McLean Research Day 2016

Full Abstracts for Poster Session

*Wednesday, January 20, 2016*

**Session 1**: 1:00-1:50pm

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

**Brief Communications**: 3:00-4:30pm
McLean Research Day 2016

Program Description

Poster # 1

Presenting Author: Elizabeth Albert, BA, McLean Hospital, Borderline Personality Disorder Training Institute

Co-Authors: Lois W. Choi-Kain, MEd, MD; John Gunderson, MD

Title: Improving Borderline Personality Disorder Care and Treatment Resources in the Dominican Republic

Key words: Borderline Personality Disorder  Training  General Psychiatric Management  Global health

Around the world the primary barrier to accessing care for Borderline Personality Disorder (BPD) is a shortage of mental health professionals who are skilled and willing to treat BPD. The BPD Training Institute at McLean is working to enhance care and build treatment resources for BPD in the Dominican Republic by training clinicians there. This capacity building program has four ongoing components: 1) intensive training in and supervision of three fellows to develop clinician leaders 2) proliferating General Psychiatric Management (GPM) in the broader mental health community 3) supervision of clinicians running a three-day partial treatment program 4) psychoeducation for individuals and families affected by BPD. This poster will further describe each of these components, will discuss successes and challenges of implementation, and will address integration of clinical capacity building with outcomes research.

Topic areas:
Borderline Personality Disorder
The role of immunological responses in the etiology of autism spectrum disorder (ASD) has long been hypothesized. Indeed, it is thought that a “multiple hit” model may apply to ASD whereby multiple immune insults early in life may increase the risk of developing an ASD. To further investigate this hypothesis, we developed a mouse model of immune-mediated ASD using a double-immune challenge approach. Pregnant mice were injected with the viral mimic poly(I:C) (20 mg/kg) on day 12.5 of pregnancy. A subset of the offspring was subsequently injected with lipopolysaccharide (LPS) (10 mg/kg) on postnatal day 9.5 to induce a bacterial infection. A battery of tests was performed in a 2x2 factorial design to characterize the behavioral phenotype of this model in relation to the core symptoms of ASD: deficits in communication and social interaction, and increases in stereotyped behaviors. To assess deficits in communication, ultrasonic vocalizations were recorded from male pups during a maternal separation test on postnatal days 10-16 and from adult males at 9 weeks in a female encounter test. In pups, postnatal LPS treatment significantly increased the number of calls emitted, independent of prenatal treatment. However, this altered communication did not persist into adulthood, with no significant difference between groups in a test involving an encounter with a female conspecific. To assess deficits in social interaction, a one-chamber social interaction test was performed using males and females at 8 weeks. In males, postnatal LPS decreased social preference independent of prenatal treatment. There was no effect of prenatal or postnatal treatment on social preference in females. To assess anxiety, both males and females at 10 weeks of age were scored on an open field test. There was a mild anxiogenic phenotype for both males and females that received postnatal LPS, irrespective of their prenatal treatment. Additionally, to assess stereotypic behavior, mice were tested in a marble-burying task at 11 weeks. In males only, postnatal LPS caused an altered pattern of behavior that was independent of prenatal treatment. Our results indicate that postnatal immune challenge with LPS causes alterations in communication, social preference, anxiety and stereotypic behavior. However, prenatal poly(I:C) did not reliably produce any of these ASD-related phenotypes, and did not increase phenotype severity when administered in combination with postnatal LPS, going against the multiple-hit hypothesis. More experiments are necessary to further characterize this model, but these data suggest that immune insults early in postnatal development may produce behavioral changes that can be used to study immune-mediated ASD.
Emerging evidence points to extracellular matrix abnormalities as key contributors to the pathophysiology of schizophrenia (SZ) and bipolar disorder (BD). Our group reported a reduction in the number of specialized extracellular matrix structures known as perineuronal nets (PNNs) in the medial temporal lobe of SZ and BD subjects. PNNs were first identified by Camillo Golgi in 1898. Today, it is known that PNNs play a critical role in both synaptic regulation and plasticity and provide neurons protection from oxidative stress during postnatal development and in adulthood. PNNs are particularly abundant in the reticular thalamic nucleus (RTN), where they surround inhibitory neurons which express parvalbumin. A region of particular importance to the pathophysiology of major psychosis, the RTN surrounds the dorsolateral portion of the thalamus, receives projections from all cortical areas and entertains massive reciprocal projections with thalamic nuclei. The RTN, is thus in a strategic position to regulate the flow of corticothalamic and thalamocortical communication. Growing evidence points to a disruption of thalamic connectivity as a significant contributor to the pathophysiology of major psychosis. Thalamic connectivity is postulated to profoundly affect perception, emotion, and cognition, thus it is hypothesized that RTN abnormalities may underlay major psychosis. With the present study, we tested the hypothesis that PNNs in the RTN are decreased in subjects with major psychosis. Our results showed a significant decrease in the number of PNNs in the RTN of subjects with SZ and BD compared to the control group. These decreases are likely to result in the disruption of corticothalamic synaptic connectivity. This disruption may potentially impact cognitive processes such as attention, and specifically the ability to filter stimuli.
Objective: This study has two purposes. The first is to determine rates of physical inactivity reported by borderline patients and axis II comparison subjects over ten years of prospective follow-up. The second is to determine the best set of predictors of inactivity in patients with borderline personality disorder (BPD).

Method: At baseline, 290 patients met DIB-R and DSM-III-R criteria for BPD and 72 met DSM criteria for another personality disorder (and neither criteria set for BPD). At six-year follow-up, we introduced an interview that assesses many aspects of physical health including physical inactivity. We re-administered this interview at five contiguous two-year long follow-up periods. Our time-varying predictors came from other interviews and self-report measures that have been administered throughout 16-years of prospective follow-up.

Results: Rates of physical inactivity were significantly more common among borderline patients than axis II comparison subjects, although they declined significantly for those in both study groups. Three variables were found to be significant multivariate predictors of inactivity among borderline patients: the severity of trait avoidance, being on disability, and being obese.

Conclusions: Physical inactivity is common among borderline patients and is best predicted by interlocking psychological, social, and physical factors.

Topic areas:
Borderline Personality Disorder
Title: The impact of impulsivity and anxiety sensitivity on abstinence self-efficacy in adults with substance use disorders.

Key words: substance use  impulsivity  anxiety sensitivity  abstinence  self efficacy

Background: Difficulty maintaining sobriety is a constant struggle for many that suffer from substance use disorders. Understanding vulnerabilities that increase an individual’s risk for relapse is of paramount importance to enhancing treatments for this population. Abstinence self-efficacy or an individual’s confidence in their ability to maintain abstinence—is a strong predictor of relapse. This confidence may be influenced by a variety of both affective and impulse-control vulnerabilities that increase difficulty resisting urges to use. The aim of this study was to examine two such vulnerabilities and their relationship with self-reported self-efficacy in maintaining sobriety. Anxiety Sensitivity is an affect vulnerability measure that gauges an individual’s negative reactivity to experiencing anxiety symptoms and is linked to greater difficulty with the physical and affective symptoms of withdrawal and early abstinence. Delay discounting measures an individual’s cognitive bias for immediate reward and is a facet of impulsivity strongly linked to substance use disorders. We hypothesized that both increased self-reported anxiety sensitivity and increased tendencies to choose immediate reward on delayed discounting tasks would predict lower ratings of abstinence self efficacy.

Methods: Data were collected from adults admitted to McLean Hospital for acute inpatient detoxification (N=308). Participants were asked to complete self-report surveys including the Anxiety Sensitivity Index and Brief Situational Confidence Questionnaire. In addition to the self-report measures, participants completed the Monetary Choice Questionnaire, which measures delay-discounting tendencies. We tested the associations between delay discounting and anxiety sensitivity and confidence maintaining sobriety controlling for sociodemographic variables, the presence of a co-occurring psychiatric disorder, and primary substance of abuse.

Results: As hypothesized, the results from a linear regression indicated a statistically significant association between delay discounting and self-efficacy in maintaining sobriety  \( B = -.32, \ SE_B = .08, t = -4.21, p < .001 \). Contrary to hypotheses, anxiety sensitivity was not significantly associated with self efficacy \( B = -.12, \ SE_B = .009, t = -1.336, p = .183 \).

Conclusion: Affect vulnerability and impulsivity have been associated with development and maintenance of substance use disorders. Understanding factors increasing susceptibility to relapse is paramount for tailoring therapeutic interventions. Our findings highlight the importance of the cognitive bias for immediate reward seen in many suffering from substance use disorders. Delay discounting may then prove a useful marker for a major cognitive risk factor separate from affect vulnerability that increases the likelihood for maintenance of substance use disorders. Future studies may examine the stability of delay discounting rates in individuals or explore the effect of increased affect during delay discounting tasks.

Topic areas:
Addiction
Anxiety
Title: Lack of Association of Morbid History with Recovery During Treatment of Major Depression in 515 Mood Disorder Patients

Key words: bipolar disorder major depression morbid history prediction treatment response

Background: There is suggestive evidence that prior episode-counts or latency to treatment lack association with response to treatment in bipolar disorder (BD) and recurrent major depressive disorder (MDD), but relationships of morbid history to treatment response in acute depressive episodes of major mood disorders require further testing.

Methods: We tested for associations of selected measures of morbid history with remission during treatment of an acute index episode of major depression in 515 mood-disorder patients (327 MDD, 188 BD), using bivariate and multivariable methods.

Results: Remission of depression was more likely with lesser initial symptom-severity and bipolar diagnosis, but was not related to years since illness-onset, to previous depressions or episodes (based on episode-counts, yearly rates, or %-of months ill) or to other indices of illness-severity (hospitalization, co-morbidity, suicide attempt).

Conclusions: The likelihood of response to standard treatments for acute major depressive episodes in MDD or BD appeared to be largely independent of past morbid history.
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Original Research - Pre-Clinical

Division of Basic Neuroscience

Presenting Author: Darrick Balu, Assistant Professor, McLean Hospital / Translational Psychiatry Laboratory

Co-Authors: Kendall Presti, Joseph T. Coyle

Title: Trace-fear conditioning alters the expression of NMDA receptor related genes in relevant brain regions

Key words: serine racemase  arc  NMDA receptor  Arc  fear conditioning

Fear conditioning is one of the most powerful and widely used models for elucidating the neural substrates of associative learning and memory formation in the mammalian brain. In this form of Pavlovian conditioning, a neutral stimulus (conditioned stimulus; CS) acquires predictive value by pairing it with an aversive, unconditioned stimulus (US; mild foot shock) that has an intrinsic value to the subject. After training, exposure of the animal to the CS or context alone elicits conditioned fear responses. The insertion of a trace interval during CS-US presentation alters the brain circuitry that mediates conditioning. There is substantial evidence that N-methyl-D-aspartate receptors (NMDARs) in the amygdala, hippocampus, and medial prefrontal cortex (mPFC) are involved in trace-fear conditioning. We previously demonstrated that D-serine, the co-agonist at forebrain NMDARs, is required for the development of contextual fear conditioning. Accordingly, we now examine whether the expression of genes related to NMDAR activity is altered after conditioning and re-exposure to the conditioning context. We used adult, male C7BL6 mice for all experiments. Mice were either: 1) naïve, 2) trace-fear conditioned and killed 60min after training, or 3) trace-fear conditioned, re-exposed to the training context the next day (no tones), and killed 30min later. We also included additional sham control groups that went through the same conditioning procedures, but did not receive foot shocks. We found that protein levels of the immediate early gene, activity-regulated cytoskeleton-associated protein (Arc; Arg3.1), were robustly increased after training and after context re-exposure. The animals exposed to sham conditioning showed a modest Arc protein increase only in the PFC after training, but no significant increase after context re-exposure. Notably, the mRNA and protein expression of serine racemase, the enzyme that converts L-serine to D-serine, was significantly increased in the amygdala after training and after re-exposure. SR protein did not change in sham mice at either time point. Using immunofluorescence, we found that SR and Arc are localized to distinct neuronal populations in the amygdala after fear conditioning. These findings demonstrate an activity-dependent regulation of SR in the amygdala and confirm that D-serine is important for the acquisition and expression of fear memory.

Topic areas:
Schizophrenia
McLean Research Day 2016

Original Research - Pre-Clinical

Division of Alcohol and Drug Abuse

Presenting Author: Claire Barkin, Technical Research Assistant; BA, McLean Hospital- Preclinical Pharmacology Program

Co-Authors: Bruce E. Blough F. Ivy Carroll Jack Bergman Stephen J. Kohut

Title: Effects of Chronic Treatment with Bupropion on Nicotine, Cocaine, and Nicotine + Cocaine Polydrug Self-Administration

Key words: Bupropion Nicotine Cocaine Nicotine + Cocaine Polydrug abuse model

Clinical reports suggest that cocaine and nicotine are often used concurrently; however, medications to manage this form of polydrug addiction are lacking. Bupropion (Zyban), a dual monoamine (dopamine/norepinephrine) transport inhibitor, is a non-nicotine-based pharmacotherapy for smoking cessation that has been approved by the FDA and is currently used medicinally. The present study was conducted to investigate the potential utility of bupropion in managing nicotine + cocaine polydrug addiction by comparing its effectiveness in decreasing intravenous (IV) nicotine, cocaine, and nicotine + cocaine polydrug self-administration. Adult rhesus monkeys responded under a second order (FR2 (VR16:S)) schedule of reinforcement for food or IV nicotine (0.001-0.0032 mg/kg/inj), cocaine (0.0032-0.01 mg/kg/inj), or nicotine (0.001-0.0032 mg/kg/inj) + cocaine (0.0032-0.01 mg/kg/inj) mixtures during four 1-hr daily sessions. The effects of chronic treatment (5-10 days) with bupropion (1.0 - 1.8 mg/kg/hr, IV) on food- and drug-maintained responding were then assessed. Consistent with our previous findings, combinations of nicotine (0.001 or 0.0032 mg/kg/inj) + a low dose of cocaine (0.0032 mg/kg/inj) were self-administered to a greater extent than either drug alone. Results further indicate that consistent or significant alterations in responding for nicotine alone or cocaine alone were not observed during chronic treatment with bupropion; however, averaged data revealed dose-dependent reductions in responding maintained by each combination of nicotine + cocaine studied. No consistent effects on food-maintained responding were observed during bupropion treatment regimens. These results suggest that bupropion deserves further consideration for its potential use in the management of nicotine + cocaine polydrug addiction.

Topic areas:
Addiction
Pharmacology
Unipolar depression is associated with episodic memory deficits, but the neurocognitive mechanisms responsible for these deficits are poorly understood. Because depression is associated with reduced hippocampal volumes, and because the hippocampus supports encoding and consolidation, it is tempting to ascribe poor memory in depression to disruptions in these two processes. However, this overlooks a potentially important role for memory retrieval. Retrieval is cognitively demanding and depends on the frontal lobes, and depression is characterized by difficulty concentrating and hypofrontality. Thus, in this ongoing study we are testing the hypothesis that depression impairs memory retrieval and weakens the fronto-parietal activation that supports it. To this end, we have thus far administered a novel source memory task to 32 healthy controls (20 females) and 17 unmedicated adults who met criteria for Major Depressive Disorder (MDD; 10 females). The task includes six encoding-retrieval cycles. During encoding, participants view words that appear on the left or right side of a computer screen above one of two questions, either “Living/Non-living?” or “Mobile/Immobile?” Participants answer each question by pressing a button. During retrieval, the words are shown again and participants indicate whether they initially appeared on the left or right (“Side” condition), and which question they were presented above (“Question” condition), thus allowing us to probe memory for perceptual and cognitive sources, respectively. As a control for visuo-motor demands and non-episodic retrieval, participants also make “odd/even” judgments for visually presented numbers (“Number” condition). Electroencephalographic (EEG) data are acquired during retrieval, and event-related potentials (ERPs) are formed by averaging the EEG in each condition. We expected a selective effect of MDD on accuracy in the difficult “Question” condition, leading to a Group x Condition interaction. Encouragingly, a linear mixed model returned the expected interaction, Z = -2.21, p < 0.03, but the nature of the result was not as predicted. Rather than performing worse in the “Question” condition (mean accuracy: controls = 73%, MDD = 74%), the depressed adults are impaired in the “Side” condition (controls = 80%, MDD = 75%). However, this may reflect a speed accuracy trade-off, as depressive slowing is magnified in the “Question” condition (mean RT: controls = 1,565 ms, MDD = 1,762 ms) vs. the “Side” condition (controls = 983 ms, MDD = 1,042 ms), leading to another Group x Condition interaction, Z = -4.65, p < 0.001. The ERP data are characterized by a sustained negativity extending from about 800 to 2000 ms post-stimulus. At right fronto-central electrodes previously implicated in retrieval monitoring, the controls show a clear separation between ERPs in the “Question” and “Side” condition that is reduced in the MDD group; we are currently determining whether this group difference is reliable and related to behavior. Overall, these initial findings indicate that depression can impair memory retrieval, but—counterintuitively—the effect is larger for perceptual source judgments than for harder, cognitive source judgments. Our preliminary analysis suggests that this result may reflect reduced differentiation of ERPs over right fronto-central electrodes.
Non-suicidal self-injury (NSSI) is the direct, deliberate destruction of body tissue without suicidal intent (Nock & Favazza, 2009). Age of onset, based primarily on retrospective reports, commonly occurs between 12 and 14 years old (e.g., Jacobson & Gould, 2007). Few studies have examined NSSI among children (except in children developmental disorders; see Minshawi et al., 2014). Recent efforts have examined NSSI among children directly (Barrocas et al., 2012; Esposito-Smythers et al., 2010). Esposito-Smythers et al. (2010) examined NSSI in an inpatient sample of bipolar youth and found approximately 34% of children with a bipolar disorder diagnosis reported lifetime NSSI. Barrocas et al. (2012) found 7.6% of third and 4% of sixth graders in a community sample had engaged in NSSI. The current study examines NSSI among a sample of children treated on a psychiatric inpatient unit. Archival chart reviews assessed current/lifetime NSSI behaviors, demographic data, current/lifetime suicidal ideation and attempts, and self-reported clinical rating scales (i.e., Multidimensional Anxiety Scales for Children [MASC & MASC-2], Children’s Depression Inventory-2 [CDI-2], Children’s Inventory of Anger [ChIA], Child-Adolescent Suicidal Potential Index [CASPI], and Trauma Symptom Checklist for Children–Posttraumatic Stress [TSCC-PTS]). The archival chart reviews included 179 children (aged 9–12) who were consecutively admitted to the unit from August 31, 2012, to September 1, 2013. Patients were excluded if they had a diagnosed psychotic disorder, a developmental/intellectual disability, or were missing self-report measures; the study was limited to 122 participants (75 boys, 47 girls). NSSI was highly prevalent in this sample; 63.9% (n=78; 47 boys, 31 girls) of inpatient children had past or current NSSI documented in their medical charts. NSSI- (n=44) and NSSI+ participants did not significantly differ in age (Mage=10.59 vs. Mage=10.64, t=.23, p=.82), race (61.5% vs. 76.1% White, χ²=1.92, p=.17), or gender (36.4% vs. 39.7% female, χ²=0.3, p=.86). Among the NSSI+ participants, headbanging was the most commonly identified method of self-injury (n=30, 24.2%), followed by hitting/slapping/punching (n=21, 16.9%), and biting (n=18, 14.5%). NSSI+ participants engaged in an average of 1.64 methods of self-injury (SD=.87), with a range of one to five methods. Forty-three participants (55%) endorsed one method while 35 participants (45%) endorsed two or more methods. In addition, NSSI+ participants were found to report significantly higher depressive scores on the CDI-2 and significantly higher anger scores on the ChIA compared to NSSI- participants (ps<.05). These findings indicate that NSSI is evident among psychiatrically impaired children as young as nine years old. In addition, depression and anger may play a role in the onset or maintenance of NSSI behavior among youth. Depression (e.g., Jacobson & Gould, 2007) and anger (Nock, Prinstein, & Sterba, 2010) have also been associated with NSSI behaviors in adolescents. Recognizing that NSSI may occur much earlier than previously thought and understanding how psychiatric distress (i.e., depression, anger) contributes to NSSI will inform better prevention and intervention treatments targeting NSSI.
Title: Attentional bias to smoking cues is associated with deficits in cognitive flexibility in nicotine-dependent smokers

Key words: attention bias  cognitive flexibility  nicotine dependence

Background: Smoking tobacco cigarettes remains one of the most preventable causes of early death in the United States, yet most attempts to quit smoking are unsuccessful. Studies have shown that greater attentional biases to smoking-related cues predict relapse vulnerability. Understanding the underlying mechanisms contributing to smoking attentional bias may guide the development of treatments targeting this relapse risk factor. In this study, we predicted greater attentional bias to smoking-related cues would be associated with poorer executive function performance.

Methods: 35 nicotine-dependent smokers (19 females) performed behavioral tests aimed at assessing attentional bias to smoking cues (Smoking Emotional Stroop task) and more general cognitive flexibility (Trail Making Task). Reaction times (RT) during Stroop performance were used to obtain attention bias scores, calculated as the RTsmoking - RTneutral, with higher scores indicating greater attentional bias to smoking-related words relative to neutral words. The Trails task is comprised of two subsets, Part A, which is a test of simple attention and psychomotor speed and Part B, which also includes an assessment of cognitive flexibility. To control for reaction time and to isolate executive function, the time to complete Trials A was subtracted from the time to complete Trails B (Trails B-A), with higher scores indicating poorer performance. A Pearson’s correlation coefficient was calculated between smoking attentional bias and executive function performance. Additionally, to identify the relationships between participant demographics and our behavioral tests, Pearson’s correlation coefficients were calculated between attention bias, cognitive flexibility, and: age, FTND, CO, pack-year, and BIS.

Results: As hypothesized, attentional bias towards smoking cues was positively correlated with Trails B-A scores (r= 0.35, P = 0.039; 95% confidence interval (CI): 0.019 to 0.611). There was no relationship between age, FTND, CO, pack-year, BIS and Stroop interference or Trails B-A scores.

Conclusion: The results indicate that a greater attentional bias to smoking cues is related to a deficit in higher-order executive function in nicotine-dependent smokers. One possible explanation is that exposure to salient drug-related cues overloads otherwise normal cognitive ability, resulting in an attentional bias in those whose executive function is on the lower end of normal.

Topic areas: Addiction
McLean Research Day 2016

Program Description

Division of Child and Adolescent Psychiatry

Division of Alcohol and Drug Abuse

Presenting Author: Olivera Bogunovic, MD, Instructor in Psychiatry, McLean Hospital

Co-Authors: Rachel Tester, PMHCNS,BC Justine Wittenauer, MD Lynn Carlson LISCW Brian Barnett, MD Kate Mchugh, Phd

Title: Clinical experience with injectable naltrexone treatment in six patients with alcohol and opioid use disorder and comorbid psychiatric disorders: retrospective case studies.

Key words: alcohol use disorder opioid use disorder co-morbid psychiatric condition Injectable naltrexone

Introduction: In 2014 McLean Hospital developed comprehensive outpatient program for medication assisted treatment for patients with opioid and alcohol use disorders. There was special emphasis for patients with co-occurring psychiatric disorders. We report rationale, design of the program with emphasis on integrated mental health/substance use treatment.

METHOD: Data was obtained by retrospective review of medical records. Injectable naltrexone was used to treat 6 patients. Two patients had a diagnosis of opioid use disorder, one patient has opioid use disorder, and three patients had both alcohol and opioid use disorders. Comorbid psychiatric disorders included PTSD, depression and anxiety disorders. All patients had never been treated naltrexone. Response was assessed by clinical observation of patients' behavior and urine toxicology screens.

RESULTS: One patient dropped out of treatment. One discontinued injectable naltrexone in favor of oral naltrexone. Four patients are actively receiving injectable naltrexone. One of the four with co-occurring alcohol and opioid use disorder reported intermittent alcohol use as evidenced by self-report and toxicology screen. There were no relapses on opiates. All psychiatric symptoms remained stable throughout treatment with injectable naltrexone.

CONCLUSION: The reduction of relapse rates gives preliminary indication that injectable naltrexone may be a safe and effective medication for treatment of patients with alcohol and opioid use disorders who have a comorbid psychiatric condition.

Topic areas: Addiction
McLean Research Day 2016

Original Research - Pre-Clinical

Poster # 13

Psychotic Disorders Division

Presenting Author: Lauren Moran, Psychiatrist-in-Charge, Instructor, Schizophrenia and Bipolar Disorders Program (Ongur)

Co-Authors: Grace A. Masters  Samira Pingali  Bruce M. Cohen  Elizabeth Liebson  R.P. Rajarethinam  Dost Ongur

Title: Prescription Stimulant Use is Associated with Earlier Onset of Psychosis

Key words: psychosis schizophrenia methylphenidate amphetamine attention deficit hyperactivity disorder

A childhood history of attention deficit hyperactivity disorder (ADHD) is common in psychotic disorders, yet prescription stimulants may interact adversely with the physiology of these disorders. Specifically, exposure to stimulants leads to long-term increases in dopamine release. We therefore hypothesized that individuals with psychotic disorders previously exposed to prescription stimulants will have an earlier onset of psychosis. Age of onset of psychosis (AOP) was compared in individuals with and without prior exposure to prescription stimulants while controlling for potential confounding factors. In a sample of 205 patients recruited from an inpatient psychiatric unit, 40% (n = 82) reported use of stimulants prior to the onset of psychosis. Most participants were prescribed stimulants during childhood or adolescence for a diagnosis of ADHD. AOP was significantly earlier in those exposed to stimulants (20.5 vs. 24.6 years stimulants vs. no stimulants, p < 0.001). After controlling for gender, IQ, educational attainment, lifetime history of a cannabis use disorder or other drugs of abuse, and family history of a first-degree relative with psychosis, the association between stimulant exposure and earlier AOP remained significant. There was a significant gender × stimulant interaction with a greater reduction in AOP for females, whereas the smaller effect of stimulant use on AOP in males did not reach statistical significance. In conclusion, individuals with psychotic disorders exposed to prescription stimulants had an earlier onset of psychosis, and this relationship did not appear to be mediated by IQ or cannabis.

Topic areas:
Child
Psychotic Disorders
Title: Cognitive Behavior Therapy for Depressed Adolescents: Normalization of Electrocortical Reactivity during Self-Referential Processing

Key words: depression adolescence ERP CBT

Background: Major depression in adolescence is common, recurrent, and debilitating (Avenevoli et al., 2015). While cognitive behavior therapy (CBT) is considered the gold standard for treatment (Webb, Auerbach, & DeRubeis, 2012), it remains unclear whether neural processes implicated in depression onset change with treatment. Thus, the current study examined whether electrocortical self-referential processes underlying adolescent depression (see Auerbach et al., 2015) normalize following CBT.

Methods: The study included healthy (HC=30) and depressed (MDD=22) female adolescents aged 13-18 years. At baseline, participants were administered a diagnostic interview and completed a self-referential encoding task (SRET) while electroencephalography (EEG) data were acquired. A subset of the MDD group (n=14) then received 12 weeks of CBT. Post-treatment and 12-week follow-up assessments were administered to the MDD and HC (n=29) groups, respectively. The SRET probed event-related potentials (ERPs), including: (a) the P1 (100-200 ms post-stimulus) indexing semantic monitoring of emotional information and (b) the late positive potential (LPP), a slow-wave component (400-1200 ms post-stimulus), reflecting encoding of emotional stimuli. We hypothesized that while the HC group would not exhibit changes in electrocortical activity over time, the MDD group would show post-treatment reductions in P1 and LPP positivity following negative words.

Results: At baseline, compared to the HC group, the MDD adolescents showed greater P1 and LPP positivity for negative versus positive words (see Auerbach et al., 2015). Consistent with our hypothesis, among HC youth, electrocortical activity in the P1 and LPP following negative words remained stable over time. Further, as hypothesized, MDD adolescents exhibited decreased P1 (t(13) = 4.52, p = .001) and early LPP (t(13) = 2.37, p = .034) positivity to negative words; MDD youth also experienced a significant decrease in depressive symptoms post-treatment, t(13) = 4.64, p < .001.

Conclusions: This is the first study to demonstrate changes in electrocortical activity following CBT among depressed adolescents. These findings suggest that effective CBT may normalize electrocortical deficits associated with depressogenic self-referential processing biases, which has important implications for identifying novel brain-behavior targets for future treatment.

Topic areas:
Child
Depression
The main purpose of this study was to describe the baseline predictors for time-to-cessation of individual therapy for borderline patients followed prospectively for 16 years.

Methods: 290 patients meeting both DIB-R and DSM-III-R criteria for BPD were interviewed concerning their use of mental health services nine times over 16 years of prospective follow-up. These blinded assessments were made every two years using a semi-structured interview of proven reliability.

Results: Only 64% of borderline patients had at least one two-year period during which they stopped participating in individual therapy. Twenty-one variables were found to be significant baseline predictors of cessation (for at least two consecutive years) of individual therapy in bivariate analyses. Seven of these predictors remained significant in multivariate analyses: younger age, being non-white, having a good vocational adjustment in the two years prior to index admission, the absence of a history of mood disorder, lower levels of neuroticism and childhood neglect, and a higher IQ.

Conclusions: Taken together, the results of this study suggest that prediction of time-to-cessation of individual therapy for borderline patients is multifactorial in nature, involving demographic factors, vocational performance, axis I psychopathology, temperament, childhood adversity, and intellectual endowment.
Lower Posterior Cingulate Cortex Glutathione Levels in Obsessive-Compulsive Disorder

Background: Several lines of evidence support the hypothesis that lower cerebral levels of glutathione (GSH), associated with increased oxidative stress, may contribute to obsessive-compulsive and related disorders. Proton magnetic resonance spectroscopy (MRS) enables the noninvasive measurement of brain GSH levels. However, no studies to date have examined GSH levels in individuals with obsessive-compulsive and related disorders. We previously used a 2D J-resolved proton MRS protocol to examine metabolite differences in the pregenual anterior cingulate cortex of individuals with obsessive-compulsive disorder (OCD) and non-OCD comparison individuals and did not detect any GSH abnormalities in OCD individuals. Because hypermetabolism has also been reported in the posterior cingulate cortex (PCC) of individuals with OCD during both cognitive challenge and at rest, we sought to determine whether abnormal PCC GSH levels are detectible in individuals with OCD. We hypothesized that: 1) OCD individuals would demonstrate lower GSH levels in PCC compared with non-OCD individuals and 2) GSH levels in PCC would be inversely associated with OCD symptom severity, as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).

Methods: Thirty individuals with OCD and 25 age-, sex-, and race-matched comparison individuals without OCD underwent single voxel 2D J-resolved proton MRS at 3 Tesla on a Siemens TIM Trio system, using a 32-channel head coil. Anatomical images were used as a guide to position MRS voxels (2 x 2 x 2 cm = 8cc) medially in the PCC. MRS data were analyzed using LCModel and a simulated basis set. Group metabolite differences, as well as relationships between metabolite levels and Y-BOCS scores, were analyzed using linear regression adjusted for age, sex, and race.

Results: One OCD participant failed to produce usable PCC MRS data. We found significantly lower PCC GSH levels in OCD participants compared with non-OCD participants ($\beta = -0.03$ [95% CI: -0.05 to -0.006]; $P = 0.014$; Cohen’s $d = .73$). PCC GSH levels were not significantly associated with total Y-BOCS score in the OCD group ($\beta = 0.0006$ [95% CI: -0.005 to 0.006]; $P = 0.83$).

Conclusion: Using 2D J-resolved proton MRS, we found lower GSH levels in PCC in individuals with OCD than in individuals without OCD. Lower PCC GSH levels may be indicative of increased oxidative stress secondary to hypermetabolism in this brain region in OCD. Peripheral oxidative stress has been reported in children and adults with OCD, suggesting that both peripheral and brain oxidative stress could contribute to the disorder. Future MRS studies are warranted to investigate GSH levels in other brain regions that comprise the cortico-striato-thalamo-cortical circuit thought to be abnormal in OCD and to determine whether lower cerebral GSH levels may represent a neurobiological diagnostic marker across other obsessive compulsive and related disorders.

