of brain activation patterns following MMJ treatment. Improvement of clinical symptoms, reduced conventional medication use and age of the MMJ patients may have contributed to the observed changes on the Stroop task. Additional research should further examine the mechanism of these MMJ-associated improvements.

Topic areas:
Imaging
Presenting Author: Belinda Zhang, Student visitor, BSc

Co-Authors: Kang, M.S., Ironside, M.A., Rutherford, A.V, Crowley, D., & Pizzagalli, D.A.

Title: Elevated glucocorticoid stress response in major depressive disorder

Key words: Stress, Cortisol, Depression

Psychosocial stress has been found to elevate risk for a range of psychiatric disorders, including major depressive disorder (McEwen, 2007). In depression, this can be associated with reward-linked symptoms such as anhedonia and apathy. As a result, understanding the differences in stress response can contribute to elucidating neurobiological mechanisms underlying reward processing deficits. Forty two unmedicated participants (18-45 years) were recruited from the community and categorized into three groups: those with current major depressive disorder (n=11), remitted MDD (n=15), and healthy volunteers (n=16). Participants completed the Maastricht Acute Stress Test (MAST), which is a stress manipulation paradigm that reliably elicits a stress response. During the MAST, participants performed cold pressor trials by immersing their hands in cold water (2-4°C). To promote social evaluation and unpredictability, these trials varied in duration (60-90 s) and were evaluated by two experimenters. Between hand immersion trials, participants were asked to perform mental arithmetic as quickly and accurately as possible, receiving negative feedback on their performance when mistakes were made. Saliva samples were collected immediately before and 38 minutes, 60 minutes, 81 minutes and 121 minutes after the onset of stressor; the five samples were later assayed for cortisol. All three groups showed significant increases in cortisol 38 minutes after the onset of stressor (F=15.92, p<0.001), supporting the effectiveness of the stress manipulation paradigm. Repeated measures ANOVA revealed main effect of time (F=7.07, p=0.001), and suggested group by time interaction (F=2.27, p=0.068). Follow-up t-test analyses revealed that cortisol levels of healthy volunteers and remitted patients returned to baseline by 81 minutes following the stressor (p>0.1). However, cortisol levels of participants with current MDD remained nearly significant for up to 81 minutes (t=1.86, p=0.093). These findings suggest that trajectory of glucocorticoid response to acute stress is altered in current major depression, but not after remission. These results may contribute to our understanding of the association between psychosocial stress and depression, and inform future development of therapeutic targets.

Topic areas:
Depression
One main goal of Universal Health Coverage proposals in the United States is to encourage better access to care, with the potential to produce both a healthier population and reduced costs. In particular, it was hoped that this venture in Massachusetts would shift vulnerable populations away from receiving care in the costly emergency medical system and towards primary and preventive care. A specific population with traditionally high rates of emergency room use and lack of access to primary care is individuals with severe psychiatric illness. People with chronic psychiatric illnesses receive poorer medical care and have higher morbidity and shorter life-expectancy. Medical care for this population is more expensive due to both an elevated risk for several chronic comorbid illnesses, including diabetes and cardiovascular disorders, and worse outcomes for these comorbid diseases. Preventive and early care for this group, particularly in the treatment of cardiac disease and diabetes, might have a significant impact on the health of patients with chronic psychiatric illness. Massachusetts implemented a Universal Health Coverage program in 2006. Success for this program’s goals can be examined by looking at rates of insurance coverage, access to a primary care physician, and lower incidence of preventable disease. This study looked specifically at success of the program among individuals with psychiatric illness severe enough to warrant inpatient hospitalization at a tertiary care academic treatment center. We examined clinical and demographic factors and noted whether a primary care physician was identified for each patient. Results from 2005 and 2008 indicated that there was a shift in insurance carried by patients admitted to McLean Hospital (p<.001) from Medicare and Medicaid/Free-Care towards commercial insurance. However, despite increased commercial insurance coverage, there was a significant decrease (p=0.004) in the number of patients admitted to the hospital with an identified PCP from 2005 (n=388, 45.6%) to 2008 (n=382, 35.6%). Furthermore, this decrease in PCP affiliation was evident across all diagnostic groups. The purpose of this poster is to see if these trends continued into 2015, or if the effect of Universal Health Coverage equilibrated over time.

**Topic areas:**
- Addiction
- Bipolar
- Depression
- Psychotic disorders
- PTSD
- Quality/Outcomes
McLean Research Day 2018

Original Research - Clinical

Poster # 75
Time: 1:00-1:50pm

Presenting Author: Blake Hilton, PsyD, Post Doctoral Clinical Fellow

Co-Authors: Monika Kolodziej, PhD; Cheryl Cronin, MBA, MA; Margaret Griffin, PhD; Rocco Iannucci, MD; Jennifer Keller, RN; Kathryn McHugh, PhD; Scott Provost, MM, MSW; Quinn Trimblay, BA; Elsie Uffelmann, PhD; Emily Volpe, LMHC; Roger Weiss, MD

Title: Role of insomnia in treatment outcomes of patients with co-occurring substance use and psychiatric disorders

Key words: Substance, Co-occurring, Psychiatric, Insomnia, Outcomes

Background: Sleep disturbances are common amongst persons with substance use disorders. Chronic sleep impairment is associated with worse treatment outcomes and increased risk for relapse. There is a current scarcity of studies examining the effects of sleep problems in patients seeking treatment for co-occurring substance use and psychiatric disorders.

Methods: This study utilized a retrospective chart review to examine the relationship between insomnia severity at treatment onset and treatment outcomes following discharge in adults enrolled in a 30-day residential program for treatment of co-occurring substance use and psychiatric disorders. Insomnia symptoms were measured at admission using the Insomnia Severity Index (ISI), and treatment outcomes were measured using the Brief Addiction Monitor (BAM) at three, six, and 12-months post-discharge.

Results/Conclusions: Findings from this study are presented as they relate to treatment for individuals suffering from insomnia and co-occurring substance use and other psychiatric disorders.

Topic areas:
Addiction
Quality/Outcomes
Presenting Author: Brent Forester, Chief, Division of Geriatric Psychiatry; Assistant Professor of Psychiatry

Co-Authors: Brent P. Forester, David G. Harper, Patrick Monette, Savannah Morehouse, Emily Mellen, Katherine Hobbs, Ipsit Vahia, Caitlin Romano, Paul B. Rosenberg

Title: Pilot Trial of Dronabinol Adjunctive Treatment of Agitation In Alzheimer’s Disease (AD) (THC-AD)

Key words: Agitation, Agression, Alzheimer’s, Tetrahydrocannabinol, Dronabinol

Agitation in Alzheimer’s Disease (AD) is a major cause of burden to patients, caregivers, and society, and current treatments are limited in efficacy and/or associated with toxicity. Tetrahydrocannabinol (THC) is known to have anxiolytic effects likely mediated through the CB1 cannabinoid receptor, and there is increasing clinical off-label use of THC in the form of the generic drug dronabinol for agitation in AD. A case series reported improved agitation in AD with mean of 7 mg of dronabinol daily (Woodward et al. 2014). A recent randomized controlled trial (RCT) of a similar THC preparation at target dose of 4.5 mg daily was null; however, this study suggested that dosing greater than 4.5 mg daily may be required for therapeutic efficacy (van den Elsen et al. 2015). We therefore propose to assess effects of THC on agitation in AD at a higher dose of 10 mg daily. THC-AD is a 3-week, double-blind, placebo controlled RCT, which will evaluate the effects of dronabinol (5-10 mg daily) vs. placebo on agitation and aggression in inpatients with AD. We plan to enroll 80 participants between 60-90 years old, who have been diagnosed with AD and are experiencing severe agitation as defined by the International Psychogeriatric Association. The participants will be inpatients at two sites (Johns Hopkins Bayview Medical Center or McLean Hospital) for the study’s duration. Agitation will be assessed weekly using the Pittsburgh Agitation Scale (PAS) and the Neuropsychiatric Inventory—Clinician Version (NPI-C) as our primary outcome measures. Currently, 9 patients have been enrolled into the study. Compared to placebo, we anticipate dronabinol treatment will be associated with a greater reduction in symptoms of agitation as measured on the PAS and the agitation and aggression domains of the NPI-C. We also believe dronabinol treatment will be well tolerated with no more than mild adverse events. THC in the form of the generic drug dronabinol has the potential to treat agitation and aggression in AD. THC-AD is the first United States RCT to assess its efficacy for this treatment target.

Topic areas:

Alzheimer’s/Dementia
Geriatric
Family Functioning as a Mediator of Outcome in Treatment of Young Adults with Borderline Personality and Recent Self-Harm

Introduction/Aims: Dialectical behavior therapy (DBT) is an empirically supported treatment for borderline personality disorder (BPD) and suicidal behaviors. The treatment is built on a transactional model that suggests that problems associated with BPD result largely from chronic emotion dysregulation that is developed and maintained through chronic and pervasive transactions between the vulnerable and dysregulated individual and his or her invalidating social and/or family environment. In a transactional model, factors influence each other over time, so increased vulnerabilities lead to increased invalidating responses, and invalidating responses exacerbate the individual’s vulnerabilities and dysregulation. Thus, reduced dysregulation is hypothesized to lead to reduced invalidating responses, and reduced invalidation is hypothesized to lead to increased emotion regulation. Thus, improvement in family functioning, even in the absence of family interventions, may be one mechanism of change in people with BPD and related disorders. This study tested whether changes in family functioning did in fact mediate outcomes, including suicidality, self-injury, and depression, in an RCT comparing comprehensive DBT with comprehensive psychodynamic treatment for young adults. Neither treatment included significant or routine family interventions of any kind.

Methods: The sample consisted of 63 young adults (mean age = 20.86 years, SD = 1.92; 81% women) with current suicidal ideation, history of at least one self-harm and/or suicide attempt, and significant features of BPD. Participants were randomly assigned to DBT or psychodynamic psychotherapy and completed measures related to family functioning (Family Assessment Device-affective responsiveness), emotion dysregulation (Difficulties in Emotion Regulation Scale), suicidal ideation and self-harm behaviors (Suicidal Behavior Questionnaire-23), and depression (Beck Depression Inventory-II) at pre-, post-, and six-month follow-up following treatment completion.

Results: Hierarchical linear modeling (HLM) analyses suggest that family functioning did not change over time in the psychodynamic treatment group (γ10 = -.03, p > .05), but the DBT group was associated with a significant decrease over time in family distress scores (γ11 = -.12, p < .01). HLM suggested that family functioning interacted with treatment condition to predict suicidal ideation (γ21 = -10.36, p < .01) and number of self-harm attempts (γ21 = -1.78, p < .001), but not depression scores (γ21 = -2.93, p > .05). In addition, when controlling for emotional dysregulation and its interaction with treatment condition, the interaction of family functioning and treatment condition remained significant for both suicidal ideation (γ21 = -7.12, p < .03) and self-harm (γ21 = -1.08, p < .01).

Conclusions: Findings showed the improvement in family functioning did mediate suicidality and self-harm outcomes (but not depression) in young adults with BPD. This supports the transactional model of BPD and emotion dysregulation: Even without treating family distress and dysfunction per se, improvements in individual functioning predicted improvements in family functioning, and family functioning mediated individual outcomes independent of family interventions or type of treatment. This suggests that there may be significant clinical value in directly including families in treatment with young adults (and perhaps all people) with BPD.

Topic areas:
BPD
Child/Adolescent
**Title:** Cognitive Insight, Symptomatology, and Quality of Life in First-Episode Psychosis Patients

**Key words:** Insight, Symptomatology, QoL, Psychosis, First-episode

**Introduction:** The first year following a first-episode of psychosis involves a number of crucial transitions, including taking new medications, managing a schedule of regular mental health appointments, and deciding long-term school and work goals that support his/her psychiatric illness. This transition period has only begun to be studied by researchers; thus, it is unknown what facilitates and inhibits a successful transition to living with a psychotic disorder. Of particular importance is the insight of patients and their symptomatology as it relates to their quality of life (QoL). Therefore, this study will explore patients’ QoL from baseline to 6 months to see if levels of insight and symptomatology impact functioning.

**Methods:** This descriptive analysis will be nested the current study exploring Neurobiological Markers as Predictors of Later Functional Outcome in First Episode Psychosis. The participants will be at least 18 years old, be within their first year following a psychotic episode and have one of the following diagnoses: schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder with psychotic features. Data will be collected at enrollment and 6 months using the World Health Organization Quality-of-Life Scale, Insight Measures, and the Positive and Negative Syndrome Scale.

**Results:** Patients with higher levels of insight and more negative symptoms have poorer QoL at six months. Patients with low insight have greater levels of subjective QoL. Other significance between variables was not observed.

**Conclusion:** The findings from this study will be used to help clinicians identify patients who are at risk for poorer subjective quality of life. Psychiatric care interventions can be developed and implemented early on to assist patients achieve better long-term outcomes.

**Topic areas:**
Psycho
tic disorders
Schizophreni

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McLean Hospital
Harvard Medical School Affiliate
**Presenting Author:** Cecilia Rush, RN, BSN  
**Co-Authors:** Dawn Miller RN, BSN, Paula Bolton, MS, CNP, ANP-BC  
**Title:** TMS and the Challenges for Nursing  
**Key words:** TMS, Nursing challenges, Complication, Brain Stimulation

**Purpose:** Transcranial magnetic stimulation (TMS) is a relatively new treatment option for patients with treatment resistant depression. Nurses play a vital role in assessment and management of patients undergoing TMS.

**Summary of evidence:** TMS has been approved as a treatment for depression since 2008. Patients are becoming familiar with this treatment option. The need for treatment centers expert in this modality is increasing.

**Description of practice or protocol:** TMS is a daily treatment lasting approximately 30-60 minutes for 6-8 weeks. Although there are relatively few contraindications and potential side effects, more evidence is being gathered on the best patient population for this type of treatment. Nurses have been involved in the development of treatment programs providing guidance for assessment and monitoring of patients.

**Validation of Evidence/Method of Evaluation:** Review of TMS side effects and complications has led to refinement of screening protocols, identification of risk factors and development of nursing case management and liaison with medical providers to reduce risk and improve outcomes. Recent cases have demonstrated challenges for more intensive monitoring of potential risks. TMS nurses assist in the careful monitoring of patients with challenging presentations. Providing patient education and monitoring, as well as case management, the TMS nurse is instrumental in the recovery process.

**Identifying and defining the role of the TMS nurse and the nursing contribution to care of the TMS patient will assist in the development of patient centered TMS programs that provide comprehensive, safe and compassionate care. The TMS nurse assesses risk factors and monitors for complications. New challenges emerge with increased experience with TMS. Challenging cases are reviewed and the role for the TMS nurse will be clearly defined.**

**Topic areas:**  
Depression
Presenting Author: Christin Mujica, Clinical Research Assistant II, B.S.


Title: Private v. Public Sector Mental Health Care: Differences and Disparities

Key words: Disparities, Public Sector, Private Sector, Outcomes

Our group is currently conducting a randomized clinical trial of cardiovascular health in patients with serious mental illness. As part of this study, we collect multiple kinds of data on clinical status and social and community functioning. Observed differences by research staff during encounters with patients revealed apparent differences in outcomes seen at “Partners” sites (McLean Hospital and Massachusetts General Hospital) and those seen at Department of Mental Health (“DMH”) sites (Massachusetts Mental Health Center and the Michael J. Gill Clinic). An exploratory data analysis was conducted to examine whether these observed differences translate to significant findings and what factors may account for these differences. A broad range of outcomes addressing socioeconomic status (food availability, utilities, housing) as well as symptom measures (MADRS, PANSS, SAPS, SANS), and a social support measure (Duke Social Support and Stress Scale) were analyzed because of their relationship to outcomes in patients with psychotic disorders. Among this larger set of measures, only those measures with notable differences between Partners and DMH sites were further pursued for deeper analysis. Because site differences can be confounded by other variables such as race and ethnicity, we examined differences between racial and ethnic groups within the DMH sites, because these sites have a more balanced representation of patients with different racial backgrounds. All other races and ethnicities were omitted because of the lack of data. Our analyses revealed that when controlling for race, there were significant differences between patients seen at “Partners” and “DMH” on three specific measures: food availability, attention, and depression.

Topic areas:
Psychotic disorders
Quality/Outcomes
Schizophrenia
**McLean Research Day 2018**

**Original Research - Clinical**

**Poster # 81**

**Time:** 1:00-1:50pm

**Presenting Author:** Elena Molokotos, Academic Credit Student

**Co-Authors:** Maya Zegel, Diego A. Pizzagalli, Amy C. Janes

**Title:** Resting-state network coupling in Major Depressive Disorder during acute nicotine administration

**Key words:** Resting-state networks, Major Depressive Disorder, Nicotine, Functional Imaging

Individuals with major depressive disorder (MDD) show disrupted functional coupling between large-scale brain networks. For instance, individuals with MDD have increased coupling between the salience (SN) and default mode networks (DMN) and decreased coupling between SN and central executive network (CEN). Effective communication between the SN, DMN, and CEN is thought to contribute to the SN’s role in shifting between cognitive states. Specifically, DMN activity dominates during internally focused attention as opposed to the CEN, which plays a larger role in externally focused tasks. Disrupted communication between the SN, DMN, and CEN may contribute to difficulties switching between these states for individuals with MDD. In nicotine dependent individuals, nicotine withdrawal leads to reduced SN-CEN coupling, which is enhanced following nicotine administration. This prior work suggests that nicotine may also strengthen the weak SN-CEN coupling noted in those with MDD. To determine the impact of nicotine on large-scale network communication in those with MDD, we administered 2 mg of nicotine to non-smoking individuals with (n = 18) and without MDD (n = 17) prior to collecting resting state functional magnetic resonance imaging (rsfMRI) data. All participants tested negative for alcohol and illicit drug use, were medication-free at the time of the study, and groups were matched on age and sex. Nicotine or placebo was administered in a double-blind, randomized, cross-over design such that peak nicotine levels were reached during fMRI scanning. Resting state networks were defined using previously published templates available from Smith et al. (2009) and the time course for each network was extracted using FSL’s dual regression tool. Correlations between networks were calculated using an in-house software. A significant group by drug interaction was observed for SN-LCEN coupling, F(1,33)= 4.50, p = .042, partial 2 = .12. Post-hoc analyses determined that acute nicotine reduced SN-LCEN coupling in those with MDD, t(33)= 2.10, p = .043, compared to HCs. MDDs also showed significantly lower SN-LCEN coupling values on nicotine compared to placebo, t(17)= -2.58, p = .020, while this effect was not seen for HCs. A main effect of nicotine was also observed for SN-RCEN coupling, F(1,33)= 6.94, p = .013, partial 2 = .17, suggesting the same pattern of reduced SN-RCEN coupling following nicotine administration in MDDs. Contrary to our hypothesis, individuals with MDD showed a reduction in SN-CEN coupling following nicotine administration. However, this finding is in line with the hypercholinergic hypothesis of depression, and the finding that nicotinic antagonists have some therapeutic value. It is plausible that nicotine administration to individuals in a hypercholinergic state may result in reduced SN-CEN coupling whereas nicotine administration under a hypocholinergic state, such as during nicotine withdrawal, may normalize SN-CEN coupling. Future research is needed to confirm this hypothesis.

