Full Abstracts for Poster Session

Wednesday, January 30, 2019

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Presenting Author: Alison Masey, Postdoctoral Fellow

Co-Authors: Stabler, Tony Psy.D.; Harper, David, Ph.D.; Patrick, Regan, Ph.D

Title: Does Color Effect Processing Speed?: A Study of Stroop Performance Among Older Adults with Mood Disorders

Key words: older adult, depression, cognition, processing speed

Objective: The Stroop Color and Word Test manual (Golden and Freshwater, 2002) states that “Occasionally, low Color scores are seen in psychiatric clients where the colors may arouse emotional rather than cognitive reactions” (p. 9). While not accompanied by any references, this statement is presumably grounded in the broader and somewhat obscure literature linking chromatic stimuli with affective valence. Review of the literature, however, reveals minimal direct support for slowed Color Naming vs Word Reading in affective disorders, with almost no studies examining this purported phenomenon in older adults. Therefore, the present study investigated whether older adults with mood disorders showed disproportionate difficulty on Color Naming vs Word Reading.

Participants and Methods: One-hundred and twenty-four older adults were selected from a database of research participants at a large psychiatric hospital in the Boston area (35 controls, 24 Major Depressive Disorder, and 65 Bipolar Disorder). All participants completed the Stroop as part of a larger neuropsychological battery. We analyzed whether trait-based (diagnostic category) or state-level (MADRS) mood disturbance differentially affected Color Naming vs. Word Reading scores.

Results: A two-way repeated measures ANCOVA controlling for age and sex did not reveal a significant group (Control, Unipolar, Bipolar) by condition (Color Naming, Word Reading) interaction (p=.56). In addition, linear regression revealed that state-level depression (MADRS) was not predictive of a Word-Color discrepancy score among patients with mood disorders (p=.173).

Conclusions: The present investigation revealed that, at least among older adults with mood disorders, neither state- nor trait-level mood disturbance was predictive of disproportionate difficulty on Color Naming vs Word Reading. These findings are not supportive of the Stroop manual’s claim that “colors may arouse emotional rather than cognitive reactions” among psychiatric patients.

Topic areas:
Bipolar Disorder
Depression
**Title:** Preliminary findings on the effect of stress and GABA on reward sensitivity

**Key words:** depression, reward, stress, GABA

**BACKGROUND** Prior work has shown attenuated reward responsivity and reinforcement learning in major depressive disorder (MDD). However, results have been mixed in individuals with remitted MDD (rMDD). In addition, there is evidence that dysfunction of the central gamma-Aminobutyric acid (GABA) system is associated with symptoms of depression and anxiety along with attentional allocation in reinforcement learning. The present study sought to examine putative effects of acute stress and GABA on appetitive reinforcement learning in those with current or remitted MDD compared to healthy controls (HC).

**METHODS** Fifty-three participants (18-25 years, 29 female) with MDD (n=10), rMDD (n=13), or HC (n=30) completed a hybrid stressor consisting of two stress-inducing tasks: the Maastricht Acute Stress Test (MAST) and the Montreal Imaging Stress Test (MIST). Ninety minutes later, the Probabilistic Reward Task (PRT) was administered, which requires that participants determine whether a short (11.5 mm) or a long (13 mm) mouth was presented on a previously mouthless cartoon face. To elicit a response bias, an asymmetric reinforcer ratio was used such that correct identification of either the short or long mouth was rewarded three times more frequently (“rich stimulus”) than correct identification of the other (“lean stimulus”). Following PRT completion, acute stress was re-introduced by informing participants they would need to repeat the MAST/MIST due to insufficient performance. The PRT (using different stimuli) was then administered a second time. A response bias was calculated with higher scores indicating greater proclivity toward the rich stimulus, and a discriminability score was calculated with higher scores indicating a greater ability to differentiate the two mouths. A learning rate was also calculated. Prior to the onset of stress, measurements of GABA in the dorsolateral prefrontal cortex (dlPFC) and rostral anterior cingulate cortex (rACC) were carried out using MEGA-PRESS magnetic resonance spectroscopy at 3T. These data were analyzed using mixed effects linear regression in R.

**RESULTS** There were no significant main effects or interactions of group (MDD, rMDD, HC), stress (pre- or post) or dlPFC/rACC GABA on PRT response bias, discriminability, or learning rate (all ps > .08). The analysis was repeated with the MDD groups collapsed (with MDD and rMDD as a single group) to increase power; however, there were also no significant effects of stress, group or GABA on PRT behavior (all ps > .08).

**DISCUSSION** These preliminary findings are drawn from an ongoing study and suffer from a relatively small sample size and diminished power. However, the lack of an effect of stress even when collapsing across remitted and current depressed patients suggests a potential absence of a trait-level difference between those with a history of depression and healthy controls on reward sensitivity or reinforcement learning following stress. The subsample of participants with GABA data was very small (n=18), therefore any interpretation of the GABA data is preliminary. Additional work with greater sample sizes will assist in further clarifying these findings.