Topic areas:
OCD
**McLean Research Day 2016**

*Theoretical/Commentary*  
Poster # 17

**Presenting Author:** Margaret Brennan, Practicum Student, B.A., OCDI, OCAR

**Co-Authors:** Leilani Webb, B.A.* Jason Krompinger, Ph.D., Jason Elias, Ph.D., Nathaniel Van Kirk, Ph.D.,* primary co-author

**Title:** How Inpatient OCD Populations Vary by Gender

**Key words:** gender OCD severity depression

**Introduction:** Research has indicated that a significant interaction exists between an individual’s obsessive-compulsive disorder symptom presentation and their gender. In a meta-analysis of 332 East-Asian men and 213 East-Asian women, men with OCD frequently had sexual and religious obsessions, pathological doubts, checking, and repeating compulsions. Women however were more likely to be married, and suffer from a higher frequency of contamination (p=0.017) related obsessions (Cherian et al, 2014). Similar results found that women generally identify more contamination obsessions and cleaning rituals, while men report obsessive slowness, as well as perfectionism (sexual purity, exactness, symmetry obsessions) and bizarre rituals (Venturello et al., 1999). Another important area of note that has been reported to correlate with gender is age of onset. In the meta-analysis previously mentioned, males had a significantly lower age of onset.

**Aim:** The purpose of our study was to evaluate the impact of gender on the presentation and treatment of severe OCD for individuals within an intensive residential setting. We hypothesized that within an inpatient setting, sexual obsessions, concerns regarding harm, and checking compulsions would be more positively correlated with men, while contamination obsessions and compulsions would be more likely to be presented by women. In a similar manner to the results of the existing literature, we also hypothesized that male patients would report earlier ages of onset.

**Methods:** We used bivariate correlations to identify whether gender affected presentation and a one-way ANOVA to determine whether gender affected the severity of OCD presentation.

**Results:** Contrary to the existing literature, results indicated that symptom presentation did not significantly differ based on gender in our sample of 274 patients seeking intensive residential treatment. Gender was not correlated with contamination (r=-.015), concerns about being responsible for harm, injury, or bad luck (r=0.057), unacceptable or scrupulous thoughts (r=-0.162), or concerns about symmetry, completeness, and the need for things to be just right (r=0.064). Between group effects of gender on OCD symptoms was evaluated using a one-way ANOVA. Results indicated there was no significant effect of gender on total symptom severity or severity of obsessions based on the Y-BOCS. However, significant effects were found for severity on the Y-BOCS compulsion subscale (F(1, 571)=4.39, p=.037) and severity of depression symptoms at admission (F(1, 571)=7.43, p=.007). The data indicated that there was no significant difference between the male and female patients in regard to age of symptom onset (r=.029).

**Conclusion:** Overall, the effect of gender on OCD symptom presentation appears to vary from outpatient to residential/intensive settings. While this study did find gender was significantly associated with different levels of compulsions and depression, with women endorsing higher levels of compulsions and greater depression scores at admission. More assessment is needed to determine the ways in which an inpatient setting arrests or equalizes any gendered effects on obsessive-compulsive disorder presentation, our study highlights the continued need for gender-related research, particularly within inpatient settings such as McLean Hospital. These preliminary analyses question why the population specific to McLean is different, and what aspects of gender drive these differences.

**Topic areas:**  
Depression  
OCD  
Women
Presenting Author: Jennifer Buchholz, Community Residence Counselor, BA, Behavioral Health Partial Program

Co-Authors: Katherine M. McHugh, LMHC, LADC, RYT-500, E-RYT200  Lynne Kopeski, MSN, PMHCNS, BC  Marie Forgeard, PhD  Courtney Beard, PhD  Throstur Bjorgvinsson, PhD

Title: Integrating Yoga with Cognitive Behavioral Therapy: Perceived Benefits, Acceptability, and Feasibility in a Partial Hospital Setting

Key words: CBT  yoga

Background: A large body of research suggests that yoga interventions are effective in treating a range of psychiatric conditions including anxiety disorders and depression. However, yoga has not been examined as a complement to cognitive behavioral therapy (CBT) treatment in a partial hospital setting. Furthermore, the majority of published studies address the impact of yoga in diagnostically homogeneous samples. The present study investigated patient perceptions of a brief yoga intervention designed to support mental health across psychiatric diagnoses.

Methods: 60 patients seeking treatment at McLean Hospital’s Behavioral Health Partial Hospital Program attended the Yoga for Wellness group offered once weekly between July and October 2015. The group’s objective was to teach breathing and grounding techniques to complement CBT skills. To that end, a certified yoga instructor and a community residence counselor led 50-minute sessions of guided mindfulness meditation and physical movement. Poses included neck openers, shoulder shrugs, standing balance postures, and gentle twists. Discussions before and after the yoga sequence connected the practice to the mental health healing process, and contextualized yoga as part of cognitive-behavioral treatment. 34 patients recorded responses to the following items on the optional Feedback and Evaluation Form: 1. Did the group meet the following objectives? a. Inform you about yoga for mental health  b. Practice yoga postures and breathing techniques  c. Provide rationale for various types of movement  d. Discuss mind and body connection through yoga  2. How helpful was this group?  3. How likely are you to try yoga in the future?  4. We greatly appreciate any negative or positive feedback about the group.  5. Any suggestions? Items 1 through 3 were rated on a 5-point scale (1 = “not at all,” 3 = “somewhat,” and 5 = “very well”). Items 4 and 5 were open-ended. We conducted both quantitative and qualitative analyses to provide descriptive statistics summarizing patient feedback.

Results: Overall, the majority of patients who responded to the questionnaire thought the group’s objectives were met very well: 70.6% selected “very well” for 1a  88.2% selected “very well” for 1b  61.8% selected “very well” for 1c  64.7% selected “very well” for 1d  70.6% of patients found the group to be “very helpful,” and 76.5% of patients reported that they were “very likely” to try yoga in the future. Four themes emerged from the qualitative data collected from items 4 and 5. They included general and non-specific positive feedback (58.8%), recommendations to increase frequency of the yoga group (41.2%), comments on the helpfulness and usefulness of the group (17.6%) and appreciation for the relaxing/calming/invigorating effect of the group (14.7%).

Conclusion: The results of quantitative and qualitative analyses suggest that yoga may hold strong therapeutic potential as a complement to CBT in a partial hospital setting. Responses from patients suggest that yoga is a highly acceptable and feasible intervention as part of a partial hospital program. Future research should investigate the impact of similar yoga interventions on clinical outcomes across diagnoses.

Topic areas: Anxiety  Depression
McLean Research Day 2016

Original Research - Pre-Clinical

Division of Basic Neuroscience

Presenting Author: Syed Bukhari, Technical Research Assistant II, McLean Hospital Translational Neuroscience Laboratory

Co-Authors: Harry Pantazopoulos  Sabina Berretta

Title: Parvalbumin Neurons in the Reticular Nucleus of the Thalamus: Potential role in the Pathophysiology of Schizophrenia

Key words: Schizophrenia  Thalamus  GABA  Brain Connectivity  Cognition

Background: Growing evidence from imaging studies points to a disruption of thalamo-cortical connectivity as a critical element of the pathophysiology of schizophrenia. Few human postmortem studies have addressed this question thus far. In the context of broader investigations on the pathological substrates of cortico-thalamic disconnection in schizophrenia, the present study focuses on the Reticular Thalamic Nucleus (RTN), a nucleus critically involved in modulating cortico-thalamic-cortical connectivity. Neurons in the RTN receive collaterals from cortico-thalamic and thalamo-cortical neurons, and in turn exert powerful inhibitory effects on these latter neurons. Thus, RTN neurons are ideally positioned to gate information flow between the cortex and the thalamus. In this context, the RTN has been postulated to enhance cognitive and emotionally relevant stimuli while suppressing irrelevant stimuli—functions that resonate with symptoms of schizophrenia, such as disruption of sensory gating and emotion processing. In support, electrophysiological and pharmacological studies in rodents suggest that RTN dysfunction may contribute to deficits in auditory gating, such as those observed in patients with schizophrenia. We are in the process of testing the hypothesis that the main RTN neuronal population, phenotypically characterized by its expression of the calcium binding protein parvalbumin (PVB), may be abnormal in subjects with schizophrenia. Such abnormalities may manifest as decreased numbers of PVB-immunoreactive (IR) neurons and/or abnormalities affecting perineuronal nets associated with these neurons (in a separate study). Subjects with bipolar disorder (BD) will be used as a psychiatric control group.

Methods: Serial sections containing the RTN from 15 SZ patients, 15 BD patients, and 20 control subjects were immunostained using antibodies raised against PVB. Computer-assisted quantitative light microscopy is being used to estimate total numbers and numerical densities of PVB-IR neurons as well as RTN volume. Linear regression models will be used to test group comparisons as well as the potential effects of confounds, such as age, gender, exposure to pharmacological agents and substance abuse.

Results: In non-psychiatric controls, PVB-IR neurons are densely represented in all portions of the RTN, creating a dense dendritic network across the nucleus. Group comparison data collection is in progress.

Conclusions: Results from these studies will be interpreted in the context of parallel investigations on perineuronal nets associated with these neurons. If our hypothesis is correct, deficits affecting RTN PVB-IR neurons may contribute to clinical symptoms of SZ, yielding insight into the pathophysiology of this disorder.

Topic areas:
Bipolar
Imaging
Psychotic Disorders
Schizophrenia
McLean Research Day 2016

Original Research - Clinical

Division of Basic Neuroscience

Presenting Author: Korine Cabrera, Clinical Research Assistant II, Cognitive and Clinical Neuroimaging Core

Co-Authors: M. Kathryn Dahlgren, Megan T. Racine, Kelly A. Sagar, Rosemary T. Smith, Ashley M. Lambros, & Staci A. Gruber

Title: Current Marijuana Use Impairs Verbal Learning and Memory In Current But Not Former Users

Key words: marijuana cognition memory verbal learning

Background: Marijuana (MJ) remains the most commonly used illicit drug in the United States. Recent survey data indicate that decreased perception of harm associated with MJ use has been linked to increased rates and earlier age of onset of MJ use. While previous research has reported cognitive deficits associated with MJ use, notably with regard to verbal learning and memory, the specific impact of age of onset of MJ use and the subsequent discontinuation of MJ use has not been fully explored.

Methods: As part of a larger study, healthy control participants, current, heavy MJ users, and former MJ users were recruited from the Greater Boston Area. The current MJ user sample was further subdivided into early onset (regular MJ use prior to age 16) and late onset (regular MJ use after age 16) MJ users. All participants completed the California Verbal Learning Test (CVLT), a serial, list-learning task designed to assess verbal learning, memory and encoding strategies.

Results: Findings suggest that current MJ use negatively impacts verbal learning and memory and the use of effective learning strategies. Current MJ users recalled significantly fewer words during the initial learning phase of the task, fewer total words over five trials, and fewer words after both a long and short delay period relative to control participants. Further, current MJ users utilized significantly fewer semantic clusters during recall relative to the control participants. No differences were detected between early and late onset MJ users, with both groups demonstrating worse performance relative to control participants. Interestingly, former MJ users performed similarly to controls; no significant differences were detected for any variable between these groups. It is of note, however, that former MJ users recalled significantly more words over five trials relative to the current MJ using group.

Conclusions: Taken together, findings support verbal learning and memory impairment in current MJ users relative to both control participants and former MJ users. Additionally, data suggest that age of onset of MJ use does not discriminate verbal memory impairment, as both early and late onset MJ users performed poorly on this task relative to non-MJ using subjects. Although preliminary, these results support the possibility that while current heavy MJ use is related to verbal learning and memory impairment, recovery of function may be associated with discontinuation of MJ use.

Topic areas:
Addiction
Binge drinking reaches a prevalence of 37.5% in individuals aged 18-25 years, and peaks at 42.8% from ages 21-25. It is therefore not surprising that the highest rate of alcohol use disorders (AUDs) also occurs within this period of emerging adulthood. Importantly, the widespread pattern of chronic, intermittent alcohol consumption seen in this age group coincides with the finalization of frontal lobe maturation, which may render emerging adults (EA) prone to neurobiological consequences of binge drinking. This study compared EA binge drinkers (BD: n=23) and light alcohol drinkers (LD: n=29) on clinical, cognitive and neuroimaging assessments. While BD demonstrated significantly greater drinking across all domains assessed, no significant differences were observed on clinical measures of depression, anxiety, impulsivity or emotional intelligence. Groups also did not differ across multiple cognitive domains, with the exception of a modest decrement in verbal learning. In contrast, multiple neurobiological differences were observed for magnetic resonance imaging and spectroscopy measures, including altered frontal lobe cortical thickness and GABA, myo-inositol and glutathione brain metabolites. Among a number of possible interpretations, altered neuroimaging measures may reflect acute neurotoxic effects of BD, which could resolve with abstinence. Alternatively, and given that BD were clinically and cognitively healthy, the neurobiological profile of BD could reflect protective neurobiological adaptations to chronic alcohol exposure. Taken together, the results suggest that while the frontal cortex is differentially sensitive to binge alcohol consumption, neurobiological alterations in BD during EA do not necessarily manifest as clinical and cognitive differences. It is plausible that neurobiological alterations observed at this stage may be early risk markers for continued hazardous drinking behaviors in young individuals who engage in frequent heavy drinking, but do not meet the criteria for AUD. Alternatively, neurobiological adaptations to a pattern of hazardous drinking may reflect compensatory measures that serve to protect the EA brain, sparing those who mature out of problematic use from adverse functional outcomes. A third possibility is a combination of these interpretations, that neurobiological adaptations protect the EA brain from immediate functional impairment, while simultaneously increasing risk for future adverse outcomes. Longitudinal studies examining antecedents to problematic alcohol use, as well as examination of neuroimaging measures as predictors of future use patterns, are currently in progress.

**Topic areas:**
Addiction
Imaging
Division of Women's Mental Health

Presenting Author: Chelsea Caracciolo, Community Residence Counselor, B.A., Gunderson Residence, Lois Choi-Kain

Co-Authors: Charlene Deming; Adam Jaroszewski; Karthik Dinakar

Title: The Valinor Project: Understanding and Intervening in Self-Injurious Thoughts and Behaviors on Social Media Sites

Key words: self-harm social media borderline personality disorder

The world of social media is ever growing and seldom patrolled for the emotional health of the end-user. Self-injurious thoughts and behaviors are regularly documented on these social media sites however, little is done to intervene and support the users. Many individuals with mental illnesses struggle with the maladaptive coping strategy of self-harm. Borderline personality disorder is one of these disorders with a staggering 70-75% of individuals engaging in self-harm (Gunderson, 2001; Linehan, 1993). The Valinor Project brings together the clinical study of self-harm and advanced machine learning, two worlds that rarely come together, to predict self-injurious thoughts and behavior and intervene to decrease the rates of self-harm. We combine and exert the power of probabilistic graphical models, decision theoretic models, and Box’s loop to better understand, intervene and predict self-injurious behavior on TalkLife. Guided by the four-function model of self-injury described by Nock & Prinstein (2004), we are working to better understand why individuals engage in these thoughts and behaviors, as well, as how we can help through the development of online interventions.

Topic areas:
Borderline Personality Disorder
Studies of psychiatric disorders such as OCD typically focus on emotional symptoms; however, neurocognitive deficits and difficulties in everyday thinking are prevalent, prominent, and independently contribute to distress and impairment (Trivedi, 2006; Millan et al., 2012). This study aimed to examine the relationship between cognitive symptoms and treatment response in individuals with severe OCD symptoms. The Montreal Cognitive Assessment, a brief cognitive screening instrument, was administered to 222 individuals who were admitted to a residential treatment program for OCD (167 performed within the normal range, 55 performed below a cutoff score associated with cognitive impairment). Individuals scoring below cutoff admitted to the program with significantly higher symptom severity (Y-BOCS mean 27.2, SD = 6.1) relative to individuals scoring within the normal range (Y-BOCS mean 24.8, SD = 6.0; p < .0011), but groups did not differ on any other admission characteristic, with the exception of disgust sensitivity (p < .05). At discharge, individuals scoring below threshold remained significantly elevated in OCD symptom severity (Y-BOCS mean 18.2, SD = 6.2) relative to individuals scoring within the normal range (Y-BOCS mean 13.7, SD = 6.5; p < .0001), and report significantly higher levels of depressive symptoms (HAM-D mean 6.1, SD = 4.9 relative to mean 3.9, SD = 4.0; p < .01), panic symptoms (PDSS mean 4.5, SD = 4.8 relative to mean 2.8, SD = 3.6), obsessive beliefs (OBQ mean 157.8, SD = 59.8 relative to mean 129.2, SD = 50.1, p < .01), rumination (mean 5.4, SD 1.7 relative to mean 4.5, SD 1.8; p < .003) and worry (mean 13.1, SD = 2.3 relative to mean 12.3, SD = 2.5; p < .05). Patients scoring below threshold also demonstrated lower distress tolerance skills (mean 10.2, SD = 4.3 relative to mean 12.2, SD = 4.0; p < .01), reappraisal skills (mean 7.5, SD = 3.1 relative to 8.6, SD = 2.5; p < .05) quality of life (QLES mean 46.0, SD =8.9 relative to mean 51.5, SD = 8.3). Percent change in Y-BOCS was significantly lower in individuals scoring below threshold on the MOCA (mean 43.2% relative to 25.3%; p < .007). These results indicate that cognitive symptoms are prevalent in this population and are associated with significantly poorer treatment outcomes. Augmenting treatment-as-usual with compensatory strategies geared toward specific deficits may help to improve treatment outcome in individuals experiencing severe OCD as well as difficulties in everyday thinking.

Topic areas:
Anxiety
Gender Differences in the Symptom Profile of Borderline Personality Disorder?: A Network Analysis Approach

Background: The relationship between gender and borderline personality disorder (BPD) has been complicated and inconclusive. Specifically, while findings regarding BPD Axis-I and Axis-II comorbidities have been relatively consistent, studies investigating gender differences in the diagnosis and symptom profile of BPD have yielded contradictory results (i.e., Grilo, 2002; Blum et al, 2007). For example, recent studies (e.g., Silberschmidt, Lee, Zanarini, & Schulz, 2014; Sansone & Wiederman, 2014) did not find typical gender differences reported in the literature, such as differences in aggression, suicidality, and substance abuse behaviors. The current study aimed to clarify the role of gender in BPD symptomatology in a heterogeneous psychiatric sample using both traditional and novel statistical approaches.

Methods: Data was obtained from 1,200 patients (51.5% female) attending the Behavioral Health Partial Hospital. We examined individual symptom endorsement in men and women, as well as the number of men and women screening positive for a BPD diagnosis on the McLean Screen Instrument for BPD (MSI-BPD). Using the novel causal systems approach and network analyses to understanding psychopathology, we also examined the network structure of symptoms using network analysis (Borsboom & Cramer, 2013). We examined whether the same central symptoms emerged in women and men, as well as whether the overall strength of relationships differed between genders. In addition, we will examine general outcome measures, depression and anxiety symptoms, and self-injurious behaviors to assess the reliability of findings in past studies.

Results: On the MSI-BPD, 328 (27.3%) patients scored above the cut-off suggesting a BPD diagnosis. Women were more likely to score above the clinical cut-off for BPD than men. Women also more frequently endorsed several individual symptoms (i.e., feeling distrustful, feeling as if things are unreal) than men. The relative importance networks (based on partial correlations) revealed similar network structure in men and women. Overall edge strength between nodes (symptoms) was the same across genders. In general, the same symptoms emerged as being most central to each network. However, in women, symptoms related to emptiness and anger were more central than in men.

Conclusions: Consistent with recent findings, our results from both traditional (symptom endorsement) and novel approaches (network analysis) revealed few gender differences overall in BPD symptom profiles. Of note, the few gender differences observed in the current sample were different from those found in prior studies. Inconsistent findings across studies may be due to differences in measurement of BPD symptoms (e.g., different scales, self-report vs clinician). Indeed, studies relying on clinician-rated assessments of BPD have been reported to be highly subject to gender biases in the diagnoses process (e.g., Becker & Lamb, 1994). A better understanding of the similar clinical profiles between genders will be crucial to ameliorate gender biases that contribute to misdiagnoses.

Topic areas:
Borderline Personality Disorder
Women
Corticolimbic dysfunction and rumination as mediating factors in the relationship between early life stress and depressive symptoms

Introduction: Previous research has shown that experiencing early life stress (ELS) can lead to significant neurobiological and cognitive changes in adulthood, and increased likelihood of major depressive disorder (MDD). For example, research comparing individuals with a history of ELS to non-stressed controls has revealed abnormalities in functional and structural connectivity between brain systems involved in regulating attention and emotion (e.g., lateral prefrontal cortex, LPFC) and systems involved in processing emotional salience (e.g., the amygdala). Individuals with ELS also report cognitive abnormalities that are theoretically related to disrupted coordination among regulatory and emotion-processing brain systems, which could be associated with higher levels of rumination. However, the research in this area is often inconsistent – with some studies showing hyperconnectivity, while others show hypoconnectivity between the amygdala and LPFC – and rarely combines multiple levels of cognitive, clinical, and neurobiological analysis in a theoretically driven model of risk.

Aim: To investigate the association between ELS and corticolimbic functioning, we focused on resting-state functional connectivity (RSFC) of the amygdala (measured with fMRI). To probe putative relationships between ELS, corticolimbic dysfunction, and cognitive style, we tested a model in which the association between ELS and rumination was mediated by amygdala RSFC. Finally, to explore the associations between ELS, corticolimbic dysfunction, cognitive style, and depression, we tested a model in which the association between ELS and depressive symptoms was mediated by amygdalar dysfunction and rumination severity.

Methods: The study included 30 women with a history of childhood adversity (ELS group: sexual, physical, emotional, or verbal abuse, or witnessing domestic violence) and 11 non-stressed control women (control group: with no significant stress history). Presence of childhood stress was determined by the clinician-administered Traumatic Antecedent Questionnaire (TAQ). Trait rumination and severity of depression were assessed using the Ruminative Response Scale (RRS) and Beck Depression Inventory, 2nd Ed. (BDI), respectively. fMRI resting state data were acquired using a 3T Tim Trio scanner and a 32-channel head coil.

Results: Women with ELS exhibited more extreme negative RSFC between the left amygdala and LPFC compared to non-stressed control women. Women with ELS also reported higher levels of trait rumination, and the relationship between ELS and rumination was mediated by stronger amygdala-to-LPFC anticorrelations. In addition, women with ELS reported higher BDI scores, indicating higher depression. An expanded mediation model revealed that stronger amygdala-to-LPFC anticorrelations and higher RRS scores, jointly partially mediated the relationship between ELS and BDI scores.

Conclusion: These findings suggest that ELS exposure is associated with more extreme antagonism between the amygdala and the LPFC, highlighting abnormally amplified down-regulation of limbic systems at rest and in the absence of emotional load. Moreover, abnormal corticolimbic connectivity was found to underlie the relationship between ELS and the tendency to ruminate. Critically, corticolimbic abnormality and ruminative tendencies may together contribute to depression among women exposed to ELS. Collectively, the preliminary findings indicate that the presence of early life stress may relate to atypical neurocognitive development, which might lead to an increase in vulnerability to depression.

Topic areas:
Depression
Impact of Acute Alcohol and Nicotine use on Emotional Impulsivity: Associations with Resting State Perfusion in Reward Circuitry

A high percentage of individuals co-use alcohol and nicotine, which together lead to more severe substance abuse disorders compared to use of either substance alone. However, cognitive and neural mechanisms that underlie the interactive effects of these drugs to facilitate co-use are still poorly understood. The current study examined the impact of acute alcohol and nicotine challenges on emotional impulsivity and cerebral blood flow (CBF) in key reward-processing brain regions, acquired at rest using PCASL fMRI. Seven males who were light to moderate smoker/alcohol drinkers completed both placebo nicotine patch + alcohol (PA) and 14mg nicotine patch + alcohol (NA) conditions in randomized order. Emotional impulsivity was measured outside the scanner via an emotional Go-NoGo task that featured negative, positive, neutral or scrambled distractor images. A repeated-measures ANOVA examining the impact of both drugs on NoGo trial accuracy revealed an increase in impulsivity (reduced NoGo accuracy) for positive trials, in response to alcohol, across both PA and NA conditions. No main effect of nicotine was observed. Nicotine and alcohol were found to increase CBF in the nucleus accumbens. In the NA condition relative to nicotine alone, the change in CBF in right nucleus accumbens was significantly correlated with reaction time on Go trials. While the small sample size of this pilot study precludes firm conclusions regarding the role of emotional impulsivity in alcohol and nicotine co-use, these findings suggest that the interplay of positive emotion, reward-related circuitry and impulsivity may have important implications for understanding how alcohol and emotion interact to increase risky behavior in young adults who co-use alcohol and nicotine.
Presenting Author: Marc Copersino, Associate Psychologist/Assistant Professor, McLean Hospital, Division of Alcohol and Drug Abuse

Co-Authors: Marc L. Copersino  Raihaan Patell  Amy C. Janes  Jenessa S. Price  Katherine H. Frost  Gordana Vitaliano  Scott E. Lukas  Roger D. Weiss  Mallar M. Chakravarty

Title: Striatal morphology is associated with frequency of recent substance use and age in substance abuse treatment patients

Key words: striatum morphology addiction patients endophenotype

A growing body of literature points to striatal volume and morphometry abnormalities as endophenotypes for various substance use disorders (SUDs). This study examined striatal volume, surface area, and surface displacement in 83 study participants, including 34 SUD patients and 49 healthy controls who received a structural MRI brain scan using a magnetization-prepared rapid gradient multi-echo sequence. Volume and morphometric data were collected via multiple automatically generated templates from a single labeled brain. In comparison to healthy controls, SUD patients had significantly less striatal gray matter volume bilaterally (p<.05). Among SUD patients, there was a significant association between right striatal volume and days of substance use in the past 30 days (p<.05), this association approached significance in the left striatum (p=.075). There was a significant interaction between substance use frequency and age on left striatal displacement [False Discovery Rate (FDR 10%)], such that older persons showed significantly greater shape deformity with displacement directionality negatively associated with substance use frequency (greatest positive displacement among older persons with lower substance use frequency, and greatest negative displacement in daily or almost daily users). These findings provide further evidence for striatal morphological abnormalities as endophenotypes for substance use disorders. Interaction effects suggest that the effect of substance use may not have exerted its influence on the still developing mesolimbic reward circuit in emerging adults. These results may also support a more state-dependent quality of striatal morphometric endophenotypes in which drug use provides a mediating factor.

Topic areas:
Addiction
Imaging
Presenting Author: Erin Corcoran, Research Student, Behavioral Health Partial Program

Co-Authors: Marie Forgeard Joey Cheung Nisha Udupa Courtney Beard Thröstur Björgvinsson

Title: Relationships between depression, self-reflective rumination and creative thinking in a transdiagnostic psychiatric sample

Key words: depression  rumination  creativity  cognition

Past research has looked at the link between depression and creativity, and has suggested that self-reflective rumination may explain why a higher prevalence of depression is found in creative samples (e.g., Ludwig, 1995; Verhaeghen, Joorman, & Khan, 2005). However, no study to date has investigated the role of self-reflective rumination in the relationship between depression and creative thinking in a psychiatric sample. In the present study, 180 participants (M age = 31.11 years, SD = 12.91, 55.6% female, 92.8% white) presenting for treatment at McLean’s Behavioral Health Partial (BHP) Program completed a measure of depressive symptoms (the Center for Epidemiological Studies Depression Scale – 10 items, CESD-10; Andresen et al. 1994), rumination (the Ruminative Responses Scale, RRS; Treynor et al., 2003), and a divergent-thinking task designed for the purpose of this study and scored according to the protocol described by Silvia et al. (2008). For this task, participants were asked to generate “one creative idea that you think could help us improve our program and the care we provide.” Sixty of the ideas generated were independently rated for creativity by a team of four trained research assistants on 3 criteria: originality, feasibility, and value. Raters achieved good levels of interrater reliability for all criteria (respectively α = .77; α = .83; α = .83). For the 60 items rated during the training phase, the four raters’ scores were averaged in order to produce a creativity score for each idea. Following the training phase, each idea was only rated by one rater. In addition, the length of each idea was computed by counting the number of characters in each idea. Contrary to our hypotheses, results of multiple regression analyses (controlling for age and sex) showed that depressive symptoms did not predict originality, feasibility, value, or length of ideas (all ps > .10). However, self-reflective rumination did predict length of ideas (standardized beta = .17, p < .01) as well as value (standardized beta = .14, p = .07), though the latter relationship only approached significance. In this study, self-reflective rumination therefore independently predicted some facets of creative thinking. These results highlight the need to conduct further research to better understand the nature of the relationship between affective disorders and creativity in psychiatric samples.

Topic areas:
Depression
McLean Research Day 2016

Original Research - Clinical
Poster # 29

Division of Basic Neuroscience

Presenting Author: Mary Kathryn Dahlgren, Senior Clinical Research Assistant, M.S., Cognitive and Clinical Neuroimaging Core

Co-Authors: M. Kathryn Dahlgren, Kelly A. Sagar, Megan T. Racine, Atilla Gonenc, Rosemary T. Smith, Korine B. Cabrera, Ashley M. Lambros, & Staci A. Gruber

Title: Highlights: Preliminary Results Indicate Improved Cognitive Control Processing with Medical Marijuana Use

Key words: medical marijuana  cognitive control  executive function  fMRI

Background: Marijuana is currently classified as a Schedule I drug by the US Drug Enforcement Administration, which is the most stringent designation and is restricted to drugs which have “no currently accepted medical use” and a “high potential for abuse.” Given this classification, marijuana remains illegal under federal law. However, over the past several years, a significant shift in public opinion regarding marijuana use has occurred, reflected in individual state laws. Currently, twenty-three states and the District of Columbia have passed laws allowing for medical marijuana (MMJ) use, and another twelve states have restricted MMJ laws in place. Despite a growing number of states allowing MMJ treatment, little research has focused on the potential impact of MMJ on measures of cognitive performance or brain function. The current study is a preliminary report assessing the impact of MMJ treatment on cognitive control processing, a type of executive functioning critical for appropriate attention allocation that has been shown to be impaired in substance abusing and psychiatric populations.

Methods: Participants were recruited from local certification centers, and included those who had been issued a certification for MMJ use but had not yet begun treatment. Participants were assessed before beginning regular MMJ use and returned for follow-up assessments after approximately three months of MMJ treatment. As part of a larger study, participants completed the Multi-Source Interference Task (MSIT) during functional magnetic resonance imaging (fMRI). The MSIT measures cognitive control processing and reliably activates the frontoparietal attention network, particularly the anterior cingulate cortex (ACC), an area associated with emotion regulation, impulse control, and reward association.

Results: Preliminary analyses from this study indicate the MMJ treatment significantly improved performance on the MSIT. Specifically, after three months of MMJ treatment, participants made significantly fewer commission errors and demonstrated trends for improved performance accuracy and decreased response time (ms) during the interference condition of the task relative to baseline performance. FMRI analyses of the treatment versus baseline contrast indicated that ACC activation during the MSIT significantly increased after three months of MMJ treatment, resulting in an activation pattern that more closely resembled activation typically observed in healthy control participants.

Conclusions: Preliminary data from this investigation suggest that three months of MMJ treatment is not associated with decrements in cognitive performance and in fact may improve cognitive control processing from both a behavioral and functional perspective. These findings have significant clinical implications, as previous studies of the impact of recreational MJ use have reported impaired cognitive control processing. Further, improved cognitive performance is often associated with improvements in overall general health as well as quality of life measures; future studies should examine this relationship in MMJ treatment. While still preliminary, these data underscore the likelihood that individuals treated with MMJ may not exhibit decrements in cognitive performance and highlight the importance of continued research in this area.

Topic areas:
Anxiety
Imaging
PTSD
McLean Research Day 2016

Original Research - Clinical

Division of Alcohol and Drug Abuse

Presenting Author: Sterling Karakula, Clinical Research Assistant, B.S., McLean Hospital, Alcohol and Drug Abuse Clinical Research Program

Co-Authors: Margaret L. Griffin, Ph.D., Roger D. Weiss, M.D., R. Kathryn McHugh, Ph.D.

Title: Delay Discounting among Inpatients with Opioid Use Disorder: Differences between Heroin and Prescription Opioid Users

Key words: opioid use disorder  delay discounting  heroin  prescription opioids

Over the past two decades, increased availability and acceptance of opioid pain medications has led to a rapid increase in prescription opioid misuse and opioid use disorder. Misuse of prescription opioids is a significant risk factor for initiating heroin use, which is associated with greater substance use severity, lower treatment retention, and less successful treatment outcomes compared to prescription opioid users who do not use heroin. Efforts to distinguish heroin users from prescription opioid users are necessary to inform the characteristics and treatment needs of these distinct populations. Delay discounting, a facet of impulsivity that reflects the degree to which future rewards are devalued based on their distance in time from the present, is one dimension in which these populations might differ. Delay discounting has been repeatedly associated with substance use and other risky behaviors. This study sought to characterize differences in delay discounting in those with opioid use disorder based on their primary opioid of use (i.e., heroin or prescription opioids).