**Topic areas:**

Depression
Imaging
**McLean Research Day 2018**

**Original Research - Clinical**

**Poster # 82**

**Time:** 1:50-2:45pm

**Presenting Author:** Elizabeth Cosby, Clinical Research Assistant II

**Co-Authors:** Jeremy G. Stewart, Erika C. Esposito, Hannah Allchurch, Randy P. Auerbach

**Title:** Self-Referential Processing and Suicidal Thoughts and Behaviors in Depressed Adolescents

**Key words:** self-referential processing, suicide, adolescent depression

Background: Suicide is a leading cause of death among adolescents and identifying markers of suicidal thoughts and behaviors (STBs) is critical. Research has shown that depressed adolescents engage in negative self-referential processing (Auerbach et al. 2015), and while this dysfunction is central to suicide theory (Wenzel & Beck 2008), little research has used objective tasks to test this relation. Therefore, the study: (a) compared self-referential processing between suicide ideators (SI) and suicide attempters (SA) and (b) tested associations between self-referential processing and STBs in depressed youth.

Methods: To date, the study has enrolled healthy (n = 22) and depressed (n = 50) adolescents aged 12 to 19 years. Participants were administered clinical interviews assessing mental disorders and lifetime STBs. Adolescents also completed the self-referential encoding task (SRET) in which they indicated whether 40 positive and 40 negative words described them (yes/no) while electroencephalogram (EEG) data were collected. Preliminary analyses focused on the behavioral data (e.g., words endorsed and reaction time [RT]).

Results: Consistent with prior research (Auerbach et al. 2015), relative to healthy youth, depressed adolescents endorsed more negative words, F(1, 68) = 165.45, p < 0.001, η²p = 0.71, and fewer positive words, F(1, 68) = 41.11, p < 0.001, η²p = 0.38, and had faster RTs to endorsed negative words, F(1, 60) = 16.80, p < 0.001, η²p = .22. Among depressed adolescents, the SI (n = 24) and SA (n = 26) groups did not differ in endorsed words or RT. However, across SI and SA groups, slower RT to endorsed positive words, but not negative words, was associated with more frequent past week suicidal ideation, p = .018, OR = 1.30, CI95 [1.05, 1.60]. Additionally, a higher ratio of negative to positive endorsed words was associated with more lifetime suicide attempts, p = .048, OR = 1.14, CI−95 [1.00, 1.30]. Future analyses will test early (P1, P2) and late (LPP) electrocortical differences among SI and SA adolescents.

Conclusion: Findings show that negative self-referent processes are associated suicide ideation and attempts in depressed adolescents. Ultimately, identifying objective markers of suicide risk may reduce preventable loss of life.

**Topic areas:**
Child/Adolescent Depression
Title: GBA haploinsufficiency is a Parkinson's disease--relevant biomarker that is phenocopied in sporadic PD--derived fibroblasts

Key words: Biomarker, Glucocerebrosidase, Parkinson's Disease, Lysosomal function, patient-derived fibroblasts

Heterozygote mutations in the GBA1 gene are one of the most important genetic risk factors for the development of familial Parkinson's disease (fPD). In the brains of sporadic PD (sPD) patients, we observed a significant decrease in the activity of the lysosomal hydrolase glucocerebrosidase (GCase, encoded by GBA1), while glycosphingolipids (GSLs) are elevated (Rocha et al., Ann Clin Transl Neurol, 2015). These changes have been linked with increased alpha-synuclein (aSYN) load in sPD patients and furthermore, pharmacological inhibition of GCase activity can induce PD--relevant neuropathology, and increase the levels of aSYN aggregates and GSLs in mice. Therefore, we are interested in understanding the relationship between GCase haploinsufficiency and sPD, and how it may be involved in driving PD--like pathological features. Stratification of sPD patients based on disease--relevant biomarkers such as GCase activity levels may aid in identification of at--risk patients as well as guiding future therapeutic interventions towards individualized PD patient’s etiologies. In our current study, we sought to determine whether changes in GCase activity observed in human PD post--mortem samples are mirrored in PD patient--derived fibroblasts. Using fibroblasts obtained from healthy subjects, sPD patients, and fPD heterozygote GBA--N370S carriers, we observed that GCase activity levels were significantly lower in sPD patient and GBA--mutant fPD patient fibroblasts (36%, and 59% respectively) compared to healthy subject fibroblasts. Furthermore, we found that GCase activity in sPD fibroblast lines was separated into two distinct populations. A subset of sPD fibroblast lines phenocopied GBA--mutant fPD lines by displaying low GCase activity levels, whereas remaining sPD fibroblast lines displayed GCase activity levels similar to healthy subject fibroblasts. Ongoing analyses will measure additional readouts of GBApathway dysfunction in GBA--mutant fPD and sPD fibroblast lines to further understand the molecular aspects of lysosomal dysfunction in PD. In summary, our data demonstrates, for the first time, that reduced GCase activity levels found in human sPD brains, can be recapitulated in sPD patient--derived fibroblasts, suggesting that GBA haploinsufficiency could potentially be used as a reportable biomarker of lysosomal function in sPD.

Topic areas:
Neurology
Presenting Author: Ellen Finch, B.A.


Title: Is treatment as usual for borderline personality disorder iatrogenic?: A meta-analysis

Objective: Standard, unspecialized care for Borderline Personality Disorder (BPD) is often thought to be iatrogenic. This leaves clinicians and patients alike facing an important dilemma: in the absence of specialized psychotherapy, should those with BPD receive standard care? Here, we quantified the effectiveness of unspecialized BPD treatment via a meta-analysis of outcomes in “treatment as usual” control groups.

Methods: Study selection and inclusion: Studies were selected through a comprehensive bibliographic search. Included studies 1) were randomized control trials of psychotherapies for adults with BPD and 2) had a “treatment as usual” control arm. Nineteen studies met our inclusion criteria and 17 provided enough data to calculate at least one effect size for an outcome in the TAU arm.

Meta-analysis: TAU outcomes included borderline symptoms, general psychopathology, self-harming/para-suicidal behavior and suicidal ideation, and global functioning. Within-group effect sizes (Hedges g) were calculated as the difference between baseline and post-treatment scores on a given measure, corrected for small sample size. Comprehensive Meta-analysis V3 software was used for computing and pooling effect sizes.

Results: Primary outcome: Hedges g showed a moderate decrease in borderline symptoms for patients in TAU conditions (g=0.388; 95% CI, 0.290-0.486). Secondary outcomes: Hedges g showed small improvement in secondary outcome measures, including general psychopathology (10 studies; g=0.167; 95% CI, 0.088-0.247), global functioning (6 studies; g=0.214; 95% CI, 0.094-0.335), and self-harm/suicidality (6 studies; g=0.224; 95% CI, 0.150-0.298).

Conclusions: Our findings rebuke the notion that standard, unspecialized care for BPD is iatrogenic. Clinicians and patients alike should feel confident that in the absence of specialized treatment for BPD, standard care is a viable and worthwhile option.

Topic areas:

BPD
An Investigation of Reinforcement Learning in Major Depressive Disorder

To test the hypothesis that Major Depressive Disorder (MDD) disrupts reinforcement learning, we acquired behavioral and fMRI data as 37 depressed adults and 41 controls completed the Probabilistic Selection Task. One of three figure pairs (AB, CD, EF) was presented on each trial, and participants chose one figure per pair; the figures yielded monetary rewards with different probabilities (80/20, 70/30, 60/40%). Next, participants rated the reward (and non-reward) feedback for valence and arousal. Finally, in a test phase the participants viewed all possible figure pairs and tried to select the more frequently rewarded figure per pair. Compared to controls, depressed adults rated rewards as less positive, $F = 3.89, p = 0.05$. However, reinforcement learning was not strongly affected by MDD. During training, both groups learned to select the more frequently rewarded stimulus in each pair (Pair x Block, $F = 3.6, p = 0.05$; no significant effects involving Group). At test, both groups consistently selected the most frequently rewarded stimulus (Choose A, t-tests vs. chance $p < 0.001$) and avoided the least frequently rewarded one (Avoid B, t-tests vs. chance, $p < 0.001$). Analysis of hypothesized group differences in striatal activation to reward feedback is currently under way.
Presenting Author: Emilia Cardenas, Clinical Research Assistant II

Co-Authors: Stefanie Nickels, Sarah Perlo, Brian Kangas, Mykel Robble, Jack Bergman, William Carlezon, Diego A. Pizzagalli

Title: Paving the way for a cross-species neurophysiological assay: Validation of feedback-related negativity (FRN) as a marker of cognitive flexibility

Key words: electrophysiology, cognitive control, event-related potentials

Cognitive control is impaired in virtually every psychiatric disorder and lacks effective treatments. Although the majority of psychiatric medications are tested on animals, there is a paucity of research bridging cognitively relevant assays for both animals and humans. This may be a key barrier in the development of novel pharmacological treatments for psychiatric disorders. The current study seeks to facilitate the development of new treatments by establishing measures of cognitive control that behave the same way in humans and rats across multiple assays. Forty-eight healthy human participants completed the Probabilistic Reversal Learning (PRL) task, a well-established measure of cognitive flexibility, during 96-channel EEG recording. The high temporal resolution of event-related potentials (ERPs) makes them an ideal measure to investigate the mechanisms underlying successful adaptation of behavior when faced with changing stimulus-reward contingencies. Analyses focused on the feedback-related negativity (FRN), found in response to negative compared to reward feedback. Participants also completed the Behavioral Rating Inventory of Executive Function (BRIEF) questionnaire, a well-validated assessment of both executive and cognitive control in everyday functioning. The first step in our investigation was to validate the PRL as a marker of cognitive flexibility on the group level. As such, we found that the PRL paradigm successfully elicited a FRN when comparing correctly identified targets that were not rewarded vs. those that were followed by a reward (t(47) = -3.6, p < .001, mean difference -.95 μV). As a second step, we investigated whether the FRN captured individual differences in cognitive flexibility. We found corroborating evidence that the FRN varies with self-report measures of cognitive flexibility. Specifically, analyses revealed a significant correlation between the BRIEF shift scale, measuring an individual’s ability to flexibly shift from one aspect of a problem to another, while at the same time tolerate change and switch or alternate attention, and the size of a participant’s FRN (r(46) = -.30; p < .04). Thus, individuals with a larger FRN reported more adaptability from one situation to the next in their daily life. There was also trending correlation between scales related to organization of materials and self-monitoring and the FRN. Current findings support the PRL as a measure of cognitive control. Upcoming analyses will compare both human and rodent electrophysiological data collected during the PRL.

Topic areas:
Pharmacology
Program Description

Poster # 87
Time: 1:00-1:50pm

Presenting Author: Emily Mellen, Research Assistant, Bachelor of Arts

Co-Authors: Hadley Heinrich, Esra Guvenek-Cokol, Hyun Jung Kim, Dost Ongur

Title: MOBILITY: Implementation of a Metformin Intervention Study in a new Adolescent Outpatient Clinic at McLean Hospital

Key words: child, adolescent, mood, lifestyle, obesity

The MOBILITY Clinic, recently launched in conjunction with a PCORI-funded multi-site MOBILITY study, aims to address the pressing need for specialized outpatient care for children and adolescents with mood and psychotic disorders. The goal of the MOBILITY study is to evaluate the efficacy of metformin treatment and lifestyle intervention for children and adolescents (age 8-19) with bipolar spectrum disorders who are taking second generation antipsychotic medications and gaining weight. In order to support the study, the Schizophrenia and Bipolar Disorder Program at McLean Hospital has expanded its outpatient capacity to include adolescents. By aligning clinical care with research opportunities, the MOBILITY Clinic aims to fulfill the shared goals of McLean Hospital and the MOBILITY study to support effective clinical care and offer practical and accessible interventions to patients and their families living with mood disorders. Both the MOBILITY study and the MOBILITY Clinic recognize the importance of early intervention in better clinical outcomes for children and adolescents with psychiatric illnesses. Our hope is that, by using the MOBILITY partnership to facilitate a direct line of communication between treatment teams and a wider research community, we may provide excellent care to a wider community of people struggling with mood disorders.

Topic areas:
Bipolar
Child/Adolescent
Pharmacology
Presenting Author: Emily Oot, Academic Credit Student; BA

Co-Authors: Jennifer T. Sneider, Julia Cohen-Gilbert, Derek A. Hamilton, Anna Seraikas, Maya Rieselbach, Carolyn Caine, Arkadiy Maksimovskiy, Lisa D. Nickerson, Sion K. Harris, Marisa M. Silveri

Title: Caudate Activation in Adolescents during Goal-Directed Memory Performance is Associated with Mood, Anxiety and Sensation Seeking

Key words: Adolescence, fMRI, Caudate, Mood, Sensation Seeking

Adolescence is a period of development characterized by rapid changes in brain structure and function. Incongruous maturation rates across brain systems during this period can manifest in both psychopathological symptoms and maladaptive behaviors, helping to explain why rates of depression, anxiety and risky activity (e.g. substance use) are elevated in adolescence. The present study aimed to elucidate the link between adolescent clinical characteristics and patterns of brain activation in the striatum. Healthy adolescent participants (n=32, 15 female) underwent functional magnetic resonance imaging (fMRI) during performance of a virtual water maze task. The task involved navigating to a hidden platform based on learning that was completed prior to imaging. Blocks of hidden trials, dependent on spatial memory, were alternated with motor control trials where the platform was visible. The caudate nucleus was examined as a region of interest due to its role in goal-directed action, as well as in spatial learning/memory. Participants also completed self-report scales of depression (CES-DC), anxiety (MASC), impulsivity (BIS) and sensation seeking (BSSS). A significant positive association was observed between caudate activation during navigation to the hidden platform and thrill seeking scores on the BSSS (p=0.026). A significant negative association was observed between caudate activation and both depression (CES-DC) and anxiety (MASC) scores on hidden (p=0.041, p=0.028, respectively) and visible trials (p=0.046, p=0.032, respectively). These findings suggest that personality and clinical characteristics may differentially influence neuronal recruitment of goal-directed motivational systems involved in learning and memory, which could in turn impact the trajectory of maturation through adolescence.

Topic areas:
Anxiety
Child/Adolescent
Depression
Imaging
Neurodevelopmental disorders (e.g. schizophrenia, autism spectrum disorders) have long been known to have a genetic component, yet the results of large genome-wide association studies demonstrate that common genetic variants collectively account for only a minority of the genetic variance underlying risk. In contrast, recent findings suggest that rare genetic variants not only contribute to a significant amount of the genetic variance in risk for complex psychiatric disorders, but also individually have much larger effects than do common variants. Rare genetic variants can occur as inherited or as de novo (spontaneous) mutations. Some are recurrent, but most are private. This study aims to identify the de novo mutations in the DNA of individuals with a psychotic disorder by sequencing DNA from the proband and both biological parents (a “trio”). Comparing the DNA of the proband with DNA of the parents will reveal changes in the DNA of the proband that were not inherited from either parent. This study is to test whether whole exome sequencing combined with anomalous neuronal expression data can identify potentially pathogenic mutations. Identifying genetic mutations that contribute to risk for psychopathology may clarify the underlying disease biology and contribute to the development of targeted treatments. Here, we report our initial progress in collecting the trios samples in collaboration with the Psychotic Disorders Division and the National Alliance on Mental Illness.
Pain is one of the leading causes of hospital visits, and presents a significant health and financial burden worldwide. µ-opioid receptor agonists are the most effective pain-management pharmacotherapies for moderate to severe pain; however, these drugs have significant adverse effects that limit their application (e.g., constipation, respiratory depression, addiction, etc.) and have spurred the search for novel approaches to pain management. Nicotine has been demonstrated to produce antinociception in preclinical models of pain, yet the extent to which nicotine also may enhance µ-opioid analgesia has not been established. Here, male squirrel monkeys (N=4) responded for 0.1 cc of 30% condensed milk (v/v in water) under a fixed ratio 10 schedule of reinforcement followed by a 30-s timeout. During each timeout period, the distal portion of the subject’s tail was immersed in either 35, 50, 52, or 55°C water and the latency to remove the tail was recorded (10 s maximum). Dose-response functions for tail-withdrawal latency and disruptions in operant responding were generated for four µ-opioid receptor agonists that varied in efficacy (fentanyl>oxycodone>buprenorphine>nalbuphine) alone or in the presence of nicotine (0.1 mg/kg nicotine). Fentanyl, oxycodone, and buprenorphine dose-dependently decreased response rate, whereas doses of nalbuphine up to 10 mg/kg did not alter rates of responding. All drugs dose-dependently increased tail-withdrawal latencies at each water temperature—with the exception of nalbuphine, which was ineffective at 55°C. Nicotine (0.1 mg/kg) did not significantly alter the dose-related effects of any of the µ-opioids on operant behavior. However, nicotine significantly increased the antinociceptive potency of oxycodone as evidenced by moderate (2-5 fold) leftward shifts in dose-response functions at all water temperatures. In subsequent studies, the nonselective nicotinic antagonist mecamylamine (0.1 mg/kg) fully antagonized the nicotine-induced increases in the antinociceptive potency of oxycodone. Nicotine also produced comparable (2-5 fold) increases in the antinociceptive potency of buprenorphine but did not significantly alter the effects of fentanyl. The effects of nicotine were most pronounced when given prior to nalbuphine: the potency of nalbuphine to produce antinociception at 50°C and 52°C was increased >50-fold and >30-fold, respectively; at 55°C, the tail-withdrawal latency of nalbuphine increased from 1 s to 5 s in the presence of nicotine. Collectively, these data demonstrate that nicotine selectively enhances the antinociceptive potency of µ-opioids, but not the rate-decreasing effects, in a manner that is related to µ-opioid receptor efficacy. Furthermore, antagonism of nicotine’s effects by mecamylamine strongly suggests that changes in the effects of µ-opioids after nicotine administration results from nicotinic receptor activation. Inasmuch as disruptions of operant responding are an indicator of behavioral impairment produced by µ-opioid agonists, these results suggest that nicotine may increase the analgesic potency of µ-opioids without concomitantly increasing some of its deleterious side-effects.
Clathrin Nanoparticles Efficiently Deliver BDNF to the Hippocampus, Enhance Neurogenesis, and Learning and Memory in a Mouse Model of HIV

**Background:** Brain derived neurotrophic factor (BDNF) promotes neuronal plasticity and restores brain functions. However, BDNF cannot easily cross an intact blood brain barrier (BBB), diffuse within the brain, and is unstable in blood. Early intervention is necessary to stop progression of chronic neurodegenerative disorders, but an intact BBB represents a major obstacle for delivering drugs to the brain. Thus, new strategies for overcoming an intact BBB must be developed to allow CNS delivery of BDNF early in the course of these diseases. However, developing an appropriate nontoxic, non-immunogenic, stable drug carrier that can cross an intact BBB and efficiently deliver BDNF to affected brain regions has been challenging. Our goal was to develop clathrin-based BDNF-nanoparticles that can bypass the BBB, target tropomyosin kinase B (TrkB) receptor rich brain regions, and reverse neurotoxic effects of HIV transactivator of transcription (Tat) protein in a mouse model of HIV.