**Topic areas:**
Depression, Imaging
Title: A Longitudinal Study of the Mismatch Negativity Event Related Potential and Functioning in First Episode Psychosis

Key words: Mismatch Negativity, Functioning, Psychosis

Introduction: Mismatch negativity (MMN) is an event related potential (ERP) that occurs approximately 200 ms following exposure to a deviant stimulus within a set of standard stimuli. MMN can be elicited automatically, and therefore reflects the preconscious detection of a deviation from the brain’s sensory memory trace (Näätänen & Alho, 1995). MMN has been identified as a robust biomarker of schizophrenia, with deficits in the ERP related to worse functioning (Light & Braff, 2005). Previous studies have demonstrated that the MMN deficit is present at first episode in both schizophrenia spectrum diagnoses (SZ) and bipolar disorder with psychotic features diagnoses (BD) (Kaur et al., 2011). The present study examined 1) the differences in MMN between patients with first episode psychosis (FEP) and healthy controls, 2) the relationships between MMN and symptom severity, 3) the relationship between MMN and a range of cognitive and social functional domains controlling for clinical symptom severity and 4) how these relationships change longitudinally after a 12-month follow-up.

Methods: FEP patients (n=39), including those with SZ spectrum diagnoses (n=19) and those with BD (n=20), and healthy control subjects (n=32) completed a duration MMN paradigm (1200 binaural 80-dB, 1000 Hz tones, inter-stimulus interval of 300 ms, 85% standard 25 ms tones and 15% duration deviant 50 ms tones). The MMN response was determined by the difference between the response to the deviant stimuli and the response to the standard stimuli at the Fz, T7, TP7, T8, and TP8 sites. Twenty-one FEP patients also completed the MMN ERP paradigm at a 12-month follow-up. To assess functioning, subjects completed the Global Assessment of Functioning Scale (GAF), Multnomah Community Ability Scale (MCAS), The Awareness of Social Inference Test Revised (TASIT), Functioning Assessment Short Test (FAST), and UCSD Performance Based Skills Assessment – Brief Version (UPSA-B). Clinical symptom severity measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), and Positive and Negative Syndrome Scale (PANSS).

Results: At baseline, differences in MMN between controls and patients were not significant at any electrode sites. At the 12-month follow-up patients with SZ had significantly smaller MMN amplitudes than controls (p = 0.006) at the Fz site, whereas patients with BD did not (p = 0.69). Longitudinally, baseline MMN amplitude at Fz could predict FAST total score at the 12-month follow-up (B = 0.64 (0.02), p = 0.03). Additionally, baseline MMN amplitude at the T7/TP7 site could predict both TASIT raw score (B = -0.75 (0.02), p = 0.009) and FAST total score (B = -0.56 (0.008), p = 0.03) at the 12-month follow-up (F(2,9) = 6.68, p = 0.02).

Conclusion: Preliminary results provide evidence supporting the MMN response as a biomarker of real-life functioning in psychosis. In addition, we found diagnosis specificity of MMN deficits at follow-up in patients with SZ. Baseline MMN responses were predictive of functional measures of FAST and TASIT at 12-month follow-up and predictive power was stronger at central (Fz) and left brain regions. Additional analyses will be performed to confirm these results.

Topic areas:
Bipolar Disorder, Psychotic Disorders, Schizophrenia
Mutations of the melanocortin-4 receptor (MC4R) are strongly linked to obesity in humans, and globally removing MC4R in mice induces obesity. MC4R is strongly expressed in the hypothalamus, but deletion of MC4R within this region does not entirely account for the obesity induced by global knockout. Neurons of the arcuate hypothalamus produce the peptides that activate and inhibit the MC4R. These cells project to the medial prefrontal cortex (mPFC), where the MC4R is also highly expressed. Furthermore, imaging data implicates mPFC in human feeding behavior and obesity, and selectively deleting MC4R from the mPFC in mice results in increased food intake and weight gain. We hypothesized that MC4R activity in the mPFC regulates food-based decision making and cognitive flexibility. Here, we used viral-mediated cre-recombinase in male mice to delete MC4R in the mPFC, then tested appetitive food-based reversal learning. We also examined whether these mice exhibited altered fear learning, exploratory behavior, and novelty suppressed feeding. We found that removing mPFC MC4R slowed reversal learning compared to controls, but did not affect initial associations. These mice also took longer to begin eating in a novel context and showed fewer eating bouts. The mPFC MC4R knockouts did not differ from control in fear memory retention or extinction, and did not show differences in exploratory behavior as measured by the open field test. These results implicate mPFC MC4R in cognitive flexibility in the context of appetitive food-related information. Given that food-based decision making is a factor in eating disorders, MC4R in the mPFC may serve as a possible target for pharmacological manipulation in humans.

Topic areas:
Anxiety
Eating Disorders
Neural Changes and Recovery after Cannabinoid Exposure.

**Key words:** Cannabis, Addiction, Adolescence, Imaging

**AIM:** Epidemiological data suggest that cannabis is the most widely used illicit substance among adolescents in the U.S. Of concern, laboratory-based human studies indicate that cannabinoid exposure during developmental periods produce alterations in brain structure and function that may endure into adulthood. Thus, there is a strong need for rigorous preclinical studies to identify persistent cannabinoid-related brain alterations. Such findings can help to develop targeted therapeutic strategies to mitigate potential long-term effects of cannabinoid exposure. The present study examined the effects of acute and chronic exposure to a high potency, long-acting CB1 receptor full agonist, AM2389, on brain morphometry in nonhuman primates.

**METHODS:** Experimentally naïve, female rhesus macaques (N=4; 3.5-4 years-old) received daily intramuscular injections of 0.01 mg/kg AM2389. Scan sessions occurred 3-hr following drug administration and T1-weighted anatomic images were acquired at baseline, on the first day (acute), after treatment for 30 days (chronic), and 30 days after AM2389 treatment was discontinued. The D99 macaque atlas was used to segment T1 data and extract regional volumetric measures (in mm³). Multiple linear regression models were used to measure the effects of drug administration on brain volume, controlling for random effects of subject and global grey-matter volume. Results were corrected for multiple comparisons and Tukey-HSD tests were used for post-hoc analyses.