Adults at an inpatient detoxification unit at McLean Hospital were recruited to complete a battery of questionnaires in this single-session research study. A total of 147 participants with a diagnosis of opioid use disorder completed the delay discounting measure, the Monetary Choice Questionnaire (MCQ). Participants were categorized based on self-reported opioid use in the 30 days prior to admission as primary heroin users (heroin group), primary prescription opioid users (prescription group), or users of both heroin and prescription opioids (combined group). Delay discounting (DD) scores were calculated and compared among the three groups.

Results from a univariate analysis of variance revealed a significant main effect of group on DD (p < .01). Post-hoc comparisons demonstrated that the heroin group (p < .05) and the combined group (p < .05) had significantly greater DD compared to the prescription group. However, the DD of the heroin and combination groups did not differ (p = 1.00). The heroin and combined groups were then collapsed and compared to the prescription group, controlling for the sociodemographic variables of age, marital status, ethnicity, and employment. Even controlling for these variables, the group difference in DD remained statistically significant (p < .01).

A sample of inpatients with opioid use disorder, elevated delay discounting was observed in those using heroin, either alone or in conjunction with prescription opioids, compared to those using only prescription opioids. This difference demonstrates a preference for immediate rewards over delayed ones in heroin users, which may contribute to their poorer treatment outcomes compared to prescription opioid users. Patients with greater delay discounting may be at an increased risk of transitioning from prescription opioid to heroin use; future longitudinal research that focuses on the lifetime course of opioid use disorder should evaluate this possibility.

Topic areas:
Addiction
The present studies were undertaken to characterize the discriminative-stimulus effects of (+)-epibatidine (EPI)–a α4β2 selective nicotinic agonist that is pharmacologically similar and structurally distinct from nicotine (NIC). Using a standard two-lever drug discrimination procedure, the effects of various nicotinic agonists and antagonists were studied in squirrel monkeys (n=4) that were trained to discriminate i.m. injections of 0.001 mg/kg (+)-epibatidine (EPI) from saline on a 10-response fixed-ratio schedule of stimulus-termination. Results show that high efficacy nicotinic agonists [(+) -EPI, (-)-EPI, NIC] substituted fully for (+)-EPI, whereas the highest doses of other nicotinic agonists produced intermediate levels of (+)-EPI-like discriminative-stimulus effects [varenicline (VAR), cytisine (CYT)] or did not substitute for (+)-EPI (lobeline). Drugs from other pharmacological classes (methamphetamine, atropine, citalopram, arecoline) did not generalize for (+)-EPI. Pretreatment studies with nicotinic antagonists show that: a) mecamylamine (non-selective) unsurmountably antagonized (+)-EPI’s effects; b) dihydro-β-erthroidine (α4β2-selective) surmountably (>3-fold rightward shift) blocked (+)-EPI’s effects; and c) methyllycaconitine (α7 selective) and hexamethonium (peripherally-restricted) failed to modify the discriminative-stimulus effects of (+)-EPI. In further studies, pretreatment with the partial nicotinic agonists VAR and CYT did not block the discriminative-stimulus effects of (+)-EPI, and in fact, CYT pretreatment shifted the (+)-EPI dose-effect curve to the left (>3-10-fold). These results suggest that the discriminative-stimulus effects of (+)-EPI are mediated through a α4β2 nicotinic receptor subtype at which the partial agonists VAR and CYT do not exert partial antagonist actions (supported by NIH DA031231).
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Title: Examining Abnormal Reward Learning In Bipolar Disorder

Key words: BD Anhedonia Hyperhedonia Reward Processing MID

Background: Bipolar disorder (BD) has been associated with dysregulated reward processing, with individuals experiencing anhedonia (reduced reactivity to pleasurable stimuli) during depressive episodes and hyperhedonia (increased pleasure seeking behavior) during manic episodes. The investigation of reward-related neural functioning within euthymic BD samples is of particular interest to identify potential reward processing dysfunctions that could act as trait markers of the illness.

Methods: In Study 1 we examined 13 euthymic individuals with bipolar disorder and 15 healthy controls during a monetary incentive delay (MID) task whilst in the fMRI scanner. In preliminary Study 2, we examined 8 healthy and 8 euthymic BD individuals during a behavioral social reinforcement learning (RL) task. During the task, participants had to choose one of the two stimuli presented on the screen in order to obtain a reward (cheer sound) or avoid receiving a punishment (boo sound). The participants had to learn, by trial and error, the changing stimulus–outcome associations. Learning rate was calculated by adding the deviation between the participants’ and pre-defined total choice across the task. Accordingly, the MID task investigated neural correlates underlying reward anticipation and consumption, whereas the behavioral RL task probed reward learning in patients and controls, allowing us to assess different subcomponents of reward processing.

Results: fMRI data were processed using FSL. The onset times of reward anticipation and consumption events were convolved with a hemodynamic response function. Parameter estimates from anatomically defined putamen and amygdala were extracted during reward anticipation and consumption and analyzed using SPSS. BD patients exhibited reduced putamen activation during reward consumption and increased amygdala activation during reward anticipation (p < 0.05). Complementing these latter findings, in study 2, we found that BD subjects had blunted reward learning when compared with healthy individuals (p < 0.05).

Conclusions: Findings across both studies converge in showing that BD patients are characterized by impaired reward learning, highlighting that reward dysfunction could be a promising trait marker of the illness. Overall, findings may translate to an impaired ability to use reward predicting cues to appropriately engage in goal-directed actions in BD.

Topic areas:
Bipolar
Imaging
Title: Lower Perceptual Sensitivity to Negative Facial Emotion Expressions in Schizophrenia

Key words: Schizophrenia  Psychophysics  Emotion Perception  Face Perception  Social Psychology

Perception of salient emotional expressions in faces is impaired in schizophrenia, yet it is unclear if this perceptual impairment emerges at subtle emotional expressions in faces. In this study, we manipulated facial emotion intensity level via morphing between facial images with highly emotive expressions and with neutral expressions. We measured accuracy of perceiving four types of facial emotion: happiness, fear, anger, and sadness at various emotion intensity levels in schizophrenia patients (n=55) and healthy controls (n=34). We also determined perceptual thresholds for detection of the facial emotions, using psychophysical methods. For accuracy, a significant interaction between group and emotion intensity was found for anger (F=2.42, p=0.035), fear (F=4.35, p=0.001) and sadness (F=3.70, p=0.003), but not for happiness (F=1.11, p=0.17). For perceptual threshold, the two groups differed for anger (p=0.01), fear (p=0.005) and sadness (p=0.003), but not for happiness (p=0.10). In patients, perceptual thresholds for anger were significantly correlated with positive and negative PANSS scores (p<0.05). Perceptual thresholds for sadness were significantly correlated with negative PANSS scores (p<0.05). These analyses indicate that patients have a greater extent of impairment for perceiving salient than subtle negative facial emotions. Also, they have lower perceptual sensitivities for detecting the presence of negative facial emotion expressions. The lower perceptual sensitivities for anger are associated with positive and negative psychotic statuses whereas the lower perceptual sensitivities for sadness are associated with negative psychotic status.
Incorporating temporal delay information about systemic physiological signals enhances noise removal from resting state fMRI data

Key words: Resting state fMRI  functional connectivity  global signal  systemic physiological noise

Introduction: Resting state functional connectivity analysis is a widely used method for mapping intrinsic functional organization of the brain. Global signal regression (GSR) is commonly employed for removing systemic global variance from resting state BOLD-fMRI data; however, GSR may introduce spurious negative correlations within and between functional networks, calling into question the meaning of anticorrelations reported between some networks.

Hypothesis: We hypothesize that the global signal in resting state fMRI is composed primarily of systemic low frequency oscillations (sLFOs) that propagate with cerebral blood circulation throughout the brain.

Method: We introduce a modified noise correction strategy, “dynamic global signal regression” (dGSR), which applies a voxel-specific optimal time delay to the global signal prior to regression from voxel-wise time series. We test our hypothesis on two functional systems that are suggested to be intrinsically organized into anticorrelated networks: the default mode network (DMN) and task positive network (TPN). We evaluate the efficacy of dGSR and compare its performance with the conventional “static” global regression (sGSR) method in terms of i) explaining systemic variance in the data and ii) enhancing specificity and sensitivity of functional connectivity measures.

Results: dGSR leads to a clear increase in the amount of BOLD signal variance being modeled and removed relative to sGSR, while reducing spurious negative correlations introduced in reference regions by sGSR, and attenuating artificial positive connectivity measures.

Conclusion: We conclude that incorporating temporal delay information for sLFOs into global noise removal strategies significantly improves noise removal from resting state functional connectivity maps, while attenuating artifactual anticorrelations.

Topic areas:
Imaging
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Title: Predictors of Rehospitalization for Depressed Adolescents Admitted to Acute Psychiatric Treatment

Key words: Depression Adolescents Rehospitalization Residential treatment Non-suicidal self-injury

Background: Although acute residential programs (~15 days) are effective in treating adolescents with severe psychopathology, approximately one-third of patients are rehospitalized within a year of discharge, with most readmissions occurring within 3 months (Barker et al., 2010; Fontanella, 2008; James et al., 2010). Rehospitalization is associated with a number of psychosocial and economic consequences (Bardach et al., 2014; Romansky et al., 2003; Noyola et al., 2014), however, the factors that predict rehospitalization remain unknown. To address this unmet gap, the present study tests whether specific demographic and clinical characteristics predict rehospitalization among depressed adolescents.

Method: Participants included 165 depressed adolescents (112 female) aged 13-19 years (M = 15.61, SD = 1.48) admitted to an acute residential treatment program over a 1-year period (November 2013 - November 2014). Within 48 hours of admission, participants completed a battery of clinical interviews and self-report questionnaires assessing: (a) demographics, (b) early life stress, (c) psychiatric diagnoses, (d) symptom severity, and (e) risky, self-injurious, and suicidal behaviors. At discharge, psychiatric symptom severity was reassessed. Predictors of readmission for acute, psychiatric care were monitored over a 6-month period following discharge.

Results: Twenty adolescents (12.1%) were rehospitalized within a 6-month period. We conducted a series of cox regression survival analyses to test demographic and clinical predictors of patients’ time to readmission. Two interesting findings emerged. First, more frequent non-suicidal self-injurious (NSSI) behaviors in the month prior to initial hospitalization was significantly associated with a more rapid time to rehospitalization, $b = .05, SE = .02, \text{Wald}(1) = 4.35, p = .037, OR = 1.05, CI95 = 1.003 - 1.10$. Second, less improvement in hopelessness during short-term psychiatric care predicted a faster time to rehospitalization at a trend level, $b = -.13, SE = .07, \text{Wald}(1) = 3.64, p = .056, OR = 0.88, CI95 = 0.78 - 1.00$.

Conclusion: It is critical to effectively manage NSSI behaviors and hopelessness during treatment of depressed adolescents, as these factors may have a profound impact on long-term clinical care.

Topic areas:
Child
Depression
Anhedonia in posttraumatic stress disorder, major depression, and their comorbid presentation

**Background:** Anhedonia, defined as an inability to experience pleasure, is a core symptom of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). However, there has been little research on how anhedonia presents in a comorbid sample and if anhedonia levels “double-load” from having both disorders. To our knowledge, there have been no studies comparing levels of anhedonia in individuals with PTSD, MDD, and comorbid PTSD-MDD. To ameliorate this gap, we examined anhedonia, as reported on the Snaith-Hamilton Pleasure Scale (SHAPS), among these three groups.

**Methods:** We used data from 74 participants, ages 18 to 50, across two studies, one on PTSD (n = 37) and one on MDD (n = 37). Twenty-four (24) participants had PTSD, 25 participants had MDD, and 25 participants had comorbid PTSD-MDD. All participants completed the SHAPS. Depression severity was assessed using the Beck Depression Inventory (BDI) in one study and using the Hamilton Depression Rating Scale (HAM-D) in the second study; hence, these scores were converted to z-scores to enable merging across studies. The z-scores failed tests of normality and were log-transformed after adding 2 to remove the negative values. The PTSD-MDD group, populated by both studies, did not fail tests of homogeneity for age and depression severity.

**Results:** An ANCOVA, controlling for depression severity, identified a significant group difference in SHAPS scores, F(3, 70) = 10.395, p < .001, partial η² = .31. Marginal mean pairwise comparisons showed that SHAPS scores were significantly higher in the MDD group than in both the PTSD group, p = .007, and the PTSD-MDD group, p = .03.

**Conclusion:** We found that SHAPS-reported anhedonia levels were higher in the MDD group than in both the PTSD group and the PTSD-MDD group. As such, even though anhedonia is a core symptom of both PTSD and MDD, it did not double-load in the comorbid sample. Additional research will be needed to replicate this finding, particularly studies that recruit the three groups concurrently with the same selection criteria. In addition, neuroimaging studies could compare neural correlates of anhedonia and reward-processing circuitry across these groups.

**Topic areas:**
Depression
PTSD
Title: Understanding the relationship between outer and inner setting implementation climate constructs to facilitate rapid adoption of mental health integration within a diverse primary care practices.

Objectives: Mild to moderate depression raises the risk of developing a number of medical conditions, interferes with patients’ self-care, and is associated with poorer outcomes, leading to a high burden for patients and health care systems alike. In response, a large integrated healthcare delivery system (Partners HealthCare) is integrating depression care within primary care across a diverse set of primary care practices. The goal of this study is to understand the implementation climate of a set of diverse primary care practices in order to support rapid adoption of practice redesign.

Methods: 135 of 190 (71%) of primary care practices completed a detailed electronic assessment of practice readiness to implement mental health integration in July-September 2014. Items addressed patient needs and resources within the practice (outer setting) as well as practice networks and communications, implementation climate, readiness for implementation and practice structural characteristics (inner setting CFIR constructs). Practices were grouped into high (greater than 15% of patients with depression) and low (<=15% depression prevalence) level of need. Relationships between level of need and inner setting constructs were explored using Chi squared tests.

Results: Structural characteristics (size, location, level of affiliation) were similar for practices with high and low levels of need. Moreover, there were no differences in measures of networks and communications (AMC affiliation, resources currently used for curbside advice or depression management, and designated staff to provide resources or liaison with BH specialists) for practices with high and low levels of need. However, practices with higher levels of need reported more positive implementation climates, including greater tension for change and relative priority of MH integration within the practice. Specifically, higher need practices were more likely to report difficulty accessing social work (57% for high vs. 32% for low need practices, p=.01), case management (56% vs. 33%, p=.03) and BH medication management (65% vs. 29%, p<.01) and were marginally more likely to report difficulties accessing curbside advice for diagnostic questions (64% vs. 50%, p=.06). High need practices also had greater interest in integrating depression care within the practice (46% interested for high vs. 24% interested for low). There were no differences in measures of practice compatibility with depression integration for low and high need practices. High need practices have lower current levels of readiness to implement BH integration, including lower levels of practice funding for BH integration (10% for high vs. 24% for low need) and are less likely to have one or more staff members trained in behavioral activation (32% for high vs. 50% for low).

Conclusions: Primary care practices with greater need for BH services have more positive implementation climates but struggle with lower levels of current readiness, including funding and training, to provide primary care based support to their depressed patients. Efforts to support rapid adoption of behavioral health integration should focus on improving funding and training for high need practices.

Topic areas:
Depression
Division of Depression and Anxiety

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Title: Resting-state medial prefrontal cortex connectivity in major depression reveals increased connectivity with the lateral prefrontal cortex and thalamus

Key words: resting state connectivity major depression medial prefrontal cortex

Background: Major depressive disorder (MDD) has been linked to altered connectivity in large-scale brain networks, as reflected by abnormal resting state functional connectivity. Results of some resting state studies suggest that MDD is associated with increased connectivity between areas of the default mode network (DN, which supports internally-oriented and self-referential thought) and regions of the frontoparietal network (FN, which supports cognitive control and emotion regulation). However, this finding has not been consistently replicated, perhaps due to variable methods used to identify seed regions-of-interest (ROI). In this study, we selected the medial prefrontal cortex (MPFC) as a seed ROI of the DN based on a recent meta-analysis, in order to examine between-group differences in brain connectivity in a sample of MDD patients and matched healthy controls.

Methods: Thirty-nine participants with MDD and 65 matched healthy controls completed a clinician-administered SCID as well as self-report questionnaires including the Hamilton Rating Scale for Depression (HRSD). A seed-to-voxel resting-state functional connectivity analysis from the MPFC was assessed using the CONN toolbox and SPM (peak threshold p <0.05, FWE cluster-corrected p < 0.05; controlling for age and sex).

Results: Compared to HC participants, MDD patients exhibited increased functional connectivity between the MPFC seed and 3 significant clusters, mainly comprised of the thalamus (k=1673) and bilateral lateral prefrontal cortices (left: k=1429; right: k=1621). Within the MDD group, HRSD scores were not significantly correlated with functional connectivity in any of the 3 aforementioned clusters.

Conclusions: Hyperconnectivity between the networks involved in self-referential processing (DN) and control systems (FN) may reflect key deficits in the top-down control of emotion processing and regulation in MDD. Our results motivate further study of “seed-networks” characterized by studies that provide meta-analytic evidence for abnormal communication among functional networks mediating the cognitive and affective biases that characterize this disorder.

Topic areas:
Depression
Imaging
Distress tolerance (DT) is often defined as the capacity to experience and withstand negative psychological states, with individuals low in DT to be more likely to overreact to distress (Simons & Gaher, 2005). Recently, DT has been investigated and linked to several psychological disorders, including borderline personality disorder and some anxiety disorders, including generalized anxiety disorder and obsessive-compulsive disorder (OCD). Specifically, studies in non-clinical samples have revealed an association between DT and obsessive-compulsive symptomatology, finding DT to be significantly correlated with obsessive-compulsive symptoms (Cougle, Timpano, & Goetz, 2012; Norr et al., 2013) and revealing that lower DT is predictive of the presence of obsessions (Cougle, Timpano, Fitch, & Hawkins, 2011; Cougle, Timpano, & Goetz, 2012). Very few studies have investigated the role of DT in OCD, especially within a clinical sample. One study in a sample of individuals with OCD revealed that DT significantly correlated with OCD symptoms (Laposa, Collimore, Hawley, & Rector, 2015). Additional research surrounding DT in a clinical sample is necessary to better understand its association to obsessive compulsive symptomatology. More importantly, no research has investigated DT and its association with treatment outcome for individuals with OCD. Therefore, this current study aims to explore the relationship between OCD and DT, and DT’s association with overall treatment outcome and changes in OCD symptoms. In the current study, 212 patients from an intensive residential treatment program for OCD were administered the Distress Tolerance Scale (DTS), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Dimensional Obsessive Compulsive Scale (DOCS), and the Quality of Life Enjoyment and Satisfaction Questionnaire (QLES), at both admission and discharge. Changes in these scores from admission to discharge were computed and correlations were conducted. Significant correlations were found between change in DTS scores and change in YBOCS scores \(r(208)=-.46, p<.001\), QLES scores \(r(208)=.44, p<.001\), DOCS concerns about responsibility for harm, injury, or bad luck subscale scores \(r(208)=.34, p<.001\), and DOCS unacceptable thoughts subscale scores \(r(210)=-.20, p=.004\). Total distress tolerance scores at both admission \(r(210)=.16, p=.023\) and discharge \(r(209)=.31, p<.001\) were also significantly correlated with change in YBOCS scores. However, when looking at both DTS scores at admission and discharge in correlation with change in DOCS subscale scores, the DTS total scores at admission were only associated with the change in DOCS concern about responsibility for harm, injury, or bad luck scores \(r(209)=.24, p<.001\). A linear regression revealed that lower DTS scores at admission, representative of lower distress tolerance, were predictive of a greater change in YBOCS scores compared to those with higher DTS scores, who showed less change in YBOCS between admission and discharge. These preliminary analyses suggest that DT is associated with OCD symptomology and change in overall OCD symptoms during treatment. DT, therefore, may be an important factor in the maintenance of OCD symptoms as well as changes in such symptoms during treatment.
Substance Use Disorders in the Elderly: Diagnosis and Treatment Challenges

In 2009 the elderly constituted 12.9% of the population, and by 2030 they will comprise 21% of the population. Substance abuse, particularly of alcohol and prescription drugs, is one of the fastest growing health problems. The substance abuse problems among the elderly are often overlooked, as symptoms mimic those of other medical and psychiatric disorders. Substance use disorders take a greater toll on affected older adults. In addition to the psychosocial issues that are unique to the elderly, aging induces physiological changes that increase susceptibility to the deleterious effects of alcohol and other illicit substances. There is a general lack of evidence based treatment approaches for substance abuse in the elderly. As a result, much of what is recommended is based on the interventions that have been validated in younger populations. It is important to understand specific ways to engage the elderly patient. Expansion of research is needed for maximum effectiveness and efficiency of the healthcare system serving these individuals. Here, we present guidelines to identifying substance use disorders in the elderly, caveats of diagnosis and treatment, and common challenges that often arise in treatment. We describe a psychotherapeutic intervention we are using at our institution to engage elders in ongoing treatment, and highlight this as a potential approach to developing substance use treatment that is tailored to the elderly.
Insula Cortical Thickness Relates to Impulse Control in Adolescents and Emerging Adults

Objective: The brain undergoes dynamic and requisite changes during adolescence that are associated with improved cognitive efficiency. Developmental reductions in grey matter thickness reflect, in part, pruning of excess neurons and maturation of synapses, which contribute to improved cognitive and behavioral development. While prefrontal maturational changes are prevalent, less is known about the role of the insula, although it has been implicated in emotional regulation, decision making, prospective thinking, and self-rated impulsivity. The current study examined impulse control and insula cortical thickness in healthy adolescents (ADOL) and emerging adults (EA). Participants and Methods: 31 ADOL and 18 EA underwent high-resolution MRI at 3T, and cortical surface reconstruction and thickness estimation were performed using FreeSurfer. Inhibitory control measures included Barratt Impulsiveness Scale (BIS), Go-NoGo and Stroop Color-Word Task. Results: Cortical thickness in superior circular sulcus of the insula was significantly greater in ADOL relative to EA: thickness on the left predicted better Go NoGo and Stroop performance and thickness on the right predicted better performance on Go NoGo and lower BIS scores (less total and motor impulsivity). Conclusions: Results from this study replicate previous evidence of an age-related association between cortical thickness in a combined anterior insula region and BIS scores, collectively suggesting that cortical thickness reductions in insula, likely via normative neuronal pruning, are associated with better impulse control. The current findings also suggest that a specific region of anterior insula, the superior segment of the circular sulcus, dissociates domains of impulsivity, with hemisphere laterality uniquely predicting neuropsychological indices of cognitive control from self-reported motor impulsiveness.
Patients with severe mental illnesses (SMI) tend to have a shorter life expectancy compared to the general population. Much of the excess mortality of SMI patients is not due to the diagnosis itself, but rather is often attributable to cardiovascular disease, which is exacerbated by chronic treatment with second-generation anti-psychotics (2GAs). Although the increased cardiovascular risks are well understood and there are safe and efficacious pharmacotherapies available, few SMI patients receive cardiovascular prevention. The main barriers to reducing cardiovascular risks for SMI patients are the fragmentation of care delivery between primary care and mental health centers, and patient adherence to medications. To address these problems, we are conducting a multi-site, open-label, randomized clinical controlled trial comparing an initial treatment strategy of free, fixed-doses of two cardiovascular prevention medications (simvastatin and losartan). This treatment will be integrated into mental health clinics and will be compared to usual treatment (i.e. patients will not receive any intervention but continued to be monitored), with a goal of enrolling 300 adult participants (18+ years old; 300 per arm) with an SMI diagnosis. For this study we have defined the SMI population as patients with a diagnosis of schizophrenia, schizoaffective, bipolar disorders, major depressive disorder, and psychosis NOS with some degree of function impairment (as evidenced by an inability to work or the receipt of disability insurance). Participants must have received a standing 2GA treatment anytime in the past six-months at one of three mental health clinics in the Boston area. We have three aims: 1) to compare the proportions of subjects who are adherent to cardiovascular drug treatment in each arm receiving cardiovascular drug treatment and are adherent to therapy during 12-months of follow-up; 2) to compare changes in composite (e.g., Framingham scores) and individual (e.g., lipid levels) cardiovascular risk factor levels using an intent-to-treat (ITT) approach; and 3) to compare risk factor levels, accounting for variation in adherence over time, using causal inference techniques to estimate the per-protocol effect of the intervention. Thus, our three aims examine whether this low cost, streamlined treatment strategy increases the numbers of subjects receiving cardiovascular prevention therapy and improves cardiovascular risk levels. Because patient adherence is a major concern in this clinical area, we will supplement the ITT assessment of risk levels by using techniques such as marginal structural models with inverse probability weighting to account for time-varying adherence. We will follow subjects for up to 12 months, and collect interview and biometric data at baseline 3-, 6-, 9-, and 12-months, and supplement these data with other sources of existing information, e.g. from electronic health records. This population-based initial treatment strategy could be an effective and efficient approach for overcoming traditional barriers to cardiovascular disease prevention within the SMI population. Findings from this study will inform efforts to improve care integration and outcomes, and enhance the survival for patients suffering from SMI.
Background: 20 million Americans are alcohol dependent or regularly drink alcohol in harmful quantities and nearly 50 million Americans smoke cigarettes. As many as 88-96% of alcoholics are smokers and approximately 60% of smokers consume alcohol in significant quantities. Individuals who are both alcohol and nicotine dependent generally have heavier use of both drugs and more severe dependence. Despite the ramifications of co-abuse of these substances, very little is known about how this drug combination acts within the brain to become so strongly paired. Alcohol and nicotine have complex interactions on the brain’s mesocorticolimbic dopamine system (MDS), which is strongly implicated in reward and addiction. Alcohol also impairs cognitive performance, whereas nicotine may enhance cognitive performance. Thus, during alcohol intoxication, we might expect to see additive effects of nicotine and alcohol in MDS structures and opposing effects of nicotine on alcohol-related alterations in cognitive control regions. To test this, we conducted a pharmacologic magnetic resonance imaging (phMRI) study of the acute effects alcohol and nicotine on cerebral blood flow (CBF) and resting state functional connectivity (RSFC) of key brain circuits implicated in addiction.

Methods: 7 healthy male light/moderate smokers and moderate/heavy drinkers participated in this within-subjects placebo-controlled phMRI study of alcohol, nicotine, and alcohol and nicotine together. Simultaneous BOLD FMRI and CBF data were collected during two separate visits. For each study session, a placebo nicotine or 14 mg nicotine patch was placed on the arm. After a three-hour uptake period, participants underwent imaging. After baseline BOLD/CBF scans participants drank an alcoholic beverage (vodka and orange juice, 0.7 g/kg of alcohol in 400 ml total volume), which was followed by post-drinking scans after a 20 min uptake period. Data were analyzed using FSL to calculate CBF in units of ml/100g/min and to assess RSFC of brain circuits using group independent component analysis with dual regression during placebo, nicotine, alcohol, and nicotine+alcohol conditions and to compare drug effects relative to placebo.

Results: Nicotine did not alter CBF in MDS structures, likely due to the route of administration (transdermal patch). Alcohol, on the other hand, showed robust CBF increases in all MDS structures (p<0.05) and the combination of alcohol and nicotine showed even larger increases in right nucleus accumbens (NAcc) and ventral tegmental area/substantia nigra (VTA/SN) relative to alcohol alone. RSFC of medial prefrontal cortex, left NAcc, and left insula with the “salience network” (SN), a key brain circuit that is involved in detecting and orienting to salient external stimuli and internal events, was decreased by alcohol (p<0.05 corrected), with these effects being diminished with nicotine on board.

Conclusion: The effects of nicotine on alcohol’s effects were to enhance alcohol effects in NAcc and to diminish alcohol effects in frontal cortex. These alterations are consistent with enhanced reward with co-use of alcohol and nicotine relative to each drug alone, and with nicotine diminishing the impairing effects of alcohol. Together, our findings provide evidence that these two factors may drive the widespread co-use of alcohol and nicotine.
Epigenetic alterations have recently been implicated in the initial consolidation of amygdala-dependent fear memories. While much work has noted the regulation of histone acetylation in fear memory processes, little is known about the specific role that histone deacetylases (HDACs), which mediate the deacetylation of histone tails, might have in fear memory consolidation. Motivated to understand the epigenetic alterations that may be associated with human clinical PTSD, our group has previously noted that CpG methylation in HDAC4 is associated with PTSD. While much work has examined the role of HDACs in learning and memory employing pan HDAC inhibitors in rodent models, very little is known about the role that specific HDACs play in mediating the initial formation of fear memories. HDAC4 is a class Ila HDAC whose subcellular localization can be cytoplasmic or nuclear and is regulated by Ca2+ and NMDAR-mediated signaling cascades; a level of regulation not yet explored in vivo with fear memory formation. Recent work in rodent models has noted that repression of HDAC4 is associated with deficits in spatial learning and hippocampal-dependent contextual fear memory consolidation (Sando et al 2012; Kim et al 2012) suggesting a role for HDAC4 in memory. Despite this progress, the role of HDAC4 in amygdala-dependent auditory fear memory has not been elucidated. Using auditory fear conditioning, we examined the regulation of HDAC4 mRNA in the amygdala 2h following tone-shock pairings and revealed training-related regulation of HDAC4 mRNA. Next, using cytoplasmic or nuclear restricted HDAC4 viral constructs in the amygdala we examined if the subcellular localization of HDAC4 impacts fear memory formation. While we found no difference in freezing during fear acquisition, 24h later mice expressing nuclear-restricted HDAC4 show impaired fear memory consolidation compared to the cytoplasmic-restricted and GFP-control animals. Given the role of HDACs in regulating transcriptional processes we examined how HDAC4 may mediate the transcriptional processes underlying fear learning and memory by examining HDAC4 occupancy at gene loci using ChIP. We found a reduction in HDAC4 occupancy at the BDNF locus following conditioning, at a timepoint when the mRNA expression of BDNF has been shown to increase with fear conditioning. These data suggest that nuclear accumulation of HDAC4 likely functions as a negative regulator of fear memory-related plasticity through impeding training-related transcriptional processes, such as the transcription of BDNF. In sum, these findings strongly suggest that HDAC4 and its subcellular localization impacts fear memory consolidation.
Parkinson’s disease (PD) is a chronic progressive disorder with motor symptoms characterized by tremor, bradykinesia, rigidity and postural instability. Currently there are nearly one million diagnosed cases in the US. Clinical studies have shown that patients can gain improved motor function with transplantation of cell preparations derived from fetal ventral midbrain. However, fetal cell sources are too limited and require immunosuppression. Induced pluripotent stem cells (iPSCs) can be generated from affected PD patients or HLA-matched individuals and differentiated to midbrain dopaminergic cells, providing opportunities for low-rejection risk or autologous transplantations. We have recently shown that dopaminergic neurons derived from iPSCs from an MPTP-lesioned cynomolgus monkey survived two years after autologous transplantation, re-innervated the host putamen and provided improved motor function (Hallett et al. Cell Stem Cell. 2015 Mar 5;16(3):269-74). We did not observe any graft-derived proliferating cells two years after transplantation, which is encouraging from a clinical standpoint. We are now in pre-clinical experiments improving our cell differentiation and transplantation paradigms in order to outline requirements and conditions for potential clinical trials. Using a xeno-free differentiation protocol (modified from Cooper et al., 2010, Mol Cell Neurosci;45(3):258-66) and feeder-free and foot-print-free human iPSC lines derived using episomal reprogramming technology, we are defining positive and negative cell-marker expression criteria of cell-preparations and cell-sorting requirements. We are also determining cell freezing and thawing strategies and pre-transplantation cell-viability criteria. For safety purposes we are preparing for scale-up and cell-dosing studies. Functional recovery and graft survival is studied in xeno-grafted rodents. These data and experiments are IND enabling efforts to establish future clinical trials.