**Methods:** GT-tg bigenic mice were treated once daily with saline (Sal; Tat-) or doxycycline (Dox, 100 mg/kg/d, i.p.; Tat+) that induces selective brain Tat expression. Concurrently, Tat+ mice also received intranasal BDNF-clathrin (BDNF-CT; 0.3 mg/kg BDNF + 2.4 mg/kg CT), BDNF, CT, or Sal. Mice were sacrificed on day 4 or 7 for western blot analysis of BDNF expression and signaling, or immunohistochemistry analysis of BrdU (50 mg/kg, delivered Q12h on day 1 and 2, i.p), Ki67 and doublecortin (DCX) which are markers for newborn cell survival, proliferation and neurogenesis respectively. Another group of mice that received Dox (Tat+) with BDNF-CT or Sal daily for 7 days were used to assess effects of BDNF delivery on learning and memory in Barnes maze and novel object recognition tests.

**Results:** Western blot and immunohistochemistry BDNF-CT, but not unconjugated-BDNF, CT or Sal, significantly enhanced mature BDNF (p<0.007), pro-BDNF (p<0.01), p-Akt (p<0.01), and Akt (p<0.002) in the hippocampus of Tat+ mice. BrdU+ (p<0.0002), Ki67+ (p<0.002) and DCX+ (p<0.001) cell densities were significantly increased in the granule cell layer of dentate gyrus in BDNF-CT treated Tat+ mice, compared to Sal treated Tat+ or Tat- mice. Learning and memory BDNF-CT treated Tat+ mice demonstrated enhanced ability to escape the maze during acquisition (p<0.04) and reversal learning (p<0.004) phase of Barnes Maze test compared to Sal treated mice. This indicates that BDNF-CT enhanced spatial learning and cognitive flexibility in Tat+ mice. BDNF-CT also increased Tat+ mice’s ability to recognize the novel object, but only when the high dose of BDNF-CT was delivered (p<0.016).

**Conclusions:** BDNF was successfully delivered to the brain using our clathrin nanoparticle formulation (Vitaliano et al. 2012) resulting in enhanced hippocampal cell survival, proliferation, neurogenesis and reversed neurotoxic effects of HIV-Tat. BDNF delivery also ameliorated cognitive deficits that are well characterized in Tat+ mice. These findings demonstrate that CT provides a highly effective nanoplatform for delivery of BDNF to the brain. This noninvasive nanotechnology may be able to enhance neuronal regeneration and plasticity and restore brain functions more quickly and completely than existing treatment methods.

**Topic areas:**
Alzheimer's/Dementia  
Pharmacology  
Technology
Context-Dependent Language Processing in Patients with Schizophrenia and Bipolar Disorder

Background: The “Phonemic Restoration Effect” is a perceptual illusion in which listeners hear a phoneme that is not actually present. When part of an utterance is replaced or masked by another sound, listeners restore the missing speech according to their contextual knowledge. For example, when an external sound replaces a phoneme in a recorded sentence, participants report hearing the missing sound (Warren, 1970). Samuel (1981a) noted that sentential predictability greatly influences phonemic restoration—listeners update their expectations about the missing sound in real-time based on the context of the rest of the sentence. Patients with schizophrenia and related illnesses experience deficits in verbal and contextual processing, and may not show these effects due to decreased ability to mobilize context quickly enough to generate predictions (Brown and Kuperberg, 2015). Thus, we aimed to examine the Phonemic Restoration Effect (PRE) in patients with schizophrenia (SZ) and bipolar disorder (BD) using a paradigm that evaluates both contextually logical and contextually illogical words.

Goals and Hypotheses: We aimed to evaluate phonemic processing and context dependent prediction in patients with SZ, BD, and healthy controls (HC) using a Phonemic Restoration paradigm. We hypothesized that in context-congruent sentences, healthy controls would have faster response times than patients, but that difference would disappear or even be reversed in the incongruent condition. We also expected that since controls preemptively predict words, they would be less accurate than patients on context-incongruent conditions. We predicted that patients with SZ and BD would exhibit abnormalities in phonemic and context-dependent processing, but SZ patients would exhibit more deficits than BD patients.

Methods: Participants with SZ (n=27) or BD (n=18) and healthy controls (n=56) were recruited from the McLean Hospital Psychotic Disorders Division as part of a larger study on language processing. Two subsets of controls were recruited, matched on sex, age, and Socioeconomic Status (SES) with the two patient groups (HC-SZ: n=29; HC-BD: n=27). Assessments included clinical and cognitive measures and a computer-based PRE task. During the PRE task, participants heard a series of sentences in which the first phoneme of the last word in each sentence was masked by white noise. After each sentence, two words were presented and participants were asked to indicate which word they had heard. Words either matched the sentence context (context congruent) or did not (context incongruent). Groups were compared on demographic, clinical, and PRE measures (accuracy and response time) using ANOVA and comparisons of 2 congruity (congruous, incongruous) interaction effects on these same measures.

Discussion: In the present study we used a PRE paradigm to evaluate language-processing deficits in patients with SZ or BD compared to matched controls. This paradigm permits evaluation of language processing both at the phonemic level (lower level processing) and in terms of context-dependent processing (higher level). Evaluating these processes separately in patients with affective and non-affective psychosis will help clarify the nature of the well-described language processing deficits across psychosis, with implications for neurobiological underpinnings and targeted treatment strategies.

Topic areas:
- Bipolar
- Psychotic disorders
- Schizophrenia
Deficits in cognitive function, such as reward sensitivity and cognitive control, are a common feature of virtually all neuropsychiatric disorders. While perturbations in cognitive control have been studied extensively in humans, it has been more challenging to examine these complex processes in model organisms. Stagnation in the development of animal-based tasks to assess these processes has coincided with a decline in the development of effective therapeutics for neuropsychiatric disorders. As part of a larger effort to create reliable and valid cross-species assays of cognitive function, we have begun developing a rodent version of the Eriksen Flanker Task to assess cognitive control. Using fading and correction procedures combined with touchscreen-based response technology, Sprague Dawley rats were trained to discriminate between several distinct pairs of visual stimuli. These stimuli included arrows (>) and letters (H/S), as well as colored stripes and more detailed pictures (cherries/leaf). While rats did not meet the required criteria of 80% response accuracy for arrow or letter stimuli, successful discrimination was observed using the red/green stripes and cherry/leaf pictures. Following training, rats were presented with flanker probe trials. Intriguingly, when increasing the number of flanked trials in a session from initially 20% to 100%, performance remained high and the Flanker interference effect of lower reduced accuracy for incongruent stimuli was confirmed. Notably, a response bias on incongruent trial types was observed in which performance on trials with a red target was reduced, regardless of stimulus type. Presently, efforts are underway to reduce this bias by altering the intensity of the green stimulus in each condition. In addition, other color schemes that may be more advantageous for visual discrimination in the rat are also being tested. Following these design modifications, EEG data will be collected during the rodent Flanker Task and the relevant ERPs will be compared to those observed in human studies. In parallel, 45 EEG data sets were collected from human subjects using the cherry/leaf stimuli and the more traditional arrow stimuli. Relevant outcome measures such as the N200 component, theta power, and the error-related negativity (ERN) were comparable across stimuli, raising confidence that the stimuli ultimately found suitable for rodents will also be appropriate for studies in humans. Cross-species behavioral and neurophysiological correspondence will serve to validate the rodent task and provide the predictive power to screen potential therapeutics for numerous neuropsychiatric conditions.

Topic areas:
Depression
Neurology
Presenting Author: James Robbins, Research Technician II

Co-Authors: Emery L. Mokler, Christopher J. McDougle, Galen A. Missig, & William A. Carlezon Jr.

Title: Maternal immune activation with a TLR7 agonist results in a distinct behavioral phenotype with relevance to neurodevelopmental psychiatric disorders

Key words: Autism, Inflammation, Autoimmune, Toll-like receptor, Behavior

Accumulating evidence suggests that maternal immune challenge during gestational and perinatal periods can have lasting effects on neurodevelopment. Previous work has demonstrated that the offspring of pregnant mice treated with immunoreactive agents can exhibit a behavioral phenotype with key features of autism spectrum disorder (ASD). This work is complemented by previous observations that some individuals with ASD exhibit atypical expression of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Previous immune challenges have primarily employed agents (e.g., PolyI:C, lipopolysaccharide) that target subtypes 3 and 4 of the Toll-like receptor (TLR) family, a class of receptor proteins that regulates the innate immune response. The current study sought to manipulate TLR7, thereby expanding the repertoire of innate immune targets studied. In addition to its novelty as a target in maternal immune activation models of autism, TLR7 is highly expressed in the placenta, its expression is developmentally regulated in the brain during the perinatal period, and its activity has been implicated in the pathogenesis of systemic autoimmune disease and preeclampsia, both putative ASD risk factors. Activation of TLR-7 by its selective agonist, imiquimod (IMQ), represents a potentially novel approach with which to model immune-mediated ASD phenotypes in mice. Pregnant dams were administered 3 subcutaneous injections of the TLR-7 agonist or saline vehicle on embryonic day 12, 14, and 16, and the offspring were subjected to a battery of ASD-relevant behavioral assays at various developmental time-points. Offspring of dams treated with IMQ exhibit a profound behavioral phenotype characterized by atypical patterns of ultrasonic vocalization, increased repetitive behaviors, reduced anxiety-like behavior, fragmented social behavior, and hyperactivity under some (but not all) testing conditions. Although there is some overlap between this phenotype and those observed in other maternal immune activation models used in the study of ASDs, it differs in several behavioral domains and therefore may enable new insights on immune involvement in other psychiatric disorders characterized by these signs.

Topic areas:
Anxiety
Bipolar
Background  The Reading the Mind in the Eyes test was a task originally created to ascertain emotion recognition ability and determine theory of mind. The original Reading the Mind in the Eyes test was created with images pulled from a variety of sources, cropped to fit just the eyes. Emotions were then decided for those images by four individuals, whose demographic data were not given. A revision of the test was created in 2001 by the original test creators, and this time four men and four women assigned emotions to the sets of eyes; once again, demographic data of the eight individuals was not given. The test itself was restricted by race, ethnicity, gender, and age. Using the platform of TestMyBrain, and by use of randomization, large-scale data, and item sampling, we have recreated the Reading the Mind in the Eyes test to be a more powerful, less biased, and reliable scientific measuring tool.

Methods  We generated a set of 37 items based on videos and images of ethnically and age diverse actors expressing different emotions, taken as part of the Act out for Brain Health project. We then used a set of 16 core items from the original test, identified based on items loading highest on the first principal component derived from principal component analysis, and administered a modified version of the test with these 16 core items and a random set of 37 out of 109 new items. These methods allowed us to identify those items with the highest correlations with the original test items, with external outcome measures of social behavior to generate a new test that avoids many of the controversial characteristics of the original test, such as high correlations with vocabulary and gendered language. Over 6,000 participants completed the test, and correct judgments were determined by consensus across an average of 1,300 participants per item.

Results  Our final product was a test of similar length to the original, but using multiethnic, age-diverse faces, across a range of facial expressions. Critically, the new test shows a similar correlation with social outcomes as the original test, similar reliability, but a lower correlation with vocabulary performance, thus improving on the psychometric characteristics of the original.

Conclusion  Here we show how large samples collected in a citizen science platform, together with random item sampling and item analysis, can be used to rapidly generate new measures that improve upon more traditional measures such as the Reading the Mind in the Eyes test. Our test provides a new tool for the research community that is useable across a broader demographic of participants and in remote testing contexts.
Introduction: Social-emotional development surveys have increasingly been utilized by student’s school support systems, including teachers, counselors and administrators to measure students’ social-emotional strengths and challenges. Ideally, student support systems use assessments to identify high-risk youth to better support students’ social-emotional needs (McKown, 2017). However, many surveys lack the necessary psychometric properties to produce meaningful results, thus justifying the importance of validated student assessments. The Holistic Student Assessment (HSA) is a validated, developmentally sensitive (Malti et al., 2017), strength-based survey designed to measure a student’s social-emotional strengths and challenges. When used in conjunction with the Strengths and Difficulties Questionnaire (SDQ), a behavioral screening assessment, the two provide valuable information regarding a student’s social-emotional needs (Goodman, 1997).

Method: The present study attempts to further validate the HSA (with SDQ) by evaluating whether responses differed between students in a clinical intervention program (INT) and students in a comparison group (COM). The HSA is a 61-item self-report assessment validated for use by students in Grade 5 and above. Students rated the 61-item HSA survey responses on a 4-point Likert scale ranging from “Not at All” to “Almost Always,”, and rated the 25-item SDQ responses on a 3-point Likert scale ranging from “Not True” to “Certainly True.” Students are categorized as having a strength or challenge on each scale based on assigning a z-score to the mean score of each scale. These z-cores were created based on a stratified random sample that grouped students by age bands (Late Childhood: ages 9.0-11.9, Early Adolescence: ages 12.0-14.9 and Middle Adolescence: ages 15.0-18.9) and gender identity (male or female). Based on the combination of strengths and challenges, students are categorized as low need (Tier 1), moderate need (Tier 2) and high need (Tier 3).

Results: A total of 1,905 students (46.9% female) in grades 6-12 completed the HSA and SDQ throughout Fall 2016 (INT, n=113; COM, n=1,792). Results indicate that the INT group reported statistically lower scores than the COM group on 10 scales, including, Emotion Control and Prosocial Behavior (p’s<0.05). The INT group reported statistically higher degrees of Assertiveness, Hyperactivity and Conduct Problems, than the COM group (p<0.05). Moreover, The INT group reported fewer strengths (M=1.7, SD=2.3) and more challenges (M=3.5, SD=2.9) than the COM group (Strengths: M=2.3, SD=3.3; Challenges: M=2.7, SD=3.1).

Discussion: These findings corroborate the need for a validated strength-based approach to measure children’s social-emotional strengths and challenges. Strength-based surveys approach social-emotional strengths as protective factors against risks such as trauma. Therefore, student support systems should address students’ strengths and challenges as a mechanism to build resiliency against risk factors. Our findings show that the HSA effectively differentiates social-emotional strengths and challenges for high-risk and lower-risk students. Developmentally appropriate assessments, like the HSA, can provide student support systems with the necessary information to effectively support the social-emotional needs of children.

Topic areas:
Child/Adolescent
Quality/Outcomes
Presenting Author: Jennifer Sneider, Associate Neuroscientist, Assistant Professor

Co-Authors: Jennifer T. Sneider, Julia Cohen-Gilbert, Derek A. Hamilton, Carolyn Caine, Maya Rieselbach, Emily Oot, Anna Seraikas, Lisa D. Nickerson, Marisa M. Silveri

Title: Unique Frontal Activation Patterns Associated with Depression Severity during Memory Retrieval in Women

Key words: depression, memory, hippocampus, frontal, fMRI

Major depressive disorder (MDD) is a debilitating disorder that interferes with normal daily functioning, and which occurs at a markedly higher rate in women relative to men. Evidence of structural and functional alterations in hippocampus and the frontal lobe also have been reported in MDD, which likely contribute to the multifaceted impact of this condition. Functional magnetic resonance imaging data were acquired at 3Tesla during a hippocampal-based spatial memory task in 15 women across a clinical spectrum of MDD, from none to current MDD. Depression severity, assessed via the Beck Depression Inventory (BDI), was examined relative to brain activation. Greater activation was observed, regardless of depression severity, in right hippocampus, bilateral fusiform, left superior-parietal lobe and occipital regions during memory retrieval relative to motor control. In contrast, there were no significant areas of activation observed for motor control relative to retrieval. Notably, despite similar behavioral performance across participants, during rest relative to retrieval, activation in superior frontal gyrus and cingulate gyrus, regions of the default mode network (DMN), was significantly associated with depression severity (BDI). The observed lateralized activation of right hippocampus during spatial navigation is consistent with previous findings reported in women. In addition, failure to suppress activity in DMN as a function of depression is consistent with a frontal lobe inefficiency that may contribute to clinical state. Linking mood, brain activation, and cognition may help to better diagnose MDD in women, as well as inform prevention and treatment efforts targeting women, thereby alleviating suffering from this debilitating condition.

Topic areas:
Depression
Imaging
Women
Title: Using a 78-year longitudinal study to examine the neuropsychiatric and pathologic outcomes of childhood head trauma

Key words: traumatic brain injury (TBI), concussion, mood disorders, cognition

Introduction: Traumatic brain injury (TBI) is a serious public health issue. The Centers for Disease Control and Prevention (CDC) defines TBI as a head blow or penetrating injury disrupting the normal function of the brain. Recent literature has shed light on chronic traumatic encephalopathy, a syndrome of progressive neurodegeneration after multiple TBIs, with clinical symptoms of behavioral changes, mood changes, and cognitive impairment. Post-concussive syndrome is a related entity, in which neuropsychiatric symptoms persist for weeks to months after a concussion. Much of the recent literature has focused on long-term pathologic and clinical changes in football players and veterans with frequent, severe head injury. Few studies have longitudinally followed more generalizable cohorts to examine the prevalence and long-term impact of mild childhood TBI on later-life neuropsychiatric and pathological outcomes in the population outside of professional sports or military.

Methods: The Harvard Study of Adult Development is a unique longitudinal study of 268 male Harvard undergraduates, recruited from 1939-1942 at age 18-19. While original selection criteria precluded the presence of physical or mental illness, prior health experiences were collected by a physician at intake. Prospective data were gathered every few years for the duration of the participants' lives via questionnaires, in-person interviews, and review of medical records. Later in life, 85 surviving members of the cohort underwent extensive neuropsychological testing, while a subset underwent head imaging with fMRI. At time of death, 13 cohort members donated their brains for neuropathological review. For the present study, data were abstracted from intake interview questions about childhood concussion, defined as head trauma with loss of consciousness, which is consistent with the modern CDC definition of TBI. Outcomes among previously abstracted data include DSM-V major depressive disorder diagnosis across the lifetime, income and job promotion as proxies for psychosocial adjustment, and age 80 Telephone Interview for Cognitive Status (TICS) score.

Results: Baseline concussion data were available for 259 men (97%). Of those, 161 (62%) never had a prior concussion, 63 (24%) had one concussion, and 35 (14%) had two or more concussions, with a maximum of five concussions per subject. 18 subjects had at least one head trauma without loss of consciousness, with 2 of these having co-occurring history of concussion and head trauma without loss of consciousness. Analyses will proceed from correlational and simple regression models to more complex modeling including potential mediators and moderators of outcomes to explore the relationships between childhood head trauma and lifetime depression trajectories, psychosocial adjustment outcomes, and later-life cognitive functioning. Among the subset with head imaging and with brain specimens available, relationships between childhood head trauma and findings on imaging and pathology will be examined.

Conclusion: Childhood head trauma data from a longitudinal study of human development could provide significant insight into the associations between early life mild head trauma and later life neuropsychiatric and neuropathological changes in a generalizable cohort. Limitations include subjective reporting by study subjects, as well as the study's homogeneous population. However, the long-term, longitudinal, and multi-modal nature of the study can provide insights despite these limitations.

Topic areas:
Alzheimer's/Dementia
Child/Adolescent
Depression
GeriatricQuality/Outcomes
Title: LRRK2 G2019S mutation modulates intracellular and ER calcium homeostasis in human iPSC-derived neurons.