**RESULTS:** Analyses revealed a significant effect of cannabinoid exposure on bilateral Posterior Cingulate Cortex (PCC) volume: F(3,1)=9.71, p<.05. Analyses did not reveal significant effects of cannabinoid exposure on other brain regions (p’s>.05).

**CONCLUSION:** These data suggest that cannabinoid exposure alters brain morphometry in a regionally-selective manner. However, changes in brain volume dissipated within 30 days following treatment discontinuation, suggesting that these alterations may be transient.

**Topic areas:**
- Addiction
- Child/Adolescent
- Imaging
- Pharmacology
Alzheimer’s disease (AD) is the most prevalent neurodegenerative disease of aging, affecting approximately 5.4 million individuals in the US, and predicted to increase to 13.8 million by 2050. Treatments for severe agitation in people with advanced AD are urgently needed. Behavioral therapies are recommended as first-line treatments for agitation in AD; however, they require substantial time to take effect and may be less efficacious for the most severely agitated patients. For these reasons, psychotropic medications, especially antipsychotics, are widely used off-label to treat agitation in AD even with documented limitations in efficacy and safety concerns. Thus, new treatments for severe agitation in AD refractory to standard interventions are timely and warranted. We will address this critical need for a new intervention to treat severe agitation in dementia by conducting a multi-site, single blind, randomized, Simulated-ECT (S-ECT) controlled trial of electroconvulsive therapy (ECT) to determine the efficacy and safety of ECT for severe agitation in moderate to severe stage AD. We will also examine the durability of the acute treatment effect in an exploratory maintenance naturalistic design. Randomized controlled trials have demonstrated the safety and efficacy of ECT for the treatment of severe psychiatric disorders of late life, including depression, mania and psychosis. We will study only inpatients with severe agitation and moderate to severe dementia, associated with high care costs and poor quality of life, who typically have already failed prior trials of psychotropic medications. Preliminary open-label data from our team suggests acute ECT treatment is safe and effective in reducing agitation in this population as measured by the Cohen Mansfield Agitation Inventory, Pittsburgh Agitation Scale, Clinical Global Impression, and adverse event monitoring. If ECT is found to be safe and effective for severe agitation in AD, the study results could have important public health implications with immediate significant benefits for both patients and families, as well as society at large.

**Key words:** Aggression, ECT, Alzheimer's, Dementia, Agitation

**Topic areas:**
Alzheimer's/Dementia
Geriatric Psychiatry
Background: Currently, 33 states and the District of Columbia have fully legalized medical marijuana (MMJ) programs and an additional 14 states offer limited access to MMJ products. Marijuana (MJ) is comprised of over 100 phytocannabinoids, including delta-9 tetrahydrocannabinol (∆9-THC), primarily responsible for the intoxicating effect of MJ, and cannabidiol (CBD), a primary non-intoxicating component which may contribute to the therapeutic benefits of MJ. Acute administration studies in both animals and humans have shown that CBD may have anxiolytic properties; however, to date, no clinical trials have assessed the impact of high CBD products on individuals who suffer from anxiety.

Methods: Patients meeting a minimum threshold of “moderate” anxiety, defined by several well-validated clinical measures, with no current use of any cannabinoid-based products were recruited for the first ever open-label to double-blind clinical trial assessing the impact of a novel, proprietary high CBD sublingual tincture on anxiety. Study visits occurred at baseline, prior to beginning CBD treatment, and weekly over the course of the 4-week treatment period; at each visit, participants completed ratings of anxiety (Beck Anxiety Inventory [BAI], Overall Anxiety Severity and Impairment Scale [OASIS], Hamilton Anxiety Rating Scale [HAM-A]), mood (Beck Depression Inventory [BDI], Positive and Negative Affect Schedule [PANAS]), and quality of life (Short Form Health Survey [SF-36], WHO Quality of Life [WHOQOL]). as well as a clinical check-in. Patients were instructed to administer a custom-formulated, whole plant-derived tincture containing approximately 10mg/ml CBD three times per day.

Results: Preliminary data from the open-label phase of the trial suggests improvement on measures of anxiety and mood following 4 weeks of treatment when compared to baseline. Specifically, patients demonstrated significant reductions in anxiety and depressive symptoms as well as improvements on several quality of life measures. In addition, the study product appears to be well-tolerated with no discernible side effect profile.

Conclusions: Findings suggest that use of a custom-formulated, whole plant-derived high CBD sublingual tincture results in less severe anxiety (OASIS) and fewer anxiety-related symptoms (BAI) following 4 weeks of treatment relative to baseline. In addition, self-reported improvements in other mood symptoms and quality of life were noted, which may result from a reduction in symptoms of anxiety. While these results are promising and reflect findings from our larger observational study of MMJ patients, results should be interpreted with caution as the open-label study is still ongoing. Furthermore, a definitive assessment of the impact of this novel treatment will be ascertained in the next phase of this trial, a double-blind, placebo-controlled phase of the study, which will provide empirically sound data regarding the efficacy of sublingual CBD for anxiety.