Topic areas:
Non-suicidal self-injury (NSSI) involves direct, deliberate destruction of body tissue in the absence of suicidal intent (Favazza, 2011). The implicit identification hypothesis describes NSSI as a behavior that is maintained through identification with NSSI as an effective means of serving particular functions (e.g., affect regulation; Nock, 2009). Despite the growing literature on NSSI prevalence and relations between NSSI, psychiatric distress, and suicidality (Klonsky et al., 2013; Washburn et al., 2012), relatively little is known about the role and impact of NSSI identity on NSSI behavior. The current study uses a multimethod approach to examine implicit identification with NSSI in an adult psychiatric sample attending a partial hospitalization program. Sixty-eight adults (54% female) with acute psychiatric concerns completed a multimethod battery of self-report measures to assess for lifetime history of NSSI and current mood, as well as the Self-Injury Implicit Association Task (SI-IAT; Nock & Banaji, 2007). The SI-IAT measures how quickly and accurately participants respond to various pairings of words and images related to NSSI and identity. Rates of NSSI were similar to those reported in previous psychiatric samples (Andover & Gibb, 2010); 34 (50%) participants endorsed a lifetime history of NSSI with an average of 1.49 methods. Picking (n = 19) was the most common method of NSSI endorsed, followed by banging (n = 18), and cutting (n = 17). Participants reported first episode of NSSI occurring between the ages of 5 and 30 (M = 15.09, SD = 5.16). The majority of participants who endorsed NSSI had engaged in self-injury within the past 30 days (n = 10). Seven participants had engaged in self-injury more than 1 year ago, 6 within the past week, 5 within the past 6 months, 5 within the last year, and 1 on the day of the assessment. At Time 1, significant differences on SI-IAT performance were observed based on NSSI status, t (64) = -3.53, p = .001. However, no significant differences were observed among participants with a history of NSSI on the SI-IAT between Time 1 and Time 2, t (29) = -.98, p = .34. Alternatively, significant differences emerged for participants with no NSSI history between Time 1 and Time 2, t (27) = -2.22, p = .04. The lack of significant difference observed for the NSSI group between Time 1 and Time 2 SI-IAT performance suggests that identification with NSSI is a relatively stable construct within the target group. Conversely, results for the no-NSSI group revealed significant differences in SI-IAT performance between Time 1 and Time 2, which suggests that the SI-IAT successfully differentiates between groups. SI-IAT scores were not significantly correlated with self-reported depression or anxiety for either group, suggesting that the impact of changes in mood on SI-IAT needs to be explored further. These results suggest that the SI-IAT – Identity Version is a valid measure of implicit NSSI identity among the target group.

**Topic areas:**

- Anxiety
- Borderline Personality Disorder
- Depression
Presenting Author: Kevin Norman, Technical Research Assistant II, McLean Hospital/ Lab of Developmental Neuropharmacology

Co-Authors: Jodi Lukkes, Britta Thompson, Sue Andersen

Title: Sex-dependent effects of juvenile methylphenidate and guanfacine on impulsive choice and cocaine self-administration

Key words: addiction development juvenile cocaine methylphenidate

Methylphenidate (MPH; a dopamine transporter inhibitor) and guanfacine (GUAN; an α2a noradrenergic receptor agonist) treatments effectively increase attentiveness and decrease impulsivity in clinical populations of adolescent ADHD. However, their long-term effects on different aspects of drug addiction, such as motivation to use drugs or sensitivity shifts, have not been thoroughly characterized. The current studies investigate the effect of juvenile to adolescent exposure to MPH or GUAN on concurrent impulsivity and later cocaine self-administration in adulthood. Male and female Sprague-Dawley rats were given MPH (2 mg/kg, p.o.) or GUAN (0.2mg/kg, i.p.) daily beginning on postnatal day (P) 22 and throughout the juvenile period. Twenty minutes following treatment, rats were placed into an operant conditioning chamber and impulsive choice was assessed using a delay discounting task (DDT; 0, 10, 20, 40, and 60 sec delay) with food reward. Beginning in adulthood (P90), rats were implanted with a jugular catheter and began cocaine self-administration on a fixed-ratio (FR1 and 5, 0.5 mg/kg) and a progressive ratio (PR, 0.25 mg/kg and 0.75 mg/kg) schedule, followed by an FR5 dose-response (0, 0.03, 0.1, 0.3, and 1 mg/kg) assessment. During DDT, MPH increased the number of large food rewards received at the 20 and 40 sec delay in males, suggesting decreased impulsivity, while both MPH and GUAN increased the number of large rewards received at the 20 sec delay in females. In adulthood, MPH and GUAN decreased cocaine intake in males, but had no effect in females. PR breakpoint was reduced by MPH and GUAN in males, but only MPH was effective in females. A downward shift in FR5 responding at 0.03mg/kg in MPH and GUAN treated male and female rats indicates decreased sensitivity to cocaine. These findings suggest that sex-dependent neural adaptations following dopaminergic and noradrenergic activation during development reduce impulsive choice and later sensitivity to and suppression of cocaine intake during adulthood.

Topic areas:
Addiction
Child
Pharmacology
Mef2c regulates cortical synaptic balance and behaviors relevant to intellectual and developmental disorders.

Key words: Mef2  Autism  mouse behavior  synapse

Autism and its common associated symptoms are thought to result from an imbalance of excitatory and inhibitory synapse function in the developing brain. Over the last decade, the Mef2 transcription factors have emerged as critical, activity-dependent regulators of excitatory synapse density and function. The MEF2C gene is highly expressed in neurons of the developing and mature cerebral cortex, and deletions or mutations in MEF2C are associated with autism and intellectual disability (ID) in humans. However, its role in cortical neuronal development remains unclear. We show here that conditional, embryonic deletion of mouse Mef2c in cortical excitatory neurons (Mef2c cKO) produces behavioral phenotypes reminiscent of autism, including deficits in communication and social interaction and increases in repetitive behaviors and motor activity, as well as severe deficits in learning and memory – a hallmark of intellectual disability (ID) in humans. Correlated with these behaviors, we observed a dramatic reduction in cortical network activity in Mef2c cKO mice – due in part to an increase in GABAergic inhibitory synapse density and a decrease in glutamatergic synapse density. Consistent with the observed E/I synapse imbalance, we observed in Mef2c cKO cortex significant dysregulation of numerous synapse- and autism-linked genes, including many RNA targets of the Fragile X Mental Retardation protein. Together, our findings reveal a novel role for Mef2c as a critical developmental regulator of both GABAergic and glutamatergic synaptic transmission, and suggest that an origin of cortical pathology can produce, at least in some cases, autistic- and ID-like behaviors in mice.
Presenting Author: Thomas Idiculla, PhD, Director & Instructor in Psychiatry, McLean, Mental Health Services Evaluation Department

Co-Authors: Austin Lee, PhD  Sarah Salcone, BA  Jason Berkowitz, BS

Title: Behavior and Symptom Identification Scale (BASIS-24): Developing Clinical Cut Scores and Effective Change for Psychiatric Patients

Key words: BASIS-24  clinical cut-scores  benchmarking  patient outcomes  evidence-based

BASIS-24 is a widely used behavioral health assessment tool. It is a twenty-four item patient self-report questionnaire designed to assess treatment outcomes by measuring symptoms and functional difficulties experienced by individuals seeking mental health services. Currently, BASIS-24 is used in over 280 hospitals and in six countries. However, clinical cut scores for BASIS-24 have not been available. This project provides clinicians with empirically-derived cutoff scores for determining how a client or patient’s BASIS-24 scores compare with various levels of care such as inpatient and outpatient. The clinical data were taken from McLean Hospital, as a part of a field test study consisting of 2,656 inpatients and 3,222 outpatients that completed BASIS-24 at admission. Among them, 1,398 inpatients and 850 outpatients had both admission and discharge completed. The normative community sample consisted of 998 cases, representative of US population. Two-step logistic regression models were employed to obtain cutoff off scores and thus classification tables for each of the subscales and the overall score: Model#1: Discriminating between low and moderate risks, we defined p = Prob[having moderate risk] vs 1 – p = Prob[having low risk]; Model#2: Discriminating between moderate and high risk. We defined p = Prob[having high risk] vs 1 – p = Prob[having moderate risk]. These models were adjusted for age, gender, race, marital status, education, and employment status. The BASIS-24 clinical cut scores were produced from logistic regression models to classify patients into low, moderate, and high risk groups. The validity of the clinical cut scores were demonstrated by the % distribution of risk groups for normative, outpatient, and inpatient samples at admission; and also at admission and discharge. The analysis also showed good to excellent predictability for the classification: (1) Sensitivity, specificity, and hit rate for all subscales and overall score indicated excellent predictability; (2) Area under the ROC was 0.88 for classification between moderate and low risk groups; and 0.71 between high and moderate risk groups. Patients with both admission and discharge scores showed clinical improvements. Furthermore, inpatients improved more significantly than the outpatient sample. These cut scores provide empirical evidence for clinicians to match patients to the appropriate level of care and also for screening purposes in the community setting. The results of this study will facilitate comparison of an individual’s mental health status to an appropriate norm group as a clinical tool for longitudinal tracking of change and for evaluating clinical meaningfulness of change. It also can be used at the aggregate level for longitudinal tracking of change and for evaluating patient outcomes.

Topic areas:
Title: Reward learning across the mood disorder spectrum

Key words: Reward learning  EEG/ERP  depression  bipolar disorder  anhedonia

Background: The current DSM diagnostic framework relies entirely on descriptions of outwardly observable signs and symptoms. Due to its reliance on purely categorical criteria, this system may fail to capture important differences in the neurobiology underlying psychiatric symptoms that occur within the same diagnostic category. As a result, DSM disorder categories tend to be poor indicators of treatment response, and it is unclear whether distinct DSM disorders have a distinct biological basis. This problem is especially pronounced in unipolar major depression and bipolar disorder, as these disorders have considerable overlap in their symptom profiles. This need for an alternative mental illness classification that better matches underlying neurobiology prompted NIMH’s RDoC initiative, which advocates a transdiagnostic research approach to investigate the underlying neural circuitry associated with specific symptom dimensions. The current study draws on this initiative, focusing on the construct of ‘Reward Learning’ within the RDoC Positive Valence Systems matrix. Previous research has shown that deficits in reward learning exist across both unipolar depression and bipolar disorder. These deficits have been specifically linked to anhedonia – a core feature of depression characterized by reduced reactivity to pleasurable stimuli. Individuals reporting high levels of anhedonia typically show blunted anticipation and response to rewards. The aim of this study was to determine whether behavioral and neural responses to reward were associated with anhedonic and depressive symptom severity across the mood disorder spectrum.

Methods: Twenty-four treatment-seeking individuals with primary mood symptoms (6 with a history of hypomania) and 12 healthy controls completed a Probabilistic Reward Task (PRT) while 128-channel event-related potentials (ERP) were collected. The PRT measures an individual’s tendency to modify behavior as a function of prior reinforcement, and has been validated as an objective measure of reward learning. Analyses focused on the feedback-related positivity (FRP), which is an ERP component generated by positive prediction errors and believed to be indicative of sensitivity to reward.

Results: Interim analyses revealed no differences in behavioral or neural responses to rewards between the control and patient groups. However in the patient group, higher levels of depression symptom severity were associated with a poorer ability to modulate behavior as a function of reward history (r = -.41, p = .049). Across the entire sample, increased reward learning (r = .34, p = .04) as well as higher scores on a self-report measure of anticipatory pleasure (r = .37, p = .03), were associated with greater FRP amplitude. Furthermore, within the patient group, greater severity of anhedonic symptoms were associated with blunted FRP following reward feedback (r = -.43, p = .04).

Conclusions: These preliminary results indicate that within a group of individuals seeking treatment for mood-related symptoms, more severe depression was associated with reduced behavioral reward learning, and greater levels of anhedonia were related to blunted neural responses to receipt of reward feedback. These findings suggest that anhedonia in mood disorders may relate specifically to abnormalities in reward processing at both behavioral and neural levels.
Severity of Substance Use, Functioning, and Overall Health in Individuals with Co-Occurring Substance Use and Personality Disorders in the Stage II Women’s Recovery Group (WRG) trial

The prevalence of co-occurring personality disorders (PDs) in individuals with substance use disorders (SUDs) varies with estimates ranging from 7-45%. Individuals with co-occurring PDs and SUDs often present with more severe SUDs and higher levels of depression. In light of this, we were interested in examining differences in physical and mental health status and functional status, among SUD participants with and without a co-occurring PD. This is a secondary analysis from a Stage II randomized clinical trial assessing treatment effectiveness of the single-gender Women’s Recovery Group (WRG) compared to mixed-gender Group Drug Counseling (GDC). Eligible participants (n=158) were over the age of 18, had alcohol or substance dependence, and had used drugs or alcohol in the 60 days prior; 15% (n=24) were diagnosed with a co-occurring PD. We hypothesized that participants diagnosed with a PD would present with more severe SUDs, higher rates of other mental illnesses, and worse overall functioning and general health, compared to those without a PD (NPD). The majority of participants in this sample were female (63%), white (94%), not married (62%), and on average, 47 years old (SD=12.2).

Results showed that, among those diagnosed with a PD, most had only one PD diagnosis (83%; range=1-4) and Avoidance PD (66%) was the most common. Participants with a PD had better baseline alcohol ASI scores (.35 vs .55; t=3.17, df=156, p<.01) and fewer heavy drinking days than NPD participants (8 vs. 13; t=2.01, df= 156, p<.05); no differences were observed for the number of days of any drug use or days of primary substance use. Significant differences were observed for the number of current and lifetime psychiatric disorders (excluding PD diagnoses), with PD participants having a higher number of current (5 vs 3; t=-3.67, df=156, p<.001) and lifetime (6 vs. 4; t=-2.08, df=156, p<.05) diagnoses. Additionally, PD participants had worse scores at baseline on the Beck Depression Inventory (21 vs. 13; t=-4.09, df=156, p<.01), the Global Assessment of Functioning (57 vs. 61; t=3.23, df=156, p=.001), and the Short Form Health Survey (65 vs. 72; t=2.048, df=156, p<.05). At 6-months post-treatment PD participants still had significantly worse scores on these 3 measures compared to NPD participants. Despite having less severe SUDs, PD participants had worse scores on overall functioning, physical health, and depressive symptoms at baseline and also at 6-months post-treatment. Further understanding of the relationship between the co-occurrence of PD and overall physical and mental health and functioning is important for targeting effective treatment in this population.

Topic areas:
- Addiction
- Women
Olfactory sensory neurons (OSNs) of the Main Olfactory Epithelium (MOE) provide a rich model to study the perception of external cues and the underlying mechanisms regulating structural plasticity within the olfactory system. Using the M71-LacZ mouse line (OSNs expressing the M71 odorant receptor can be visualized by LacZ immunohistochemistry (Vassali et al., 2002)), we have demonstrated an increased number of M71+ OSNs in the olfactory epithelium following cue-specific olfactory fear conditioning to acetophenone (Jones et al., 2008), an odorant shown to specifically activate the M71 receptor. Furthermore, this increase in M71+ OSNs was directly correlated with an increase in the M71+ glomerular cross-sectional area and volume within the olfactory bulbs. Notably, when animals receive the same odor-shock pairing to another odorant that does not activate M71, there are no detectable changes in the M71 neuron population or glomeruli. Functionally, mice exhibit enhanced freezing to the conditioned odor stimulus following olfactory fear conditioning. These previously published data indicate that the olfactory nervous system responds both structurally and functionally to olfactory fear, however, it is unknown whether previously acquired responses to the conditioned cue can be reversed by cue-specific fear extinction. We sought to determine whether the behavioral (increased freezing) and structural (increased number of M71+ OSNs and M71+ glomerular area) changes observed after olfactory fear conditioning may be reversed with extinction training. Additionally, using native chromatin immunoprecipitation (N-ChIP) protocols on the MOE, we investigate the dynamic alterations in permissive and repressive histone marks around the M71 gene locus following both olfactory fear acquisition and extinction. Male mice were trained to associate mild footshocks with acetophenone using a session consisting of 5 odor-shock pairings (1 session/day for 3 days). 3 weeks after the last conditioning session, animals were handled only or exposed to an extinction session that involved the presentation of 30 acetophenone-only presentations (1 session/day for 3 days). 3 weeks after the last extinction session, animals were sacrificed. We demonstrate that extinction training specific to the conditioned odorant cue reverses the conditioning–associated increases in freezing and M71-specific OSN number and glomerular area. Furthermore, we demonstrate a dynamic regulation of histone marks around the M71 locus associated with both cue-specific fear learning acquisition and extinction. Our observations shed light on how the olfactory sensory system responds dynamically to extinction learning after fear conditioning.

Topic areas:
PTSD
Program Description

Presenting Author: Linda Flaherty

Co-Authors:

Title: Promoting Recovery Oriented Practice: Partnering with our Patient/Family Advisory Council

Key words: Recovery oriented practice  Patient/Family Advisory Council  Patient/Family Engagement

This poster will describe the process of engaging our Patient and Family Advisors in the roll-out of Recovery Oriented Practice (ROP) in an acute care psychiatric hospital. The Substance Abuse Mental Health Services Administration (SAMHSA) funded the Recovery to Practice project in 2009. A major component of the program was to support the development and dissemination of recovery oriented training materials for mental health professionals. The national behavioral health provider associations were funded to develop educational material to train psychiatric nurses, social workers, psychologists, psychiatrists and peer specialists. The content was released in 2014. In 2010, the hospital initiated the Patient/Family Advisory Council (PFAC). Objectives of the group are to communicate the perspectives of patients and their families regarding the care experience and work in an advisory role to enhance the care experience. Using content from the Recovery to Practice (RTP) curriculum developed by the American Psychiatric Nurses Association, an on-line training module was developed for the clinical staff. Advisors from PFAC reviewed and endorsed the training module. Clinical staff were required to review the material. To reinforce learning, advisors participated in unit staff meetings by sharing their narratives of receiving care at the hospital. Over 130 staff participated in the meetings. To promote on-going dissemination of ROP, an interdisciplinary group has been formed. Membership includes PFAC advisors and peer specialists from Waverley Place. Recent topics have included using patient/family centered language and a review of shared decision making concepts.

Topic areas:
Severe or prolonged stress can trigger psychiatric illnesses including mood and anxiety disorders. Social withdrawal, defined as diminished interest or participation in social activities, is a core feature of these disorders. Preclinical studies have shown that exposure to an aversive stimulus (e.g., exposure to predator odor) can disrupt normal social interaction (SI) behaviors in rats, but the mechanisms of how stress disrupts SI is unknown. Pituitary adenylate cyclase-activating polypeptide (PACAP) is a highly conserved neuropeptide that has recently been identified as an important regulator of the effects of stress and is implicated in the pathophysiology of mood disorders. We recently demonstrated that PACAP administration produces increases in anxiety-related behavior and anhedonia (reduced ability to experience reward), and reductions in attention and social behavior. The present studies were designed to further investigate how PACAP (0, 0.25, 0.5, 1.0 µg, administered intracerebroventicularly [ICV]) affects social interaction behaviors. One week after ICV cannula implantation, rats were infused with PACAP and placed in a 60 x 60 x 40 cm Plexiglas chamber with a weight-matched partner rat 1 hr later. PACAP administration produced acute dose-dependent decreases in active SI (i.e. approach and reciprocal behaviors). PACAP treatment dysregulated SI behavior up to 1 week later, producing a phenotype opposite to that seen with acute treatment, suggesting “over-shoot” of recovery. Little is known about the mechanisms that underlie PACAP’s regulation of stress responses, but PACAP is known to activate adenylate cyclase and therefore may activate the transcription factor cAMP response element binding protein (CREB), which is known to induce neuroplasticity and regulate depressive and anxiety-like behaviors. Thus, we used western immunoblotting to assess PACAP-mediated CREB activation in the nucleus accumbens (NAc) shell, a brain region involved in encoding reward and aversion, and the central amygdala (CeA) and bed nucleus of the stria terminals (BNST), brain regions previously implicated in PACAP stress-related signaling. Surprisingly, we found that PACAP treatment significantly decreased pCREB expression in the NAc shell, with nominal increases in the CeA and no changes in the BNST. We further examined whether altering CREB levels using viral-mediated gene-transfer specifically within the NAc can mimic central PACAP effects in the SI test. Elevated CREB produced increases in active SI and decreases in anxiety-related behavior in the SI test compared to disruption of CREB function, consistent with our PACAP immunoblotting data. The role of stress-related NAc CREB-signaling is unclear; CREB overexpression produces depressive-like effects such as anhedonia and behavioral despair, but has also been shown to reverse anxiogenic effects of social isolation stress. This may be due to differential influences of CREB signaling depending on topographical organization, cell-type specificity, or the state of the animal. Lastly, we examined whether the effects of central PACAP can be recapitulated by restricted microinfusions in the NAc, CeA, and BNST. Preliminary data suggests that PACAP dysregulates social behaviors when directly infused into the NAc. A more comprehensive understanding of PACAP signaling in stress-related behaviors will elucidate how stress contributes to psychiatric illness, and facilitate the development of new medications for stress-related disorders.
Program Description

Division of Depression and Anxiety

Presenting Author: Paula Bolton, MS, ANP-BC, McLean Hospital Psychiatric Neurotherapeutics Program

Co-Authors:

Title: The Evolving Role for Nurses in Neuromodulation Services

Key words: ECT TMS Nurse Roles

The McLean Hospital Psychiatric Neurotherapeutics Program has expanded its services involving neuromodulation therapies (including ECT and TMS). The Treatment Team includes psychiatrists, anesthesiologists, certified nurse anesthetists, advanced practice psychiatric nurses, staff nurses, mental health specialists and administrative staff. Nurses play an important role at all levels of care and are especially skilled at assisting with transition issues (including inpatient to outpatient coordination, and acute to continuation/maintenance phase of treatment) and moving between services. As our services grow, the need for specialized nursing practice grows as well and nurses (both advanced practice and registered nurses) are uniquely positioned to assist patients transitioning to all levels of care within our program. A case study is presented along with a description of the various roles nurses play in our Program to provide safe, effective and excellent care for patients and families.

Topic areas:
Depression
Division of Depression and Anxiety

Presenting Author: Lauren Lebois, Research Fellow in Psychiatry, McLean Hospital/Harvard Medical School

Co-Authors: Lauren Lebois, Justin Baker, Lauren O’Connor, Jonathan Wolff, Richard Juelich, Nina Lewis-Schroeder, Matt Robinson, Megan Racine, Kelly Sagar, Staci Gruber, Kerry Ressler, Sherry Winternitz, & Milissa Kaufman

Title: Neurobiology of dissociative and non-dissociative responses to chronic childhood abuse and neglect

Key words: dissociation  PTSD  childhood trauma

Individuals exposed to chronic childhood abuse and neglect can develop a long-term tendency to experience perceptual and cognitive disruptions (i.e. dissociation) outside the original traumatic setting. Trauma-exposed individuals with this dissociation tendency may show changes to large-scale neural network architecture distinct from trauma-exposed individuals who do not dissociate. Alternatively, dissociation could reflect a more continuous, albeit severe, disturbance of a single neural system affected to varying degrees in different trauma-exposed individuals. Characterizing the unique and shared substrates of neural architecture changes in these varied presentations could therefore reveal the underlying neurobiology of dissociation, by accounting for more general responses to chronic trauma. We explored this idea in a cross-diagnostic cohort of women with histories of childhood abuse and neglect. Participants also carried Structured Clinical Interview for DSM-IV Dissociative Disorders verified diagnoses of dissociative identity disorder (projected N = 20) and/or Clinician-Administered PTSD Scale for DSM-5 verified post-traumatic stress disorder (PTSD), either with dissociation (projected N = 20) or without (projected N = 20). We probed large-scale network architecture changes in individuals with and without dissociation using 3T brain MRI, and a modified version of the Common Acquisition Protocol (Buckner et al.), including a T1-weighted high-resolution structural image (MultiEcho MPRAGE), resting-state fMRI, and task-based fMRI. In particular, we assessed integrity both within and between several large-scale intrinsic networks (e.g., Default), defined on the basis of a priori studies in healthy individuals (Yeo et al., 2011). In preliminary analyses, patients reporting dissociation showed reduced connectivity (p<0.01) within both the Ventral Attention Network (VAN) and Default Mode Network (DMN), with increased connectivity between these two networks (p<0.01), compared with matched control participants. These changes in VAN and DMN indicate that dissociation symptoms could arise from (or potentially lead to) increased cross-talk between brain systems subserving roles in behaviorally relevant external attention and self-referential processing, respectively. Our findings will help provide a basic neurobiological understanding of clinical heterogeneity in response to chronic trauma, and provide a network perspective on the neurobiology of dissociation.

Topic areas:
PTSD
Division of Alcohol and Drug Abuse

**Presenting Author:** Thomas Ledoux, Psy.D., Postdoctoral Fellow, Addiction Psychology, McLean Hospital/McLean Fernside

**Co-Authors:** Rachel Tester, PMHCNS, BC; Patricia Diaferio, LICSW; John Rodolico, PhD; R. Kathryn McHugh, PhD; Roger Weiss, MD; Hilary Connery, MD, PhD; & Brendon McCue, BA

**Title:** Trauma and Self-Medication: A psychotherapy group for first-responders with co-occurring psychiatric and substance-use disorders.

**Key words:** Self-medication  Emotional management  Avoidance  Emotional identification  Group cohesion

In 2014, McLean Hospital developed comprehensive mental health services designed to meet needs of law enforcement, active duty military, and emergency responders (LEADER). A recent addition to the LEADER program, Trauma and Self-Medication, is a psychotherapy group that aims to address the relationship between trauma (e.g. duty-related) and management of distressing thoughts and emotions through substance use. The Trauma and Self-Medication psychotherapy group aims to accomplish the following goals: (a) strengthen management and validation of emotions, (b) increase insight and awareness of self-medicating behaviors, and (c) increase capacity to share distress with others. These goals are accomplished through the following objectives: (a) emotional identification (b) discussion of salient thoughts and emotions amplified and avoided through substance use, and (c) reinforcement and validation of patients sharing their substance-related thoughts, emotions, and behaviors within a structured therapeutic setting. The poster will present the rationale for the group’s format, goals, objectives, and discussion topics reviewed during weekly sessions. Feedback from group members in addition to satisfaction data will also be presented.

**Topic areas:**
Addiction
Psychotic Disorders Division

Presenting Author: Eve Lewandowski, Director of Clinical Programming; Assistant Professor, McLean Hospital/Harvard Medical School

Co-Authors: Dost Ongur  Lesley A. Norris  Richard Juelich  Julie M. McCarthy  Justin T. Baker

Title: Cognitive Variability in Psychosis: Cluster Solution Replication and Association with Resting State Networks

Key words: schizophrenia bipolar disorder cognition cluster fMRI

Objective: Substantial cognitive variability exists across the psychoses, and a clear profile of cognitive strengths and weaknesses has not emerged. Cluster analysis permits data-driven grouping of individuals, in contrast to use of predetermined grouping criteria. Cognitive clusters may reveal stronger associations with biological variables; however, clusters solutions are dependent upon the measures used to generate them. We aimed to: a) replicate a cross-diagnostic cluster analysis using a different cognitive battery in a separate sample and b) examine associations between clusters and resting state networks using fMRI.

Participants and Methods: Subjects with psychosis (n=120) and healthy controls (n=31) were assessed using the MATRICS Battery, clinical measures, and fMRI resting state connectivity (RSFC) analysis. MATRICS data were analyzed using a K-means cluster approach and canonical discriminant function analysis. RSFC data were acquired using fMRI. Clusters were compared on diagnosis and measures of clinical symptoms, community functioning, and network connectivity.

Results. A four-cluster solution provided adequate fit, and – similar to our previous report – yielded a ‘neuropsychologically normal’ cluster, a globally and significantly impaired cluster, and two clusters of mixed cognitive profiles. Clusters differed on several clinical variables; diagnoses were distributed amongst all clusters, although not evenly. In terms of RSFC, Clusters 2, 3 and 4 showed network disconnectivity compared to the neuropsychologically-normal cluster (Cluster 1) and healthy controls, particularly in fronto-parietal control regions. All patient clusters, including Cluster 1, differed from healthy controls in default mode connectivity.

Conclusions. This replication in an independent sample using a different but related cognitive battery suggests that cognitive clusters identify meaningful groupings and are not simply a function of the measures used to derive them. Clusters were associated with RSFC in networks associated with relevant cognitive processes; regardless of cognitive profile, patient status was associated with abnormalities in default mode connectivity. Identification of groups of patients who share similar neurocognitive profiles may help pinpoint relevant clinical and neural abnormalities underlying these traits.

Topic areas:
Bipolar
Imaging
Psychotic Disorders
Schizophrenia
Program Description

Presenting Author: Nina Lewis-Schroeder, PhD, Clinical Psychologist/Instructor in Psychology, McLean Hospital/The Dissociative Disorders and Trauma Research Program

Co-Authors: Matthew A. Robinson, PhD  Diane Bedell, LICSW  Lauren Lebois, PhD  Stephanie Rickey, PhD  Milissa Kaufman, MD, PhD

Title: Development of an Outpatient Trauma Treatment Program: Meeting the Needs of LEADER (Law Enforcement, Active Duty, Emergency Responder) Men and Women Exposed to Traumatic Events

Key words: PTSD  Program development  Trauma treatment  Assessment  Outpatient treatment

First responders and active duty military personnel are regularly confronted with traumatic events, including potentially life-threatening situations, death, and grave injuries. Evidence indicates that prevalence rates of Post-traumatic Stress Disorder (PTSD) are significantly higher among firefighters (Corneil et al., 1999), active duty personnel and veterans (Schoenbaum et al, 2014), police officers exposed to critical incident stressors and personal threats (Carlier et al., 1997), and emergency medical technicians (EMT) (Berger et al., 2012) compared to the general population in the United States. McLean Hospital leadership faced numerous requests to provide consultation to the community for the treatment of PTSD and trauma spectrum disorders following the April 15, 2013 Boston Marathon bombings. Among those requesting support was the Boston Police Department Peer Support Unit. Under the leadership of Dr. Joseph Gold, the McLean Hospital Law Enforcement, Active Duty, Emergency Responder (LEADER) Adult Outpatient Trauma Track in the Adult Outpatient Clinic was developed in September 2014. The goal of this program is to provide trauma consultation services as well as individual and group outpatient trauma-focused treatment for men and women within the LEADER Program. Our objective is to provide support for comprehensive assessment as a critical step in the treatment of PTSD and other trauma spectrum disorders. We hypothesized that the majority of LEADER patients referred for trauma consultation through the Adult Outpatient Trauma Track would present with a history of multiple traumatic events, including childhood abuse and neglect, critical factors that influence decision-making about psychotherapeutic treatment modalities. We present data from 48 trauma consultations completed since September 2014 using data from the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013). Results show that 52 percent of LEADER patients do report significant histories of childhood abuse and neglect. We also provide a detailed overview of the trauma-consultation-referred LEADER patients clinical presentations since the inception of the Adult Outpatient Trauma Track in September 2014. These findings will assist clinicians providing trauma-focused treatment to first responders and active duty military personnel in understanding the importance of comprehensive assessment of PTSD prior to initiating treatment.

Topic areas:
Dissociative Disorders
PTSD
Title: Effects of maternal immunoactivation on neurotransmission in mPFC-amygdala circuits

Key words: Autism Spectrum Disorders (ASD) maternal immunoactivation (MIA) mPFC basolateral nucleus of amygdala (BLA) synapse

Both the medial prefrontal cortex (mPFC) and the amygdala were repeatedly implicated in etiology of autism-spectrum disorders (ASDs). Presently, there is significant evidence that autism is the neural network phenomenon, which may reflect dysregulation of functional interactions between certain regions of the brain, including the mPFC and the amygdala. The amygdala receives strong projections from the mPFC and contributes to regulation of social behaviors. As the deficit in social behaviors is one of the hallmarks of autism, it is possible that the functional connectivity between the mPFC and amygdala may be affected during the development of ASDs. We explored this possibility by assaying the effects of Poly I:C-triggered maternal immunoactivation (MIA), an animal model of ASD, on neurotransmission in projections from the mPFC to the basolateral nucleus of the amygdala (BLA) in the offspring of immunoactivated female mice. The BLA was targeted in the course of these recordings because it is most densely innervated by prefrontal fibers. Using optogenetic techniques, we found that MIA was associated with the increased synaptic strength in glutamatergic projections from the mPFC to neurons in the BLA without affecting functional expression of channelrhodopsin. Potentiation of synaptic responses was not accompanied by changes in the paired-pulse ratio, suggesting a postsynaptic expression mechanism. In contrast, the magnitude of GABAergic inhibitory postsynaptic responses resulting from activation of local circuit interneurons in the BLA by prefrontal fibers was diminished in the offspring of immunoactivated mice. Therefore, the balance between excitation and inhibition in mPFC-BLA projections was shifted toward a greater functional efficiency of excitation. The latter, resulting in the enhanced probability of neuronal firing in the BLA in response to incoming afferent signals arising from the mPFC, could potentially contribute to autistic-like behavioral modifications in the offspring of immunoactivated mice.