Key words: Parkinson disease, human iPSC-derived neurons, LRRK2, G2019S mutation, endoplasmic reticulum, calcium homeostasis

The Leucine-Rich Repeat Kinase (LRRK2) G2019S gain of function gene mutation is one of the most prevalent mutations contributing to Parkinson’s disease (PD) pathogenesis. Using human induced pluripotent stem cell (iPSC)-derived neurons carrying the LRRK2 G2019S mutation, we and others have shown that the LRRK2 mutation, which increases LRRK2 kinase activity, alters axon outgrowth, intracellular trafficking, mitochondrial health and autophagy. We have also shown that this mutation contributes to an increased vulnerability of iPSC-derived neurons to PD-associated cell stressors and can be rescued by treatment with LRRK2 inhibitors (Cooper et al., 2012, Sci Transl Med. 2012, 4;4(141):141ra90.). Previously we described that human iPSC-derived neurons carrying the LRRK2 G2019S mutation challenged with the sarco/endoplasmic reticulum Ca2+ -ATPase (SERCA) uptake blocker thapsigargin (THP), exhibit an increase in depolarization-induced calcium influx and a modified calcium decay (interpreted as buffering capacity), when compared to neurons derived from healthy subject controls. Here, we show that endoplasmic reticulum (ER) Ca2+ levels, measured using an ER specific calcium-measuring organelle-entrapped protein indicator (Cepia-ER), are lower in iPSC-derived forebrain and midbrain dopamine neurons carrying the LRRK2 G2019S mutation compared to healthy subject controls. The lower level of ER calcium in LRRK2 G2019S neurons is still present even after THP-induced SERCA block. This phenotype was ameliorated by the treatment with antisense oligonucleotides targeting LRRK2 sequence. qPCR analysis of key ER Ca2+ channels and regulators, and membrane Ca2+ channels, known to regulate store operated calcium entry (SOCE), indicates altered expression in LRRK2 G2019S neurons. In summary, these data suggest that the LRRK2 G2019S mutation alters intracellular calcium homeostasis, which could contribute to PD-specific neuronal dysfunction. Further studies will identify specific targets of the ER homeostasis pathway affected by the LRRK2 G2019S mutation.

Topic areas:
Neurology
Depression is associated with episodic memory deficits, but the underlying neural mechanisms are poorly understood. Therefore, we conducted a time-frequency analysis of electroencephalography (EEG) data collected from 24 unmedicated adults with Major Depressive Disorder (MDD) and 24 control subjects as they retrieved the encoding task (Question condition) and spatial position (Side condition) of neutral words studied earlier. In a semantic memory control condition, participants made odd/even judgments for numerals (Number condition). A prior analysis of event-related potentials (ERPs) from this task indicated that episodic retrieval elicits a robust positive potential from 400-800 ms over left parietal scalp, as well as a sustained late posterior negativity (LPN) from 800-2000 ms over midline occipital regions; the LPN extended over left frontal scalp in the Question condition only. Given the lack of prior EEG studies of source memory in MDD, we focused our time-frequency analysis on these scalp regions and time windows. Time-frequency analysis was conducted by applying a complex Morlet wavelet to epochs time-locked to the presentation of encoded words at retrieval (-200 to 2000 ms). We extracted power in the theta (4-7Hz), alpha (8-13Hz), and beta (16-30Hz) frequency bands, and computed Group x Frequency x Condition (Question, Side, Number) ANOVAs, with Time (800-1400 ms, 1400-800 ms) as an additional factor for analyses over midline occipital and left frontal scalp (for left parietal scalp, a single 400-800 ms interval was analyzed). Over left parietal and left frontal sites, significant Group x Frequency interactions were observed, ps < 0.03. These corresponded to reduced power in depressed vs. healthy adults in the theta band over left parietal sites and reduced power in both the alpha and theta bands over left frontal sites. By contrast, no group differences were observed over midline occipital sites; data from these electrodes were characterized by a Condition x Frequency interaction (p = 0.05), driven by increased alpha power in the Question condition. The main effect of Frequency was significant at all sites due to a steady decrease in power across the theta, alpha, and beta bands (ps < 0.001). Models of source memory retrieval posit separate search and monitoring processes, and extensive neuroimaging data in healthy adults has aligned those processes with left parietal cortex and the frontal lobes, respectively. Consistent with this, our EEG data reveal a relatively early increase in power over left parietal scalp that is followed by increased power over occipital and left frontal sites. The results of this analysis indicate that MDD is marked by reduced power in the theta band at left parietal sites and both theta and alpha bands at left frontal sites. Although additional research is needed, these data suggest that reduced oscillatory power in neural networks that support retrieval may play a key role in episodic memory deficits in MDD.
Presenting Author: Margaret Gardner, Clinical Research Assistant

Co-Authors: Fei Du, Virginie-Anne Chouinard, Dost Ongur

Title: A systematic review of interventions in neurological and psychological disorders targeting oxidative stress.

Key words: Oxidative Stress

Oxidative stress has been implicated in the etiology of numerous psychological and neurological disorders, including psychotic disorders, mood disorders, Alzheimer’s disease and multiple sclerosis. This review systematically compares the efficacy of interventions targeting oxidative stress, in terms of clinical and biological outcomes, and attempts to draw conclusions about which interventions may be most appropriate for each disorder in which oxidative stress likely plays a key role.

Topic areas:
Neurology
Pharmacology
Quality/Outcomes
PRESENTING AUTHOR: Victoria Lawlor, Student Intern

Co-Authors: Victoria Lawlor, Christian Webb, Ph.D., Madhukar Trivedi, M.D., Maurizio Fava, M.D., Patrick J McGrath, M.D., Myrna Weissman, Ph.D., Ramin Parsey, M.D., Ph.D., Melvin McInnis, M.D., Maria A Oquendo, M.D., Ph.D., Cristina Cusin, M.D., Patricia J. Deldin

Title: Drift-Diffusion Modeling of Reward Learning in Depression

Key words: Depression, Modeling, Decision-making, Reward

Background: Major Depressive Disorder (MDD) has been associated with disrupted reward learning, but the underlying neurocognitive mechanisms are poorly understood. For example, relative to healthy controls, adults with MDD typically show poorer performance in the probabilistic reward task (PRT), but the reason for this group difference remains unclear. Therefore, we applied the Hierarchical Drift Diffusion Model (HDDM) to three PRT datasets. The HDDM decomposes behavioral data into component cognitive processes, and we sought to identify which processes are affected by MDD.

Methods: PRT data from healthy controls and depressed participants were analyzed. The HDDM was used to extract three decision-making parameters: drift rate, decision threshold, and prepotent bias.

Results: In all three samples, the HDDM revealed slower drift rates and higher decision thresholds in depressed versus healthy adults. HDDM parameters mapped onto standard PRT outcome variables: drift rate and threshold explained discriminability, while prepotent bias explained response bias. Discriminability, the ability to differentiate between task stimuli, predicted the number of rewards received better than response bias.

Conclusions: These findings indicate that the PRT is readily modeled as a perceptual decision-making task, and they highlight key roles for discriminability and drift rate (in addition to response bias) in task performance. Conceptualizing the PRT in this way may forge a link between studies of reward learning in depression and extensive work on evidence accumulation in non-human primates. Most importantly, these results provide insight into aberrant decision-making in depression, by linking MDD to slow evidence accumulation and conservative threshold settings.

Topic areas:
Depression
**Title:** A Novel, Behavioral Task for Measuring Stressor-Induced Changes in Palatable Food Consumption

**Key words:** Emotional Eating, Binge Eating, Eating Disorders, Emotion, Social Exclusion

**Introduction:** Stressful events (“stressors”) can predict a variety of eating-related behaviors, including extreme dietary restriction (e.g., in anorexia nervosa) and objective binge-eating episodes (e.g., in binge-eating disorder). Valid, within-person measures are needed to advance our understanding of how stressors might differentially affect eating behavior across individuals. Thus, we describe the development and initial validation of a novel, behavioral paradigm for use in laboratory-based studies of stressor-induced changes in food intake.

**Methods:** The Cyberball-Milkshake (CM) task is designed to measure how social exclusion, a clinically relevant interpersonal stressor, affects consumption of palatable food. Participants play a modified version of the computerized Cyberball throwing game, which includes 6 inclusion and 6 exclusion rounds, and also sip a participant-determined amount of milkshake between rounds. Negative affect is assessed via repeated self-report and continuous physiological recording (e.g., skin conductance).

**Results:** Results for pilot subjects suggest that social exclusion (vs. inclusion) induces negative affect and changes in caloric intake that vary substantially across individuals. We will also present preliminary results from an initial validation study (n = 40) conducted in women ages 18-30 years old.

**Conclusions:** The CM task may provide a valid, objective measure of stressor-induced changes in palatable food intake for use in future research.

**Topic areas:**
Eating Disorders
Women
**Presenting Author:** Kristin Serowik, Doctoral Student  
**Co-Authors:** Ruth Reibstein, Olivera J. Bogunovic, Hilary Connery, R. Kathryn McHugh  
**Title:** The Impact of Mindfulness on Affect and Craving Following a Group Therapy Session  
**Key words:** Substance Abuse, Mindfulness, Craving, Affect

**Introduction:** Meta-analytic findings demonstrate that mindfulness is an efficacious treatment for substance use disorders, specifically resulting in reductions in both the frequency and severity of use and intensity of craving. The aim of this quality improvement initiative was to develop a mindfulness group for adults with substance use disorders and to examine its feasibility and impact on affect and craving.

**Methods:** Participants were 71 adults diagnosed with a substance use disorder who participated in a mindfulness group therapy session in McLean Hospital’s Alcohol and Drug Abuse Treatment Program Partial Hospital Program. The typical length of stay in the program is two weeks and treatment consists of group therapy, case management, and medication management. A mindfulness-based group was developed based on evidence-based mindfulness approaches and added to the program as a once weekly hour-long group. At the beginning of the mindfulness group, participants rated their affect, using the PANAS-20, and craving, on a scale of 1-5 (very slightly/not at all to extremely). The mindfulness group included psychoeducation about the definition and practice of mindfulness and a brief guided meditation. At the end of the group, participants again completed the PANAS-20 and provided a rating for current craving.

**Results:** Correlational analysis revealed moderate significant associations between ratings of craving and negative affect both before (r = .41, p<.001) and after (r = .32, p <.001) the mindfulness group. Results of paired-sample t-tests indicated significant reductions in negative affect, t(70) = 5.73, p <.01, and increases in positive affect, t(69) = -3.36, p <.01, after the mindfulness group when compared to before group. A Wilcoxon test indicated a significant decrease in reported craving, z = -3.62, p <.01.

**Conclusion:** The results of this analysis demonstrate that a brief guided mindfulness exercise, coupled with psychoeducation, is associated with changes in affect and craving. These findings extend prior research illustrating the benefits of mindfulness for improving mental health and craving by suggesting that even brief experiences with mindfulness can improve affect and reduce substance use cravings. Future research could examine important factors that may influence such changes, such as prior experience with mindfulness practice, as well as examining the extent that these changes persist over time.

**Topic areas:**  
Addiction
Original Research - Pre-Clinical

Presenting Author: Kyung Joon Park, Research Associate

Co-Authors: Kyung Joon Park and Vadim Bolshakov

Title: Synaptic encoding of context-dependent mechanism underlying fear memory extinction

Key words: Fear extinction, Amygdala, Ventral hippocampus, Synaptic mechanism

In Pavlovian fear conditioning, fear memory is formed after pairing the conditioned stimulus (CS) with the unconditioned stimulus (US), so that a presentation of the CS after the CS-US pairing evokes fear responses (e.g., freezing). When the CS is repeatedly presented without the US, fear responses gradually decrease, reflecting the new learning processes termed fear extinction. An important feature of fear extinction memory is its context dependence, restricting the stability of extinction memory, as an exposure to the CS in a novel context results in renewed fear memory. Certain brain regions such as prelimbic and infralimbic cortex and amygdala are parts of neural circuits underlying fear extinction. However, it remains unclear how this context dependence is encoded. To explore this, we focus on the connection between the ventral hippocampus (vHPC) and basolateral amygdala (BLA). Using optogenetic tools, we found that vHPC sends projections to the BLA and these projections contribute to the mechanisms of fear learning and fear extinction. Additionally, we showed that vHPC sends direct monosynaptic GABAergic projections to the BLA, which also could contribute to control of extinction memory. Taken together, our findings indicate that projections from the vHPC to the BLA play essential roles in fear control.

Topic areas:
Anxiety
PTSD
Accurate perception of information conveyed by a face is fundamentally adaptive, increasing our changes of survival by allowing us to interpret dynamic and potentially threatening situations. From an ecological perspective, facial expressions guide us to take social action (Gibson, 1979; Reed, 1996). Since facial expressions are an accurate predictor of future behavior, correctly identifying and avoiding an angry face may allow us to avoid harm, and greeting a happy face openly may incur greater resources and reproductive fitness (Andrew, 1963; Harris et al., 2016). A vast literature has reported an age-related shift in the ability to recognize negative emotions. A recent review confirmed that older adults are less accurate in recognizing anger, sadness, and to some extent, fear (Isaacowitz et al., 2007). In a cross-sectional study exploring age-related differences in emotion recognition ability, results revealed that decline in recognition of sadness and anger start around 30 years of age (Mill et al., 2009). Most behavioral tasks were not designed to cleanly dissociate between emotion categories, as responses are confounded across emotion types. The current study aimed to examine sensitivity to the intensity of emotional face expressions (emotional sensitivity: ES) across the lifespan, in a set of three tasks that were matched for sensitivity and reliably and could cleanly dissociate between these three emotion categories. In the ES tasks, participants had to discriminate which of a pair of faces was more fearful (fear sensitivity task), angry (anger sensitivity task), or happy (happiness sensitivity task). Participants were 9546 visitors to the website http://testmybrain.org. Average age of our sample was 27.59 (SD = 12.33, range = 10-85). To evaluate both development and aging, we analyzed data based on age group: 10-30 (development), 31-85 (aging). We expected that the development group would show better ES scores with age, and that aging group would show a decline in ES for anger and fear. We also explored the impact of gender, ethnicity, and education on ES. Results showed a curvilinear relationship between age and ES. In the development group, participants had significantly higher ES scores for angry, fearful, and happy faces (p < .001) as they aged. In the aging group, we saw the opposite trend; increased age was associated with decreased ES (p < .01). Effects were stronger for anger and fear than for happiness, despite comparable psychometrics. Women were more emotionally sensitive than men for angry and fearful expressions, but the difference in ES between genders did not occur for happy faces. ES scores by face type will be presented graphically across the lifespan. Clinical and theoretical implications of the results will be discussed.

**Topic areas:**
- Anxiety
- Depression
- Technology
Scrupulosity and Guilt in Intensive/Residential Treatment (IRT) for Obsessive-Compulsive Disorder (OCD)

Introduction: Previous research has identified the presence of elevated guilt within those with OCD (Shapiro & Stewart, 2011); however, this evaluation has been largely focused within scrupulosity based symptoms. Further, there is limited research addressing the role of guilt and how its interaction with other conscience related factors (C-RFs) may impact OCD severity and treatment outcome. A better understanding of these relationships can be very helpful in understanding the development/maintenance of OCD symptoms. Furthermore, the role of C-RFs in maintaining symptoms and associated beliefs across OCD subtypes (e.g., contamination, sexual, symmetry/exactness) has not been studied in depth, especially in IRT samples. Most previous studies have utilized non-clinical samples or those with mild/moderate severity.

Methods: The overall objective of this study was to assess whether unaddressed conscience-related factors (C-RFs) such as guilt and scrupulosity contribute to OCD severity and impact treatment. More specifically, this study aims to examine the effects of guilt, scrupulosity and their interaction on the general obsessive-compulsive (OC) symptomatology as well as treatment outcome. 125 patients receiving IRT for severe OCD completed the Interpersonal Guilt Questionnaire, Pennsylvania Inventory of Scrupulosity-Revised Questionnaire (PIOS-R), Dimensional Obsessive-Compulsive Scale (DOCS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), at admission/discharge.

Results: Linear regression analyses indicated that omnipotent guilt (β=.257, t(115)=2.850, p=.005) and survivor guilt (β=.196, t(114)=2.129, p=.035) were significantly associated with overall symptom severity at admission. Further, those with high levels of scrupulosity (as measured by a PIOS score of 24 and above) had significantly higher OC symptom severity (F(1,114) = 4.547, p = .035) as well as depressive symptoms (F(1,115) = 10.834, p = .001) at admission. However, significant differences in omnipotent and survivor guilt were not seen between groups. Furthermore, among individuals who endorsed obsessions concerning responsibility for harm/injury/bad luck and unacceptable obsessive sexual/violent/religious thoughts (measured by the 2nd and 3rd domains of DOCS-4), those with high scrupulosity presented with significantly higher severity of symptoms at both admission (DOCS 2: F(1,115) = 13.425, p = .000; DOCS 3: F(1,115) = 33.687 p = .000) and discharge (DOCS 2: F(1,97) = 5.681, p = .019; DOCS 3: F(1,97) = 12.775 p = .001). Of note, higher omnipotent guilt and survivor guilt were correlated with higher DOCS 2 and DOCS 3 domains.

Discussion: Results suggest elevated feelings of guilt and the presence of significant scrupulosity symptoms were both related to greater overall OCD severity. However, no significant differences in reported guilt was observed between those with high vs. low scrupulosity symptoms. Further, with the significant relationship between guilt and OCD severity across the DOCS 2 and 3 domains it reinforces that elevated guilt is a broader aspect of OCD symptomatology, and not related to scrupulosity symptoms alone. Findings suggest that individuals with increased scrupulosity have higher symptoms on the DOCS-2 and DOCS-3 domains throughout treatment. Results support the importance of considering the role of scrupulosity in symptom severity/presentation for individuals with OCD. Further investigation is warranted to address how treatment may be augmented to ameliorate these C-RFs.
Presenting Author: Lindsay Appleman, Clinical Research Assistant II

Co-Authors: Jessica Bachetti; Diego Pizzagalli, Ph.D.; Christian Webb, Ph.D.

Title: The Effects of Mindwandering on Adolescent Affect: An Ecological Momentary Assessment Study

Key words: mindwandering, affect, EMA, adolescents

Background: In a highly cited ecological momentary assessment (EMA) study, Killingsworth & Gilbert (2010) reported that healthy adults spend approximately half (46.9%) of their waking hours thinking about something other than what they are doing (i.e., mind wandering). Importantly, mind wandering was found to be a stronger predictor of lower mood than the activities in which participants were engaged at the time of the EMA surveys. Research has yet to examine the role of mind wandering within adolescent populations experiencing higher levels of low mood. The present study used EMA to investigate the affective correlates and consequences of mind wandering in adolescents with low mood (LM) and healthy controls (HC).

Methods: The study included 38 adolescents aged 13 – 18 years (25 HC and 13 with LM). Participants downloaded a smartphone application (Metricwire) for EMA data collection. Over the course of one week, participants received surveys on their phone two to three times a day. Each survey prompted adolescents to report on their current positive and negative affect (PA & NA) (Positive and Negative Affect Schedule; PANAS), cognitions, and activity.