Topic areas:
Anxiety, Quality/Outcomes
**Presenting Author:** Crystal Blankenbaker, Clinical Research Assistant, MRes

**Co-Authors:** Elyssa Barrick, Habib Rahimi Eichi, Ian Barnett, Dost Öngür, J-P Onnela, Randy Buckner

**Title:** Circuit dynamics underlying longitudinal fluctuations in mood and cognition in bipolar patients

**Key words:** Digital-phenotype

Research on bipolar illness is hampered by a lack of basic understanding of the course of dynamic circuit properties in living individuals that might underlie fluctuations in mood and cognition. Longitudinal studies are essential for gaining an understanding of the biological and experience-dependent factors that exacerbate and ameliorate affective illness. This study aims to recruit 30 participants to use mobile behavioral tracking technology and actigraphy devices to characterize the natural course of changes in mood and cognition and associated environmental variables in individuals with severe bipolar disorder or severe affective illness. Coupled with MRI, we hope to characterize changes in structural brain anatomy and functional network architecture that occur over the span of weeks to months within these same individuals. With this data, we aim to explore symptom-circuit relationships by linking changes in neuroanatomical systems to changes in specific symptom and/or processing domains. Data collection is currently ongoing and preliminary results will be discussed.
McLean Research Day 2019

Original Research - Pre-Clinical
Poster # 9
Time: 1:00-1:50pm

Presenting Author: Bin Song, Postdoctoral Research Fellow
Co-Authors: Bin Song; Pierre R. Leblanc; Melissa Feitosa; Kwang-Soo Kim; Jeffrey S. Schweitzer
Title: Columnar Injection for Intracerebral Cell Therapy
Key words: Cell therapy, dopaminergic neurons, stereotaxy

Background: Surgical implantation of cellular grafts into the brain is of increasing importance as stem cell-based therapies for Parkinson’s and other diseases continue to develop. The effect of grafting technique on development and survival of the graft has received less attention. Rate and method of graft delivery may impact the cell viability and success of these therapies. Understanding the final location of the graft with respect to the intended target location is also critical.

Objective: We describe a “columnar injection” technique, designed to reduce damage to host tissue and result in a column of graft material with greater surface area to volume ratio than traditional injection techniques.

Methods: Using a clinically relevant model system of human embryonic stem cell-derived dopaminergic progenitors injected into athymic rat host brain, we describe a novel device that allows separate control of syringe barrel and plunger, permitting precise deposition of the contents into the cannula tract during withdrawal. Controls consist of contralateral injection using traditional techniques. Graft histology was examined at graft maturity.

Results: Bolus grafts were centered on the injection tract but were largely proximal to the “target” location. These grafts displayed a conspicuous peripheral distribution of cells, particularly of mature dopaminergic neurons. In contrast, column injections remained centered at the intended target, contained more evenly distributed cells, and had significantly more mature dopaminergic neurons.

Conclusion: We suggest that this columnar injection technique may allow better engraftment and development of intracerebral grafts, enhancing outcomes of cell therapy, compared to fixed point injection techniques.

Topic areas:
Neurology
McLean Research Day 2019

Original Research - Clinical

Poster # 10
Time: 1:50-2:45pm

Presenting Author: Eleanor Schuttenberg, Clinical Research Assistant II

Co-Authors: Julia Cohen-Gilbert, Maya Rieselbach, Elena Stein, Dana Sarvey, Jessica Feinberg & Marisa M. Silveri

Title: Suicidality and emotional inhibitory control in dually diagnosed adolescents

Key words: Suicidality, Emotion, Impulsivity, Adolescents, Dual-Diagnosis

Inhibitory control, a critical aspect of self-regulation, is reduced in adolescents with substance use disorders and in individuals at an elevated risk for suicide attempts. Dual diagnosis refers to a substance use disorder co-occurring with at least one additional psychiatric diagnosis. The current study explores relationships between suicidality and inhibitory control in a sample of dually diagnosed adolescents, assessed upon their admission to the McLean Hospital Acute Residential Treatment program. All participants included in the current analyses reported some lifetime suicidal ideation. Participants (N=335, 196 female, age=16.9±1.2) performed an emotional Go-NoGo task to measure inhibitory control in the presence of distracting images that were emotionally negative, neutral, positive or scrambled. Results showed individuals who reported at least one lifetime suicide attempt (N=164) had significantly lower accuracy on inhibitory (NoGo) trials across all background conditions. In patients reporting suicidal ideation within the past month (N=201, 124 female, age=16.9±1.2), a significant group x background interaction effect was observed (p=.012) with individuals reporting suicide attempts (N=69) within the past month showing significantly increased impulsive errors on negative background trials (p=.020) and neutral background trials (p=.025). These data demonstrate that inhibitory control measures may be helpful in identifying adolescents at highest risk for attempting suicide and that inhibitory control in negative and neutral emotional contexts is particularly associated with recent suicidal actions. Further studies are necessary to parse out relationships between suicidality, inhibitory control and emotion, in order to develop interventions that may help reduce suicidality in dually diagnosed adolescents.