Topic areas:
Child
Psychotic Disorders
Division of Alcohol and Drug Abuse

Presenting Author: Austin Lin, Chief Resident, Harvard South Shore Psychiatry Residency Program

Co-Authors: Hilary Connery, MD, PhD John Rodolico, PhD Kathryn McHugh, PhD Rachel Tester, APRN Patricia Diaferio, LICSW Robert Drozek, LICSW

Title: Descriptive data of a male mental health residential treatment service for law enforcement, active duty military and emergency responders (LEADER) after one year

Key words: Addiction PTSD First responder Residential treatment

Mental health and substance use issues have been well-studied in the civilian and veteran populations. However, there has been a paucity of data for first responders, defined here as law enforcement (police and correction officers), firefighters, and emergency medical services personnel. These men and women experience repetitive exposure to traumatic events in their line of work duties, thereby increasing vulnerability to stress-related problems such as sleep disorders, mental illness, substance use disorders, and chronic medical illnesses. For instance, the prevalence of Posttraumatic Stress Disorder (PTSD) in firefighters and police officers are 22% and 13% respectively, compared to 1-8% in civilians.1,2 To help address this need, in May 2014 McLean Hospital developed a comprehensive men’s residential treatment program providing culturally sensitive psychiatric evaluation, medication management, skills development, housing milieu, integrated peer supports, and outpatient maintenance step-down options for first responders. Here we report descriptive data for patients entering the 6-bed men’s residential LEADER program between August 2014 and August 2015. Our objective is to identify patients’ clinical needs and risk factors, the prevalence of psychiatric and substance use disorders, and the quantity of patients amenable to medication-assisted treatment (MAT) for substance use disorders and continuing their care in the McLean outpatient LEADER program. Retrospective chart review data for 122 patients consecutively admitted was abstracted using a chart review template developed on the Research Electronic Data Capture (REDCap) website. Variables extracted include demographics, mode of referral, prior treatment, psychiatric and substance use diagnoses, psychosocial stressors, length of stay, discharge diagnoses, type of MAT, and receipt of aftercare. Data is currently being abstracted. Completion of data collection is anticipated by December 15, 2015. We hypothesize that patients in the LEADER residential program will demonstrate high prevalence of co-occurring PTSD and substance use disorders, and that receipt of MAT for alcohol use disorder will be more frequently accepted than receipt of MAT for opioid use disorder. These findings will assist in further optimizing the effectiveness of treatment engagement with LEADER populations in need of evidence-based therapies addressing stress-related disorders.

Topic areas:
Addiction
Pharmacology
PTSD
**Division of Depression and Anxiety**

**Presenting Author:** Isobel Green, Student Visitor, BA Candidate, Harvard University, Laboratory for Affective and Translational Neuroscience

**Co-Authors:** Elizabeth Parsons  Liliana Capitao  Poornima Kumar

**Title:** Impaired Social Reward Learning in Dysphoria

**Key words:** dysphoria  reward  learning

**Background:** Studies suggest that individuals with depressive symptomology show blunted neural responses to rewarding stimuli. However, few studies have investigated whether this altered activation reflects an impairment in hedonic capacity or merely an inability to learn stimuli-outcome associations. This study investigates reward learning utilizing socially relevant feedback in a sample of individuals with dysphoria (individuals with elevated depressive symptoms) compared to healthy controls.

**Methods:** The present study sample consisted of 42 (mean age: 25.12 ± 8.60; mean BDI: 0.90 ± 1.19) healthy controls and 28 individuals with dysphoria (BDI > 14; mean age: 24.83 ± 7.80; mean BDI: 16.70 ± 6.40). All participants completed a Social Reward Learning task, in which they were presented with two stimuli and had to learn which stimulus was associated, at any given moment, with a reward (cheers) or a punishment (boos). The associations of stimuli with feedback changed throughout the task and had to be learned through trial and error. Each individual completed three blocks of the task: a block in which they received rewards or neutral feedback (Reward Block), a block in which they received punishments or neutral feedback (Punishment Block), and a block in which they received both reward and punishment feedback (Mixed Block). Order of the Reward and Punishment blocks was counterbalanced.

**Results:** A 2x2x2 ANOVA with Group and Order as between-subjects factors and Valence (Reward Block / Punishment Block) as within-subjects variables on accuracy scores showed a significant main effect of Group (F(1, 59) = 4.12, p = .047). State Anxiety was entered into this ANOVA as a covariate due to a significant between-group difference (t(62) = -7.19, p < .001) in individuals with state anxiety scores recorded (38 controls, 26 dysphorics). Post-hoc independent t-tests within the whole cohort revealed the main effect of group to be driven by a significant difference in Reward Block Accuracy, with dysphorics significantly less accurate than controls (t(1,68) = 2.107, p = .039). No significant difference emerged between controls and dysphorics in Punishment Block Accuracy (t(1,68)=1.056, p = .295), and the between-groups effect of order was not significant (F(1, 59) = 2.114, p = .151).

**Conclusions:** The present study extends understanding of the differential reward processing exhibited by individuals with dysphoric symptoms and healthy controls. Specifically, it demonstrates that individuals with dysphoria are less proficient in learning reward-based stimulus-outcome associations than healthy controls, as evidenced by their decreased accuracy during the Social Reward Learning Task. The study demonstrates that this differential ability to learn from rewards, previously investigated in the context of monetary rewards, extends to social rewards as well. Notably, the present study suggests that this deficiency does not extend to punishment-based stimulus-outcome learning. As such, this study suggests that the neural processing of rewarding and punishing stimuli may be dissociable, and that individuals with dysphoria may have a specific impairment in the process governing reward-based, but not punishment-based, learning.

**Topic areas:**

Depression
Beliefs about mental illness affect how individuals suffering from psychological difficulties cope with their symptoms, by influencing their cognitions and their willingness to seek help (Segal et al., 2005). Past research examining such beliefs has generally focused on internalized stigma, including harmful stereotypes, prejudice, and discrimination individuals may direct against themselves because of their psychological difficulties (Corrigan, 2002). The present study sought to extend our understanding of beliefs about mental illness by developing and testing a measure of positive beliefs about mental illness (PBMI) in a sample of 395 adults (53.92% female, M age = 33.2 years, SD = 13.46) presenting for partial hospitalization for variety of acute psychiatric conditions. PBMI refer to possible advantages or positive qualities individuals may perceive in their mental illness, such as increased creativity, meaning, or strength (among others). Based on prior findings from the internalized stigma literature, we expected women and older individuals to have higher levels of PBMI than others. Based on clinical experience, we also expected individuals with a history of mania/hypomania to have higher levels of PBMI than others. Participants completed our new 6-item PBMI scale, the Internalized Stigma about Mental Illness scale (ISMI-10), the MINI diagnostic interview (Sheehan et al., 1998), the Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2002), the Generalized Anxiety Disorder Scale (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006), the Schwartz Outcome Scale (SOS; Blais et al., 1999), and the Behavior and Symptom Identification Scale (BASIS-24; Cameron et al., 2007) at the beginning and at the end of treatment. As expected, an exploratory factor analysis confirmed that PBMI and internalized stigma are different constructs (r = -.28), and that our PBMI scale was reliable (α = .91). Contrary to our hypotheses, age was negatively associated with PBMI (r = -.26, p < .001). In addition, women had lower levels of PBMI than men (F (1, 359) = 9.72, p = .002, Cohen’s d = .33), even when controlling for depressive symptoms. Consistent with our hypotheses, individuals with a history of mania/hypomania had higher levels of PBMI than others (F (1, 278) = 16.37, p < .001, Cohen’s d = .57). Baseline levels of PBMI predicted depression, well-being, depression/functioning, and self-harm (all p < .05). History of mania/hypomania also moderated the relationship between baseline PBMI and emotional lability only (p < .05). For individuals without a history of mania/hypomania, higher levels of PBMI predicted reduced emotional lability. For individuals with such a history, higher levels of PBMI predicted increased emotional lability. These results suggest that PBMI are a distinct set of beliefs that meaningfully relates to demographic and diagnostic characteristics, as well as clinical outcomes. Future research is needed to determine whether changes in PBMI predict changes in clinical outcomes, as well as whether interventions designed to address PBMI may affect outcomes.
Sleep dysfunction is highly prevalent among first responders. Poor sleep is particularly problematic for these individuals, who are chronically exposed to traumatic events, and who often work irregular hours. Sleep deprivation increases the likelihood of developing posttraumatic stress disorder (PTSD) after exposure to a traumatic event, and also appears to result in poorer treatment outcomes for those with PTSD. Moreover, poor sleep has significant impact on job safety, and risk for physical and psychological illness. However, relatively little is known about the impact of treatment for sleep on functioning in first responders. The aim of this poster is to report initial results on sleep disruption in first responders from the Law Enforcement Active Duty and Emergency Responder (LEADER) Program at McLean. The LEADER Men's Residential Program provides pharmacotherapy for sleep disruption and weekly group on sleep health, as well as the opportunity to stabilize the sleep schedule over the residential stay. Weekly groups focus on psychoeducation, sleep hygiene, and stimulus control, with a focus on topics specific to first responders (e.g., shift work). Patients presenting to the LEADER Men's Residential Program complete self-report measures of insomnia and fatigue, and record daily sleep diaries to complement objective measurement of sleep quality and duration (actigraphy watches). In this poster, we will report initial results from both self-report and actigraphy measures during the LEADER Program. In addition, we will discuss the association between sleep dysfunction and related presenting symptoms (e.g., substance use, depression). The importance of addressing sleep in LEADER populations and future directions for the program will be discussed.
McLean Research Day 2016

Original Research - Clinical

Division of Depression and Anxiety

Presenting Author: Analise McGreal, Clinical Research Assistant, B.S., Center for Depression, Anxiety, and Stress Research; McLean Hospital/ Harvard Medical School

Co-Authors: Rena Fukunaga, Elizabeth A. Olson, Jason T. Haberman, Scott L. Rauch, Isabelle M. Rosso

Title: Childhood trauma relates to resting state connectivity between the amygdala and hippocampus in trauma-exposed adults

Key words: Amygdala  Hippocampus  Resting state  Childhood trauma  PTSD

Background: Research on functional brain connectivity in PTSD has demonstrated decreased resting state connectivity between the amygdala and hippocampus. Early life trauma is a known risk factor for PTSD; however, the role it may play in altered brain network connectivity is relatively unknown. Therefore, the present study examined the association of childhood trauma with resting state connectivity in the amygdala-hippocampus in a sample of adults with trauma exposure and healthy controls.

Methods: Thirty-nine trauma-exposed adults with varying levels of posttraumatic stress symptoms and 26 healthy adults completed the Childhood Trauma Questionnaire (CTQ), and a resting state functional MRI at 3T. Trauma participants were interviewed using the Clinician Administered PTSD Scale (CAPS). Resting state analyses used the amygdala and hippocampus as regions of interest. Linear regressions and correlations examined CTQ and CAPS scores in relation to functional connectivity Z scores. All analyses were corrected for age and sex.

Results: In trauma-exposed participants, weaker connectivity between the left amygdala and left hippocampus was correlated with significantly higher CTQ scores ($r(38) = -.404, p = .012$), and significantly higher CAPS scores ($r(38) = -.369, p = .023$). When entered as simultaneous predictors in a multiple regression analysis, CTQ scores were significantly associated with resting state connectivity between the left amygdala and left hippocampus ($t = -2.43, p = .02$), but CAPS were not ($t = -1.98, p = .056$).

Conclusions: Altered resting state functional connectivity between the left amygdala and left hippocampus was related to the severity of childhood trauma in trauma-exposed adults. The relationship of childhood trauma with amygdala-hippocampus connectivity was significant even after accounting for correlation with PTSD symptom severity. These results motivate further study of early life stress as a risk factor that may contribute alongside illness characteristics to altered functional brain connectivity in traumatic stress disorders.

Topic areas:

Anxiety
Imaging
PTSD
McLean Research Day 2016

Original Research - Pre-Clinical

Poster # 66

Presenting Author: Patrick McGuinness, Research Assistant, Laboratory of Genetic Neuropharmacology

Co-Authors: Patrick S. McGuinness Rachel A. Foster Jing Liu Johanna Cobb Rebecca Benham Vautour Elif Engin Deborah L. Levy Uwe Rudolph

Title: A 9p24.1 copy number variant (CNV) associated with psychosis results in prepulse inhibition and latent inhibition deficits in mice

Key words: Psychosis Schizophrenia Bipolar disorder copy number variation genomic engineering

Copy number variations (CNVs) are widely recognized to contribute to both normal genomic variability and risk for human
diseases, including neurodevelopmental/neuropsychiatric disorders such as schizophrenia (SZ), autism spectrum disorders (ASD) and bipolar disorder (BD). Recent genome-wide studies of CNVs have enhanced our understanding of the genetic bases of those disorders. Strong and reproducible disease associations have been observed for the most recurrent rare CNVs, e.g.,
chromosomal regions 1q21.1, 15q11.2, 15q13.3, 16p11.2 and 22q11.2. Other CNVs are even more rare, making a connection to risk for neurodevelopmental disorders less straightforward. A duplication/triplication in the 9p24.1 chromosomal region has been identified in a family studied at McLean Hospital in which two members have diagnoses of schizoaffective disorder or bipolar disorder with psychotic features. In these patients, 13 genes in the 9p24.1 region are duplicated, while two genes, UHRF2 and GLDC, are triplicated. GLDC, which encodes the glycine decarboxylase enzyme, may be particularly relevant to the pathophysiology of this mutation. It degrades glycine, which is a co-agonist at the NMDA receptor. Increased copy numbers of this gene would be expected to result in lower glycine levels in the brain, contributing to NMDA receptor hypofunction, which has been strongly implicated in the pathophysiology of schizophrenia. To determine whether 9p24.1 copy number variations are sufficient to cause changes in behavioral domains relevant to disorders such as schizophrenia, we generated mice with duplications (3 copies), triplications (4 copies) and deletions (1 copy) of this chromosomal region using gene targeting and trans-allelic recombination. We assessed whether 9p24.1 copy number corresponds to the amount of Glde protein. Western blotting using hippocampal and liver samples indicates that copy number is linearly related to Glde protein level. The triplication mice express approximately twice as much Glde protein as wild type mice, and deletion mice express approximately half as much. Using behavioral testing, we observed that both deletion and triplication mice have a deficit in prepulse inhibition (PPI) of acoustic startle, whereas duplication mice are indistinguishable from wild type mice. Similarly, in a latent inhibition (LI) to conditioned freezing paradigm, both deletion mice and triplication mice have a deficit in LI, whereas the duplication mice are indistinguishable from wild type mice. All genotypes performed comparably in hippocampal-independent delay fear conditioning, but on hippocampal-dependent trace or contextual fear conditioning tasks, only triplication mice displayed more freezing than wild type mice, indicating a change in hippocampal function. In summary, our preliminary studies reveal that 9p24.1 copy number is correlated with the amount of Glde protein, and that deletion and triplication mice have PPI and LI deficits analogous to those described in schizophrenia. Although the behavioral phenotypes of the triplication mice might be explained by increased Glde protein (and likely activity), the mechanism causing the same deficits in the deletion mice is less obvious. The observation that these phenotypes are present in the triplication,
but not in the duplication mice, indicates that triplication of Glde is sufficient to induce these changes but duplication is not.

Topic areas:

Bipolar
Psychotic disorders
GABAergic dysfunction in schizophrenia (SZ) is associated with a marked decrease in the expression of GAD67 in interneurons found in the stratum oriens (SO) of sector CA3/2 of the hippocampus (HIPP). A microarray-based gene expression analysis of laser microdissected (LMD) human hippocampus has suggested that GABA neurons in the SO of CA3/2 may contain a network of differentially regulated genes that are involved in GAD67 regulation. Several of these genes may contribute to the highly significant decrease of GABAergic activity at the SO-CA3/2 locus in SZ. To validate the role of this network in GAD67 regulation, both in vitro and in vivo studies in which shRNAi and lentiviral vectors have been used to explore how changes in the expression of GAD67 may be influenced by two other genes, HDAC1 and DAXX, that have been specifically implicated in the proposed network could potentially influence the expression of GAD67. Toward this end, knockdowns of HDAC1 and DAXX expression were induced both in vitro (in HiB5 cells with a GABAergic phenotype) and in vivo (in GABA cells of the SO of CA3/2 following selective stereotaxic infusions of the vectors). Suppression of HDAC1 and DAXX expression was associated with a highly significant increase of GAD67 expression; however, neither gene was associated with changes in the expression of its respective co-repressor (i.e. DAXX or HDAC1, respectively). Viral vector knockdowns of both HDAC1 and DAXX did, however, induce significant changes in the expression of other putative GAD67 regulatory genes, such as Runx2 and PAX5. Taken together, these findings suggest that both HDAC1 and DAXX are components of a complex network of genes identified in GABAergic neurons at a key locus of the trisynaptic pathway where significant abnormalities have been observed in patients with SZ. HDAC1 and DAXX are known co-repressors of methylation reactions at CpG islands and may be contributing to transcriptional regulation of GAD67 expression. In summary, these experiments have provided validatory information suggesting that there is a complex network of interactive genes that play a complex role in both normal and abnormal GABA cell function in the hippocampus.

Topic areas:
Bipolar
Pharmacology
Schizophrenia
Men are more likely to use alcohol and other drugs in their lifetime and have higher rates of alcohol and substance use disorders (SUDs) compared to women. Group therapy is the most common form of treatment for SUDs and is most often delivered in a mixed-gender format. Gender-specific group therapy for SUDs has primarily focused on women. However, there is evidence that men with SUDs may benefit from gender-specific group therapy as well. Research shows that there are important gender-specific topics specifically related to relapse and recovery for men. Group therapy for men with SUDs has been developed for specific sub-groups, but not for a general population of men. The aim of this study is to develop a gender-specific, manual-based, group therapy for men with SUDs. The first phase of the study was to inform manual development by conducting focus groups. All focus groups were transcribed and coded for themes. Seventeen men (> 18 years of age who had used substances within the past 60 days) were recruited from outpatient (n=12; 71%) and inpatient (n=5; 29%) treatment. Men ranged in age from 20-40 years old (M=35 years, SD=9.4). The majority of men were never married (53%), primarily White (88%), and generally well educated (59% attending some college; 12% graduating college). Eight men (47%) identified alcohol as their primary substance, 8 men (47%) identified other drugs as their primary substance, and one man (6%) indicated that both drugs and alcohol were equally problematic. On average in the past 30 days, participants drank alcohol 8.8 days (SD=9.3), drank alcohol to intoxication 7.7 days (SD=9.1), and had 9.9 heavy drinking days (SD=9.3). The most common substances other than alcohol that participants reported using were sedatives, prescription opioids, cocaine, and street opioids. Only four participants (24%) had ever been in an all-male group therapy. With regard to preference for gender-composition of groups, 41% preferred all-male groups, 24% preferred mixed-gender groups, and 18% felt that they could benefit from engaging in both all-male and mixed-gender group therapy. Of the men who preferred all-male groups, reasons included that they feel more comfortable with men, feel that they can be more open and honest with men, and that there are gender-specific issues that are important to recovery that can best be discussed in an all-male group. The men also described how societal expectations of men, financial pressures, and family obligations affect their recovery. When asked what topics the men would include in an all-male recovery group, the men listed: relationships, sexual behaviors, financial stress, employment issues, feelings of shame and guilt, and parenting. These results support the need for a gender-specific, group therapy for men with SUDs. These data will inform manual development of a 12 session, CBT-based, gender-specific group for men with SUDs. Although, previous studies demonstrate that gender-specific interventions in certain sub-groups of male patients with SUDs can be effective, this will be the first study of a manual-based, gender-specific group therapy for a heterogeneous group of men with SUDs such as those who typically present for treatment at community-based substance abuse treatment programs.

**Topic areas:**
Addiction
Comorbidity and functioning of substance dependent women with sexual abuse history in the Stage II Women's Recovery Group therapy trial

The Women's Recovery Group (WRG) Study is a Stage 2, RCT comparing single-gender group therapy (WRG) to mixed-gender group therapy (Group Drug Counseling; GDC) for substance use disorders (SUD). Women were randomized to the WRG (n = 52) or Group Drug Counseling (GDC; n = 48), and men were assigned to GDC (n = 58). Characteristics of women with a history of sexual abuse were examined in these post-hoc analyses. Participants ≥18 years with SUDs were included if they used substances in past 60 days. Sexual abuse (SA) history was assessed using the Life Experiences Questionnaire; functioning with the Global Assessment of Functioning (GAF) scale; and the CIDI was used to determine psychiatric diagnoses. Of the 100 women in the trial, 39% reported a history of SA. Compared to women without a history of SA, those with a SA history had lower GAF scores (t=2.7, df=98, p<.01) and higher rates of major depressive disorder (85% vs. 64%; χ²(1)=5.05, p<.05), PTSD (39% vs. 13%; χ²(1)=8.63, p<.01), and panic disorder (26% vs. 8%; χ²(1)=5.68, p<.05). We divided women into 3 groups: (1) no history of SA, (2) SA either before OR after age 16, and (3) SA before AND after age 16. Women with abuse before and after had the lowest GAF scores (M=56, SD=4.7), followed by those with one type of abuse (M=59, SD=5.7); women with no history had the highest GAF scores (M=61, SD=5.3). Women assigned to the GDC group who had a history of SA rated the helpfulness of having men and women in the group as significantly lower than those without a history of SA (t=−2.4, df=40, p<.05); women in the WRG rated the helpfulness of the all-women group composition as high regardless of SA history. Women with SA history had lower functioning and greater psychiatric comorbidity. Single-gender SUD group composition was endorsed as helpful by those with and without SA history but may be especially important for those who have experienced sexual abuse.
In humans, exposure to severe stress in early life significantly contributes to the pathophysiology of psychiatric disorders in adulthood. While stressful and even traumatic events are common in childhood, only a minority of exposed individuals develop a disorder, which is presumably modulated by genetic predisposition through gene by environment interactions (GxE). Many studies have characterized the GxE of FKBP5 (FK506 binding protein 5) and childhood trauma on the risk for post-traumatic stress disorder (PTSD) and other phenotypes. We recently identified an epigenetic mechanism that induces long-lasting changes in FKBP5 DNA methylation, which contributes to the deregulation of the HPA axis and thus leads to an increased risk of developing PTSD (Klengel et al., Nat Neurosci., 2013). Although highly controversial, exposure to environmental factors may lead to the transmission of information to subsequent generations through the gametes. Thus, the ancestral environment may influence disease risk in non-exposed generations. The present study aimed to extend our findings to a non-human primate model of infant maltreatment in rhesus macaques using a cross fostering paradigm. We found strong effects of ancestral infant maltreatment on intergenerational FKBP5 DNA methylation that correlate with neurodevelopmental, behavioral and endocrine phenotypes. In summary, this study provides evidence for the influence of ancestral environment on the functional epigenetic imprint at the FKBP5 locus in rhesus monkeys.
Posttraumatic Stress Disorder as a Predictor of Opioid Use Disorder, Mood Symptom Severity, and Suicidality in Adolescents

Background: Adolescent opioid misuse and overdose is a significant public health concern in the United States. Opioid use is more common in adolescents having co-occurring psychiatric disorders, such as posttraumatic stress disorder (PTSD) and major depressive disorder (MDD). Here we investigate PTSD as a potential predictor for adolescent Opioid Use Disorders (OUDs) in an acute residential treatment setting. Methods: As a part of a clinical quality assurance initiative, patients voluntarily complete a structured clinical interview (MINI-KID) to establish DSM-V diagnoses and also complete multiple self-report assessments at admission and discharge to the McLean Hospital Acute Residential Treatment (ART) and Landing programs for adolescents with co-occurring disorders. We sampled 185 participants admitted between 2012 and 2015. Patients who met criteria for PTSD (PTSD+ : n=43, age=16.9) were compared to patients who met criteria for MDD but not PTSD (PTSD-/MDD+ : n=142, age=17.0). Both groups met criteria for multiple other psychiatric and substance use disorders; as is typical of this treatment-seeking population. Results: PTSD+ exhibited significantly higher rates of OUD than PTSD-/MDD+ (p<.05). While both groups met criteria for co-occurring mood disorders, PTSD+ scored significantly higher than PTSD-/MDD+ on the CES-D (Center for Epidemiologic Studies—Depression) scale and the DERS (Difficulties in Emotion Regulation Scale), p<.001. PTSD+ also exhibited more severe suicidality than PTSD-/MDD+ (p<.05), as quantified by the MINI-KID. Correspondingly, PTSD+ patients were significantly more likely to report a lifetime suicide attempt than PTSD-/MDD+ (p<.05). Conclusions: Adolescents with a current PTSD diagnosis demonstrate a greater likelihood of also meeting criteria for OUD, as well as increased mood symptom severity, and suicidality. This symptom cluster suggests that adolescents with a PTSD diagnosis are at higher risk of intentional or accidental overdose. Screening of adolescents with a PTSD diagnosis for opioid use is warranted, and may be an important prevention strategy for opioid overdose deaths.

Topic areas:
Addiction
Child
Depression
PTSD
Intracranial self-stimulation (ICSS) is a technique that can be used to examine the sensitivity of brain reward systems to a variety of manipulations. It has been previously established that treatments which produce anhedonia (reduced sensitivity to reward) and/or dysphoria (aversion) in humans increase thresholds for ICSS in mice, which suggests that the amount of stimulation that previously produced sustained responding is no longer effective as a result of the treatment. We recently reported that chronic social defeat stress (CSDS) causes progressive elevations in ICSS thresholds, suggesting that this stress can produce a key sign of depression (anhedonia) in mice. Due to the highly prevalent co-morbidity between depressive-like states and drug abuse, we used ICSS to assess if CSDS alters the rewarding impact of cocaine. In addition, we also examined sensitivity to the aversive effects of the kappa-opioid receptor agonist U50,488 (U50), which reportedly mimics key aspects of stress. Wild-type C57BL/6 mice underwent surgery to have a stimulating electrode implanted into the lateral hypothalamus (LH). These mice were then trained until their ICSS thresholds were stable for 5 consecutive days, which was defined as baseline (BL). The subjects then underwent a 10-day CSDS regimen, during which their ICSS thresholds were measured after the defeat session. In addition, following these threshold assessments, sensitivity to cocaine (5.0 mg/kg, IP) was evaluated before defeat, and on defeat days 1, 5, and 10. Following the end of the CSDS regimen, the mice were tested for an additional 10 days to determine if the elevations in ICSS thresholds would recover. On post-defeat day 11, the mice were treated with U50 (3 mg/kg, IP) to determine sensitivity to the aversive effects of the drug. We found that CSDS does not change general sensitivity to the threshold-altering effects of cocaine. However, whereas cocaine significantly lowered thresholds in the control mice, it only restored thresholds to normal levels in mice with CSDS-induced anhedonia. There were no group differences in sensitivity to the aversive-effects of U50. When considered together, these data support a “self-medication” hypothesis in humans, whereby an addictive drug is used to restore normal motivation.
Psychotic Disorders Division

Presenting Author: Nora Mueller, Clinical Research Assistant II, McLean Hospital, Schizophrenia and Bipolar Disorder Program

Co-Authors: Sonal Mallya, Kevin M. Spencer, Kathryn Eve Lewandowski, Lesley A. Norris, Deborah L. Levy, Bruce M. Cohen, Dost Öngür, Mei-Hua Hall

Title: Relationships Between Auditory Gamma Oscillations and Symptom Severity in Patients with Psychosis

Key words: Gamma Oscillations  Psychosis  Community Functioning  Mood

Introduction: Cortical oscillations are important for the transmission and integration of information among brain regions and across neural networks. Previous studies have reported auditory steady-state response (ASSR) deficits within the gamma frequency range (30-100 Hz) in patients with schizophrenia (SZ). However, little is known about ASSR gamma oscillations in other psychoses, especially psychotic bipolar disorder (BPD), or the relationship between ASSR gamma oscillations and clinical symptom severity. This study examined whether patients with psychotic BPD show ASSR deficits similar to those observed in SZ patients and whether impairments in ASSR gamma oscillations are associated with clinical variables and symptom severity.

Methods: EEG was recorded from 428 participants, including healthy controls (HC; n=156), patients with SZ (n=131) and BPD (n=141) during 3 minutes of 40-Hz binaural click trains (1-ms white noise clicks, 500-ms duration, 1100-ms stimulus onset asynchrony). ASSR phase locking factor (PLF) was analyzed with the Morlet wavelet transform. All participants completed a clinical assessment using the SCID, medication usage, clinical scales including the Multimodal Community Ability Scale (MCAS), the Snaith–Hamilton Pleasure Scale (SHPS), and the Mood and Anxiety Symptom Questionnaire (MASQ). Statistical Analyses: Linear regression analyses were used to compare ASSR responses between groups (HC, SZ, BPD). Age, gender, and education were included as covariates. Statistical significance was set to be p ≤ 0.017 (Bonferonni corrected for multiple measures). Associations between ASSR PLF, antipsychotic medication dose (in chlorpromazine (CPZ) equivalents & D2 Blockade) and clinical symptoms (MCAS, SHPS, and MASQ) were examined using Pearson partial correlations controlling for age, sex, and education.

Results: ASSR PLF was significantly reduced in both patient groups compared with controls (SZ: r=-0.06, p<0.001; BP: r=-0.07, p<0.001); no difference was found between the SZ and BPD groups (r=0.00 p = 0.82). Years of education (p=0.019) and age (p<0.001) were significantly associated with PLF. Controlling for age, sex, and education, PLF was significantly correlated with the MCAS total score (partial r=0.17, p=0.04). This relationship was particularly strong in the SZ group (partial r= 0.27, p=.02), and trending but non-significant for those in the BD group (partial r =0.12, p=0.27). Also, PLF was significantly associated with the MASQ total score (partial r=-0.14, p=0.009). Medication, age of onset, lifetime and current smoking status were not significantly associated with ASSR PLF.

Discussion: Gamma oscillation deficits are present in both SZ and psychotic BPD, suggesting that the neural circuitry abnormalities underlying the gamma ASSR deficit may be nonspecifically associated with psychosis. In addition, the strength of the gamma oscillations was significantly correlated with severity of depression/anxiety, such that more impaired the gamma oscillation was associated with higher the anxiety/depression scores , indicating that abnormal mood may be associated with an impaired ability for neurons to fire in synchrony. Furthermore, the significant positive relationship between the MCAS score and gamma oscillation suggests that basic integrated neural network activity is an important substrate for brain activities necessary for effective community functioning and that more persistent psychosis may exacerbate this dysfunction.

Topic areas: 
Bipolar  
Imaging  
Psychotic Disorders  
Schizophrenia
Presenting Author: Beth Murphy, Medical Director, CEC and Clinical Instructor,

Co-Authors: Wendy Currie

Title: Depression in First Responders at McLean: Clinical Characteristics

Key words: depression first responders LEADER comorbidity risk

To date, the LEADER (law-enforcement, active duty national guard, emergency responder) program at McLean has treated several hundred individuals in first-responder occupations. In order to further develop appropriate services, understanding the needs of this population is critical. As one are of potential need, we looked at characteristics of individuals presenting for treatment with depression. Many of the individuals presenting for treatment of depression have significant medical and psychiatric comorbidity. Specific comorbidities, some consistent with the general population and others group specific, may be associated with depression. Factors, such as age, marital status, childhood trauma may play either a protective or perilous role in mediating depression risk. In addition, a history of multiple concussions, the development of physical debility, administrative conflict, or work performance issues may add to the risk of depression. Multiple occupational groups (police officers, fire fighters, emergency medical technicians, national guard, and correctional officers) are represented within this program, and may represent distinct sub-populations in their characteristics and risk factors. Specific stressors and types of traumatic events have both commonalities and distinct differences in the occupations represented within the LEADER program. Where numbers permit an examination, this data will serve as pilot data for further examinations.

Topic areas:
Depression
Psychotic Disorders Division

Presenting Author: Emily Ness, Clinical Research Assistant II, B.A., Schizophrenia and Bipolar Disorder Research Program

Co-Authors: Emily Ness, Sonal Mallya, Kathryn Eve Lewandowski, Lesley A Norris, Deborah L. Levy, Bruce M. Cohen, Dost Öngür, Mei-Hua Hall

Title: Mismatch Negativity in Schizophrenia and Bipolar Disorder and its Association with Smoking and Clinical Variables

Key words: Schizophrenia  Bipolar Disorder  EEG  Mismatch Negativity  Smoking

Background: MMN is an auditory event-related potential (ERP) component that is passively evoked in response to unattended changes in background auditory stimulation. While chronic schizophrenia (SZ) patients exhibit robust MMN deficits, MMN reduction in bipolar disorder (BPD) is a less consistent finding. In SZ, there is evidence that MMN deficits are associated with impairment in neurocognitive processes, illness progression and poor psychosocial functioning. Studies also found that nicotine transiently normalizes MMN deficits in SZ. The current study aims to 1) compare MMN between patients with SZ and BPD and 2) to assess the relationship between MMN, smoking and clinical variables in patients.