Results: The frequency of mind wandering was high in our adolescent sample, in particular for LM (71.7% of EMA samples) relative to HC (58.1% of samples) participants (F(1,36) = 5.61, p = .02). Moreover, LM participants were more likely to mindwander to unpleasant (46.7%) - relative to pleasant (22.8%) or neutral (30.4%) - content. In contrast, HC participants were more likely to mindwander to pleasant content (48.4%) (unpleasant = 16.8%, neutral = 34.8%). Importantly, participants reported significantly lower PA (F (1,304) = 5.79, p = .02) and higher NA (F (1,304) = 6.37, p = .01) when their minds were wandering than when they were not, even when controlling for current activity, social companion, and day of the week. Participants were no happier when mindwandering to pleasant topics than when focused on their current activity (NA: F(1,206) = 1.30, p = .26; PA: F(1,206) = 2.01, p = .16) and were less happy when thinking about neutral topics (for NA: F(1,192) = 14.01, p < .001; for PA: F(1,192) = 3.88, p = .05) or unpleasant topics (for NA: F(1,179) = 24.36, p < .001; for PA: F(1,179) = 20.62, p < .001). Finally, a time-lagged analysis indicated a directional relationship between mindwandering and PA/NA over time (F (3,83) = 3.49; p = .02), suggesting that mindwandering may be a cause – and not merely a consequence or correlate – of low mood.

Conclusion: Rates of mind wandering among adolescents were high, especially among those endorsing low mood. Results also suggested that mind wandering may contribute to decreased positive affect and increases in negative affect. In contrast to traditional laboratory-based paper-and-pencil questionnaires, the sampling density of repeated, daily smartphone-delivered EMA surveys allows for a more fine-grained and ecologically valid assessment of the temporal relationship between cognition and affect in real time and in the real world.

Topic areas: Child/Adolescent Depression
Depression is the most common psychiatric disorder in the United States, with an estimated 16.1 million American adults suffering at least one depressive episode in 2015. Antidepressant pharmacotherapies have primarily targeted the biogenic amine neurotransmitter systems, but available treatments have a slow onset and fail to satisfactorily treat up to 30% of patients. A growing body of evidence, however, suggests that the cholinergic neurotransmitter system may play a role in the pathophysiology of depression. Emerging clinical findings show that scopolamine, a muscarinic acetylcholine receptor antagonist, rapidly relieves symptoms of depression, with effects persisting beyond the drug’s duration of action. Importantly, preliminary studies also suggest that scopolamine may be effective in treating refractory depression. Unfortunately, scopolamine also has well known cognition-impairing effects, which may limit its clinical safety. In the present studies, we investigated the effects of scopolamine and arecoline (a prototypical muscarinic receptor agonist), on cognitive performance in rats to elucidate the effects of these drugs and to anticipate potential barriers to the development of novel cholinergic antidepressants. Rats (n=3-5/group) were trained in touchscreen chambers to respond for a food reinforcer in either a Titrating Vigilance task, a visual attention task, or a Progressive Ratio task, a task used to assess motivation. Once baseline performance was established, subjects were exposed to acute drug tests up to twice per week, contingent on daily baseline performance. Scopolamine (0.032-3.2 mg/kg) and arecoline (1-10 mg/kg) each dose-dependently impaired performance in the Titrating Vigilance task; however, distinct within-session patterns of responding were produced by each drug in a dose-dependent manner. Pretreatment with scopolamine shifted arecoline’s dose-response function down, consistent with its antagonist profile. In the progressive ratio task, doses of scopolamine below 1.0 mg/kg produced a dose-dependent increase in break point, while doses above 1.0 mg/kg produced a decrease in break point. Doses of arecoline above 0.32 mg/kg eliminated progressive ratio responding, and scopolamine pretreatment attenuated this effect. In sum, these data indicate that scopolamine and arecoline both impair attention, but in qualitatively different ways. Additionally, scopolamine may produce an increase in motivation under some doses. These data will serve as benchmarks which will be used in future studies to evaluate the cognitive side effects of novel muscarinic antagonists designed to have fewer adverse effects but retain antidepressant action.
**Title:** Impact of Intensive DBT Parent Skills Training on Adolescent Treatment Outcomes

**Key words:** DBT, adolescents, suicide, parent skills training, emotion dysregulation

**Aim:** To evaluate the impact of a DBT weekend parent skill training intensive “workshop” on adolescent outcomes and parent-teen relationships.

**Introduction:** Individual and family functioning are reciprocally connected. When an adolescent is struggling with emotion dysregulation that leads to a suicidal and self-injurious behavior, the family environment is also negatively impacted, and parent-teen relationship problems, and parent invalidating responses, negatively affect their adolescents (Fruzzetti et al., 2005). Parents of suicidal and self-harming teens report significant difficulty responding effectively (Hoffman et. al, 2005), contributing to parent burn out and distress (Hoffman et. al, 2007). Without targeted intervention, parents can struggle to provide adequate support to their children as they navigate treatment. The present study sought to examine the impact of an intensive weekend DBT family skills program based on the Family Connections program, an empirically supported program for family members, on outcomes for adolescents receiving residential Dialectical Behavior Therapy (DBT), and on parent-teen relationships. All adolescents also received comprehensive residential DBT treatment, including weekly individual therapy, group skills training at least 3 times per week, skill coaching available at all times, weekly family therapy, and clinicians participated in a weekly DBT consultation group.

**Method:** 112 adolescent (ages 13-17) in a residential Dialectical Behavior Therapy (DBT) program, and their parents participated in the study. Parents were randomly assigned to either participate in the intensive parent skill training weekend (treatment condition), or a waitlist control condition. Adolescents completed a series of questionnaires at the beginning of treatment (T1), at 4 weeks post intervention or end of waiting period (T2), and in the week prior to discharge (T3). Outcome measures included measures of emotion regulation (DERS), psychological distress, including depression and anxiety (DASS-21), parent levels of validating and invalidating responses to their teens (VIRS), and parent emotion availability (LEAP).

**Results:** Parents in the parent skills condition were rated by their teens as significantly increasing their validating responses compared with parents in the waitlist condition. Additionally, parents in the parent skills condition were rated as more emotionally available for both positive and negative experiences. Improvements in validating parent responses correlated with adolescents’ reduced difficulties with emotion regulation and decreased depression at discharge. 23% of parents were unable to attend the intensive parent skills weekend during the study period. A post-hoc analysis indicated that adolescents whose parents attended the parent skills weekend at any time (compared to those who did not) reported greater improvements in emotion regulation and family communication, above and beyond the gains achieved through the standard comprehensive DBT treatment program.

**Conclusion:** Findings support both the importance and efficiency of parent skills training in improving outcomes for suicidal and self-harming adolescents. Even in a 4-week period, adolescents whose parents participated in the parent skill weekend reported reduced invalidating and increased validating responses, and showed improved outcomes overall on their depression scores and problems regulating their emotion.

**Topic areas:**
- BPD
- Child/Adolescent
- Depression
- Quality/Outcomes
Coping Strategy Use in Individuals with Sexual Abuse Histories and Substance Use Disorders

A significant proportion of individuals who seek treatment for substance use disorders (SUDs) endorse a history of sexual abuse (SA). Studies have shown that individuals who have SA histories are prone to maladaptive and avoidant coping, and that those who engage in more avoidant coping are more likely to use alcohol in response to stress when compared to individuals who use more active coping. There are also gender differences in coping strategies in response to stress, with women using more active coping strategies (like emotional support) when compared to men. This secondary analysis of a randomized control trial (N=158) that compared two group therapies for SUDs—the Women’s Recovery Group and Group Drug Counseling—explores the different coping strategies used by participants with a history of SA versus those with no SA history, as well as gender differences in coping, using a modified version of the Brief COPE. Eligible participants were >18 years of age, substance dependent, and had used substances in the past 60 days. We hypothesized that participants without a history of SA would endorse more active coping strategies (i.e., active coping, positive reframing, acceptance, religion, and emotional support), whereas participants with a history of SA would endorse more avoidant coping strategies (i.e., denial, behavioral disengagement, and self-blame). Among the subgroup reporting a history of SA (n=49), we hypothesized that avoidant coping styles would be associated with worse substance use severity at baseline and worse SUD outcomes at end of treatment (12 weeks) and that women would endorse more coping strategies, particularly the use of emotional support. Contrary to our hypotheses, at baseline, participants with a history of SA were significantly more likely to report using two types of active coping strategies: positive reframing (t=-2.2, df=156, p=.03) and acceptance coping (t=-2.3, df=156, p=.02) compared to participants without SA histories. At end of treatment (12 weeks), participants with a SA history were still significantly more likely to report using coping strategies that are considered active: emotional support (t=-2.1, df=128, p=.04) and active coping (t=-3.2, df=114.9, p=.00); however they were also more likely to use two types of avoidant coping strategies: denial (t=-2.7, df=128, p=.01) and self-blame (t=-2.3, df=128, p=.02). Baseline substance use of participants with SA histories was not associated with baseline coping strategies; however at 12 weeks (end of treatment) use of denial strategies was significantly correlated with number of heavy drinking days (r=.37, p=.02) and number of drinks per drinking day (r=.65, p=.01). There were no significant gender differences in coping at baseline; however at 12 weeks (end of treatment), women with a history of SA were more likely to endorse using denial strategies (t=-2.7, df=39, p=.01) when compared to men with SA histories. Use of denial as a coping mechanism at end of treatment is associated with increased alcohol use. Women with a history of SA may be more likely to use such strategies even after completing treatment. Assisting women with SA histories in SUD treatment to learn more adaptive coping may be one strategy to improve SUD treatment outcomes.

Topic areas:
- Addiction
- Gender Differences
- Women
Program Description

**Presenting Author:** Melissa Moses, Assistant Psychologist

**Co-Authors:** Monika Kolodziej, PhD, Rocco Iannucci, MD, Ken Gilman, Emily Volpe, PsyD

**Title:** Technology-Assisted Dual-Diagnosis Support and Education for Family Members

**Key words:** Dual-Diagnosis, Family Members, Technology-Assisted, Support, Group

**Aim:** To explore feasibility of a multifamily psychoeducation group with some family members participating in-person and others participating via video-conferencing.

**Introduction:** The importance of family support in a patient’s recovery from addiction has been well-established. While some treatment programs offer family programming, it is often difficult or impossible for loved ones to travel to receive services on-site. At McLean Fernside, we developed a program of support and psychoeducation to assist family members in navigating both the treatment and early recovery of their loved ones.

**Methods:** We developed an accessible family program by offering a video-conferencing option in addition to on-site participation, facilitating the involvement of families who live out-of-state or overseas. In developing the family support program, we researched topics that would be most helpful to address and decided upon self-care, boundaries, positive communication, and psychoeducation about addiction. Upon rolling out the program, we asked participants to complete Likert Scale survey evaluations of the topics. Participants also offered feedback about the experience in general.

**Results:** We found that the mix of video-conferencing and in-person participation was appreciated. Group members enjoyed hearing the experiences and perspectives of others regardless of venue. The family program was highly rated by participants and we served more families by offering direct support rather than referring them elsewhere.

**Conclusions:** Multifamily group support using a blend of simultaneous in-person interactions and videoconferencing is a feasible approach that could be adapted to extend treatment to remote locations.

**Topic areas:**
- Addiction
- Technology
Introduction: Arterial Spin Labeling is an MRI technique used to study cerebral blood flow and hemodynamics. In this project we use static ASL to assess hemodynamic parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and bolus arrival time. In order to simulate pathology we perform these measures in healthy controls while breathing medical air (MA), Oxygen (100% O2), or Carbogen (5% CO2 / 95% O2). Oxygen is a vasoconstrictor and carbon dioxide is a vasodilator; and we expected both increases and decreases in hemodynamic parameters to occur under these gas challenges. We expect O2 to have minimal effects on CBF and CBV; we expect Carbogen to cause increases in CBF and in bolus arrival time.

Methods: We collected multi-delay PCASL data using a 3D Gradient and Spin Echo (GRASE) sequence on a Siemens 3T Prisma MR system. 3D GRASE provides higher resolution within achievable scan times. The acquisition used 8 single volume delays with TE=30ms, TR=4s, TI = 1.6s, 2.0s, 2.4s, 2.8s, 3.2s, 3.6s, 4.0s and 4.4s; the tag duration was 1.5s (within TI); isotropic voxels were 3.5mm with a matrix of 64x64x40; scan time was 5:30. Three acquisitions were made. Subjects were breathing either MA, O2 or Carbogen through an MR compatible portable tank-based apparatus utilizing a demand regulator during each scan. The sequence provided both tag and control images as well as M0 images. A standard 3D anatomic image was also acquired for registration. Data were acquired from five healthy subjects. Calibrated ASL processing was performed using FSL BASIL software (Oxford FMRIB v5.0.10) which provided maps of voxel wise bolus arrival time, quantitative CBF and quantitative CBV. Assessments were made of the three hemodynamic parameters in a gray matter (GM) region and in a region containing the basal ganglia and thalamus (BG). These two regions were selected because they represent different tissue vasculature and variability for comparison. Regional mean values were compared for CBF and CBV, while voxel wise maps of the relative change in arrival time from MA to O2 and MA to Carbogen were made to assess change in bolus arrival time.

Results: Changes in CBF were apparent with a reduction in regional CBF observed under O2 as compared to MA, 18.5% in both GM and the BG; there was an increase in CBF under Carbogen in GM (16.5%) and in the BG (6%). CBV increased under the influence of both gases, with a 13.8% increase under O2 in GM and a 27.8% increase under O2 in the BG, and an increase by 26.8% under Carbogen in the GM and by 45% in the BG. Arrival times were unchanged in both regions under O2 and were decreased by 3% in the GM and by 2% in the BG under Carbogen. The regional mean changes are shown in the figures below (CBF and CBV) as well as the mean voxel wise change in bolus arrival time.

Discussion: The repeatability and robustness of these results demonstrate that the 3D GRASE sequence can be used to detect the desired changes in cerebrovascular reactivity. Reduction in CBF under the influence of O2 occurred as expected, and the increase in CBF under the influence of the carbon dioxide in the Carbogen mix was also as expected. The increase in CBV under both gases was not expected and further modeling will be performed to explain this. The changes in bolus arrival time were small but robust.

Topic areas:
Imaging
**Title:** First Human Trial of Stem Cell Engraftment in Complex Arrays for Stroke Patients Using the Intracerebral Microinjection Instrument (IMI)

**Key words:** neural transplantation, basal ganglia stroke, stem cell therapy, neurosurgery, Intracerebral Microinjection Instrument

**Introduction:** The Intracerebral Microinjection Instrument (IMI) has been developed for delivery of restorative therapeutics within the human CNS. Preclinical trials in pigs and non-human primates have shown the IMI to be safe and effective in delivering stem cells, viral vectors, and microspheres. This trial evaluated the ability of the IMI to strategically distribute deposits of human neural stem cells in the vicinity of a stroke lesion.

**Materials/Methods:** The IMI was engineered to deliver cell suspension via a microcannula that extends from a guide cannula at a 22o angle and with an arcing trajectory. Using surgical planning software and precision manipulation of the guide and micro-cannulas, multiple cell deposits were placed in three-dimensional (3D) space. As part of a Phase I clinical study, 3 neurologically stable subjects with lenticulostriate artery strokes of the basal ganglia, 3-24 months prior to surgery, and with Fugl-Meyer Assessment scores of <55, were enrolled in the study. MRI and DTI imaging was used in surgical planning for delivery of the human-derived neural stem cell line, NSI-566, which has been shown to restore function in ischemia-injured spinal cord along the ipsilateral corticospinal tract and internal capsule.

**Results:** Deposits of NSI-566 cell suspension were placed at targets surrounding the infarcted region as well as in and around the internal capsule affected by ischemia. Each patient received 45 (+5) strategically placed deposits during a single operation using imaging data and surgical planning software. The procedure was well-tolerated by all patients and they recovered without complications. The IMI was determined to be user-friendly, safe, and effective for cell delivery.

**Discussion:** The IMI design allows the injection of multiple sites in 3D space using a single overlying penetration of the guide cannula. The diameter of the delivery microcannula is minimized to allow discrete brain regions to be targeted as well as to reduce trauma in the local environment. Precision targeting combined with reduced inflammation and reactive gliosis results in a more suitable environment for therapeutic efficacy. An unprecedented number of cell deposits were safely implanted during a single operative session.

**Conclusions:** After extensive preclinical testing, the IMI and its surgical planning software were successfully used for human neural transplantation for the first time. The IMI technology offers a safe and reliable method for efficiently delivering therapeutics to multiple predetermined targets while minimizing potential trauma. The IMI may be used in restorative therapies for diverse neuropsychiatric diseases, including neurodegeneration, epilepsy, trauma, and stroke.

**Topic areas:**
Neurology
Technology
Presenting Author: Min Su Kang, Clinical Research Assistant II

Co-Authors: Min Su Kang, Maria Ironside, Ashleigh Rutherford, Sean Boyden, David Olson, Cristina Cusin, & Diego A. Pizzagalli

Title: Effect of acute stress on model-based learning in depression

Key words: Depression, Stress, Magnetic Resonance Imaging, Model-based Learning, Reward

Background: Functional and structural abnormalities within mesolimbic reward pathways – which play a key role in reward processing and decision-making – are strongly implicated in the pathophysiology of major depressive disorder (MDD), particularly in the presence of anhedonic symptoms. A promising endophenotype of MDD is blunted response to rewarding stimuli, which has been observed both on the behavioral and neural levels. Although several neuroimaging studies have shown the effect of stress on response to reward, little is known about its influence on complex decision-making processes that are ultimately driven by these reward pathways. Using functional magnetic resonance imaging (fMRI) and two-step reinforcement learning task, this study aimed to model the neurobiological changes in reward sensitivity after exposure to acute stress in MDD.

Methods: During high temporal resolution fMRI acquisition, 27 unmedicated adults (11 with current MDD) completed a sequential two-step reinforcement learning task (“two-armed bandit”) using reward points before and after exposure to a stressor. For the learning task, participants were given a choice between two options, which preferentially (70%) transitioned to one of two subsequent states, where choices were rewarded stochastically. Model-based decisions included trials in which participants chose the common (70%) transition option despite having won a reward in a rare (30%) transition in the preceding trial, suggesting an evaluative decision-making process informed by overall transition probabilities. The stress manipulation paradigm (the Maastricht Acute Stress Paradigm) consisted of interleaved blocks of hand immersions in cold water (2-4°C) and difficult arithmetic task under social evaluation with unpredictable trial duration. Saliva samples were collected immediately before and 38 minutes after the onset of stressor, and later assayed for cortisol. fMRI data were preprocessed and analyzed using SPM12 with a voxel height threshold of p=.005 and a cluster extent cutoff of >10 voxels. Contrasts of interest compared activations during model-based decisions pre- and post-stressor.

Results: Significant increases in cortisol confirmed the efficacy of stress manipulation (F=15.92, p<0.001). Compared to the healthy volunteers, the MDD group had lower activations during model-based decisions in the right pallidum, right hippocampus, parahippocampal gyrus, and subgenual anterior cingulate cortex prior to the stressor. Conversely, following the stress paradigm, the MDD group, relative to healthy volunteers, showed greater activations in the right putamen and parahippocampal gyrus, as well as in the left amygdala and insular cortex. Further group-level contrast analyses comparing pre- and post-stressor activations revealed that the MDD group was characterized by greater activations in the left putamen, hippocampus, thalamus, and medial orbitofrontal cortex after stress.