Topic areas:
Addiction
Child/Adolescent
Depression
Presenting Author: Eliza Passell, Clinical Research Assistant II
Co-Authors: Lauren Rutter, Luke Scheuer, Laura Germine
Title: Can Current Behavioral Methods Measure Threat-Related Attentional Bias?
Key words: threat, attention, trauma, PTSD, psychometrics

Attentional bias in perception and processing of threat-related stimuli has been linked to the development and maintenance of anxiety disorders, including post-traumatic stress disorder (PTSD). Of particular interest in relation to these disorders is the relationship between threat bias and cognitive control, the ability to adaptively direct information processing, cognition, and behavior towards a goal; the impairment of cognitive control in the presence of threatening stimuli has been hypothesized to play a role in the development of PTSD following trauma. The AURORA study, a longitudinal study of trauma survivors that examines factors that may play a role in the development of PTSD and other mental disorders, thus includes threat-related bias as one of its cognitive traits of interest in order to examine the relationship between threat bias and psychopathology following trauma. However, while many paradigms have been designed to measure threat-related attentional bias, reliability is rarely reported, making it unclear whether such tasks are appropriate for measuring individual differences. As part of the AURORA study, we examine the reliability of two tasks commonly used to measure threat-related attentional bias: a threat/neutral Sternberg working memory test and a threat/neutral dot probe test. Analyzing internal reliability for these tasks in both trauma-exposed samples and the general population, we found that both paradigms display little to no reliability. Thus, these tasks are not suitable for the study of individual differences or change over time in attentional bias to threatening stimuli. In order to study the role of threat-related attentional bias in PTSD and other anxiety disorders, reliable paradigms for measuring individual differences and change over time in threat-related attentional bias will need to be identified.

Topic areas:
Anxiety
Cognitive Sciences
PTSD
Technology
Background: Short-term treatments for depression underscore the importance of intact executive functioning (EF) abilities, and EF deficits are related to worse treatment outcomes in adults (Dunkin et al. 2000). Given that adolescence is a critical period of neurodevelopment for the prefrontal circuitry that underlies EF (Blakemore and Choudhury 2006), the present study examined the role of EF in adolescent treatment outcomes. Specifically, we tested whether interference control (i.e., suppressing task-irrelevant information) and conflict monitoring (i.e., translating the detection of conflicting information into compensatory adjustments in control) predict depression symptom reduction in the context of short-term (i.e., ~14 day) inpatient treatment.

Methods: Depressed adolescents (n = 97) recruited from a short-term inpatient treatment program were administered diagnostic interviews, and at intake and discharge completed: (a) self-report depression symptom measures and (b) the Eriksen Flanker Task. Analyses tested whether interference control (reaction time (RT) to incongruent – congruent trials) and conflict monitoring (RT to congruent trials that follow incongruent trials (iC) - congruent trials that follow congruent trials (cC)) (Gratton et al. 1992; Botvinick et al. 2001) predicted depression symptom reduction.

Results: Analyses controlled for baseline depression symptoms, age, ADHD diagnosis, and length of stay in treatment. Consistent with prior research (Schuch and Koch 2015), all analyses were restricted to trials with correct responses; additionally, conflict monitoring analyses were restricted to trials following a correct response. In line with our hypothesis, greater conflict monitoring was related to greater depressive symptoms at discharge ($\beta = 0.31, t(91) = 3.42, p = .001$). However, interference control did not predict depressive symptoms post-treatment ($\beta = -0.06, t(91) = -0.69, p = .495$).

Conclusion: Greater conflict monitoring during the Flanker Task was associated with poorer treatment outcomes. Conflict monitoring is enhanced during negative mood, perhaps due to the fact that conflict is an inherently aversive signal and thus a more salient stimulus during negative mood states (Dreisbach and Fischer 2012). Greater conflict monitoring may reflect enhanced attentional bias towards negative stimuli, which may contribute to the persistence of depression symptoms (Rude et al. 2002).

**Topic areas:**
Child/Adolescent
Depression
Quality/Outcomes
Suicide is a leading cause of death among American youths and young adults. Research has identified associations between characteristics of personality and suicidality. An “under-controlled” personality pattern, characterized by low measures of conscientiousness and agreeableness paired with elevated neuroticism and impulsivity, is associated with an elevated suicide risk. The link between this personality pattern, often associated with Cluster B personality disorders, and suicide are relatively well explored. However, there are a number of studies that show a similarly elevated risk for people that score low on impulsivity, but high on measures of neuroticism and introversion. This so-called “over-controlled” personality pattern is more commonly associated with Cluster A and C personality disorders. These “over-controlled” individuals have different symptomology and problematic behaviors that influence suicide risk. This review investigates research on individuals with over-control personality characteristics to clarify the presentation of suicidality in this population, as well as potential risk factors.
McLean Research Day 2019

Original Research - Clinical
Poster # 14
Time: 1:50-2:45pm

Presenting Author: Elliot Kuan, Technical Research Assistant
Co-Authors: Xi Chen, Talia Cohen, Kathryn Nielsen, Margaret Gardner, Dost Ongur, and Fei Du
Title: Anti-correlated Networks and GABA concentrations in Healthy Controls and Psychosis Patients

Key words: Psychosis, Schizophrenia, fMRI, MRS, GABA

Background: Large-scale neuronal networks such as the default mode network (DMN) and the frontoparietal executive control network (CN) are involved in the normal function and organization of the human brain. Neuronal networks are defined as brain regions that show coordinated activity and are composed of many neural structures from disparate regions of the brain. In addition, large-scale neuronal networks can exhibit coordinated or differential activity with other networks. The DMN shows activity at rest and becomes deactivated during external processing. The CN is anti-correlated with the DMN and becomes activated in response to cognitive tasks. The amount of DMN deactivation is also proportional to the cognitive task load, suggesting a dynamic modulation of coordinated brain activity resulting in a suppression of default brain activity to allocate resources. DMN-CN anti-correlation strength is associated with cognitive performance and decreased DMN-CN anti-correlation has been observed in neuropsychiatric disorders like schizophrenia.