Method: EEG was recorded from 159 participants, including healthy controls (HC; n=50), patients with SZ (n=73) and BPD (n=36). MMN was elicited by a duration auditory oddball task using four blocks of 400 binaural 80 dB stimuli (ISI: 0.3 sec) from two EEG recording devices (BioSemi N=102; Neuroscan N=59). Statistical Analyses: Linear regression analyses were used to compare MMN responses among groups (HC, SZ, BPD). Age, gender, EEG device were included as covariates. Statistical significance was set to p ≤ 0.017 (Bonferroni corrected for multiple measures). Associations between MMN, smoking status (current smoker, past smoker, non-smoker), antipsychotic medication dose (in chlorpromazine (CPZ) equivalents & D2 blockade potency) and clinical symptoms (MCAS, SHPS, and MASQ) were examined using Pearson partial correlations controlling for age, sex, and EEG device.

Results: Patients with SZ showed a significantly reduced MMN response at Fz (F (5,145) = 17.36, p = 0.011) compared with HC. Patients with BP exhibited a similar deficit, but only at a trend level (F(5,145) = 17.36, p = 0.038). Partial correlation analysis revealed a trend toward a significant association between lifetime cigarette smoking (past and current smoker) and increased MMN amplitudes in SZ (r = -.27, p = 0.041) but not in BPD. At the T8 site, reduced MMN was observed in both SZ (mean = -1.20, SD = 0.86; p = 0.06) and BPD (mean = -1.39, SD = 0.95; p = 0.07) at a trend level compared with controls (mean = -2.03, SD = 1.13). No group differences in MMN were found at the T7 site. No other associations between MMN amplitude and clinical variables were observed.

Discussion: Consistent with the literature, the present study found evidence of an impaired MMN response in SZ. The non-significant MMN deficits in BP patients may be reduced power secondary to the small sample size. In addition, patients with SZ who have smoked during their lifetime had significantly larger MMN responses compared to nonsmokers. This result is consistent with previous findings that nicotine normalizes MMN and supports the hypothesis that nicotine use may be an attempt to treat some underlying biological pathology. Contrary to previous findings suggesting greater MMN impairments in the left side, the current study found suggestive evidence for a more impaired response in the right temporal region in both SZ and BPD. Larger samples are being collected to confirm these results.

Topic areas:
Bipolar
Psychotic Disorders
Schizophrenia
INTRODUCTION: Schizophrenia (SZ) is a severe mental disorder with heritability estimated at ~80%. Genetic variants in contactin-associated protein-like 2 (CNTNAP2) (also known as Caspr2) have been reported in SZ and autism spectrum disorders. This gene is critically involved in normal neuronal synchronization and myelin production. Deletions in this gene would therefore be expected to impact white matter (WM) integrity. Compromised WM integrity in the corpus callosum (CC) has been implicated in SZ and may also be a heritable biomarker. In order to help characterize the genetic components of WM changes in SZ, we examined two carriers of a large heterozygous deletion in CNTNAP2 with discordant clinical phenotypes.

METHOD: Two subjects, a 59 year old female proband who met DSM-IV criteria for a diagnosis of schizo-affective disorder (depressed subtype) and her clinically unaffected 90 year old father, completed a neuroimaging protocol that included diffusion kurtosis imaging acquisition on the McLean Imaging Center Siemens 3T system. In addition, three unrelated non-psychiatric controls (mean age: 68.67±4.51 years; two females) completed the same imaging protocol. Induced pluripotent stem cell (iPSC) lines from skin biopsies of both carriers were generated and differentiated in vitro to oligodendrocytes.

RESULTS: Fractional anisotropy (FA) and the radial kurtosis (RK) were reduced, and radial diffusivity (RD) was increased, in the genu of the CC of the proband, consistent with substantial compromise of WM integrity and implicating a demyelinating process. The clinically unaffected father closely resembled elderly non-psychiatric controls in the genu of the CC. In the whole brain analysis, FA and RK were reduced, and the RD was increased, in the proband and the father compared with the controls, more substantially in the proband than in the father. Preliminary results from the in vitro differentiation suggest impairment of oligodendrocyte formation in the proband compared with the father.

DISCUSSION: These preliminary data suggest that WM integrity is compromised in the CC of the affected patient, possibly due to a demyelinating process that may be associated with SZ, but that may be independent of this specific mutation. These findings complement the molecular and cellular phenotypes of the hiPSC neural cells derived from these carriers and support the role of brain imaging in helping to potentially elucidate objectively measurable neuroanatomic phenoypotypic consequences of genetic variant susceptibility. Further analyses are underway to investigate other brain regions.

Topic areas:
Schizophrenia
Background: Chondroitin sulfate proteoglycans (CSPGs), one of the main components of the brain extracellular matrix, were found to be altered in the medial temporal lobe, prefrontal cortex and olfactory epithelium (OE) of people with schizophrenia (SZ). These molecules are robustly expressed in the olfactory system, where they regulate neuronal differentiation and axon guidance. Interestingly, odor identification deficits have been observed in patients with SZ and first-degree relatives. Together, these observations suggest that a disruption of CSPG expression in the olfactory system may contribute to the olfactory deficits observed in SZ. As a first step toward testing this hypothesis, we are investigating the pattern of CSPG expression in the olfactory mucosa (OM) and bulb (OB) of healthy individuals. More precisely, we are testing the hypothesis that distinct CSPGs surround olfactory axon bundles, forming channels that guide them through the OM to their odor-specific glomeruli within the OB.

Methods: Dual and triple antigen immunofluorescence was used on OM and OB sections from healthy human subjects to label the axons of olfactory receptor neurons (ORN), and investigate their relationship with CSPGs, as labeled with the lectin, wisteria floribunda agglutinin (WFA), or Aggrecan and 6- sulfated (CS56) CSPG-immunodetection.

Results: In the OM, CSPGs form complex, channel-like structures that tightly surround ORN axon bundles. Distinct channel-like structures were labeled by different CSPGs with no detectable overlap, suggesting CSPG-specific segregation of ORN axon bundles. In the OB, CSPG-labeling surrounds incoming axonal bundles along the superficial olfactory nerve layer in addition to their corresponding glomeruli. However, consistent with the pattern in the OM, distinct CSPGs showed preferential and non-overlapping distribution patterns, for instance, CS56-IR was found only superficially, exclusively surrounding ORN axon bundles but not the glomeruli, while WFA-IR showed opposing medial expression patterns.

Conclusion: Our results show that non-overlapping CSPGs form channel-like structures that surround ORN axon bundles. Although preliminary, our results suggest that, in the human olfactory system, distinct CSPGs guide these ORN axon bundles to their corresponding odor-specific glomeruli. If so, disruptions of CSPG expression in the olfactory system of patients with SZ may contribute to the pathophysiology underlying odor identification deficits observed in this disorder. These results provide useful insights into the role CSPGs play in regulating axon guidance during brain development.
Objective: The subjective value of monetary rewards declines with increasing delays. Accelerated delay discounting (DD) occurs in individuals with externalizing problems and impulse control disorders. There is growing interest in DD as a marker of altered decision-making in stress-related disorders, including posttraumatic stress disorder (PTSD). We hypothesized that steeper DD would be associated with greater symptom severity and reduced reward sensitivity (anhedonia) following trauma exposure, as well as with altered resting state functional connectivity of the nucleus accumbens (NAcc), a reward-sensitive region.

Methods: Participants were 22 adults who endorsed a DSM-IV PTSD Criterion A traumatic event. They completed the Clinician Administered PTSD Scale (CAPS), the Snaith-Hamilton Pleasure Scale (SHAPS), and a computerized DD task. Resting state functional connectivity from the nucleus accumbens seed to the rest of the brain was assessed in CONN, using a seed-to-voxel approach (peak threshold p < 0.05; FDR-corrected p < 0.05), controlling for age, sex, and total CAPS.

Results: Accelerated DD was associated with increased self-reported anhedonia on the SHAPS. Anhedonia and accelerated DD were positively but non-significantly associated with symptom severity on the CAPS. Accelerated DD was associated with increased resting state functional connectivity between the NAcc and multiple cortical regions, including bilateral temporal/insular cortex and posterior cingulate cortex.

Conclusions: These results contribute to an emerging body of evidence regarding alterations in the DD rate in stress-related disorders. Higher DD rates are associated with anhedonia following trauma exposure; we provide evidence that this is related to altered functioning of reward-related brain regions including the NAcc. These findings are discussed in terms of the potential for inclusion of DD as a candidate intermediate phenotype.

Topic areas:
PTSD
Impulsivity and abnormalities of the brain’s reward system have been associated with varying levels of alcohol misuse. The current study examined delay discounting, a marker of impulsive decision making, in relation to the volume of the nucleus accumbens (NAcc), a key region in brain reward circuitry, and aimed to identify differences between binge drinkers and light drinkers. Magnetic resonance imaging datasets were acquired at 3T in 18-24 year old binge alcohol drinkers (BD; n=18; 9 male) and light alcohol drinkers (LD; n=19; 9 male). Cortical reconstruction and volumetric segmentation were performed using Freesurfer. Participants completed a battery of neuropsychological measures that included the Monetary Choice Questionnaire (MCQ), which assesses reward valuation and delay discounting. BD were significantly more likely than LD to discount delays (prefer smaller but more immediate rewards) on large-reward trials. In addition, smaller right NAcc volume was strongly predictive of a higher impulsive choice ratio for small, medium and large rewards in the BD group, but not in the LD group. Although BD and LD showed no significant differences in NAcc volumes in either hemisphere, right NAcc volume was significantly predictive of MCQ responses in BD. The finding that this relationship is specific to the BD group suggests that the behavioral outcomes of binge drinkers depend more heavily on reward system morphology than the outcomes of their LD counterparts (possibly due to impaired functioning of other brain regions involved in regulatory control). Characterization of reward system morphology and behavioral outcomes associated with binge alcohol consumption may help identify unique risk factors for the later manifestation of alcohol abuse and dependence in young individuals who are heavy, frequent drinkers.

**Topic areas:**
Addiction
Imaging
Acute and chronic effects of cannabidiol on Δ9-tetrahydrocannabinol (Δ9-THC)-induced disruption in stop signal task performance

Key words: Δ9-Tetrahydrocannabinol (Δ9-THC) Cannabidiol (CBD) Cognition Chronic Drug Combinations

Recent clinical and preclinical research suggests that cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC) can have interactive effects on cognition; however, the nature of such interactions is not well characterized. To address this question, the effects of Δ9-THC and CBD were studied independently and in combination with therapeutically relevant dose combinations of 1:1 and 1:3 Δ9-THC:CBD in adult rhesus macaques (n=6) performing a stop signal task (SST). Additionally, the development of tolerance to the effects of THC on SST performance was evaluated by determining the effects of acutely administered Δ9-THC (0.1-3.2 mg/kg), during a 24-day chronic Δ9-THC treatment period with Δ9-THC alone or combined with CBD. Results indicate that, during acute treatment, Δ9-THC (0.032 - 0.32 mg/kg) dose-dependently decreased ‘go’ success but did not alter ‘go’ reaction time or stop signal reaction time (SSRT); CBD (0.1 - 1.0 mg/kg) was without effect on all measures and, when co-administered in a 1:1 or 1:3 dose-ratio, did not systematically alter the effects of Δ9-THC. Rightward shifts in ED50 values for the effects of Δ9-THC on SST performance were apparent during chronic Δ9-THC treatment, with little evidence for modification of changes in sensitivity by CBD. These results indicate that CBD, when combined with THC in clinically available dose ratios does not systematically alter THC’s behavioral effects, suggesting that CBD may not exacerbate unwanted effects of Δ9-THC in therapeutic preparations.

Topic areas:
Addiction
Pharmacology
Kappa opioid receptors (KORs) in the brain play an important role in mood regulation. Increasing evidence indicates that activation of KORs within stress- and reward-related neural circuits has mood-dampening effects whereas inhibition of KORs has antidepressant- and anxiolytic-like effects. Recently, our group identified 12-epi-salvinorin A (12-epi-salvA) as a selective KOR partial agonist with moderate potency in vitro. Because partial agonism enforces a chronic mid level of stimulation at a receptor, we hypothesize that a KOR partial agonist would have a stabilizing effect on mood: dampening euphoric or manic-like states and also reducing anhedonic or depressive-like states. To test this hypothesis, we examined how intracerebroventricular delivery of 12-epi-salvA affects both enhancement and suppression of brain stimulation reward in male and female Sprague Dawley rats using intracranial self-stimulation (ICSS), an operant behavior that measures reward function in real time. In one study, we measured effects of 12-epi-salvA on cocaine-induced facilitation of ICSS, a model of the pathologically increased reward function that characterizes mania and stimulant intoxication. In a second study, we measured the effects of 12-epi-salvA on KOR agonist (U50,488)-induced suppression of ICSS, a model of the pathologically decreased reward function that characterizes unipolar and bipolar depression. We found that 12-epi-salvA on its own did not affect brain stimulation reward. However, it attenuated cocaine-induced facilitation of ICSS in male, but not female, rats. Preliminary data indicate that 12-epi-salvA initially reduce U50,4880-induced suppression of ICSS. Taken together, these initial studies support evidence that 12-epi-salvA acts as a partial agonist at KORs. A KOR partial agonist might stabilize mood and, thereby, have a greater potential than either a full KOR agonist or antagonist for the treatment or prevention of specific symptoms of mood, anxiety or other stress-related disorders.
Division of Alcohol and Drug Abuse

Presenting Author: Alyssa Peechatka, Graduate Research Fellow, Functional Integration of Addiction Research Lab

Co-Authors: Nadeeka Dias, Ph.D. Amy Janes, Ph.D.

Title: Insula reactivity to negative stimuli is associated with daily cigarette use: a preliminary investigation using the Human Connectome Database.

Key words: Nicotine Insula Emotion Negative Affect Smoking

Individuals who smoke larger volume of cigarettes per day are at greater risk for developing smoking-related illness and have more difficulty quitting. Withdrawal-related negative mood is one factor thought to motivate drug use. However, heavy smokers are more sensitive to the experience of negative affect regardless of origin, not just negative emotion stemming from withdrawal. One possibility is that individual differences in how the brain processes negative affective stimuli may relate to smoking volume. Given the wealth of data implicating the insula in nicotine dependence and affective processing, we hypothesize that the number of cigarettes an individual smokes per day will relate to insula reactivity to negative stimuli. A functional magnetic resonance imaging (fMRI) emotional processing task collected by the Human Connectome Project was assessed in 21 daily tobacco smokers who reported smoking between 5-20 cigarettes per day. The number of cigarettes smoked per day was correlated with right and left anterior insula reactivity to faces expressing a negative emotion relative to a control. This anterior insula region of interest has been associated with treatment outcome and smoking cue-reactivity in our prior work. Individuals who smoked more daily cigarettes showed greater right insula reactivity to negative stimuli ($r = 0.564, p = 0.008$). Left insula reactivity was not associated with cigarettes smoked per day. Smokers who use more cigarettes per day have greater right insula reactivity to negative stimuli. As the role of the bilateral and left insula in nicotine use is more clearly defined, these results further the field’s understanding of the right insula’s involvement in nicotine use and suggest a mechanism contributing to higher rates of daily smoking. Furthermore, treatments focused on affective regulation may be particularly beneficial to heavier smokers.

Topic areas:
Addiction
Presenting Author: Angela Pisoni, Research Assistant, Child and Adolescent Mood Disorders Laboratory

Co-Authors: Poornima Kumar, Diego A. Pizzagalli, Randy P. Auerbach

Title: Adolescent Depression: Probing Neural Mechanisms Underlying Social Reward Processes

Key words: Adolescents  Depression  fMRI  Reward

Background: Adolescent major depressive disorder (MDD) is a major public health concern (Birmaher et al., 2002; Avenevoli et al., 2015), and presently, the neural mechanisms underlying adolescent MDD remain largely unknown. Previous research indicates that depressed adolescents may be characterized by blunted neural responsiveness to reward (Forbes et al., 2009). To date, the vast majority of research has examined currently depressed adolescents, however, such an approach is unable to determine whether reward dysfunction is a cause or effect of depression. Therefore, the present study tested whether reward-related deficits prospectively predict depression onset in never-depressed youth.

Method: The study included healthy, low-risk (LR) and high-risk (HR; owing to a maternal history of MDD) female adolescents aged 12-14 years. During the initial study visit, adolescents and parents completed a diagnostic interview and self-report measures assessing current symptom severity. At the second study visit, adolescents (LR = 37, HR = 14) completed an ecologically valid peer feedback task (i.e., peer acceptance versus rejection), the Chatroom Task, while functional magnetic resonance imaging (fMRI) data were collected. Then, participants completed 1-, 3-, and 6-month follow-up assessments of disorder onset and symptom severity. Baseline and follow-up data collection remains ongoing (Target: LR = 40, HR = 20).

Results: Preliminary analyses examined a subset of the fMRI data collected (LR = 23, HR = 7). At baseline, a Group (LR, HR) x Valence (Acceptance, Rejection) interaction emerged in the rostral anterior cingulate cortex (rACC; $x = 4$, $y = 36$, $z = 10$; cluster size = 264; $p < 0.05$ uncorrected). Parameter estimates were extracted to conduct post-hoc analyses. Relative to the HR group, the LR female adolescents exhibited increased activation in response to social acceptance, $t(28) = 2.65$, $p = .01$. Conversely, relative to the LR group, the HR adolescents showed increased activation to rejection at the trend level, $t(28) = 1.66$, $p = .11$). Across groups, after controlling for baseline anhedonia symptoms, lower rACC activation following peer acceptance was associated with higher levels of anhedonia at the 6-month follow-up, trend: $r = -.538$, $p = .058$).

Conclusion: These findings suggest potential differences in social reward valuation, which may have important implications for the onset of depressive and anhedonic symptoms. Results from the current study are expected to advance our understanding of neurobiological mechanisms that prospectively predict depressive disorders in youth.

Topic areas:
Child
Depression
Imaging
Sex differences in insula volume in cannabis dependence and association with emotion and cognition

Background: Behavioral and imaging studies have suggested sex differences in cannabis use disorders. Specifically, women with cannabis dependence (CD) have more mood disorders, and have shown larger amygdala volume, a brain region involved in emotion processing. In contrast, men with CD have more comorbidity of other psychiatric and substance use disorders, and have shown smaller volumes of prefrontal cortex, which is correlated with cognitive dysfunction. The Insula is one brain region that is engaged in both emotion and cognitive function, suggesting that we may see a sex difference in this region in CD that correlates with mood symptoms and emotion processing in women and cognitive function in men.

Methods: Insula volumes and clinical/behavioral measures of mood symptoms (depression and anxiety), emotion processing using the Penn Emotion Recognition Test (PERT) and cognitive processing using the Dimensional Change Card Sort (DCCS) for CD (12 females/12 males) and healthy controls (HC, 12 females/12 males) were drawn from the Human Connectome Project (HCP) data. The HCP data are a large comprehensive dataset collected in nearly 900 individuals to map the human brain connectome. These data are available to the public (http://humanconnectome.org). ANOVAs were conducted for the comparison of insula volumes and clinical/behavioral measures. Spearman correlations were used to test associations of insula volume with clinical/behavioral measures.

Results: Significant group (CD vs. HC) by sex interactions were found for right insula volumes (p=0.040) but not left insula volumes (p=0.500). Further analysis found that the group by sex interaction was driven by a sex effect (p=0.036), not by group effect (p=0.316). Females with CD had larger right insula volumes as compared with the other three subgroups, while there was no difference among the other three subgroups. Significant positive correlations of right insula volumes with depression (p=0.003) and anxiety (p=0.019) symptom scores were observed in all females together, but not in males. Right insula also showed a weakly significant negative correlation with identification of angry faces in the PERT in females with CD (p=0.087) but not in males with CD. In males with CD, there was a significant negative correlation with the DCCS score (p=0.017) that was not present in females with CD.

Conclusions: Our findings that sex-specific factors are associated with insula volume – with mood symptoms and emotion processing being related to insula volume in females and measures of cognitive processing being related to insula volume in males – shed insight into how cannabis dependence may affect emotion and cognitive processing. Further imaging studies including different modalities are needed to identify mechanisms of insula and insula related network dysregulation in men and women with CD.

Topic areas:
Addiction
Imaging
Women
Neurodevelopmental disorders such as Autism Spectrum Disorders (ASDs) affect millions of individuals worldwide, with a prevalence of 1 in 68 newborns. Emerging evidence has demonstrated that mechanisms which control the proper balance between excitatory and inhibitory synaptic signaling in the brain are critical for the establishment of neuronal circuitry during development. Consequently, deficits in either excitatory or inhibitory synapse development have been proposed to underlie ASD, Epilepsy, and other neurodevelopmental cognitive disabilities. We have previously demonstrated that the myocyte enhancer factor (MEF2) mediates activity dependent synapse elimination in the mammalian brain. Recently, mutations in the MEF2 family member MEF2C have been identified in patients who suffer from severe intellectual disability, Epilepsy, and ASD, implicating MEF2C as an important genetic link between MEF2 and neurodevelopmental disorders. To examine the role of MEF2C in synapse elimination and autism-related phenotypes, we generated a conditional knockout (cKO) of the MEF2C gene throughout excitatory neurons of the forebrain and performed RNAseq to identify changes in gene expression in the cortex of MEF2C cKO mice. We observed a 2.5-fold increase in the α5 subunit of the inhibitory synaptic GABAA receptor suggesting a shift in the balance of inhibitory signaling in MEF2C cKO mice. Acute slice recordings from somatosensory cortex demonstrate that MEF2C cKO mice display a reduction in both the duration and amplitude of cortical UP-states as well as an increase in mIPSC frequency and amplitude revealing an increase in inhibitory tone in MEF2C cKO mice. We also observed that cultured cortical neurons from MEF2C cKO mice display a 2-fold increase in GABAergic synapse density compared to WT littermates, demonstrating that MEF2C drives GABAergic synapse elimination in the mammalian cortex. Behaviorally, MEF2C cKO mice demonstrate a variety of significant autism-like phenotypes, including reduced social preference, deficits in social communication (ultrasonic vocalizations) as well as hyperactivity, all of which are analogous to behavioral deficits observed in patients with MEF2C haploinsufficiency syndrome. Ongoing studies will investigate the specific contribution of increased GABAA R α5 mediated inhibition in MEF2C cKO mice by exploring the effect of α5 inverse agonists on both behavioral and electrophysiological phenotypes resulting from MEF2C loss of function. Taken together, our data reveals a unique role for MEF2C in the regulation of GABAergic dependent inhibition and autistic-like behavioral phenotypes, and as such can serve to provide novel insight into the molecular mechanisms which underlie neurodevelopmental disorders such as ASD.
Division of Alcohol and Drug Abuse

Presenting Author: Curtis Rheingold, Technical Research Assistant, McLean Hospital, Preclinical Pharmacology Laboratory

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Title: Increases in Locomotor Activity during Spontaneous Cannabinoid Withdrawal in Mice

Key words: cannabinoid withdrawal  THC  AM2389  tolerance  locomotor activity

The consequences of repeated exposure to cannabinoids such as Δ9-tetrahydrocannabinol (THC) are poorly understood, in part because of a lack of strong evidence of cannabinoid withdrawal in laboratory subjects. We investigated the effects of daily cannabinoid injections, as well as cessation of the daily injection regimen, on a behavioral measure - locomotor activity - and a physiological measure - body temperature - in CD1 and C57BL/6 mice. Mice were implanted inter-abdominally with emitters that allowed constant monitoring of movement and core temperature via a telemetry system while animals remained in their individual home cages. Data were recorded every fifteen minutes over periods of 15-20 days, encompassing a 5-day baseline period, 5 days of drug exposure, and 5-10 days post-drug exposure. After establishing baseline values, mice were injected either once or twice daily for five days with saline or one of the following drugs: 0.03 - 0.1 mg/kg AM2389 (a full CB1 agonist), 10 - 30 mg/kg THC, or 10 mg/kg morphine. The first injection of either AM2389 or THC dose-dependently decreased body temperature from 1 - 10°C and also decreased locomotor activity to 10-65% of control levels of activity. These effects lasted up to 36 hours after injection. Tolerance to the hypothermic effects of cannabinoids was evident after the 2nd injection was administered whereas the drugs continued to suppress locomotor activity throughout the 5-day injection period. Cessation of the daily injections with AM2389 did not alter body temperature, but did result in increases in locomotor activity. Likewise, cessation of the THC injections had no effect on body temperature and, at best, produced only small increases in locomotor activity. Morphine induced mild hyperactivity during the five injection days but had no effects following the final injection. These data suggest that sub-chronic injections of either a cannabinoid full or partial agonist is sufficient to induce tolerance to its effects on temperature and locomotor activity. In contrast, spontaneous withdrawal appears only following exposure to a full agonist.

Topic areas:
Addiction
Pharmacology
Effects of voluntary nicotine self-administration on fear conditioning in rats

Nicotine can facilitate learning and cognitive performance while also relieving feelings of stress. These two actions may have opposing effects on vulnerability to stress-related illness such as post-traumatic stress disorder (PTSD). The present experiments examined the effect of nicotine self-administration (SA) on the development and expression of PTSD-like symptoms in rats using the fear-potentiated startle (FPS) paradigm. FPS has elements that model an index trauma and enables quantification of exaggerated startle response and extinction deficits, two characteristics observed in humans with PTSD. Long-Evans rats were allowed to self-administer nicotine (0.03 mg/inj) or saline in 12hr (overnight) extended access sessions in standard operant conditioning chambers for a minimum of 14 sessions. Criteria for nicotine dependence was determined by SA of >0.7 mg/session for 4 out of 5 sessions and observable signs of spontaneous withdrawal 11.5 hrs post SA session. After criteria were met, rats were fear conditioned at one of two time points: either immediately after or 11.5 hrs after their last SA session. Fear conditioning consisted of 10 pairings of a 4-sec light (conditioned stimulus; CS) co-terminating with a 0.5-sec 0.6 mA footshock. Two different patterns of post-training nicotine intake were examined: for some rats, nicotine exposure was discontinued between fear conditioning and testing, whereas for others nicotine SA continued. At 10-12 days after fear conditioning, rats were tested immediately after SA three times, each test 48 hrs apart. Two metrics were examined in each of the test sessions: Context-potentiated startle (CPS) and Fear-potentiated startle (FPS). %CPS was expressed as the percent change in startle after exposure to the conditioning context relative to a pre-training baseline. %FPS was expressed as the percent change in startle elicited in the presence of the light CS relative to trials without the CS. Rats that received fear conditioning immediately after SA sessions plus no further nicotine exposure showed reduced %CPS and normal %FPS, whereas those that continued nicotine SA showed normal %CPS but reduced %FPS. In contrast, rats that were fear conditioned during nicotine withdrawal plus no further nicotine showed elevated %CPS and normal %FPS. Rats that received fear conditioning during nicotine withdrawal plus continued nicotine SA also showed enhanced CPS, but reduced %FPS as well as enhanced extinction. Our data suggest that, under certain conditions, nicotine can reduce behavioral responsiveness to cues associated with a stressful (trauma-like) event, whereas nicotine withdrawal can enhance these same metrics.
Biases in interpretation play a role in the maintenance of a wide range of emotional disorders. Cognitive Bias Modification computer training tasks targeting interpretation (CBM-I) have successfully changed interpretation bias in anxiety and depression, with positive effects on symptoms and behavior. CBM-I has great potential for dissemination as it targets a transdiagnostic mechanism, is computerized, can be reliably administered across settings, does not require clinician contact, and does not require patients to apply complicated concepts. However, few studies have tested CBM-I’s efficacy in clinical samples or its effectiveness in real-world settings. Given that CBM-I targets similar cognitive mechanisms, it may be an ideal adjunctive therapy to CBT. The current study tested the effectiveness of CBM-I as a transdiagnostic, adjunctive treatment in a CBT-based partial hospital. Patients completed a word-sentence association paradigm (WSAP) that provided reinforcement for making benign interpretations and rejecting negative interpretations. Patients completed the 10-minute task daily while attending the partial hospital (average duration = 8 days). Results (n=62) indicated that patients successfully learned the interpretation contingencies in the task (i.e., significant increase in benign interpretations and decrease in negative interpretations). CBM-I patients who demonstrated an interpretation bias at baseline reported significantly greater overall improvement compared to patients assigned to a neutral version of the same task. Moreover, patients found CBM acceptable, reporting that it complemented CBT groups well. The WSAP has the potential to improve outcomes in an acute and comorbid population. We will present qualitative data speaking to acceptability and perceived mechanisms of action. We will also describe refinements made to the protocol and control condition based on patient feedback and present preliminary data from the new and improved treatment.
Program Description

Division of Geriatric Psychiatry

Presenting Author: Cindy Ruscitti, Nurse Director, MSN RN, McLean Hospital--inpatient

Co-Authors: no co-author

Title: Older Adults Embracing Mindfulness, Meditation and New Technologies

Key words: treatment relaxation smartphone apps patients

Herbert Benson has laid the groundwork for the benefits of relaxation response and traditional groups, led by a staff member to help patients on the unit. They ask for ways to use the techniques on their own and when they are discharged. We use smartphone/tablet applications that are specific to relaxation and meditation techniques and connect a radio via Bluetooth to facilitate a group. We use wireless headphones to help patient relax individually in their rooms and instruct them in the use of smartphones and tablets for discharge. Many older adults already have lap tops, smartphones and tablets. These apps, such as Relax M and Calm, Spotify, and Instagram are adjuncts to the therapies they receive on the inpatient unit. Patients are calmer, use these tools for sleep, to decrease the effects of auditory hallucinations, and aid in their recovery. These tools are useful in recovery, decrease incidents of seclusion and restraint on the unit, and promote patient-centered care.

Topic areas:
Geriatric
DNA methylation implicates zinc finger transcription factors and WNT signaling in functional distinction of phenotypically similar neuronal populations in human hippocampus

The myriad distinct neuronal subtypes within the brain assemble to form a complex cytoarchitecture with neurons in distinct microcircuits performing specific tasks in unique tissue environments. These neuronal subpopulations support the circuit specific tasks underlying diverse cognitive functions, and are differently affected by the pathophysiology of disease states. A role for chromatin modification in the generation and maintenance of neuronal diversity within the brain, as well as neuronal physiology in health and disease, is beginning to take shape. What epigenetic studies of postmortem human brain have been lacking to date is spatial resolution beyond the level of large-scale brain structures or cortical regions. The Illumina HumanMethylation450 BeadChip was used to contrast genome-wide methylation profiles in highly specific populations of GABAergic interneurons sampled using laser-microdissection from stratum oriens of CA1 and CA3 of postmortem human hippocampus, comparing these two regions in eight healthy controls as well as eight patients with schizophrenia and eight patients with bipolar disorder. These neuronal populations are phenotypically highly similar and are differentiated by their functioning within microcircuits supporting distinct cognitive functions. Methylation differences were greater between hippocampal subfields than between diagnoses, although there were significantly more individual CpG sites of significant methylation change in bipolar disorder. Investigation of differentially methylated regions identified 11 significant regions with FWER < 0.05 across all cases. The 11 genes associated with these regions form a group with high face validity that includes three of the five members of the ZIC gene family, four genes found within divergently transcribed tandem gene pairs, four zinc finger transcription factors and multiple other genes important for CNS development and function including the WNT signaling pathway. The present findings demonstrate the deep complexity of chromatin dynamics in neuronal diversity and physiology operating distinctly in highly similar populations of GABAergic interneurons in a single cellular layer performing discrete functions in separate hippocampal subfields.