Conclusion: These results suggest that acute stress differentially impacts neural activation during model-based decision-making in depression. Furthermore, these findings support prior literature that through this hypersensitivity to stress, these circuits over time may become downregulated by chronic stress and ultimately result in blunted response to reward, which is a core feature of depression underlying anhedonia. These findings may contribute to our understanding of depression and stress-related disorders, and serve as a potential target for therapeutic interventions.

Topic areas:
Depression
Presenting Author: Kathryn Nielsen, Clinical Research Assistant II

Co-Authors: Roscoe Brady, MD, PhD, Alison Margolis, Esin Asan, Mei-Hua Hall, PhD, Dost Ongur, MD, PhD

Title: Contributing Factors to Social Anosognosia in Patients with Psychotic Disorders

Key words: Psychosis, Insight, Social functioning, Schizophrenia, Bipolar Disorder

Background and Significance: Patients with psychotic disorders often experience anosognosia, or limited insight into the nature of their disease. A substantial body of research links psychotic disorders to social cognitive impairments, which mediate broader functioning. It is unclear whether patients with psychotic disorders have insight into their own social functioning and other impairments in this domain. The present analysis seeks to clarify the extent to which patients possess insight into their own social functioning and whether this acknowledgement of social functioning varies between patients with different psychiatric diagnoses. We will also examine the influence of social insight on treatment outcomes in patients with psychosis.

Methods: Patients with psychotic disorders were recruited from the Schizophrenia and Bipolar Disorder Program. In this analysis, we compare self-report measures of social function (World Health Organization Disability Assessment Schedule (WHODAS)) to informant/observer ratings of social function (Multnomah Community Ability Scale (MCAS))- utilizing objective and subjective ratings within subjects to examine the association between patient self-report and independent observer report.

Results: We found that patients with psychotic disorders rate their own social functioning similarly to observers (t(59)=-1.397, p=0.168). However, patients with bipolar disorder demonstrate impaired ‘social acceptability’- navigating social environments without attracting negative attention- compared to patients with either schizophrenia or schizoaffective disorder (F(2,58)=3.678, p=0.031). Further, patients with bipolar disorder display significantly poorer insight into their psychiatric symptoms, in general, than patients with either schizophrenia or schizoaffective disorder (F(2,58)=10.092, p<0.001).

Discussion: Results from this project contribute to the development of innovative therapeutic interventions for patients with psychotic disorders. While correcting social cognition necessitates interventions beyond realization of social deficit, encouraging social self-awareness may be a critical initial step to facilitate other positive treatment outcomes.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia
McLean Research Day 2018

Theoretical/Commentary

Poster # 117
Time: 1:00-1:50pm

Presenting Author: Nara Nascimento, Clinical Research Assistant II


Title: Optimizing magnetic resonance spectroscopy protocol for GABA on a 3T Prisma: A methodological overview

Key words: Depression, Magnetic Resonance Spectroscopy, Sex Differences, GABA

Despite epidemiological evidence pointing to the higher prevalence of major depressive disorder (MDD) in women when compared to men (Kessler, 2003), little is known about the neurobiological mechanisms behind this sex difference. Preclinical evidence raises the possibility that gamma-Aminobutyric acid (GABA) signaling deficits might be sex-dependent in MDD (Tobet, S. et al., 2009) and could lead to a better understanding of the higher female risk for MDD. The main goal of this preliminary study was to evaluate the reliability of the MEGAPRESS magnetic resonance spectroscopy (MRS) protocol for GABA on a 3T Prisma. MRS data were initially collected from three regions relevant to sex differences: 1) rostral Anterior Cingulate Cortex (rACC) 2) left Dorsolateral Prefrontal Cortex (DLPFC); 3) right Hippocampus using a MEGAPRESS sequence for detection of GABA. Initial results showed high variability, with an initial signal to noise ratio of <8 and ~20% CRLB (obtained in LCModel), owing to difficulties shimming (unsuppressed water linewidth more than 40Hz in some cases) and eddy current effects. However, parameters were optimized using an eddy current effect test to find the combination of spoil gradient length and strength that minimized noise. In addition, for the DLPFC voxel, modifications were made to voxel placement and size to improve shim quality and reduce lipid effects. This optimization resulted in substantial improvements in MRS data outcomes with an increase in signal to noise ratios (>40), decrease in fitting errors (<10% CRLB), and an increase in shimming quality (<20hz). The hippocampus voxel was discarded because of persistent shimming difficulties (>40Hz), which needs further improvement. Since optimization of the acquisition protocol, the MRS component has been launched in the larger study and test-retest reliability was excellent (<3% variability). The improved MRS protocol will allow the team to measure rACC and DLPFC GABA in males and females with MDD and demographically matched healthy controls and thus add to the knowledge of how GABA signaling deficits may lead to the sex difference in MDD. This work is dedicated to Dr. Eric Jensen, who spearheaded many MRS methodological developments at the McLean Imaging Center, and whose untimely passing left a void among his colleagues and friends.

Topic areas:
Depression
A substantial proportion of psychiatric inpatients are re-admitted after discharge. Readmissions are disruptive for patients and families, and are a key driver of rising healthcare costs. Predicting readmission risk in patients with first episode of psychosis (FEP) is a key NIH priority as the early phase of psychosis also offers a “window of opportunity” during which treatment may achieve disproportionately favorable outcomes. A challenge in reducing readmission risk is the difficulty in developing a model for extracting risk factors associated with readmission. Clinical narratives in electronic health records (EHRs) contain detailed descriptions about a patient’s illness presentation, prior course, and treatment plans. Natural language processing (NLP) tools to automatically extract information from EHRs have been proposed, but have not been widely applied in psychiatry. It is particularly difficult for such EHR tools to automatically identify what a clinical narrative is about. To address this challenge, previous research has used document similarity metrics, which take two or more documents as input, and output a score representing how similar the documents are. Models using these metrics have revealed associations between certain topics and readmission risk (McCoy et al. 2015). Previous models have typically relied on corpora constructed from clinical journal abstracts or web search results. This study investigates whether models constructed from clinical narratives in EHR data can better predict patient readmissions.

Aims: The aims of the present study are to: 1) Use the Research Patient Data Registry (RPDR) and other EHR data to construct specialized corpora for the following domains: mood, attention/concentration, substance use, thought process, thought content, and employment; 2) Standardize the documents with vectorization, thereby building a model for revealing domain distribution patterns in clinical narratives; 3) Evaluate the model by investigating the associations between each domain and hospital readmission, modifying the approach in McCoy et al. (2015); and 4) Compare the performance of our model trained on clinical corpora vs. previously published models trained on web pages, e.g. McCoy et al. (2015).

Methods/Design: We use text-mining techniques to build sets of EHR ‘megadocuments’ for each domain. We then apply TF-IDF vectorization to each megadocument set. This provides us with a document similarity model: we use vector similarity measurements to compare each paragraph in the clinical narrative to each megadocument set, with each similarity score representing the domain coverage of the paragraph. We then use the model output as the features for training a classifier to predict 30-day psychiatric readmission.

Data: To extract the clinical narratives, we use Meditech software to extract EHRs from 50 patients. To construct the megadocuments, we use the RPDR query tool to download EHRs for patients visiting New England hospitals for reasons related to psychiatric symptoms, diagnoses, or treatment. Training data is based on approximately 30,000 relevant EHR documents.

Conclusion: We are testing two hypotheses: first, compared to models constructed from web search data, our model provides better insights into which risk factor domains are most closely tied to patient readmission; and second, that our document similarity model trained on EHR data will perform better than similar models used in previous research, which were trained on general web search results rather than domain-specific EHR data.

Topic areas:
Psychotic disorders
Quality/Outcomes
Technology
Increasingly both clinicians and clinical researchers are incorporating digital technologies into their work. It is unclear, however, which technology solutions carry the most appeal or urgency for clinicians and investigators, and are therefore the highest priority for validation and translation. To that end, we are surveying clinicians and investigators at a large psychiatric hospital (McLean Hospital) from across multiple clinical programs and levels of care. While data collection is ongoing, initial results reveal substantial interest and engagement with digital tools among clinicians and investigators. The digital technologies most in demand are those that facilitate symptom self-report and assessment (92%). After that, clinicians and investigators are interested in mobile measures of stress, cognitive functioning, and activity (46%). Finally, a substantial proportion are seeking digital means to automatically assess emotion, sleep, diet, social interaction, and vital signs (15% - 30%). Research that helps clarify applications, validity, and best practices in the implementation of digital technology will be useful to providers and organizations seeking to adopt them safely and effectively.

**Topic areas:**
- Quality/Outcomes
- Technology
Multimodal functional magnetic resonance imaging (fMRI) studies have suggested that dynamic, systemic low frequency oscillations (LFOs) measured in the periphery contribute to fluctuations in the blood-oxygenation-level-dependent (BOLD) signal in similar spatial patterns as observed during resting-state fMRI (rsfMRI). It is currently not well understood in which manner these blood-borne oscillations contribute to the BOLD signal. Observing the behavior of these LFOs under different gas manipulations during rsfMRI may shed light on their association to physiological underpinnings of the BOLD signal. Of particular interest are how oxygen (O2) and carbon dioxide (CO2) affect BOLD signal parameters, such as delay time in healthy and compromised tissue. To that end, our laboratory is currently collecting multimodal imaging data, including rsfMRI and arterial spin labeling, end-tidal CO2 and O2, and peripheral near-infrared spectroscopy (NIRS) in 60 individuals to generate normative data characterizing LFO behavior in a generally healthy community sample. So far, we have collected data of 10 participants, and in eight of them examined rsfMRI data obtained under different gas manipulations with the aim to determine the effects of O2 and CO2 on the BOLD signal delay. We hypothesize that the BOLD time delay under O2 will be the longest due to vasoconstriction, the shortest under CO2 due to vasodilation, and intermediate under medical air.
Presenting Author: Sarah Hill, Clinical Research Assistant II; B.A. degree

Co-Authors: Laura Ward, M.B.A., Lauren A.M. Lebois, Ph.D., Jonathan D. Wolff, B.S., Kerry J. Ressler, M.D., Ph.D., Milissa L. Kaufman, M.D., Ph.D.

Title: Trauma History and the Medical Setting: Patient Perspectives and Experiences

Key words: trauma, PTSD, women

Background: Patients with a history of exposure to traumatic events may receive inadequate care when trauma history is overlooked or not discussed in a medical setting. To date, patients’ perspectives and preferences regarding disclosure of trauma history have not been well represented in the literature. Engaging patients in research that assesses their experiences and preferences regarding disclosure of trauma history could lead to more effective screening protocols, treatment preferences and outcome measures.

Method: Participants in this study were 19 patients at McLean Hospital’s Hill Center for Women, age 18-62 (M = 39.63). All participants experienced some form of childhood trauma as measured by the Childhood Trauma Questionnaire (CTQ) (Bernstein, et al., 1997). However, some reported an experience from adulthood as their “worst” traumatic event. All participants completed the Connection Between Childhood Trauma and Physical Health Patient Survey (PS-CTPH) (Ward, Hill, et al., 2016), a 15-item questionnaire designed to collect information about perceived connections between physical health and trauma exposure, experiences of disclosure, provider preference, influence of trauma exposure on willingness to seek medical care, and beliefs around disclosure and stigma.

Results: Participants noted they were less likely to self-disclose if not asked by a provider, yet believed it was important for medical providers to ask about a history of trauma (M = 8.53, SD = 1.90). They reported they were most comfortable disclosing trauma with Primary Care Providers (PCPs), and least comfortable disclosing in Urgent Care settings. Although participants believed that it was most important for PCPs and Gynecologists (GYNs) to screen for trauma compared to other medical providers, 58% reported their PCPs rarely or never asked about trauma history, and 42% reported their GYNs rarely or never asked. Nearly every participant believed that more routine discussion about trauma and abuse in medical settings could reduce stigma associated with disclosure (M = 8.79, SD = 2.02).

Conclusion: This study of treatment-seeking women with trauma histories suggests strong patient preferences to disclose in the medical setting, yet it is somewhat uncommon for these providers to routinely screen for history of trauma. Based on patient perceptions, it seems that more routine discussion about trauma in medical settings could potentially improve care and help to reduce the stigma often associated with disclosing a trauma history. Enhanced clarity and further study is needed around language, outcome measures, and practices that medical providers can use to screen for trauma, and treat and manage symptoms and conditions related to their trauma history. Additionally, further research is needed to understand what type of information and resources might be beneficial to those who have disclosed a history of trauma. Data collection for this research study is currently ongoing, and we expect to have data from approximately n=25 participants by the time this poster is presented.

Topic areas:
PTSD
Women
Background: Disrupted stress circuitry has been implicated as a key contributor to major depressive disorder. Extensive piloting was required to develop an effective stress paradigm while concurrently collecting fMRI data. Due to the scanning environment setup, traditional implementation of the original Maastricht Acute Stress Test (MAST) during fMRI scans was unfeasible. This project aimed to elicit a cortisol response to confirm the effectiveness of a modified stressor for in-scanner use.

Methods & Results: Pilot 1: A Medoc device delivered hot and cold stimulation using a MR safe thermode according to the iMAST protocol (Quaedflieg, Meyer, & Smeets, 2013). Pilot fMRI data were collected from three healthy control subjects who received hot and cold pulses while completing arithmetic problems. Pilot 1 results: Verbal responses to math problems led to subject movement exceeding 6mm, rendering the data unusable. Pilot 2: A second hybrid stressor, combining the iMAST with the Montreal Imaging Stress Test (MIST), was administered in a mock scanner. This task did not require verbal responses and was designed to reduce the movement observed in Pilot 1. Eleven participants completed self-report questionnaires, VAMS, STAI-S, PANAS, and TCQ pre-and post-stress. Salivary cortisol was obtained pre-stress, and 20 and 40 minutes post-stress. Pilot 2 results: Repeated measures (rm) ANOVA revealed a significant interaction of time and emotion on PANAS scores, p=.014. In addition, the stressor significantly increased state anxiety scores (STAI-S), p=.009. Finally, a rm-ANOVA revealed a significant interaction of time and emotion on visual analogue mood scales of relaxation, friendliness, and happiness (p=.001). However, a rm-ANOVA revealed no effect of stress on salivary cortisol among the three timepoints (p=.114). Pilot 3: To increase stress potency, the traditional MAST was combined with blocks of the MIST arithmetic for a third round of piloting. Twelve healthy participants completed VAMS, STAI-S, PANAS, and TCQ questionnaires, followed by an easy block of the MIST. Participants’ heart rates were recorded using a finger sensor during the traditional MAST. They then completed two additional blocks of the MIST. Salivary cortisol was collected 20 minutes after participant arrival, immediately prior to the MAST, and 20 minutes and 40 minutes post-stress onset. Half of the sessions were conducted in the morning and half in the afternoon to account for diurnal fluctuations in cortisol. Pilot 3 results: A paired t-test showed a significant increase in cortisol (ug/dL) from mock scanner baseline to post stress induction (p=.040, one tailed). Heart rate increased during the mental arithmetic portions of the MAST, as well as during the final block of the MIST following negative feedback from evaluators. There were significant increases in state anxiety and negative affect and decreases in positive affect (all p<.01). VAMS showed significant increases in tenseness (p=.02) and hostility (p=.001) post-stressor.

Conclusions: The combination of the MIST and traditional MAST elicited a significant cortisol response and is easily implemented in the MRI scanner. These three rounds of piloting emphasize the importance of troubleshooting prior to study launch. The hybrid version (MIST_MAST_MIST) has been successfully administered on 17 participants to date.

Topic areas:
Depression
Imaging
Even in this increasingly secular age, more than eight in ten Americans profess belief in God or a universal spirit (Gallup Poll, 2016). Further, studies have shown that more than 50 percent of patients receiving medical or psychological care desire to discuss spiritual matters with their health care providers (Rosmarin et al., 2015), and it is common for individuals to turn to spirituality in coping with distress (Pargament, Koenig & Perez, 2000). However, the combined mental health disciplines have historically neglected this domain in both research and practice. The McLean Hospital Spirituality and Mental Health Program is bridging these gaps through a variety of activities. We recently developed and implemented a robust but flexible “Spirituality & Treatment” group protocol for use within our inpatient, partial and residential units. This clinical innovation has successfully facilitated the provision of evidence based, spiritually-integrated care throughout the hospital’s divisional structure, with more than 500 patients to date. This poster will present the protocol for the “Spirituality & Treatment” group, discuss our process of implementation and adaptation to meet the needs of individual McLean units, and highlight future applications and research.

**Topic areas:**
Quality/Outcomes
Sustained attention is a transdiagnostic phenotype that has been linked with most forms of psychopathology. We sought to understand factors that influence the development of sustained attention, by looking at the relationship between childhood adversity and adult sustained attention.

Participants were 5,459 TestMyBrain.org visitors from English-speaking countries who completed a continuous performance task (gradCPT) of sustained attention and a childhood adversity questionnaire. The questionnaire assessed exposure to childhood adversities including physical and sexual abuse. Scores on the gradCPT were significantly related to childhood adversity exposure, with participants who experienced more adversity in childhood showing poorer sustained attention ($\beta=-0.031$, $p<0.03$). This result held when controlling for age, gender, parental education level, and socioeconomic status ($\beta=-0.043$, $p<0.01$). Results were similar for US-participants only ($N=3,585$; $\beta=-0.037$, $p<0.05$) and in the full international sample ($N=14,610$; $\beta=-0.041$, $p<0.01$).

These findings suggest that childhood adversity can lead to adult differences in sustained attention, years after adversity exposure. These results, paired with the well-documented associations between sustained attention and psychopathology, indicate that sustained attention may be an important mechanism for understanding early influences on mental health.
Presenting Author: Sarah Withey, Postdoctoral Fellow

Co-Authors: Sarah L. Withey, Katherine A. Sullivan, Carol A. Paronis and Jack Bergman

Title: Assessment of the Priming Strength of Opioids Before and During Chronic Naltrexone Treatment in Squirrel Monkeys

Key words: Oxycodone, Naltrexone, Self-administration, Relapse, Reinstatement

Opioid addiction is characterized as a chronic relapsing disorder in which renewed drug-seeking behavior during abstinence can be provoked by exposure to an opioid or opioid-associated cues. In laboratory subjects, drug-seeking behavior similarly can be reinstated by priming with the drug or drug-related stimuli. Naltrexone, a µ-opioid receptor antagonist is most commonly used in the treatment of a suspected opioid overdose but is also used in the treatment of opioid addiction. Vivitrol™ (a slow release formulation of naltrexone) is given as a single injection every 28 days in the treatment of opioid dependence, however naltrexone’s ability to reduce reinstatement behavior in laboratory subjects is not well understood. In the present studies squirrel monkeys (n=4) were trained to self-administer i.v oxycodone. Full dose-effect curves for the priming strength of different opioids (i.e. number of injections self-administered when only vehicle is available) were determined before (baseline) and during chronic naltrexone treatment. Baseline data revealed that an i.m. pre-session priming injection of either full opioid agonists (oxycodone, heroin and methadone) or partial agonists (buprenorphine, butorphanol and nalbuphine) reinstated drug-seeking behavior in a dose-dependent manner. Externalized programmable mini-pumps (iPrecio™) were used to deliver naltrexone continuously through a sub-cutaneous catheter during chronic treatment and the priming strength of each full and partial opioid agonist was reassessed during chronic naltrexone treatment to investigate changes in priming strength. Preliminary data (n=2) suggests 0.2mg/kg/day naltrexone produces rightward shifts in the dose effect (D-E) functions for the full opioid agonists, oxycodone and heroin, and rightward and downward shifts in the D-E functions for partial opioid agonists, buprenorphine, nalbuphine and butorphanol. Methadone-induced reinstatement was variable between the subjects but the data suggests a rightward shift in the D-E function. Any reduction in the priming strength of opioid drugs (rightward and/or downward shift in D-E function) would represent a reduction in the ability of these drugs to provoke relapse in naltrexone-maintained individuals.