Methods: In this study, resting-state functional MRI (rsfMRI) and magnetic resonance spectroscopy (MRS) were used to characterize DMN-CN neuronal activity and GABA concentrations in medial prefrontal cortex (mPFC), respectively, in healthy controls (HC, n=23) and subjects with first episode psychosis (FEP, n=19). rsfMRI was used to measure the whole-brain BOLD signal in structures within the DMN and CN (mPFC and dLPFC respectively). FEP subjects were scanned at baseline and one year after initial treatment (n=12).

Results: The rsfMRI showed that there was strong DMN-CN anti-correlation in HC and that DMN-CN anti-correlation was compromised in FEP at baseline. However, there appears to be a restoration of some DMN-CN anti-correlation in FEP at the one-year follow-up scan. GABA concentrations in the mPFC were associated with anti-correlation between DMN and CN at resting-state in HC. The association between GABA and anti-correlation in FEP generally follows the same trend as that observed in HC, with altered levels that are potentially modulated by treatment.

Conclusions: These results suggest that GABA levels in the mPFC are responsible for the disrupted DMN-CN anti-correlation seen in FEP. GABA in the mPFC is involved in modulating inter-network brain activity at resting-state.

Topic areas:
Imaging
Psychotic Disorders
Schizophrenia
Religiosity and spirituality (RS) are aspects of diversity that can be neglected in the research, assessment, and treatment of individuals with co-occurring substance use and psychiatric disorders. Yet, the inclusion of RS in the assessment and treatment planning with this population of patients is necessary from empirical clinical and clinical standpoints. For example, spirituality is one of four themes supporting recovery in women with co-occurring disorders who had survived trauma; spiritual support is one of six themes in the lived experience of patients with co-occurring substance use and bipolar disorder; and spiritual practices is a significant mediating variable between Alcoholics Anonymous attendance and better recovery outcomes for individuals with alcohol use disorders. Furthermore, the inclusion of RS in the assessment and treatment of individuals in recovery from substance use disorders is suggested by the Massachusetts Department of Public Health’s (MA DPH) Bureau of Substance Abuse Services (BSAS). The BSAS Principles of Care for Prevention, Treatment and Recovery identify patient spirituality as a core component of responding to a whole person with substance-related disorders.

While difficulties in operationalizing the terms “religiosity” and “spirituality” are inherent in RS research, it is possible to allow patients to self-identify as religious or spiritual, and so examine whether behavioral healthcare professionals identify and respond to patients’ self-defined religious and spiritual needs. For example, patients were surveyed about spirituality in the McLean Hospital’s Behavioral Health Partial Hospitalization Program, and they indicated that spirituality is “somewhat or definitely important in their life (92.9%) and plays a central role in their mental health (87.9%)”.

The purpose of this quality improvement effort is to examine RS-related assessment practices at McLean Fernside, a 30-day residential treatment program for co-occurring substance use and psychiatric disorders in Princeton, Massachusetts. Specifically, it will be a retrospective record review of the most recent (20) patients to examine whether and how assessments include any focus on the religious and spiritual practices and/or interests of patients. The main goal of this initiative is to generate baseline data which may be part of a future quality improvement effort that might take a trajectory of the following: (1) researching the extent to which spirituality is included in assessment; (2) providing feedback to staff; and (3) reassessing in the future to develop a “control chart” to follow the process of assessment with regard to spirituality over time.

**Topic areas:**
Addiction
Quality/Outcomes
Adolescence is a period of development characterized by rapid changes in brain structure and function. Incongruous maturation rates across brain systems during this period can manifest in maladaptive behaviors, helping to explain why rates of risk-taking (e.g. initiation of alcohol use) are elevated in adolescence. Developmental studies have identified functional brain activation patterns observed during blood oxygen level dependent (BOLD) fMRI that are associated with risk for initiating alcohol use. Less is known, however, about the developmental profile and implications of cerebral blood flow (CBF), which through neurovascular coupling is more closely related to neuronal activation than the BOLD signal. Accordingly, healthy adolescent participants (n=52, 25 female) between ages 13-14, who were alcohol and drug naïve, underwent pseudo-continuous arterial spin labeling (pCASL) at 3.0T and completed demographic questionnaires, the Brief Sensation-Seeking Scale (BSSS, self-report of sensation seeking) and the Barratt Impulsiveness Scale (BIS, self-report of impulsiveness). pCASL data were pre-processed, including motion correction, using FSL. Subtraction images, calculated by subtracting the pre-processed control-label images, were used to calculate CBF maps in units of ml/100g/min using Equation 1 from Alsop et al. 2014. Global CBF values were then calculated using a whole brain mask. Consistent with previous studies, whole brain GM CBF was significantly higher in girls than boys (p=.001). GM CBF was also significantly negatively associated with baseline age (p<.002, controlled for sex), which ranged from 13.05 to 14.98 (FWE corrected p < 0.05). There were no significant differences between girls and boys for BSSS or BIS scores, nor did scores significantly vary as a function of age. There was a significant relationship (controlling for sex and family history of AUD) between GM CBF values and BSSS disinhibition scores, with higher CBF associated with less disinhibition. No other significant relationships between GM CBF and self-report measures were observed. CBF may make important contributions to the underlying neurocircuitry mediating risk and reward during adolescence, which changes rapidly during the second decade of life, and in a sex-specific manner. Furthermore, quantification of CBF is necessary to reconcile functional brain activation patterns, observed during rest or task performance, that may serve as biomarkers of risk for initiation of use during adolescence, as well as for the manifestation of alcohol use disorder later in life.
Pain catastrophizing is a cognitive response that is characterized by the interpretation of pain as harmful or intolerable. Higher pain catastrophizing is associated with greater pain reactivity, pain disability, and emotional distress in patients seeking treatment for chronic pain. The current study characterized pain catastrophizing and its demographic and clinical correlates in a sample of individuals receiving inpatient substance use disorder treatment who also endorsed current chronic pain (N=244, 67.6% female). In a series of regression models, we tested the associations between pain catastrophizing and functioning, specifically pain-related phenomena, substance use severity, and mental health variables. Higher pain catastrophizing was associated with greater pain interference (β = 0.10, SE = 0.01, p < .001), higher levels of craving (β = 0.04, SE = 0.01, p = .009), and greater mood and anxiety symptoms (β = 0.20, SE = 0.05, p < .001 and β = 0.11, SE = 0.02, p < .001). These relationships remained significant when pain severity was included in the statistical models. Elucidating how pain catastrophizing relates to pain interference, substance use, and mental health among individuals with a current substance use disorder is important because pain catastrophizing could be targeted therapeutically to improve treatment outcomes.
Embedding medical alert technology into primary care practice to combat self-injury mortality