Topic areas:
Bipolar
Psychotic disorders
Schizophrenia
Bipolar Disorder is a severely debilitating psychiatric disorder that affects 5.7 million American adults. In geriatric populations, bipolar disorder affects approximately 1.4 million elderly. Bipolar disorder causes unusually large fluctuations between manic and depressed mood states resulting in functional and cognitive impairment. Because of suicide and comorbid medical ailments such as obesity, type-2 diabetes and cardiovascular disease, life expectancy in bipolar disorder patients is 30% shorter than the general population. Despite excess mortality, recurrent episodes of mania and depression persist into later life with adverse effects on cognition, daily functioning and quality of life. Currently bipolar disorder is diagnosed using clinical criteria defined in the DSM 5. However, neuroimaging could be a tool for more accurate and earlier diagnosis. Discovering brain regions involved in bipolar disorder may also direct novel therapeutic interventions. Previous cross-sectional neuroimaging studies have found structural changes in the cortical, subcortical and limbic brain regions of bipolar patients. Studies regarding the globus pallidus are limited and findings inconsistent. The aim of this study was to use enhanced MRI imaging methods to determine volumetric group differences in the basal ganglia, globus pallidus and caudate nucleus between geriatric bipolar subjects and controls. We hypothesized a 337 mm3 volumetric decrease in these brain regions for bipolar subjects with 80% power, $p < 0.05$ and 15 subjects per arm. To test this hypothesis we did a retrospective study using MRI imaging collected with a Siemens 3T Trio scanner equipped with a 32-channel, phased array coil. We used FSL software for volumetric analysis of T1 weighted images and JMP Pro 10 for multiple regression analysis with diagnosis and total brain volume set as predictors. $p < 0.05$ was considered statistically significant. Interim analysis did not show a statistically significant volumetric difference between bipolar (n=10) and controls (n=11) in the globus pallidum, caudate or basal ganglia regions ($t(18)=0.62; p=0.5413$); $t(18)=1.13; p=0.2731$) and $t(18)=1.37; p=0.1877$), respectively. However, all three regions demonstrate a trend toward lower volumetric sizes in bipolar patients (globus pallidum: controls= 3710.10 mm3, bipolar= 3548.17 mm3; caudate: controls= 6732.34 mm3 bipolar= 6343.04 mm3; basal ganglia: controls= 70539.70 mm3 bipolar= 6684.10 mm3). In conclusion, volumetric differences in the globus pallidus, caudate and basal ganglia regions were not statistically significant between bipolar patients and normal controls. A small sample size may have limited our power to detect group differences in basal ganglia volume. Next steps planned are to increase the sample size for follow-up volumetric analyses and then initiate a functional connectivity analysis of motor networks in the basal ganglia region of bipolar patients.

**Topic areas:**
- Bipolar
- Geriatric
- Imaging
Do Locus of Control and Scrupulosity Predict OCD Treatment Outcome?

**Study Objective and Purpose:** A pilot study is underway to assess whether locus of control is a treatment factor in patients whose OCD has not responded to standard clinical intervention, and the extent to which an internal or an external sense of control affects treatment outcome. Locus of Control (LOC) is a construct that addresses an individual’s perception about whether they have, or do not have, control over what happens to them. People with internal LOC believe that their own behavior, capacities, or attributes effect the course of their lives, while those with external LOC believe that their lives are under the control of powerful others, luck, chance, fate, etc. Another study examined pre- and post treatment outcome between patients by religion who met criteria for scrupulosity who attended a weekly scrupulosity group and those who did not.

**Method:** Locus of Control was measured by Rotter’s Internal-External Scale. Scrupulosity was measured by the Pennsylvania Inventory of Scrupulosity-Revised. OCD symptom severity was measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

**Results:** In the current sample, a significant reduction was found in PIOS-R total score ($t(256)=5.52, p=.000$), sin subscale ($t(256)=5.37, p=.000$), and god subscale ($t(256)=4.39, p=.000$) across religions. There was not a significant association between religion and OCD severity at admission, with the exception of those identifying as Buddhists who had a lower severity at intake ($r(377)=-.16, p=.002$). Further analyses will evaluate how decreases in scrupulosity symptoms across treatment differed based on identified religion and inclusion in a scrupulosity focused treatment group. Additionally, pilot data currently being gathered in a clinical OCD population will be evaluated to determine the impact of LOC on this change and the effects of identified religion on LOC.

**Conclusion:** Overall, scrupulosity symptoms appear to decrease significantly across time in intensive/residential OCD treatment, regardless of their inclusion in a scrupulosity specific group or identified religion. This is in line with previous finding suggesting a significant effect of time in IRT on scrupulosity symptoms (Shapiro et al., 2011). Additionally, it is hypothesized that locus of control may further determine treatment outcome. Those with internal LOC are predicted to have better outcome scores than those with external LOC. Those with external LOC may be hampered by their belief that response prevention may have a negative effect on the reality of their loved ones, and that as a result, they are vulnerable to retribution from the forces outside of themselves (luck, authorities, God).

**Topic areas:**

OCD
Presenting Author: Arthur Siegel, Director, Internal Medicine; associate professor of medicine, HMS, McLean and MGH

Co-Authors: Sophie S. Forte, C.N.P. Nasir A. Bhatti, M.D. Steven E. Gelda, M.D.

Title: Drug-Induced Hyponatremic Encephalopathy

Key words: hyponatremia encephalopathy adverse drug reaction SIADH

Background: Drug-induced hyponatremia characteristically presents with subtle psychomotor symptoms due to compensatory adjustments to hypo-osmolality in the central nervous system facilitated by a slow onset. Due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH), this condition readily resolves upon discontinuation of the responsible pharmacological agent in contrast to life-threatening neurological symptoms characteristic of a rapid onset, which requires emergent infusion of intravenous hypertonic (3%) saline to reverse cerebral edema.

Case: We describe herein a 63 year old female admitted for inpatient psychiatric care for refractory depression with a normal physical examination and laboratory values including a serum sodium [Na+] of 144 mEq/L. She developed seizures followed by unresponsiveness within days after initiating treatment with the dual serotonin and norepinephrine reuptake inhibitor [SNRI] duloxetine in usual and customary doses while also receiving a thiazide-containing diuretic prescribed for a stable hypertensive disorder. Emergent infusion of intravenous hypertonic (3%) saline was initiated immediately following determination of a serum sodium [Na+] of 108 mEq/L. Urine osmolality and urine [Na+] were measured at 314 mOsm/kg H2O and 12 mEq/L, respectively. Correction of hyponatremia in accordance with recommended guidelines resulted in a full recovery with return to her baseline mental status.

Conclusion: Life-threatening hyponatremic encephalopathy was drug-induced in this case by co-occurring SIADH and sodium depletion due to duloxetine and a thiazide-containing diuretic agent, respectively. While prompt diagnosis and management based on severity resulted in recovery without neurological complications, co-administration of pharmacological agents which confer risk for hyponatremia by alternative mechanisms should be avoided.

Topic areas:
Division of Depression and Anxiety

Presenting Author: Ölafía Sigurjónsdóttir, Phd candidate, McLean Hospital, BHP

Co-Authors: Inga Dröfn Wessman, MS, Kean Hsu, PhD, Lara Rifkin, BSc, Courtney Beard, PhD, Thröstur Björgvinsson, PhD, ABPP

Title: Must I Accept before I can change?

Key words: Rumination Acceptance Depression Anxiety Treatment outcome

Two types of ruminative response styles, reflection vs. brooding have been differentially related to depressive symptom improvement. Reflection is thought to indicate purposefully turning inward to engage in cognitive problem solving and has been found to be related to a decrease in depressive symptoms over time. Brooding in contrast is thought to reflect passive comparison of one’s current situation with some unachieved standard and has been linked to more persistent depressive symptoms (Treynor et al 2003). Acceptance and commitment therapy (ACT) is theorized to increase acceptance of internal experiences, which then facilitates symptom change. The construct of reflection may have common factors with acceptance strategies and facilitate more adaptive problem solving, leading to symptom reduction over time. The aim of this study was to examine changes in utilization of cognitive-affective acceptance strategies, willingness, cognitive defusion and dysfunctional thinking, and their relation to different rumination styles and treatment outcome. It was hypothesized that reflection would be related to higher utilization of acceptance strategies and enhanced treatment outcomes; and that alternatively brooding would be related to less utilization of acceptance strategies and worse treatment outcome. Participants included 165 patients (52% female, mean age=32.45, SD=13.41) in a partial hospital program presenting with severe psychopathology. Participants completed the Before Session Questionnaire (BSQ; Forman, Chapman, Herbert, Goetter, Yuen, & Moitra, 2012), Ruminative Responses Scale (RRS; Treynor, Gonzalez & Nolen-Hoeksema, 2003), Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer & Williams, 2001), Generalized Anxiety Disorder Scale (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006) and Schwartz Outcome Scale (SOS-10; Blais et al., 1999). Regression analyses will be used to assess the relationship of acceptance and change strategies, ruminative responses and treatment outcome. An appropriate model will be selected by comparing the model fit criteria, or the AIC (Akaike Information Criterion), and significance tests results for main and interaction effects between models.

Topic areas:
Anxiety
Depression
McLean Research Day 2016

Original Research - Pre-Clinical

Poster # 95

Division of Basic Neuroscience

Presenting Author: Laura Smith, Instructor, Harvard Medical School, McLean Hospital, Integrative Neurobiology Laboratory

Co-Authors: Laura N. Smith, Rachel D. Penrod, Jaswinder Kumar, Jakub P. Jedynak, Morgane M. Thomsen, Makoto Taniguchi, Christopher W. Cowan

Title: Essential role for Arc in cocaine addiction-related behaviors and synapse plasticity

Key words: Arc  cocaine  CPP  sensitization  self-administration

Exposure to drugs of abuse induces lasting alterations in the brain function of vulnerable individuals, and these changes are thought to maintain maladaptive behaviors characteristic of addiction. Understanding the molecules that mediate such responses to drug experience is critical to developing successful treatment and prevention strategies. Acute cocaine exposure transiently upregulates mRNA and protein expression of the immediate early gene, activity-regulated cytoskeleton-associated protein (Arc), in the striatum of rodents, an effect that becomes more persistent after multiple exposures. As a key regulator of structural and functional synaptic features that are altered by cocaine treatment and withdrawal, including AMPA receptor surface expression, and as an early responder to cocaine exposure, Arc is well positioned to mediate aspects of drug addiction. Therefore, our aim in this study was to determine how loss of Arc affects drug-related behavioral and synaptic plasticity. Using separate cohorts of mice lacking Arc (i.e., Arc KO) and their wild-type (WT) littermates, we observe that KO mice show significantly enhanced locomotor activity in response to moderate doses of cocaine, an effect that is present upon the first exposure. Perhaps relevant to the basal sensitivity of Arc KO mice to cocaine, and consistent with Arc’s reported role in activity-dependent endocytosis of synaptic AMPA receptors, KO mice display increased AMPA receptor surface expression and synaptic strength on medium spiny neurons of the nucleus accumbens (NAc). In contrast, naïve Arc KO mice show normal place preference to various doses of cocaine compared to WT littermates, but after receiving repeated cocaine administration followed by 10 days of drug abstinence Arc KO mice display a significantly sensitized cocaine place preference score. There was no difference between drug naïve and cocaine-experienced WT mice in place preference. Given Arc’s importance for learning and memory, the observation of normal, and especially enhanced, place conditioning is unexpected; however, consistent with previous studies, we find that these mice have deficits in contextual fear conditioning, suggesting a unique role for Arc in drug-related learning and memory. When we examine the response of Arc KO mice to natural rewards in the sucrose two-bottle choice assay and acquisition of sweetened liquid food self-administration, they do not differ from WT littermates. Ongoing studies indicate possible differences between WT and Arc KO mice in the cocaine self-administration assay. Together, our results demonstrate that mice lacking Arc have enhancements in basal AMPA receptor function in the NAc, as well as in reward-related behavioral plasticity following prior cocaine experience. Future studies addressing the role of this protein in behaviors that are thought to drive continued abuse and addiction, such as cue-induced craving and relapse, are warranted.

Topic areas: Addiction
Title: Measures of Impulsivity in Healthy Controls, Current and Former Marijuana Users

Key words: marijuana  impulsivity  frontally mediated behavior

The prevalence of marijuana (MJ) use has doubled over the last ten years, with 9.5% of all adults and 21.2% of emerging adults endorsing past-year MJ use. As MJ use becomes more widespread, it is increasingly important to examine the behavioral differences, particularly impulsivity, that may exist between MJ users and non-users. Impulsivity has been reported to be increased in substance abusing populations, and is associated with deficits in executive function. We recently examined self-report measures of frontally mediated behavior using the Barratt Impulsiveness Scale (BIS-11), Eysencks’s Impulsivity Inventory (IVE), and the Frontal Systems Behavior Scale (FrSBe). The sample included healthy controls, current chronic, heavy MJ users (minimum of 5 times per week), and former MJ users. The current MJ users were further subdivided into early onset (regular MJ use prior to age 16) and late onset (regular MJ use after age 16) users. Results revealed that current MJ users reported significantly higher levels of total impulsivity scores on the BIS-11, higher impulsivity and venturesomeness ratings on the IVE, and higher disinhibition, executive dysfunction, and overall total scores on the FrSBe relative to healthy controls. Early onset users reported higher non-planning and total scores on the BIS-11, as well as higher disinhibition scores on the FrSBe compared to late onset users, indicating that those who initiate use prior to age 16 report increased impulsivity compared to later onset users. Significant differences also emerged between current MJ users and former MJ users. Specifically current MJ users reported significantly higher attention, non-planning, and total impulsivity scores on the BIS-11, and higher impulsivity ratings on the IVE compared to the former MJ users. Interestingly, no significant differences were observed between control participants and former MJ users on any of the impulsivity scales. Taken together, findings suggest that current MJ users endorse higher levels of self reported impulsivity and executive dysfunction relative to healthy controls. Further, early onset users appear to exhibit higher levels of impulsivity and disinhibition relative to their later MJ onset counterparts. Data from this investigation is consistent with reported neuropsychological findings in MJ users, including difficulty with inhibition and executive function, which have been correlated with earlier age of onset of MJ use. Further, while quite preliminary, these data indicate that former users may exhibit a greater ability to appropriately inhibit impulsive behavior after cessation of MJ use. Future studies will address this issue with larger sample sizes for more appropriate comparisons.

Topic areas: Addiction
A high percentage of individuals co-use alcohol and nicotine, which together lead to more severe substance abuse disorders compared to use of either substance alone. Despite established findings of alcohol-related memory alterations in animal and human studies, little is known regarding the underlying neurobiological mechanisms of co-administration. This study examined memory performance on a virtual water maze task (vWMT) and cerebral blood flow (CBF) acquired at rest using PCASL fMRI following nicotine and alcohol challenges. Six males who were light/moderate smoker/alcohol drinkers were randomized into placebo nicotine patch + alcohol (PA) and 14mg nicotine patch + alcohol (NA) conditions. Offline vWMT performance and CBF data were acquired prior to (baseline) and following an oral acute alcohol challenge during scanning. Breath alcohol levels (BrAL) achieved prior to vWMT testing were 0.077±0.026 (PA) and 0.075±0.016 (NA). Relative to the baseline, in the PA condition, significantly worse memory retention (-11%) was observed, which correlated with higher BrALs. Significantly lower resting state hippocampal CBF also was observed in the PA condition (-15%) relative to the baseline. No significant memory or CBF decrements were observed in the NA condition. Impaired memory retention associated with acute alcohol exposure is consistent with previous animal studies. Further, alcohol-related memory impairment was not observed when alcohol and nicotine were co-administered, suggesting that nicotine may mask some of alcohol's impairing effects, as well as minimize effects on resting state CBF. Such masking may enhance co-use of these substances, which during acute exposure may be advantageous, but under chronic co-use conditions may have more significant consequences, such as greater severity of substance abuse disorders and higher rates of relapse.

**Topic areas:**
Addiction
The degeneration of substantia nigra (SN) dopamine (DA) neurons in sporadic Parkinson’s disease (PD) is characterized by disturbed gene expression networks. Micro(mi)RNAs are post-transcriptional regulators of gene expression and there is increasing evidence that they are involved in the molecular pathogenesis of neurodegenerative disorders, including PD. Here, we document a comprehensive analysis of miRNAs in SN DA neurons from postmortem brains of PD patients and healthy controls. Our data show that miRNAs are dysregulated in disease-affected neurons and are differentially expressed between male and female samples with a trend of more up-regulated miRNAs in males and more down-regulated miRNAs in females. Unbiased Ingenuity Pathway Analysis (IPA) revealed a network of miRNA/target-gene associations that is consistent with dysfunctional gene and signaling pathways in PD pathology. Based on our findings from the miRNA profiles and computational data analysis, we started to functionally analyze miRNAs of interest. To this end, we studied miR-126, which was upregulated in PD and has been implicated in regulating Insulin/IGF-1/PI3K signaling, a pathway that was also dysregulated in the PD DA neurons. Our data show that miR-126 may play a profound role in neuronal cell survival to toxic insult by regulating growth factor (GF)/PI3K/AKT and MAPK/ERK signaling cascades. Altogether, our data provide evidence for an association of miRNAs with the cellular function and identity of neurons in general and SN DA neurons in particular, and with deregulated gene expression networks and signaling pathways related to neurodegenerative diseases, including PD, that may be sex-specific. Further functional characterization of miRNA/target gene relationships in neurons may lead to the identification of novel therapeutic targets for the treatment of neurological and age-related disorders.

Topic areas:
Geriatric
Title: Modulation of theta oscillations by fear conditioning and extinction during simultaneous EEG and fMRI

Key words: fear conditioning extinction theta simultaneous EEG/MRI

Human studies using fMRI and EEG as well as animal studies indicate that the amygdala and the anterior midcingulate cortex (AMC) are involved in fear expression. Moreover, the AMC has been found to generate theta oscillations (4-8 Hz), which have been associated with fear expression in both animals and in humans. The aim of the present study is to establish an experimental paradigm to bridge findings from prior animal, human electrophysiological (EEG) and human neuroimaging (fMRI) studies by recording fMRI and EEG simultaneously during the recall of conditioned and extinguished fear. Specifically, the goal of the current analysis is to establish the feasibility of the design to detect oscillatory EEG correlates when EEG is recorded during MRI and scanner artifact reduction procedures have to be applied to the EEG signal.

Twenty-one healthy participants underwent a 240-trial differential fear conditioning and extinction paradigm with a recall test 24h later. Neutral faces were used as conditioned stimuli (CS), while electric shocks served as unconditioned stimuli (US). fMRI and SCR recordings were collected during all experimental phases, while EEG was measured simultaneously during the recall test on day 2. By comparing extinguished (CS+/-E, i.e., presented during extinction) and nonextinguished CS (CS+/-N, i.e., not presented during extinction) on day 2, both recall of extinction learning recall of conditioning learning can be assessed.

Subjective CS ratings (valence and arousal) as well as SCRs showed successful fear acquisition on day 1. Conditioned fear measured by ratings was also successfully recalled on day 2, but not modulated by day 1 extinction. Conversely, SCRs and EEG activity on day 2 showed significant interactions with day 1 extinction: Differential SCRs (CS+ vs. CS-) were stronger for nonextinguished vs. extinguished CS during the first half of the recall test. Importantly, oscillatory theta activity at the frontal midline channel Fz showed a significant contingency (CS+ vs. CS-) x extinction (CS+/-E vs. CS+/-N) interaction on day 2 (F(1,17) = 5.22, p = .035), indicating decreased differential theta activity for extinguished vs. nonextinguished stimuli. Follow-up t-tests confirmed that only nonextinguished stimuli showed an increased differential (CS+ vs. CS-) theta response, while this effect was absent for extinguished stimuli. The results converge with previous findings reporting modulations of prefrontal theta by conditioned and extinguished fear when EEG was recorded outside the MRI scanner (Mueller, Panitz, Hermann, & Pizzagalli, 2014). In conclusion, these findings show that oscillatory EEG activity within the theta frequency is a valuable tool to study fear conditioning and extinction, including in the MRI environment. Moreover, in the present study, only physiological (theta, SCR), but not subjective (arousal, valence) measures were modulated by fear extinction during day 2 recall test. Consequently, these measures may be feasible to study symptoms in anxiety disorders which are associated with rather nonconscious (vs. conscious; LeDoux, 2014) fear processes and may lead to the development of new treatment approaches. Ongoing analyses and studies are assessing how theta activity is related to BOLD activity during fear learning and whether it is altered in anxiety patients.

Topic areas:
Anxiety
Imaging
Title: Adolescent co-occurring disorders: Opioid use and motivation to change.

Key words: Adolescence Opioid Use Disorder Motivation Treatment outcomes

Background: Adolescent illicit opioid use continues to be a public health concern in the United States. Many adolescents with opioid use disorders (OUDs) also have co-occurring psychiatric disorders, as well as poorer psychosocial and health outcomes, including overdose deaths and suicide. As an earlier onset substance use is associated with worse outcomes, effective interventions, particularly during adolescence, are of critical importance. The objective of this investigation was to characterize substance use progression between adolescents with OUDs and those with other substance use disorders, in order to identify potential unmet needs of adolescents with OUDs within a residential treatment setting.

Methods: As a part of a clinical quality assurance initiative, 106 patients from the McLean Hospital Acute Residential Treatment and Landing programs for adolescents with co-occurring disorders underwent a structured clinical interview (MINI-KID) and completed self-report assessments, including the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES). Adolescents who met criteria for an opioid use disorder (OUD+: n=53, age= 17.2) were age- and sex-matched to adolescents who did not meet criteria for an opioid use disorders (OUD-: n=53, age= 17.2). Both groups met criteria for multiple other psychiatric and substance use disorders, as is typical of the patient population studied.

Results: OUD+ exhibited significantly higher readiness to change as measured on the SOCRATES, including greater recognition of a drug problem, ambivalence towards their drug use, and taking steps to reduce drug use, as compared to OUD- peers (p<.001). Furthermore, OUD+ adolescents reported a significantly younger age of initiation of alcohol use (p=.05, mean(SD)=13.5(.3) in OUD+ vs. 14.3(.3) in OUD-) and cannabis use (p=.001, mean(SD)=12.4(.5) in OUD+ vs. 14.3(.3) in OUD-) than OUD- adolescents.

Conclusions: Adolescents with OUDs demonstrate unique clinical characteristics, including an earlier initiation of alcohol and cannabis use, and a greater readiness to change their substance use during residential treatment. These findings suggest that OUD+ adolescents tend to progress more quickly in their substance use disorder trajectory than OUD- peers.

Summary: In a residential treatment setting, adolescents with opioid use disorders report an earlier age of substance use initiation. However, despite great motivation to change, adolescents with OUDs have a high rate of relapse. Therefore, it is critical that efficacious treatments are implemented for adolescents with OUDs that target the specific needs of this high-risk population.

Topic areas:
Addiction
Child
Division of Child and Adolescent Psychiatry

Division of Depression and Anxiety

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**Title:** Unpacking Differences in Attentional Biases for Emotional and Suicide-Related Words Among Adolescent Suicide Ideators and Attempters

**Key words:** Adolescents Suicide Cognition Attention Inpatients

Suicide is the second leading cause of death among American adolescents, and approximately 4% of youth make a suicide attempt before age 19 (Nock et al., 2013). Although both mental illness and suicidal ideation are robust correlates of attempts, only a minority of youth with these risk factors ultimately attempts suicide. Therefore, it is critical to identify objective markers of suicide attempts within psychiatric samples of adolescent ideators. Adult research has found that the tendency to selectively attend to suicide-related stimuli (i.e., suicide attentional bias) reliably differentiates suicide attempters and non-attempters and predicts future attempts (Becker et al., 1999; Cha et al., 2010; Williams & Broadbent, 1986). However, no study to date has: (a) examined suicide attentional bias among adolescents or (b) compared suicide ideators and attempters, which is essential as only one third of ideators make an attempt (Nock et al., 2013). To address these empirical gaps, we recruited 99 (71 female) adolescent inpatients, all reporting current suicidal ideation. Thirty-nine participants had made a past suicide attempt (“attempters”) and 60 had no lifetime attempts (“ideators”). Participants completed an interview capturing current and lifetime suicidality (i.e., ideation, plans, attempts), a diagnostic interview, and self-report measures of psychiatric symptoms. We used a modified Stroop task to probe participants’ reaction time (RT) to indicate the color of neutral, negative, positive, and suicide-related words. Attentional bias scores [(emotion word RT – neutral RT) / neutral RT] were computed for each non-neutral stimulus. Compared to ideators, attempters showed greater attentional bias to both positive, t(97)=2.63, p=.010, d=.534, and suicide-related, t(97)=2.04, p=.044, d=.414, but not negative, stimuli. Follow-up analyses revealed that, for both positive and suicide-related words, multiple attempters showed greater attentional biases than ideators (p=.001 and p=.003) but single attempters did not (p=.834 and p=.670) [F(2,95)=6.93, p=.003, ηp2=.127 and F(2,95)=4.54, p=.013, ηp2=.087, respectively]. Finally, only positive attentional bias was associated with suicide attempt recency. Together, our results (a) highlight unique patterns of attentional bias to emotional stimuli that may characterize suicidal adolescents versus adults and (b) identify valuable markers of suicide risk among adolescents at high risk to attempt suicide.

**Topic areas:**

Child

Depression
Temporal Unfolding of Positive and Negative Affect following an Ecologically Valid Social Stressor

Background: Failure to experience and sustain positive affect following rewarding experiences is a core dysfunction of many psychiatric disorders. By better characterizing the behavioral profiles that accompany these impairments, research may help identify other risk factors for developing psychopathology. The current study sought to examine individual differences in recovering to baseline levels of positive affect following an ecologically-valid laboratory stressor. Of particular interest were differences in stress reactivity, as stress is well-known to precede the development of mental illness.

Methods: Seventy-nine healthy females, ages 18-45, underwent a modified version of the Maastricht Acute Stress Test (MAST). Individuals were instructed to perform a challenging series of mental calculations under time constraints, while intermittently completing trials of a cold pressor test. To increase the socio-evaluative threat of the situation, participants were given negative feedback by two evaluators. At the conclusion of the test, they were informed that their performance was poor and that they would be required to repeat the tasks. A heightened and prolonged state of stress was induced, from which subjects were relieved at the end of the session.

Results: Participants experienced an acute increase in negative affect (F (1.17, 94.17) = 24.51, p < .001) and decrease in positive affect (F (1.90, 104.504) = 11.244, p < .001) following the administration of the stress manipulation. Following relief, individuals were able to successfully recover to baseline levels of negative affect, yet continued to experience a reduction in positive emotion. Interestingly, those individuals who exhibited increased reactivity to the socio-evaluative stressor, as measured by salivary cortisol, also demonstrated greater difficulty in reestablishing positive affect as compared to their less-reactive counterparts (F(1.793, 134.49) = 3.374, p = .042).

Conclusion: These findings raise the possibility that stress may confer vulnerability to psychopathology by disrupting an engagement with positive emotional experiences, and furthermore, that sensitivity to stress may put individuals at increased risk by posing greater challenges in recovering positive affect. Further analysis of our clinical and physiological measures will be critical in understanding other characteristics that differentiate those individuals who experience difficulties in recovering from stressful experiences and reestablishing positive emotion.

Topic areas:
Depression
McLean Research Day 2016

Original Research - Pre-Clinical

Division of Basic Neuroscience

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Title: Magnetic resonance spectroscopy evidences striatal magnetic abnormalities in young adult SAPAP3 knockout mice

Key words: MRS SAPAP3 Translational research Obsessive compulsive disorder

Background: Obsessive compulsive disorder (OCD) is a debilitating condition with lifetime prevalence of 1-3%. OCD typically arises in youth but delays in diagnosis impede optimal treatment and developmental studies of the disorder. Research using genetically modified rodents may provide models of etiology that enable earlier detection and intervention. The SAPAP3 knockout (KO) transgenic mouse was developed as an animal model of OCD and related disorders (OCRD). KO mice exhibit compulsive self-grooming behavior analogous to behaviors found in people with OCRD. Striatal hyperactivity has been reported in these mice and in humans with OCD.

Methods: Striatal and medial frontal cortex 9.4 Tesla proton spectra were acquired from young adult SAPAP3 KO and wild-type control mice to determine whether KO mice have metabolic and neurochemical abnormalities. Mice were anesthetized during MRS sessions. Proton (1H) MRS spectra were acquired using an ultra-short echo-time STEAM sequence of TR=4 s and TE=3 ms. The short echo time allows minimal relaxation of the metabolites resulting in a rich spectrum. MRS spectra were processed and fitted with LCMODEL. Ratios relative to the unsuppressed water peaks were estimate from the LCMODEL outputs.

Results: Young adult KO mice had lower striatal lactate (P=0.006) and glutathione (P=0.039) levels. Among all mice, striatal lactate and glutathione levels were associated (R=0.73, P=0.007). No group differences were detected in medial frontal cortex metabolites. At the age range studied, only 1 of 8 KO mice had skin lesions indicative of severe compulsive grooming.

Conclusion: Young adult SAPAP3 KO mice have striatal but not medial frontal cortex MRS abnormalities that may reflect striatal hypermetabolism accompanied by oxidative stress. These abnormalities typically preceded the onset of severe compulsive grooming. Our findings are consistent with striatal hypermetabolism in OCD. Together, these results suggest that striatal MRS measures of lactate or glutathione might be useful biomarkers for early detection of risk for developing compulsive behavior disorders.

Topic areas:
Imaging
Recent preclinical studies in rodents suggest that tobacco constituents other than nicotine (NIC) also exhibit pharmacological properties that may play a role in maintaining tobacco consumption. The present studies were conducted to evaluate, respectively, the NIC-like discriminative-stimulus (Sd) and reinforcing effects of minor tobacco alkaloids [e.g., nornicotine (NOR), anabasine (ANA), anatabine (ANAT), myosmine (MYO), and cotinine (COT)] in nonhuman primates. In drug discrimination (DD) studies, the ability of minor tobacco alkaloids to engender NIC-like Sd effects was determined in squirrel monkeys (n=4) trained to discriminate a highly potent NIC-like agonist [(+)-epibatidine; EPI] from vehicle. In IV self-administration (SA) studies, second-order fixed-interval (SO-FI) schedule procedures in NHP (n=3) were utilized to determine whether selected minor tobacco alkaloids (e.g., NOR, ANAT, and MYO) exhibit NIC-like reinforcing effects. Results from DD studies show that: a) NIC and minor tobacco alkaloids engendered full (NOR, ANA, MYO, ANAT), or no (COT) substitution for EPI. Results from our SA studies show that NIC (0.0032–0.032 mg/kg/injection) reliably produced dose-related IV SA behavior under the SO-FI schedule, with peak rates of responding during availability of the unit dose of 0.01 mg/kg/injection. In contrast, NOR (0.032–0.18 mg/kg/injection) and ANAT (0.01–0.18 mg/kg/injection) produced response rates that are between those engendered by nicotine and those during saline availability; MYO (0.32–5.6 mg/kg/injection) failed to maintain IV SA under the SO-FI schedule; response rates were no greater than for vehicle. Taken together these findings suggest that non-NIC tobacco constituents may differentially produce nicotine-like addiction-related effects that contribute towards maintaining long-term tobacco consumption (DA-031231 – NIDA/NIH).

**Topic areas:**
- Addiction
- Pharmacology
- Schizophrenia
Npas4, novel HDAC5 target gene, mediates its role in limiting cocaine reward-related behavior

Environments associated with the use of abused substances often develop into long-lasting triggers for drug seeking and taking behaviors even after long periods of abstinence. Nuclear accumulation of the transcriptional repressor, histone deacetylase 5 (HDAC5), in the adult nucleus accumbens reduces cocaine reward behaviors. We show here nuclear HDAC5 reduces the association between cocaine reward and context, independent of cocaine sensitivity, and in self-administering rats, nuclear HDAC5 selectively reduces reinstatement of drug seeking behavior. Using an unbiased, genome-wide analysis (ChIP-seq) of HDAC5 genomic binding sites, we identify Npas4 as an important nuclear target of HDAC5 in striatal neurons. We show that nuclear HDAC5 inhibits activity-dependent induction of Npas4 in striatal neurons, and in wildtype mice, Npas4 levels are rapidly and transiently induced in a discreet population of neurons in the NAc following administration of cocaine or exposure to novel environment. Reduction of Npas4 in the adult NAc reduces cocaine reward behavior, but not cocaine sensitivity, fear-related contextual memory, preference for food reward, or anxiety-like behaviors. Taken together, our data reveal Npas4 as a novel target of nuclear HDAC5 and indicate an important role for induction of Npas4 in the development of drug reward-context associations.
McLean Research Day 2016

Original Research - Clinical

Poster # 106

Division of Child and Adolescent Psychiatry

Presenting Author: Naomi Tarlow, Clinical Research Assistant, Child and Adolescent Mood Disorders Laboratory

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Title: Self-Referential Processing in Adolescents with Borderline Personality Disorder

Key words: borderline personality disorder adolescent self-referential processing

Background. Borderline Personality Disorder (BPD) is characterized by self-referential processing deficits – particularly relating to negative self-views. Previous research indicates that adults with BPD exhibit a negative evaluation bias (Winter, et al., 2015); however, research among adolescents with BPD is limited. Therefore, the present study tested behavioral and neural self-referential processing deficits that may underlie BPD in adolescents.