Topic areas:
Addiction
Pharmacology
Alzheimer’s Disease is a dementia whose hallmark pathology is progressive neurodegeneration that is not a feature of normal, healthy aging. As the disease advances, it becomes increasingly debilitating—mentally, physically, emotionally, socially, and economically. The prevalence of Alzheimer’s Disease among adults aged 65 and older is exponentially increasing; in the United States alone, 5.4 million people are currently living with Alzheimer’s, and this figure is expected to triple by 2050. The significant caregiver burden of the disease in conjunction with its rapidly escalating prevalence constitutes Alzheimer’s Disease as a global public health problem which demands the development of new treatments to effectively cure and/or improve the prognosis of this disease. Current approved treatments for Alzheimer’s are focused on palliative care, demonstrating modestly effective control of cognitive symptoms but without altering the course of the illness. The Geriatric Psychiatry Research Program at McLean Hospital engages in the global effort of Alzheimer’s research by running innovative clinical trials that investigate new putative disease-modifying treatments which aim to delay the overall disease decline through targeting the problematic cerebral accumulation of Amyloid-β plaques that is core to the aetiology of Alzheimer’s itself. The Aducanumab (Biogen) and Crenezumab (Genentech) studies are two industry-sponsored Phase III, randomized, double-blind, placebo-controlled, parallel-group outpatient clinical trials assessing the efficacy and safety of two different monoclonal antibody therapeutics in the treatment of Alzheimer’s Disease. Aducanumab is a fully-human monoclonal antibody directed against the fibrillar Amyloid-β plaque build-up. However, Aducanumab may also incite microglial activation, which can cause Alzheimer’s-Related Imaging Abnormalities (ARIA). Crenezumab is a humanized monoclonal antibody which targets oligomer and fibrillar forms of Amyloid-β. Unlike Aducanumab, the structure of Crenezumab includes an IGG4 backbone which prevents microglial activation and transitorily, ARIA. The Aducanumab Trial lasts 1.5 years (78 weeks) and is enrolling adults aged 50-85 years old; enrollment is expected to close March of 2018, with the last patient completing the study in October 2019. The Crenezumab Trial lasts 2 years (105 weeks) and is enrolling adults aged 50-89 years old; the last subject is expected to enter in December 2018 with last completion in December 2020. In both studies, the primary measurement of treatment efficacy is global improvement from baseline on the Clinical Dementia Rating (CDR)- Sum of Boxes (SB) by the end of the respective treatment period. Of the Alzheimer’s-specific studies run by the Geriatric Psychiatry Research Program (GPRP), McLean is not the only research site; as the Aducanumab and Crenezumab trials are multicenter, the GPRP thus strives to contribute to a greater web of information about Alzheimer’s disease and to serve as one research center advancing global clinical knowledge. Alzheimer’s Disease is a burdensome reality which afflicts many individuals and their families across the globe; however, through efforts and advances in clinical research conducted by dedicated programs akin to McLean’s Geriatric Psychiatry Research Program, a safe and effective cure or method of control will one day be a clinical reality.
Program Description

Poster # 127
Time: 1:00-1:50pm

Presenting Author: Scott Provost, Sr. Clinical Project Manager; Research Associate

Co-Authors: R. Kathryn McHugh, Ph.D., Margaret L. Griffin, Ph.D., Hilary Smith Connery, M.D., Ph.D., Garrett M. Fitzmaurice, Sc.D., Shelly F. Greenfield, M.D., M.P.H., Roger D. Weiss, M.D.

Title: Fifteen Years of the National Drug Abuse Treatment Clinical Trials Network at McLean Hospital (2002 - 2017)

Key words: Addiction, Clinical Trials, Community Programs, Effectiveness, Substance Use

Background: The National Drug Abuse Treatment Clinical Trials Network (CTN) “provides an enterprise in which NIDA, treatment researchers, and community-based service providers work toward new treatment options in community-level practice.” The CTN was established in 2000 based on recommendations from an Institute of Medicine report showing gaps between research and practice. Continuously funded through this cooperative agreement grant mechanism since 2002, McLean Hospital/Harvard Medical School researchers, researchers from Yale University School of Medicine, and other researchers and clinicians throughout New England have been at the forefront of this nationwide collaborative project testing the effectiveness of behavioral and pharmacotherapeutic interventions, both individually and combined, in a variety of community treatment programs. Dissemination of their research findings have helped to move empirically-supported treatments into community practice. CTN Structure and Studies: The CTN is comprised of 13 Nodes, a centralized Clinical Coordinating Center responsible for regulatory oversight and Quality Assurance monitoring, and a centralized Data and Statistics Center responsible for overseeing an electronic data capture system and providing statistical support. McLean Hospital/Harvard Medical School along with researchers from Yale, compose the New England Consortium Node. The CTN organizational arrangement provides an adaptable infrastructure for deployment of multi-site testing of promising evidence-based treatments in community treatment programs and healthcare settings across the country. Recently, the CTN has evolved in response to changes in healthcare technology (e.g., use of electronic medical records and web-based treatment tools), policy and delivery from a network comprised of mainly specialty substance use disorder treatment programs to a diverse network including general healthcare settings such as Emergency Departments and general hospitals. CTN study designs have ranged from conventional clinical trials comparing an intervention to treatment-as-usual to more complex studies, including adaptive treatment designs, a comparative effectiveness trial, longitudinal follow-up studies, and effectiveness-implementation science designs. McLean Hospital researchers led the 10-site Prescription Opioid Addiction Treatment Study (POATS) – the largest clinical trial that has been conducted of treatment for prescription opioid dependence (N=653). The CTN also presents opportunities for important secondary data analyses and research across studies based on a standardized battery of outcome measures. Some of these secondary analyses include studies led by McLean Hospital researchers through the CTN Gender Special Interest Group. Since 2002, McLean Hospital has been involved in 16 studies through the CTN, including 13 multi-site clinical trials, one study of a semi-automated performance improvement system, and two survey studies. Publications from New England Consortium researchers have been some of the most highly cited throughout the entire CTN. This poster presentation will describe these studies conducted through McLean Hospital showcasing the productivity of our node and the important impact of the CTN.

Discussion: The CTN provides an adaptable platform for deploying research resources for studying the effectiveness of substance use disorder treatments in a variety of diverse settings, including specialty substance use treatment programs and general medical settings to expand access to promising, empirically-supported substance use treatments. In doing so, it fosters a community of practice between researchers and clinicians seeking to improve substance use treatment.

Topic areas:
Addiction
McLean Research Day 2018

Theoretical/Commentary

Presenting Author: Serdar Aslan, Research Fellow – Postdoc
Co-Authors: Blaise Frederick
Title: PCA based Correlation Analysis of the Resting State fMRI for Improved Blood Vessel Territory
Key words: Principal component analysis, correlation analysis, global systemic oscillations

AIM: Previous work from our group has presented compelling evidence that systemic low frequency oscillations (sLFOs), the major constituent of low frequency global systemic noise overlying resting state functional networks, propagate dynamically throughout the brain with cerebral blood circulation [1]. More specifically, it has been demonstrated that sLFOs travel with the bulk cerebral blood flow with voxel-specific arrival time delays, and their spatiotemporal pattern changes in a way that tracks cerebral blood flow dynamics [2]. We are interested in using the Human Connectome Project (HCP) dataset to determine normative blood flow delays throughout the brain. Time delay maps were obtained by the Regressor Interpolation at Progressive Time Delays (RIPTiDe) method [3], which was applied to 487 subjects of the HCP 500 subjects release data. While the procedure generates extremely clean mean delay maps, the individual delay maps are quite noisy. Because the circulation delays should in general be slowly varying in space, PCA noise reduction is a natural choice to preserve the spatial structure of the delay maps while removing random noise points.

INTRODUCTION: The three-dimensional time delay maps of all of the resting state scans for the entire set of subjects can be summarized in a matrix form \(X\). Rows of the matrix represent different subjects, columns represent the voxels, and each value in the matrix is the corresponding time delay. In the HCP 500 subject release, there are 487 subjects with complete resting state acquisitions. Since each subject has two resting state scan, the whole data set is in the size of 974x902629. By PCA, we decompose the data covariance \(X^TX\) matrix of size 902629x902629. However, the direct application of PCA is problematic. Because the feature size is very high and sample size is low. For that reason, we applied PCA to the transpose data matrix \(X^T\) as suggested by [4]. The data covariance matrix of the \(XX^T\) which is only size of 974x974. In order to determine the main components of data covariance matrix, we plot the eigenvalues. We selected the components where the plot has a hinge. Subsequently, the whole data is projected in the selected principal components.

RESULTS: The plot of eigenvalues of the PCA methods is a nice shaped figure as seen in Figure 1. The hinge occurs at the 39'th component. Hence, first 39 components are chosen to describe the whole data. Remaining components are taken as noise. After applying noise reduction by PCA method, our noisy figures are smoothed as seen in Figure 2.

DISCUSSION: Direct application of the RIPTIDE algorithm to the resting state fMRI data can result in noisy delay maps. In order to improve signal to noise ratio, we used the rich Human Connectome Project data set. By applying PCA to the delay maps, we performed noise reduction. The noise removed figures are smooth. After PCA noise reduction, we have also delay maps which are compatible with the expected physiological expected delay ranges. Because the major source of variation between subjects should be between the individual arterial territories, we also performed linear regression analysis towards the average territory map given by Tatu et. al. [5]. The error in linear regression for the PCA applied RIPTIDE was around 17-percentage better. By compactly representing each delay maps with 39 PCA coefficients (rather than 902629 voxels), the delay maps are more amenable to being used as inputs for other machine learning techniques in our subsequent works. For example, we hope to use deviation from the smooth variation of the PCA delay map representations as a method for discerning vascular anomalies such as strokes.

CONCLUSION: Regressor interpolation at progressive delays (RIPTiDe) method is used to obtain time delay maps to the human connectome project (HCP). These maps contain a good deal of redundant information, and are amenable to substantial compression using PCA decomposition into a relatively small set of spatial components. The PCA decomposition method chosen is suitable for low sample high feature sizes. The outputs are smoothed versions of the formerly noisy figures. (See poster for references)

Topic areas:
Imaging
Sex Differences in Brain Network Connectivity Subserving Theory of Mind in Individuals with Alcohol Use Disorder

Alcohol use disorder (AUD) is associated with impairments in Theory of Mind (ToM), which is the ability to infer actions and emotions of self and others. Converging evidence that ToM may be more impaired in males (M) versus females (F) with AUD has been reported, yet sex differences in the neural correlates of ToM are understudied in those with AUD. To address this issue, we analyzed resting state functional connectivity (RS-FC) data from 104 participants (52 F) with AUD (matched for tobacco/marijuana use) and 104 healthy controls (HC) matched for sex, age, menstrual cycle factors, and family history of drug/alcohol disorders. RS-FC was analyzed using group independent component analysis (GICA) with dual regression (p<0.05, corrected). Interactions between sex and AUD were evaluated using two-way ANOVAs in ToM-related brain networks. Importantly, a sex-by-AUD interaction (F>M for AUD, F<M for HC) was found for RS-FC of the dorsal attention network (dAN) with the bilateral temporo-parietal junction (TPJ), a key region in the default-mode network (DMN) implicated in ToM. Increased RS-FC in AUD relative to HC was found within the DMN itself (in dorsomedial prefrontal cortex, left superior temporal gyrus and TPJ). Alterations in the RS-FC within the DMN in individuals with AUD and a sex-by-AUD interaction in the connectivity of the TPJ, a key node of the DMN, with the dAN, suggest that processing involved in orienting to social stimuli via dAN in the context of mentalizing, and ToM via DMN/TPJ, may be differentially affected by sex and AUD.
McLean Research Day 2018

Literature Review

Presenting Author: Shane Shucheng Wong, Child Psychiatry Fellow

Co-Authors:

Title: Medical Uses of Cannabis in Children and Adolescents: A Systematic Review

Key words: Cannabis, Marijuana, Review, Pediatrics, Children

CONTEXT: The legalization of medical marijuana in many states has led to a widening gap between its accessibility and the limited evidence for medical cannabinoids as a treatment of pediatric populations.

OBJECTIVE: To systematically review published reports to identify the evidence base of cannabinoids as a medical treatment in children and adolescents.

DATA SOURCES: Based on preferred reporting items for systematic reviews and meta-analyses guidelines, a systematic search of PubMed, Medline, and the Cumulative Index to Nursing and Allied Health Literature databases was conducted in May 2017 to identify primary research that investigated the benefits of cannabinoids for clinical indications in a child and adolescent patient sample.

STUDY SELECTION: Searching identified 2743 citations, and of these, 103 full texts were reviewed.

DATA EXTRACTION: Searching identified 21 articles that met inclusion criteria, including 22 studies with a total sample of 795 participants. Five randomized controlled trials, 5 retrospective chart reviews, 5 case reports, 4 open-label trials, 2 parent surveys, and 1 case series were identified.

RESULTS: Evidence for benefit was strongest for chemotherapy-induced nausea and vomiting, with increasing evidence of benefit for epilepsy. At this time, there is insufficient evidence to support use for spasticity, neuropathic pain, posttraumatic stress disorder, and Tourette syndrome.

LIMITATIONS: The methodological quality of studies varied, with the majority of studies lacking control groups, being limited by small sample size, and not being designed to test for the statistical significance of outcome measures. Studies were heterogeneous in the cannabinoid composition and dosage and lacked long-term follow-up to identify potential adverse side effects.

CONCLUSIONS: Additional research is needed to evaluate the potential role of medical cannabinoids in children and adolescents, especially given increasing accessibility from state legalization and potential psychiatric and neurocognitive adverse effects identified from studies of recreational cannabis use.

Topic areas:
Child/Adolescent
McLean Research Day 2018

Original Research - Clinical

Poster # 131
Time: 1:00-1:50pm

Presenting Author: Thomas Idiculla, Director, PhD

Co-Authors: Austin Lee, PhD, Sarah Salcone, BA, Jason Berkowitz, BA, Shannon O’Brien, MA

Title: Development of the Behavior and Symptom Identification Scale in an Adolescent Psychiatric Population (BASIS-T)

Key words: BASIS-24, Adolescent, Outcomes, Self Report, Measurement

Background: Many existing scales for the adolescent population (12-18) are completed by the clinician or parent/caregiver, are too long, diagnostic specific or are designed for screening purposes, therefore they are less useful for outcome measurement. In 2014, the BASIS-24 Adolescent Pilot Project sought to research if BASIS-24, a 24-item patient self-report questionnaire designed to assess treatment outcomes by measuring symptoms and functional difficulties experience by individuals seeking mental health services, was an acceptable and reliable measure for the adolescent population. While BASIS-24 was a reasonable fit for screening and analysis, some items were missing that were specific to the adolescent population. The tool was then revised and new questions were added that specifically addressed the needs and prevalent diagnoses to the adolescent population.

Objectives: The objective of this study, sought to examine the psychometric properties of the adolescent population; and develop a comprehensive, yet brief self-reported outcomes measure for the adolescent population.

Methods: Data consisted of an adolescent, national sample (N=1466) obtained from 13 mental health facilities from October 2016 to October 2017 across all levels of care. BASIS-T was assessed using a Varimax Rotated Exploratory Factor Analysis. Factors derived from principal components analysis were assessed for internal consistency and construct validity with other scales including: BPRS-S, Y-PSC, PSC. Canonical correlation analysis was conducted to see if significant canonical correlations for at least one pair of canonical variates would indicate information-sharing between two metrics and summarize the extent of association between the metrics.

Results: Factor analysis using Varimax rotation of the admission data yielded 5 factors: Attention/Anxiety, Depression, Social Anxiety, Substance Use, and Emotional Lability which reflects symptoms of the most prevalent disorders in adolescence Internal consistency of the subscales ranged from 0.90 to 0.72, and for the full scale was 0.93. Concurrent and discriminant validity analyses indicated that the BASIS-T scores successfully discriminated patients hospitalized six months before admission from those living in the community, and with their overall rating of physical health. Internal Discharge/follow-up scores indicate that the BASIS-Teen is sensitive to changes in adolescents’ symptoms and functioning.

Conclusions: BASIS-T yielded 5 factors using a Varimax Rotation. Cronbach alpha analysis and item-scale correlations support the internal-consistencies of the tool. Overall, BASIS-T provides a comprehensive, yet brief self-reported, standardized outcome assessment measure for the adolescent population. Future implications of BASIS-T is anticipated use in research and clinical settings for the psychiatric adolescent population. This study is an active research study. Data collection and the conclusion of the study will be December 31, 2017. Further analysis will be performed to determine construct validity of the instrument.

Topic areas:
Child/Adolescent
Quality/Outcomes
Presenting Author: Uwe Rudolph, Director, Laboratory of Genetic Neuropharmacology; Professor of Psychiatry


Title: Marker Chromosome Architecture and Temporal Origin Revealed in a Family with Pleiotropic Psychiatric Phenotypes

Key words: schizophrenia, bipolar disorder, genetics, Chromosomal abnormalities, Copy number/structural variation

Small supernumerary marker chromosomes (sSMC) are chromosomal fragments that are inherently difficult to genetically characterize due to their small size and abnormal genetic structure. Here we detail a mother and proband who present with neuropsychiatric disorders and a marker chromosome that segregates with disease. We explored the genomic architecture of this marker and investigated its temporal origin in the family. A customized array comparative genomic hybridization (aCGH) revealed 3 duplications and 3 triplications that spanned the short arm of chromosome 9, suggesting a chromoanasynthesis event. Subsequent FISH analysis showed the DUP/TRP segments were present on the marker and droplet digital PCR (ddPCR) revealed the presence of mosaicism. The discovery that the mother had two different subsets of cells, one carrying the marker (blood DNA) and one not carrying the marker (lymphoblastoid cell line (LCL)) provided a unique opportunity to distinguish between these two genotypes. A SNP array was performed in the distinct cell types; and using SNPs that were homozygous in the mother’s LCLs, but heterozygous in her blood, we were able to delineate the genotype of the marker. Examining those same positions across the family, we were able to infer that the chromosomal fragments of the marker likely were inherited from the grandmother, who does not carry the marker itself, suggesting it was formed during a germline level event. Additional ddPCR assays were used to interrogate the junctions present and showed a duplication of breakpoints. To understand the exact architecture of the fragments on the marker, we performed whole genome sequencing (WGS) of the blood DNA from the mother, proband and grandmother. Using genomic locations derived from the aCGH, we located those regions in the WGS data and found reads with mate-pairs matched to regions on the other side of a breakpoint. This nucleotide resolution allowed for Sanger-sequencing of 5 out of 6 breakpoints and facilitated the creation of a proposed genomic architecture for the marker. The combination of multiple copy number gains as well as the complex rearrangement is indicative of chromoanasynthesis via a DNA replicative repair mechanism such as FoSTeS/MMBIR. While CNVs have been previously associated with neuropsychiatric disorders, here we detail their precise architecture on a marker. A better understanding of how these changes can contribute to disease may provide avenues for targeted therapies.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia
Presenting Author: Victoria Joyce, Clinical Research Coordinator

Co-Authors: Christopher D. King, EdM, Carol C. Nash, MS, Lauren A.M. Lebois, PhD, Kerry J. Ressler, MD, PhD, Ralph J. Buonopane, PhD

Title: Predictors of inpatient psychiatric rehospitalization in adolescents: A retrospective analysis

Key words: Rehospitalization, Adolescence, Risk factors, Inpatient, Suicidal ideation

Objective: In adolescents treated for psychiatric disorders, repeat hospitalizations serve as markers of negative post-discharge outcomes, cause severe psychological distress, and use tremendous healthcare resources. The present study investigated a wide range of clinically relevant variables to determine predictors of psychiatric rehospitalization for adolescents within two years after discharge.