Background: Primary care practitioners are unprepared to respond effectively to the 30% increase in suicides and the opioid abuse epidemic as intersecting crises causing Americans to die younger for 2 years in a row. Novel approaches are urgently needed on the front lines of office practice to reduce the devastating impact of these causes of premature mortality on families and societal functioning. Objective: We propose to design a medical alert system for primary care clinicians to prescribe for patients at risk for life-threatening emergencies due to psychiatric and substance abuse disorders. Shown to reduce morbidity and mortality for general medical conditions, such technology can be transposed into the behavioral health domain to address life-threatening emergencies.

Methods: Primary care practitioners and behavioral health experts can collaborate with providers of medical alert systems to design a product specifically for life-threatening behavioral health emergencies.

Results: We propose to create a medical alert system that primary care practitioners can offer to patients for activation in potentially life-threatening situations such as an impending suicidal act or overdose with substances of abuse. The ability to offer such a safety net may encourage clinicians to engage patients in risk assessment and thereby enhance their willingness to accept evidence-based treatments such as agonist therapy for opioid dependency. When treatment fails, this intervention enables patients during ambivalent pre-suicidal moments to activate a rescue response. Such systems provide an indirect wireless connection 24/7 to a known clinician via a necklace-type push-button call device or to the National Suicide Prevention Lifeline (1–800–273–TALK (8255)] which received more than 2 million calls in 2017. Mobile units can initiate an emergent response to a location identified by GPS anywhere in the United States where GSM cellular phones operate. Providing parity for potentially lethal behavioral health situations similar to the immediate medical attention available for suspected medical emergencies, a dedicated behavioral health response system would also facilitate optimal case-specific interventions by first responders.

Conclusion: Combating stigma, medical alert technology can be incorporated into primary care practice to mobilize emergency responses for potentially life-threatening behavioral health emergencies. Once feasibility is demonstrated by acceptance on the part of patients and families, the efficacy of this strategy can be determined prospectively by tracking the outcome of emergency responses and relevant demographics.

Topic areas:
Addiction, Child/Adolescent, Depression, Education, Technology
Title: Repeated Δ9-Tetrahydrocannabinol (THC of Marijuana) Promotes Dramatic Changes in Dopamine Signaling Parameters in Basal Ganglia: Cannabidiol (CBD) Attenuates the Changes

The composition of marijuana remains largely unregulated, even though consumption is rising in parallel with rising evidence of harm. The marijuana plant produces over 100 different cannabinoids, including the structurally distinct principals, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC concentrations in retail marijuana have risen dramatically, while CBD levels have declined, with THC:CBD ratios now 8 times greater than before. THC and CBD engender markedly different or even antagonistic molecular, pharmacological and neuropsychiatric effects. High concentrations of THC and high ratios of THC:CBD in marijuana are associated with more robust euphoria, anxiety, and psychotic symptoms, whereas CBD mitigates the effects of THC by attenuating anxiety, cognitive deficits or psychosis. In contrast to THC, no comparable evidence implicates CBD in engendering euphoria, psychosis, cognitive impairment, anxiety, or addiction. Their contrasting pharmacology is poorly understood, but heavy marijuana users self-report blunted “high”, with evidence of attenuated dopamine signaling. We postulated that repeated THC will promote dopamine system neuroadaptation and that co-administered CBD will blunt the responses. 

AIMS: In nonhuman primates, we investigated whether THC altered D1-D2 dopamine receptor heteromers, signal transduction mechanisms and whether combined THC and CBD altered the responses elicited by THC alone. D1-D2 heteromer activation produces aversive behaviors, manifest by reduced hedonic value of psychostimulant drugs and by rodent behaviors consistent with depression and anxiety. D1-D2 heteromer disruption amplifies stimulant reward and promotes rodent anxiolytic, antidepressant behaviors.