Method. The current study included healthy, female adolescents (HC = 33) and youth diagnosed with BPD (BPD = 26) aged 13-22 years. During the initial assessment, participants completed a diagnostic interview assessing psychopathology. Additionally, participants completed a self-referential encoding task (SRET) while electroencephalographic (EEG) data were recorded. The SRET is designed to elicit event-related potentials (ERPs) probing: (a) the P2 (200-300 ms post-stimulus), indexing semantic monitoring of emotional information and (b) the late positive potential (LPP) (600-1200 ms post-stimulus), reflecting encoding of emotional information. We hypothesized that relative to the HC group, the BPD youth would exhibit greater P2 and LPP positivity for negative versus positive words.

Results. As hypothesized, a significant Group x Condition interaction emerged when examining the P2, F(1,53) = 4.38, p = 0.041, ηp2 = 0.08. No between-group effects emerged for positive (p = 0.48, ηp2 = 0.01) or negative words (p = 0.63, ηp2 = 0.004). However, within-group effects found that BPD female participants showed greater positivity for negative versus positive words (p = 0.03, ηp2 = 0.09); no within-group effects emerged in the HC group (p = 0.44, ηp2 = 0.01). Similarly, a significant LPP Group x Condition interaction emerged, F(1,53) = 9.57, p = 0.003, ηp2 = 0.15. No between-group differences for positive (p = 0.36, ηp2 = 0.02) or negative (p = 0.13, ηp2 = 0.04) words emerged. However, the HC group exhibited sustained positivity for positive versus negative words (p = 0.05, ηp2 = 0.07), while the BPD participants showed the opposite effect (p = 0.02, ηp2 = 0.11) Conclusion. These findings suggest that negative self-relevant information may be more salient among BPD youth, and potentially, may contribute to psychiatric severity. Identifying neural substrates that underlie these processes may ultimately lead to innovative brain-behavior targets for future treatment.

Topic areas:
Borderline Personality Disorder
Child
Women
Perfectionism, a phenomenon characterized by exceedingly high expectations coupled with distress when these standards are not met, is a rampant phenomenon affecting much of the population. Within the scope of obsessive-compulsive disorder (OCD), much of the extant literature suggests that perfectionism is more prevalent among people with OCD compared to healthy controls, and that it may play a primary role in the presentation of OCD. The Obsessive-Compulsive Cognitions Working Group (1997, 2001) has identified perfectionism as a key component in the development and maintenance of OCD. Further research supports the notion that perfectionism does not exist as a single, negative concept, but as a multidimensional phenomenon. Although the literature disagrees on the number of subgroups of perfectionism, Hamachek's (1978) early argument for normal and neurotic perfectionism (i.e. health and unhealthy (Stumpf & Parker, 2000), adaptive and maladaptive (Rice & Slaney, 2002)) is now widely accepted. The Revised Almost Perfect Scale (APS-R) is a valid and reliable measure of perfectionism across three domains of perfectionism: high standards (HS), ordering (O), and discrepancy (D) (Slaney, et al., 2001). Correlations between the High Standards subscale and measures of wellbeing, including depression, worry and student’s grade point averages (GPA), suggest that HS may be a measure of adaptive perfectionism. Additionally, scores on the Discrepancy subscale were found to be correlated with these measures of wellbeing suggesting that the Discrepancy subscale may be an appropriate measure of maladaptive perfectionism (Rice & Ashby, 2007; Rice & Slaney, 2002; Sironic & Reeve, 2012). Additionally, maladaptive perfectionism has been linked to an increase in OC-related behaviors including checking, doubting, and excessive hand washing (Rice & Pence, 2006). Identification and analyses of perfectionism subgroups is necessary to effectively treat perfectionism within the context of OCD. In this study, 215 patients at an intensive residential treatment facility for OCD completed a battery of measures, including the APS-R, at admission and discharge to measure change over the course of treatment. This study is a continuation of previous presentations examining the implications of perfectionism in treatment. This study is aimed at examining maladaptive versus adaptive perfectionism and identifying the role of each in treatment. Preliminary analyses show a decrease in scores on the APS-R over the course of treatment (M = 8.7, SD = 17.3, t(214) = 7.4, p < .001) suggesting that patients experience a relief in overall perfectionist tendencies. Scores on both the High Standards (M = .90, SD = 5.6, t(214) = 2.3, p = .02) and Discrepancy subscale (M = 7.11, SD = 12.67, t(214) = 8.23, p < .001) decreased significantly. Additionally, Discrepancy scores, but not High Standards, correlated significantly with measures of OCD severity at 1-month and 6-month follow-ups (r = .301, p = .004; r = .296, p = .027). It is hypothesized that adaptive perfectionism will be more indicative of treatment success and maladaptive perfectionism will predict relapse of symptoms in follow-up analyses. Further analyses are warranted to determine the role perfectionism plays across the course of treatment within different OCD symptom domains.
Introduction: Both alcohol use disorders (AUDs) and depression are national public health issues as evidenced by their prevalence rates in the general population, 7.06% and 8.46% respectively (Grant et al., 2004), and their debilitating effects on the individual and society. AUDs and major depression have a high comorbidity rate. Within individuals with depression, 40% have a lifetime diagnosis of an AUD (Lai et al., 2015). Although numerous studies have examined comorbidity rates, fewer studies have compared age of onset for these two disorders. The developmental course of these comorbid disorders may facilitate understanding of risk factors, as well as treatment implications. For example, one study showed in men, depression preceded alcoholism, whereas in women, alcoholism preceded depression (Helzer & Pryzbeck, 1988). The current study aimed to examine the order of onset for these comorbid disorders specifically in a psychiatric population, as well as examine gender differences.

Methods: Data was collected from the Behavioral Health Partial Hospital Program. The MINI (Mini-International Neuropsychiatric Interview) was administered to assess for lifetime history of Major Depressive Disorder and current alcohol dependence. Age of onset was obtained for any diagnoses assigned.

Results: Of 1606 patients attending the partial hospital, 182 had comorbid lifetime MDD and alcohol dependence. A paired t-test indicated that age of onset was significantly younger for lifetime MDD (M = 18.88) compared to alcohol dependence (M = 23.81), t(127) = -6.51, p < .001. 72% of individuals reported that depression preceded alcohol dependence; 19% reported that alcohol dependence preceded depression, and 9% reported the same age of onset for both disorders. This pattern was the same across genders, and average age of onset did not significantly differ between genders for MDD or alcohol dependence. Of females, 75% reported that depression preceded alcohol dependence; 11% reported that alcohol dependence preceded depression; and 14% reported the same age of onset. Of males, 68% reported that depression preceded alcohol dependence; 24% reported that alcohol dependence preceded depression; and 9% reported the same age of onset.

Conclusion: The results indicate that overall the age of onset for lifetime depression most often precedes that of alcohol dependence for both males and females. However, contrary to expectations, there were substantially more males who reported alcohol dependence preceding depression compared to females. The findings highlight the importance of examining age of onset from multiple approaches (average age for each disorder vs frequency of each onset order). This pattern of comorbidity is not surprising given that this partial hospital setting does not treat primary AUDs. Thus, we might expect to see the opposite pattern of age of onset in a primary substance abuse treatment setting. Regardless of setting, these results highlight the potential need for integrated treatment. Additionally, given that depression more often preceded alcohol dependence in this psychiatric sample, treatment providers should assess for AUD risk and focus on prevention of AUDs. Limitations of this current study include the dichotomous assessment of gender. Future studies should include individuals who identify as transgender or other gender identities.

Topic areas:
Addiction
Depression
Women
Background: Previous studies have implicated anhedonia and negative bias as core features of major depressive disorder (MDD). These studies have shown that MDD participants display blunted reinforcement learning (RL) and striatal activation in response to reward. However, there is very little research probing RL in response to punishment. The present study utilizes a social RL task to investigate the neural correlates of both reward and punishment learning in depression. This study also uses a pharmacological manipulation to assess how dopamine abnormalities in MDD play a role in RL.

Methods: Twenty-four healthy and 26 unmedicated individuals with MDD completed a social RL task whilst in the fMRI scanner, and current analyses include 14 healthy and 16 MDD participants. During the task, participants had to choose one of the two stimuli presented on the screen in order to obtain a reward (cheer sound) or avoid receiving a punishment (boo sound). The participants had to learn, by trial and error, the changing stimulus–outcome associations. Each individual completed three blocks of the task: a reward block in which they received rewards or neutral feedback, a punishment block in which they received punishments or neutral feedback, and a mixed (R&P) block in which they received both rewards and punishments. Order of the reward and punishment blocks was counterbalanced. Both behavioral and fMRI analyses were restricted to the R&P block. For the behavioral analysis, learning rate was calculated by adding the deviation between the participants’ and pre-defined total choice across the task, and a Group x Order ANOVA of learning rate was conducted. fMRI data were processed using SPM8 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 were analyzed using SPSS.

Results: Behavioral analyses revealed a main effect of block order (Order 1: Punishment block preceded R&P block; Order 2: Reward block preceded R&P block) on learning in the mixed (R&P) block (F(1,42) = 7.99, p < .01), with no other significant effects. Post-hoc tests indicated that performance on the R&P block depended on the prior block. If the reward block was prior to the mixed block, better learning was displayed on the mixed block than when the prior block included punishments (t(44) = 3.16, p = .003). The Group x Valence (Reward/Punishment) ANOVA of beta weights from the left NAc showed a main effect of Group at a trend level (F(1,28) = 4.01, p = .055). Exploratory post-hoc t-test indicated that MDD individuals showed a blunted response to both reward (t(28) = 2.24, p = .03) and punishment (t(28) = 1.56, p = 0.13 (trend)) in the left NAc. However, no significant effects were observed in the right NAc.

Conclusion: Consistent with previous findings, MDD participants displayed a more blunted neural response to reinforcement learning. Further behavioral results show that both healthy and MDD participants learned better when they were primed in a rewarding context.
Introduction/Background: Behavioral inhibition has been shown to be impaired in individuals with obsessive-compulsive disorder (OCD; Bannon et al., 2002; Penades et al., 2007). Additionally, previous research has demonstrated that in healthy participants, repeated checking behaviors were associated with behavioral inhibition impairments (Linkovski et al., 2015). Taken together, this suggests that specific symptom subtypes in OCD may be associated with impairments in one’s ability to stop responses, which may be a cognitive vulnerability in OCD, and may influence symptom severity. Furthermore, these abilities and symptom subtypes may be differentially influenced by cognitive functioning (Rachman 2002). However, few studies have examined the association of behavioral inhibition performance and symptom subtype in relation to cognitive functioning and treatment outcomes in individuals with severe OCD. Aims/Objective: Our aim was to examine relationships among behavioral inhibition, as measured by performance on a stop-signal task (SSRT; Logan et al., 1984), symptom subtype, cognitive functioning and treatment response in severe, treatment-refractory OCD.

Methods: 104 individuals (45 women; mean age 32.37) with severe, treatment-refractory OCD performed the SSRT, a cognitive screening assessment, and a number of self-report questionnaires of their symptoms while engaging in intensive residential treatment program.

Results: At admission, global OCD symptom severity as measured the Yale-Brown Obsessive Compulsive Disorders Scale (YBOCS; Goodman et al., 1989) indicated that self-reported compulsions but not obsessions were significantly associated with impairments in behavioral inhibition when taking into account performance on a cognitive screener (Montreal Cognitive Assessment; MOCA; Nasreddine et al., 2005). At discharge, the YBOCS was not associated with behavioral inhibition. Regarding OCD symptom subtype, preliminary findings indicated that at admission, on the Dimensional Obsessive-Compulsive Scale (DOCS; Abramowitz et al., 2010), increased symptoms of concerns about germs and contamination was significantly associated with impaired performance on the SSRT. At discharge, responses on the DOCS were not associated with performance on the SSRT. However, at discharge, when taking into account performance on the MOCA, impairments in behavioral inhibition were significantly associated with increased symptoms of concerns about germs and contamination as well as symmetry, completeness, and the need for things to be “just right” on the DOCS. Preliminary results suggest that cognitive functioning as measured by the MOCA may influence the relationship between behavioral inhibition performance and self-reported symptoms on the DOCS, particularly for symptom subtypes of symmetry, completeness, and the need for things to be “just right.”

Conclusions: Our findings align with previous research suggesting impairments in behavioral inhibition in OCD (Bannon et al., 2002; Penades et al., 2007), and extend these findings for individuals with severe, treatment-refractory OCD. Additionally, our findings suggest that assessment of cognitive functioning may inform our understanding of relationships among impaired behavioral inhibition and symptom subtype within the course of intensive treatment for OCD. Given that orbitofrontal brain regions have been shown to underlie executive functions of behavioral inhibition (Bonelli and Cummings, 2007), further examinations involving assessments of specific domains of cognitive functioning, including executive functioning in particular, are necessary to characterize relationships among behavioral inhibition impairments and severity of symptom subtype in OCD.
Intensive/residential treatment (IRT) programs provide a unique opportunity to systematically evaluate factors that influence change in OCD in a longitudinal manner. While the efficacy of OCD treatment has been well established, we still have limited understanding of the role emotional/cognitive processes play in treatment. In order to continue to enhance the efficacy of OCD treatment for complex/treatment refractory cases, a better understanding of how these the processes relate to change is necessary. This presentation will discuss novel findings regarding the relationship between emotion regulation (ER) and worry and how they relate to symptom change in IRT.

274 OCD patients, seeking IRT at the OCD Institute at McLean Hospital were administered self-report measures at admission and discharge, including: 1) Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Dimensional Obsessive-Compulsive Scale (DOCS), 3) Emotion Regulation Questionnaire (ERQ), 4) Penn State Worry Questionnaire (PSWQ). The ERQ, Y-BOCS, and PSWQ were also administered weekly across treatment. In line with previous findings, degree of worry at intake correlated with intake Y-BOCS \( r(225)=.336, p=.000 \) and symptom reduction across treatment \( r(146)=.240, p=.003 \). Interestingly, when evaluating individual symptom dimension, degree of worry was only significantly related to Unwanted Thoughts and Reduction of Harm. With regard to ER, the use of re-appraisal strategies was related to lower symptom severity at intake \( r(225)=-.254, p=.000 \) but did not significantly correlate with any individual dimensions, while the suppression subscale was correlated with the Unwanted Thoughts dimension. Regression analysis indicated that changes in emotion regulation strategies across treatment, specifically reduction in suppression strategies \( \beta=.192, t=2.445, p=.016 \) and increases in re-appraisal \( \beta=.304, t=3.945, p=.000 \) predicted symptom reduction across treatment. When controlling for the impact of worry, only increases in the use of re-appraisal strategies predicted symptom change above and beyond the impact of reduction in worry \( \beta=.228, t=3.293, p=.001 \). Overall, IRT appears to have significant effects on the underlying processes related to ER and worry. These changes appear to have significant implications for the process of change across treatment, along with their interactions with each other. Implications of these findings for both research and clinical practice will be presented, along with longitudinal models of change demonstrating when these changes occur in the treatment process.
Division of Alcohol and Drug Abuse

Presenting Author: Gordana Vitaliano, Instructor, Brain Imaging Nanotechnology Group, MIC

Co-Authors: Gordana D. Vitaliano*, Franco Vitaliano, Jose D. Rios, Tatyana Kramer, Perry F. Renshaw, Martin H. Teicher

Title: Clathrin Nanoparticles Efficiently Deliver Antibodies to Targeted Dopamine Brain Regions

Key words: Neurotechnology  Clathrin nanoparticles  CNS antibody delivery  Dopamine 3 receptor imaging

Background: Antibodies (Abs) have great promise for detection and treatment of central nervous system (CNS) disorders. However, the blood-brain barrier (BBB) is a major impediment to effective delivery. Only 0.1% of plasma Abs enter the CNS. Abs may take days to diffuse only a few millimeters and CNS concentrations may still be insufficient for therapeutic efficacy. Our goal was to develop a new nanotechnology method for efficient noninvasive intranasal delivery of antibodies to targeted dopamine brain regions.

Method: Dopamine-3 receptors (D3R) in rats have a restricted CNS distribution and D3R antagonists may be of value in treatment of drug dependence and psychosis. Thus, D3R Abs were selected, PEGylated and conjugated to clathrin triskelia through cysteine residues. Transmission electron microscopy and dynamic light scattering determined nanoparticle size and shape. Nanoparticle immunoreactivity was tasted by Western Blot. Low doses (64 µg/kg) of nanoparticles were delivered intranasally in rats. Control animals received D3RAbs or saline. Animals were perfused and sacrificed three hours after intranasal administration and immunohistochemistry analyses were performed. ELISA was used to quantify D3RAbs in different brain regions. Rhodamine-PEGs were then attached to D3RAb-nanoprobes and their in vivo stability was tested with confocal microscopy.

Results: D3RAb-nanoprobes (42.3 nm) remained immunoreactive after the modifications. Three hours after intranasal administration D3RAb-nanoprobes were found only in D3R brain regions in rats. Fluorescent and light microscopic examination confirmed specific targeting of CNS D3-receptors with D3RAb-nanoprobes. The highest nanoprobe concentration (2,753 ng/g) was detected in basal forebrain (islands of Calleja and ventral pallidum) and nucleus accumbens (1,028 ng/g). Low concentrations were detected in the cerebellum. D3R Abs delivered intranasally but without clathrin did not enter the brain. Confocal laser microscopy confirmed integrity of the nanoparticles in rat brain. Clathrin and D3RAb fluorescence co-localized in the D3R brain regions.

Conclusions: Clathrin-nanoprobes successfully bypassed an intact BBB after intranasal administration. Nanoprobes were able to target D3 receptors and deliver adequate concentrations of Abs inside neurons (17.2% ID/g) by using doses 300 times smaller than previously reported in BBB technologies studies. This nanotechnology holds promise for delivering antibodies to treat neurodegenerative disorders, to suppress neuroinflammation, infection or cancer growth, to regulate GPCR receptors, and serve as nanoprobes for diagnosis and monitoring of cellular events.

Topic areas:
Imaging
Pharmacology
Perceived Barriers to Smoking Cessation among Adults with Substance Use Disorders

Introduction: Among individuals with substance use disorders (SUDs), cigarette smokers experience more severe SUD symptoms, poorer SUD treatment outcomes, and higher mortality relative to non-smokers. SUD treatment provides an opportunity to address smoking cessation in this population. However, few patients engage in smoking cessation programs during SUD treatment, and many SUD treatment facilities do not even offer this service. The aims of present study are to (1) identify perceived barriers to smoking cessation among individuals in SUD treatment; (2) compare perceived barriers between distinct substance using populations (males and females, opioid use disorder [OUD] and alcohol use disorder [AUD]); and (3) identify correlates of perceived barriers.

Methods: Adults receiving inpatient detoxification treatment were recruited for a study examining characteristics of individuals in SUD treatment; 208 individuals identified themselves as current smokers and were included in the present analysis. Participants completed a battery of self-report measures including the Barriers to Quitting Smoking Scale (BQSS), the Motivation to Change Scale (MCS), the Anxiety Sensitivity Index-3 (ASI-3), and the Fagerstrom Test for Nicotine Dependence (FTND).

Results: Participants reported smoking an average of 16.1 (SD = 9.5) cigarettes per day and had a mean FTND score of 4.5 (SD = 2.5), corresponding to a low to medium level of nicotine dependence. Out of 11 possible barriers, participants endorsed an average of 5.9 (SD = 3.2) perceived barriers. The most common barriers endorsed were feeling anxious (81.2%), feeling tense/irritable (75.8%), harder to say sober when quitting during SUD treatment (69.1%), and feeling restless/can’t concentrate (63.8%). Total number of perceived barriers did not differ by gender, but women were more likely to endorse feeling anxious as a barrier (p<.05). Individuals with primary AUD and primary OUD did not differ on number or type of barriers reported. Total number of perceived barriers was associated with number of cigarettes smoked per day, severity of nicotine dependence, lower importance of changing smoking, lower readiness to change smoking, and lower confidence in ability to change smoking (p<.05). When controlling for these variables, confidence in ability to quit smoking was strongly associated with total number of perceived barriers (p<.05). Correlates of a greater number of perceived barriers included younger age, more severe nicotine dependence, and higher anxiety sensitivity (all ps<.05).

Conclusion: Despite the high prevalence of smoking and smoking-related consequences among individuals with SUDs, smoking cessation services in SUD treatment settings are underutilized. An array of perceived barriers to smoking cessation among this population may contribute to a reluctance to engage in smoking cessation services during treatment. The most common perceived barriers reported in our sample were affective and substance related. Notably, 63% of participants had the perception that smoking cessation during SUD treatment would make it more difficult to stay sober. This is in contrast to literature indicating that smoking cessation during SUD treatment does not increase risk of relapse. Psychoeducational interventions providing corrective information regarding smoking cessation and SUD treatment outcomes may be necessary to encourage quit attempts among individuals in SUD treatment.

Topic areas:
Addiction
**Title:** Treatment of prescription opioid dependence: long-term follow-up

**Key words:** opioid dependence treatment prescription opioids follow-up

Background: Despite the growing prevalence of prescription opioid dependence, no longitudinal studies to date have examined long-term response to treatment in this population. The current study thus examined outcomes over a 42-month follow-up period among participants from the Prescription Opioid Addiction Treatment Study (POATS), conducted through the NIDA Clinical Trials Network.

Methods: POATS was a multi-site randomized clinical trial of buprenorphine-naloxone and counseling for prescription opioid dependence. A subset of participants (N=375 of 653) enrolled in a follow-up study. Measures of opioid and other substance use and treatment utilization were administered by telephone interviews approximately 18, 30, and 42 months after enrollment in the main trial.

Results: The majority of follow-up participants were no longer opioid-dependent at Month 18; less than 10% met criteria for current opioid dependence at Month 42. Participants who reported a lifetime history of heroin use at study entry were more likely to be opioid-dependent at Month 42 (OR=4.56, 95% CI=1.29-16.04, p<.05). Sixty-one percent reported past-month abstinence from opioids at Month 42. Approximately one-third of the sample received opioid agonist treatment during follow-up; engagement in agonist treatment was associated with a greater likelihood of abstinence at Month 42. Eight percent (n=27/338) used heroin for the first time during follow-up; 10.1% reported first-time injection heroin use.

Conclusions: Long-term outcomes for those dependent on prescription opioids demonstrated clear improvement from baseline. However, a small subgroup of participants exhibited a worsening course, characterized by the initiation of heroin use and/or injection opioid use.

**Topic areas:** Addiction
Division of Depression and Anxiety

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Title: Psychometric Properties and Clinical Utility of the McLean Assessment of Rejection Sensitivity

Key words: Rejection Sensitivity Psychometric Properties Reliability Validity Clinical Utility

Rejection sensitivity (RS) may be defined as a disposition to anxiously expect, easily perceive, and intensely react to rejection. RS is related to mental health issues and disorders; for example, a core diagnostic feature of borderline personality disorder (BPD) is fear of abandonment. The study aim is to assess psychometric properties and clinical utility of an 11-item self-report inventory measuring RS (i.e., McLean Assessment of Rejection Sensitivity; MARS) among patients in a partial hospital program presenting with severe psychopathology. The sample (N = 512) mostly consists of non-Hispanic whites, and includes almost equal percentages of females and males with a mean age of around 35. According to the results, the measure appears to have good internal consistency (i.e., Cronbach α’s is .84). Item analysis will be conducted to assess item difficulty and item discrimination (i.e., the degree to which each item discriminates between total scores), and item response patterns (i.e., the utilization of item response options). The results of factor analysis showed that two factors underlie RS (as determined by the Kaiser criterion and scree plot) and account for 52% of the total variance. However, only reversed items load on the second factor. MARS total scores correlate moderately with anxiety (Generalized Anxiety Disorder-7 GAD-7; r (503) = .35, p < .001), depression (Center for Epidemiologic Studies-Depression, CES-D; r (505) = .36, p < .001), borderline personality features (McLean Screen Instrument for BPD, MSI-BPD; r (503) = .37, p < .001), and psychological health (Schwartz Outcome Scale, SOS; r (505) = -.41, p < .001). To further establish construct validity, the association between MARS total scores and total scores for items measuring difficulties related to RS on the MSI-BPD will be assessed. Additionally, the degree to which MARS total scores discriminate between scores on the Personality Disorder Questionnaire (PDQ-IV), which measures features of different personality disorders, will also be assessed. Finally, predictive validity will be established by assessing the degree to which baseline total scores on the MARS predict treatment outcome. Assessing the psychometric properties and clinical utility of the MARS is a necessary step in the construction of the inventory. The preliminary findings indicate that the psychometric properties of the MARS are good.

Topic areas:
Anxiety
Borderline Personality Disorder
Depression
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Title: Risk factors for increased length of stay in child emergency psychiatry visits

Key words: emergency psychiatry  length of stay  child psychiatry

Objective: To characterize child psychiatry visits and assess risk factors for longer lengths of stay (LOS) in a large psychiatric emergency department (ED).

Method: We identified the electronic health records of children age 4-17 years who presented to our urban, academic, tertiary referral medical center in Massachusetts and who were evaluated by a psychiatrist. We calculated these patients’ LOS and extracted demographic and clinical features including prior outpatient or emergency psychiatry visits and chief complaint. We applied quantile regression to assess potential risk factors for association with increased LOS.

Results: The cohort included 2,829 visits involving 2,127 children and adolescents between November 2008 and March 2015: median age was 15 years (IQR=12-16). Median LOS was 8.2 hours and 90th percentile was 24.1 hours (IQR=5.4-16.0). In multivariate quantile regression, older age, more recent year of presentation, and lack of commercial insurance were strongly associated with increased LOS; all were significant at both 50th and 90th percentiles (p<5x10^{-4}) and all three effects were significantly larger at the 90th percentile (p<.005). Chief complaint of suicidality was associated with increased median LOS (p=0.001), but not 90th percentile.

Conclusions: During the years 2009-2015, LOS in the ED for children with psychiatric emergencies increased substantially, with a disproportionate effect seen on prolonged stays. Specific demographic and clinical features, including age, insurance type, and chief complaint, identified those children at risk for longer ED stays.

Topic areas:
Child
Title: Efficacy related modulation of behavioral effects of opioids during chronic buprenorphine treatment in squirrel monkeys

Key words: Opioid  Buprenorphine  Addiction  Behavior

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. Buprenorphine (BUP), a partial agonist at the μ opioid receptor, is commonly prescribed for the management of opioid addiction but its ability to reduce reinstatement behavior in laboratory subjects is not well understood. In the present studies, squirrel monkeys (n=4) were trained to respond under a drug/food choice procedure (i.e., concurrent FR schedules of i.v. oxycodone and milk delivery). Next, the priming strength (i.e., % injection lever responding when the choice was between i.v. saline or milk) of different opioids was determined before and during chronic BUP treatment (0.1 or 0.32 mg/kg/day). Results thus far indicate that: 1) despite decreased potency, indicative of tolerance, full agonists (oxycodone, methadone) maintain priming strength during chronic treatment whereas 2) the priming strength of partial agonists (nalbuphine, butorphanol) is dramatically decreased. These results suggest a reduction in the ability of lower efficacy, but not high efficacy, agonists to provoke relapse in BUP-maintained people. The extent to which these findings may reflect efficacy-related differences in other opioid endpoints (e.g. analgesia) during BUP maintenance remains to be determined.
Division of Alcohol and Drug Abuse

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Title: The Role of Case Management in an Outpatient Buprenorphine Program

Key words: Case Management  Buprenorphine  Outpatient  Groups

Introduction: Case management has been shown to improve outcomes for a spectrum of addictive disorders. (1) Individuals in methadone programs who are assigned to additional case management miss fewer doses of medication, more regularly attend physician appointments and have a reduced number of substance positive urine drug screens. (2) However, the role of case management for opioid addiction has mainly been explored through its use in methadone programs. Specifically, there is limited research regarding its use in outpatient buprenorphine treatment, and even less information about the demographics of those who are most likely to benefit from additional case management in these programs.

Aim: The proposed work will examine a series of patients who entered the buprenorphine outpatient program at McLean Hospital over a six-month period from 4/1/2015-10/1/2015. The format of this tailored treatment includes an average of 16 weeks of twice-weekly case management with a Licensed Clinical Social Worker, in addition to weekly appointments with an Advanced Practice Registered Nurse who receives oversight by a Board Certified Addiction Psychiatrist. Referrals to the program are provided through multiple outlets, including intensive outpatient partial programs, residential admissions, and detoxification units. Demographic characteristics of age, gender, type of substance use, length of dependency in years, and referral source are used as descriptive variables. Outcome measures include adherence to treatment as determined by the number of no-show appointments to case management/groups and the number of buprenorphine positive urine drug screens. The rate of abstinence is measured by the number of negative urine drug screens. Urine drug screens that did not contain buprenorphine are counted as positive. The final outcome measure is treatment completion determined as the point in which the patient meets criteria to be transitioned from the more acute buprenorphine stabilization group to a buprenorphine group maintenance level, where urine drug screens and scripts are provided on a monthly basis. This transition occurs after a series of negative urine drug screens and consistent group attendance for a minimum of 6 weeks. This project hopes to inform the allocation of case management resources.

Methods: Six patients began treatment through the outpatient buprenorphine clinic at McLean Hospital from 4/1/2015-10/1/2015. Provided the small sample size of this growing program, a within subject analysis will focus on describing how the cohort of people receiving the same type of treatment (case management) perform in the selected outcome measures. The online medical record system, Meditech, was queried for further demographic information of the patients. Clinigen Labs, the laboratory contracted with McLean Hospital was used to accurately report the number of positive versus number of negative results over the designated time period.

Conclusions: The projected outline for completion of results is 1/1/16

Topic areas:
Addiction
Title: Differences in delay discounting across the mood disorder spectrum: A high-density event-related potential study

Key words: Bipolar disorder MDD FRN Delay discounting

Background: Current diagnostic classification systems often fail to differentiate bipolar disorder (BD) from unipolar major depressive disorder (MDD) due to their overlapping symptom profiles. Therefore, improving diagnostic precision requires moving beyond purely descriptive categories of symptoms and examining phenotypes that better map onto underlying neurobiology. Emerging evidence indicates that dysfunction within brain reward pathways, in particular the ventral striatum and anterior cingulate cortex (ACC), may underpin symptoms that are specifically elevated in those with BD, particularly increased reward sensitivity and impulsivity. Therefore, examining the neural correlates of reward sensitivity and impulsivity in individuals with MDD and BD may point to more reliable biomarkers that can improve mood disorder diagnosis. This study aimed to directly compare neural reward responses, as well as changes in the magnitude of these responses when there was a delay until reward receipt, across MDD and BD. Decreases in the subjective value of delayed rewards (known as delay discounting) is a robust measure of impulsive choice, so we hypothesized that individuals with BD would show greater reductions in neural responses to delayed rewards than individuals with MDD or healthy controls.

Methods: Participants with BD (n=7), MDD (n=10) and healthy controls (n=17) completed a novel delay discounting task while 128-channel high-density event-related potentials (ERPs) were recorded. ERPs were time-locked to receipt of rewards and losses that were delivered immediately or after a delay. We focused our ERP analysis on the feedback-related negativity (FRN). This is a negative-going ERP component involved in early outcome evaluation, thought to arise from phasic reward-related signaling that originates in the striatum and projects to the ACC. FRN amplitude has been found to be more negative for more unfavorable outcomes.

Results: As expected, across the entire sample FRN amplitude was smaller to rewards than to losses (F1,33=5.68, p=.02, ηp²=.15). However, distinct patterns of FRN activity emerged for responses to delayed rewards and losses. Specifically, although individuals in the control and MDD groups showed smaller FRN amplitudes for delayed rewards relative to delayed losses (F1,26=9.94, p=.004, ηp²=.28) (indicating that rewards received after a delay were valued more favorably than losses received after a delay), individuals with BD showed FRN amplitudes to delayed rewards that were almost identical to the neural responses that they showed to delayed losses (p=.97). Furthermore, a smaller difference in FRN amplitude to delayed rewards and losses was associated with higher scores on the Barratt Impulsivity Scale (r=-.45, p=.01).

Conclusions: These interim findings indicate that individuals with BD show greater devaluation of delayed rewards (reflected in reduced FRN amplitudes) relative to those with MDD and controls, and this devaluation may be associated with abnormalities in reward feedback monitoring regions involving the ACC. Furthermore, this reduction in neural activity was correlated with increased levels of impulsivity, indicating that abnormalities in processing the value of delayed rewards may be a mechanism driving the impulsive behaviors commonly observed in BD mania, such as spending sprees, substance abuse and risk-taking. These findings contribute toward a better understanding of the neurobiological differences that distinguish BD from MDD.

Topic areas:
Bipolar
Depression
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