Methods: In this retrospective chart review, medical records of 787 adolescents (550 females) aged 12-19 years (mean = 15.1, SD = 1.7) discharged from an inpatient psychiatric hospital between January 1, 2012 and December 21, 2013 were reviewed. Rehospitalization to the same inpatient unit was monitored for two years following the index discharge.

Results: The cumulative rehospitalization rate within two years post-discharge was 26.3%. We constructed a series of Cox regression analyses to test demographic and clinical predictors of patients’ time to rehospitalization. In our final model, posttraumatic stress disorder (β=0.61, SE=0.23, Z= 2.73, CI=1.19-2.87, p=0.026) and patients at risk to self, based on suicidal ideation (SI) history (β=0.24, SE=0.09, Z=2.71, CI=1.07-1.52, p=0.007) were significantly associated with greater likelihood of rehospitalization. Notably, lack of treatment alliance at time of admission (β=-0.23, SE=0.09, Z=-2.64, CI=0.67-0.94, p=0.008) was significantly associated with less likelihood of rehospitalization. Risk severity based on SI history was associated with the likelihood of rehospitalization; patients at severe risk were most likely to be rehospitalized over the two-year period, except within the first 118 days post-discharge, when patients at moderate risk were most likely to be rehospitalized.

Conclusions: It is crucial to understand the role of PTSD, the trajectory of SI, and specific self-injurious thoughts and behaviors in adolescents in psychiatric crisis, as these variables are directly related to post-hospital discharge outcomes. Additionally, it is essential to examine post-discharge services, particularly the post-discharge level of care as part of an overall episode of care, in any longitudinal evaluation of outcomes.

Topic areas:
Child/Adolescent
Assessing the role of Ska2 in stress-associated psychiatric disorders

Background: Mood and anxiety disorders represent a major disease and social burden worldwide, but the underlying molecular mechanisms are still poorly understood. In recent years, evidence has emerged for the crucial role of genes involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, especially in the context of stress-related psychopathologies such as anxiety and depression. The glucocorticoid receptor (GR) is the main mediator of the negative feedback loop of the HPA axis in response to stress. The Ska2 gene, encoding the spindle and kinetochore associated complex subunit 2, has previously been identified as GR interaction partner. Interestingly, single nucleotide polymorphisms and epigenetic status within the Ska2 gene, as well as gene expression alterations, have been associated with posttraumatic stress disorder and suicide risk in several studies in the past. Yet, little is known about the underlying molecular mechanisms and the role of Ska2 in the brain. Therefore, we set out to further investigate the role of Ska2 in the CNS and validate it as a potential candidate gene in the context of stress-associated psychiatric disorders.

Methods: We performed Immunohistochemistry (IHC) to study the expression pattern of Ska2 in human postmortem amygdala samples and in the mouse brain. In addition, we conducted western blot analysis to investigate Ska2 protein expression in basolateral amygdala (BLA) samples of individuals with bipolar depression and matched controls. Stress-induced changes in Ska2 mRNA expression in mice were investigated via qPCR following fear conditioning.

Results: IHC analyses in postmortem human amygdala samples revealed a prominent expression of Ska2 protein in Vglut1-positive, glutamatergic pyramidal, neurons. Furthermore, we detected significantly increased Ska2 protein levels in the BLA of individuals with bipolar depression compared to matched controls (ANCOVA, F = 5.83, p < 0.025, n=14 per group). Detailed mapping and co-labeling studies in mice also revealed a distinct pattern of Ska2 expression in neurons of the BLA, as well as in the hippocampus (HC), medio-dorsal thalamus, the paraventricular nucleus of the hypothalamus and throughout the cortex. Most of the Ska2-positive neurons also expressed the GR. Consequently, we assessed whether stress is able to modulate Ska2 gene expression. Using qPCR, we found dynamic changes of Ska2 mRNA expression four hours after stress (fear conditioning, 5 tone/foot shock pairings). Stressed mice showed significantly decreased Ska2 mRNA levels in the HC (T18 = 2.446, p < 0.05, n = 8 (ctrl), n = 12 (stress)) and increased levels in whole amygdala punches (T15 = 2.693, p < 0.05, n = 5 (ctrl), n = 12 (stress)) compared to baseline controls (home cage group).

Conclusion: Together these findings suggest that Ska2 is expressed in GR-containing neurons throughout regions involved in emotion processing and that the Ska2 gene is dynamically regulated in these brain areas following stress exposure. Collectively, our results point to an important, and thus far unappreciated, role of Ska2 in stress-related psychiatric disorders, which is relevant to our understanding of the molecular mechanisms underlying such diseases. We further aim to manipulate Ska2 gene expression in the mouse brain using viral vectors in order to investigate its causal role in regulating stress- and anxiety-related behaviors.

Topic areas:
Bipolar
PTSD
Presenting Author: Wei Tang, PhD, Research Fellow

Co-Authors: Wei Tang, Suzanne N. Haber

Title: Corticostriatal networks reveal the role of the dACC in mediating cortical outputs and their integration in the striatum

Key words: dACC, striatum, anatomy, network, connectivity

Aim: Hub regions in the brain form high degree of connectivity with other regions. They are central in neural integration and involved in a diverse set of functions. Previously, we identified a hub region in the monkey dorsal anterior cingulate cortex (dACC), which receives diverse input from all divisions of the prefrontal cortex (PFC). The goal of this study is to compare the dACC outputs to the striatum and test whether the hub differs from non-hub regions in its striatal projection patterns.

Methods: To identify inputs to the dACC, tracers were injected into dACC areas 24 and 32 in macaque monkeys. Cell labeling was quantified by stereology using light microscopy. To measure outputs to the striatum, tracers were injected into 49 locations in the PFC. Terminal fields of the PFC and the dACC projections were charted throughout the striatum using light microscopy.

Results: Connectivity patterns between the PFC, the dACC and the striatum were identified for the 4 dACC injections. Injection site 1 in the ventral part of area 32 receives major inputs from the ventromedial PFC (vmPFC); it projects to ventral striatal zones similar to those of the vmPFC-striatal projections. Injection site 2 in the rostral dorsal part of area 24 receives major inputs from the orbitofrontal cortex (OFC); it projects to ventral striatal zones similar to those of the OFC-striatal projections. Injection site 3 in the caudal dorsal part of area 24 receives major inputs from the premotor cortex; it projects to lateral caudate and putamen, similar to those of the premotor-striatal projections. Injection site 4 at the rostral tip of the cingulate sulcus, which is a hub region, receives diverse inputs from the PFC and projects to the ventral striatal zones similar to those of the frontal pole-striatal projections.

Conclusion: Direct striatal projections from different PFC divisions occupy different striatal zones. The projections from different dACC regions also occupy different striatal zones. In addition, different PFC divisions indirectly project to the striatum via the dACC. Generally, the direct PFC-striatal connections and those via the dACC target the same striatal region, and thus, form a triangular pattern. However, in spite of its diverse inputs from all divisions of the PFC, the dACC hub projects to striatal regions that are primarily occupied by terminals of the frontal pole projections.

Topic areas:
Depression
OCD
Technology
Title: Late-onset Alzheimer's disease is associated with inherent changes in bioenergetics profiles

Key words: Late-onset Alzheimer's disease, bioenergetics, skin fibroblasts, glycolysis, mitochondrial dysfunction

Body-wide changes in bioenergetics, i.e., energy metabolism, occur in normal aging and disturbed bioenergetics may be an important contributing mechanism underlying late-onset Alzheimer's disease (LOAD). We investigated the bioenergetics profiles of fibroblasts from LOAD patients and healthy controls, as a function of age and disease. LOAD cells exhibited an impaired mitochondrial metabolic potential and an abnormal redox potential, associated with reduced nicotinamide adenine dinucleotide metabolism and altered citric acid cycle activity, but not with disease-specific changes in mitochondrial mass, production of reactive oxygen species, transmembrane instability, or DNA deletions. LOAD fibroblasts demonstrated a shift in energy production to glycolysis, despite an inability to increase glucose uptake in response to IGF-1. The increase of glycolysis and the abnormal mitochondrial metabolic potential in LOAD appeared to be inherent, as they were disease- and not age-specific. Our findings support the hypothesis that impairment in multiple interacting components of bioenergetics metabolism may be a key mechanism contributing to the risk and pathophysiology of LOAD.

Topic areas:
Alzheimer's/Dementia
Neurology
The effects of immune activation on dendritic morphology in the basolateral nucleus of the amygdala

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders, associated with a disruption of the development of neural circuits responsible for social interactions and emotionality. Results from brain imaging and postmortem studies of human subjects suggest the existence of abnormalities at cellular and circuit levels in specific brain regions, including mPFC and amygdala. However, the neural mechanisms of neuropathological changes underlying core behavioral symptoms of ASD remain unknown. Thus, we previously performed functional studies focusing on the effect of early-age immune activation on neurotransmission between prelimbic medial prefrontal cortex (PL-mPFC) and the basolateral nucleus of the amygdala (mPFC-BLA projections). Recently, we analyzed the mPFC projection patterns in subnuclei of the amygdala, development of dendrites and spine morphology in BLA neurons in the same groups of immunoactivated mice. We found that the fluorescence density of ChR2-eYFP-expressing mPFC projections in BLA much stronger than that in the lateral nucleus of the amygdala (LA) and central amygdala (CeA), which remained unchanged by immune activation. Sholl analysis of dendritic morphology showed that the dendritic surface area was significantly increased in postnatally immunoactivated mice. This was accompanied by a significant increase in the soma size. The analysis of dendritic spines in sampled dendritic segments revealed multiple clusters of thin spines (one of three major spine types: stubby, thin and mushroom spines) were formed on dendritic branches of BLA neurons in mice, which received both prenatal and postnatal immunoactivation (“two-hits” model). These observations show an impact of early-life immunoactivation on the development of dendritic morphology and the spatial distribution of dendritic spines in BLA neurons.
Behavioral rigidity is a major symptom in autism spectrum disorders, schizophrenia, anxiety disorders, and mood disorders, which affect an estimated 30 million people in the US alone. While these disorders have various underlying genetic, epigenetic, environmental and physiological causes, it is possible that some of the common behavioral pathology, such as cognitive rigidity, are caused by multiple genetic pathways converging on a few physiological mechanisms. For instance, GABA system, and the expression and function of GABAA receptors, have been shown to be impaired in all of the above disorders. Several lesion, genetic and optogenetic silencing studies have shown that the dentate gyrus is a crucial brain area for pattern separation; i.e., the brain’s ability to distinguish between similar contexts and stimuli, and to direct the organism to act appropriately given the current set of contingencies. This ability is required for behavioral flexibility. Computational models have noted that the high level of tonic inhibition and the resulting sparse activation patterns in the dentate gyrus are crucial for pattern separation and behavioral flexibility. To test this directly, we developed mice that lack the subunit containing GABAA receptors (GABAARs) in dentate gyrus granule cells (DGKO mice). Engin et al., 2015 has shown that these mice had lowered tonic inhibition and hyperactivity in the dentate gyrus. As predicted by computational models, DGKO mice had a specific and consistent behavioral rigidity phenotype; e.g., impaired context discrimination, impaired reversal learning, impaired extinction of learned fear. In our current studies, we are examining the changes in the neurophysiological dynamics of the hippocampal circuits that may underlie behavioral rigidity in DGKO mice by recording both local field potential and single cell activity in the hippocampus of freely behaving mice. We are expecting to see a subdued hippocampal novelty response and patterns of activity indicating a tendency toward retrieval rather than encoding in the hippocampus. We also expect to see rigid patterns of awake hippocampal replay in the DGKO mice. Our studies have identified a specific molecule and a specific brain area that is essential for healthy behavioral flexibility. With our current studies, we are hoping to clarify how the genetic deletion of GABAARs changes single cell and population activity in the hippocampus during tasks that require behavioral flexibility. We speculate that the hyperactivity of the dentate gyrus caused by a reduction in GABAAR (or other extracellular GABAAR) expression, and the resulting neurodynamic changes in the hippocampus may be the common underlying cause of behavioral rigidity in multiple disorders.
McLean Research Day 2018

Original Research - Clinical

Poster # 139
Time: 1:50-2:45pm

Presenting Author: Huanjie Li, Postdoc fellow

Co-Authors: Huanjie Li, Staci Gruber, Stephen M Smith, Scott E Lukas, Marisa Silveri, Kevin P Hill, William D. S Killgore, Lisa D. Nickerson

Title: Combining Multi-Site/Study MRI Data: A Novel Linked-ICA Denoising Method for Removing Scanner and Site Variability from Multi-Modal MRI Data

Key words: Multi-site/study, Linked ICA, Denoising, Multi-modal MRI

Introduction: Large multi-site studies that pool magnetic resonance imaging (MRI) data across research sites present exceptional opportunities to advance neuroscience and enhance reproducibility of neuroimaging research. However, scanner/site variability is confounds that hinder pooling data collected across different sites or across different scanner software on the same hardware, even when all acquisition protocols are harmonized. We propose a novel denoising approach for multi-site, multi-modal MRI data that implements a data-driven linked independent component analysis (LICA) to efficiently identify scanner/site-related confounds for removal.

Methods: Data: Data from 133 subjects (62 chronic heavy marijuana smokers and 71 healthy controls (HC)) from 6 different studies were used. All data were collected using the same Siemens 3T Trio, but with 3 different scanner software versions (SSWV). Thus, the main confounds for combining data were SSWV and STUDY variability. Data processing: Modality-specific preprocessing pipelines were used to produce seven modalities outcome images for each participant, including: modulated grey matter (GM), vertex-wise cortical thickness (CT) and pial surface area (PSA), fractional anisotropy (FA), mean diffusivity (MD) and tensor mode (MO), and brain activation maps estimated by analysis of fMRI data collected during Multi Source Interference Task. For each modality, a subject-series was created by normalizing all images to MNI152 space, then concatenating across all participants into a single data file. Denoising: Subject-series for all 7 modalities were analyzed simultaneously using LICA to derive 15 multi-modal spatial components. Subject-loadings (SL) for each component that related only with SSWV and STUDY were identified for denoising. Two approaches for LICA-denoising were tested: LICA-R1, which applies a single multivariate regression (MVR) of the SL for all noise components against the participant-series for each modality to remove the noise effects, and LICA-R2, which uses a two-stage MVR to remove noise components by regressing the LICA spatial maps against each subject-series to obtain subject-specific regression weights that are then regressed against the subject-series to remove the noise effects. Two other approaches for addressing scanner confounds were used to compare the performance: a higher-level GLM with a site/study covariate included in the group-level model, and modality-specific ICA denoising. We constructed test data for each modality by splitting the data from HC into two “groups”, defined based on SSWV and STUDY variables. Thus any observed differences when comparing the two groups can be attributed to differences introduced by SSWV or STUDY. Group differences in each modality were assessed using two-group t-tests with permutation testing in FSL’s Randomise with 5000 permutations to achieve an FWE-correct p < 0.05.

Results and Conclusion: Three noise components were identified for LICA-R1/R2 denoising. The first revealed global effects in FA and MD and region-specific effects in GM, fMRI, CT and PSA. The second revealed region-specific effects in FA, MD, GM, CT and PSA, while the third revealed effects in GM. Our results showed that LICA-R1 showed superior performance over all methods in denoising scanner effects, removing them completely for each modality. LICA-R1 has great potential for large-scale multi-site studies to produce combined data free from study/site confounds.

Topic areas:
Imaging
Technology
**Title:** The relationship between a social-emotional assessment and a behavioral screening assessment, and the impact of support need

**Introduction:** Self-report assessments are increasingly used to provide educators and support staff insight about students’ academic, behavioral, and social-emotional needs. One such measure is the Holistic Student Assessment (HSA), a 14-scale survey of students’ social-emotional development within three domains: Resiliencies, Relationships, and Learning/School Engagement. The HSA is frequently used in conjunction with the Strengths and Difficulties Questionnaire (SDQ), a five-scale behavioral screen of Hyperactivity/Inattention, Conduct Problems, Peer Relationship Problems, Emotional Symptoms, and Prosocial Behavior (Goodman, 1997). Previous studies have compared several HSA scales to SDQ scales, and have found theoretically expected associations between the two (Noam et al., 2012; Malti et al., 2017). The present study investigates the relationship between all HSA and SDQ scales, as well as trends in the self-reported strengths and challenges on both assessments for students with different support needs.

**Methods:** Utilizing a national database, we report on first-time responses of school day students who completed both the HSA and SDQ surveys between January 2012 and November 2017. Students rated the 61-item HSA survey responses on a 4-point Likert scale ranging from “Not at All” to “Almost Always,” and rated the 25-item SDQ responses on a 3-point Likert scale ranging from “Not True” to “Certainly True.” Students were categorized as having a strength or challenge on a scale based on transforming each HSA and SDQ scale into a z-score, standardized by gender and grade. Based on the combination of strengths and challenges, students were categorized as low need (Tier 1), moderate need (Tier 2) and high need (Tier 3). Correlational analyses, regression analyses, and ANOVAs were conducted to investigate the relationship between the HSA and SDQ. The top three self-reported strengths and challenges on the HSA and top challenges on the SDQ were evaluated by level of support need.

**Results:** The sample consisted of 17,146 students (48.9% female) in grades 5-12. The strongest correlations between HSA and SDQ included a positive association between Empathy and Prosocial Behavior (ρ=0.622) and a negative association between Emotion Control and Conduct Problems (ρ=-0.631) (p’s<0.001). Interestingly, the top strengths for Tier 1 students were among some of the top challenges for Tier 2 students (i.e., Empathy), and Tier 3 students (i.e., Perseverance, Learning Interest). A One-Way ANOVA found that Tier 2 and Tier 3 students had significantly higher z-scores than Tier 1 students for four of the SDQ scales (p’s<0.001).

**Discussion:** Our findings corroborate previous research regarding several associations between the HSA and SDQ scales (Noam et al., 2012; Malti et al., 2017) and provide insight into which HSA and SDQ scales most strongly relate to one another. Furthermore, identifying differences between support-need levels in SDQ scores and top strengths and challenges could help educators provide more targeted prevention and intervention services to students. For instance, intervention services that target Tier 3 students may want to focus on strengthening perseverance and learning interest, as these are some of the most prevalent challenges for students with the highest need, but are also the most prevalent strengths for students with the lowest need.

**Topic areas:**
Child/Adolescent
Quality/Outcomes
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