METHODS: Adult male rhesus monkeys (n=3/group) were administered (a) THC (0.32-1.0 mg/kg) for 24 days), (b) THC (0.32-1.0 mg/kg over 24 days) and CBD (1-3 mg/kg) for 16 days, (c) vehicle daily for 24 days. RESULTS: THC produced profound neuroadaptive changes in dopamine signaling cascades within the caudate-putamen (CP) or nucleus accumbens (NAcc). CBD attenuated these responses. THC increased: 1. D1-D2 heteromer expression in CP and NAcc; co-administration of CBD markedly attenuated the THC-induced response. 2. expression of pCaMKIIα in NAcc, but not in CP; CBD abolished this effect in NAcc. 3. Thr75-DARPP-32 phosphorylation in NAcc and CP neurons; CBD abolished this response. 4. ΔFosB in NAcc and CP; CBD abolished this effect. 5. phosphorylation (activation) of BDNF receptor tropomyosin kinase B (pTrkB) in NAcc and CN; CBD attenuated this response. THC decreased: 1. phosphorylation of both subunits of pERK1/2 in NAcc; CBD restored pERK2 phosphorylation and partly reversed THC effects on pERK1. 2. phosphorylation of both subunits of GSK3 in NAcc; CBD blocked this effect. 3. Ser845-GluA1 phosphorylation in the NAC; CBD did not attenuate THC effects. SUMMARY and CONCLUSIONS: THC and CBD produced opposing effects on proteins involved in dopamine signal transduction mechanisms, warranting further comparisons of the pharmacological and pathological consequences of high/low THC:CBD ratios and whether CBD can attenuate the effects of a range of THC doses, especially after prolonged use. Except for cannabidiol-specific products, most retail marijuana strains contain immoderately high concentrations of THC and scant CBD levels. Accumulating research documents the pitfalls of an unregulated industry, operating without a foundation of informed science.

Topic areas:
Addiction, Pharmacology, Psychotic Disorders
McLean Research Day 2019

Presenting Author: Dawn Sugarman, Assistant Psychologist, Alcohol and Drug Abuse Clinical and Health Services Research Program; Assistant Professor, Harvard Medical School

Co-Authors: Laurel E. Meyer, Meghan E. Reilly, Scott L. Rauch, and Shelly F. Greenfield

Title: How Can Technology Enhance Mental Health Treatment for Transitional Aged Women with Co-occurring Substance Use?

Key words: technology, addiction, comorbidity

Transitional aged youth (usually defined as age 16-26 years) have the highest rates of substance use and substance use disorders (SUDs) of any age group. Although men historically have higher rates of SUDs than women, research shows that this gender gap is narrowing, and rates of substance use are nearly equivalent for transitional aged men and women. Moreover, transitional aged youth with comorbid psychiatric disorders are at increased risk for developing an SUD. Despite this risk, mental health treatment often does not adequately address substance use in patients receiving care for a comorbid diagnosis. Technology-based interventions (TBIs) could overcome barriers to addressing substance use in a psychiatric treatment setting. This study utilized a user-centered design process to better understand how technology could be used to address substance use in transitional aged women receiving psychiatric care. All participants were in treatment (inpatient, residential, or partial hospitalization) for a psychiatric disorder, but not formally engaged in treatment for an SUD. We conducted qualitative interviews and administered self-report surveys on substance use and technology use. Interviews were audio-recorded and transcribed. Transcripts were analyzed using thematic analysis in NVIVO 11. Fifteen transitional-aged women (mean age=22, SD=2.8; 87% White; 14% Hispanic or Latino) were recruited from five treatment programs at McLean Hospital. Primary reason for admission to treatment included anxiety (71%), depression (64%), eating disorder (43%), and posttraumatic stress disorder (36%). Participants indicated that alcohol (86%) and marijuana (43%) were the two substances that have caused them the most problems in the past year. Few participants (14%) had ever received treatment for an SUD. However, most participants (79%) indicated that they would engage with a TBI focused on substance use as part of their mental health treatment. Four key themes emerged from the qualitative data: (1) gaps in treatment, (2) important topics to address, (3) technology solutions, and (4) technology preferences. Regarding gaps in current treatment, participants reported a lack of integrated care addressing substance use and co-occurring disorders, and concern that disclosure of substance use to treatment providers would jeopardize their status in treatment. Participants identified several important topics related to women their age including substance use and sexual assault, stigma and shame, difficulties staying sober while maintaining social relationships with peers, and negative emotions as a trigger for use. Regarding the TBI, there was a preference for a mobile-based platform, a desire for a digital peer-support component, and the importance of including personalized feedback. These data provide preliminary evidence that a TBI may be a feasible way to address salient topics related to substance use for transitional aged women in a psychiatric setting.

Topic areas:
Addiction
Technology
Women
McLean Research Day 2019

Original Research - Pre-Clinical

Presenting Author: Debkanya Datta, Assistant Neuroscientist; Instructor in Psychiatry

Co-Authors: Sivan Subburaju, Jugajyoti Baruah, Sarah Kaye, Anju Vasudevan

Title: Human forebrain endothelial cells: new avenues for interneuron-based therapy of neuropsychiatric disorders

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

Abnormalities in GABAergic interneurons are implicated in the pathology of severe brain disorders like schizophrenia and epilepsy, for which effective treatments are still elusive. Transplantation of human stem cell-derived interneurons is a promising cell-based therapy for treatment of these disorders. In mouse xenograft studies, human stem cell derived-interneuron precursors could differentiate in vivo, but required a prolonged time (up to seven months) to migrate from the graft site and integrate with the host tissue. This poses a serious roadblock for clinical translation of this approach. For transplantation to be effective, especially for very sick or severe patients, grafted neurons should migrate to affected areas at a faster rate. Our group has previously discovered in mouse that endothelial cells of the periventricular vascular network act as physical substrates, and provide valuable guidance cues for migrating GABAergic interneurons in the developing forebrain. In this study we translated this discovery into human, with significant therapeutic implications. We generated human periventricular endothelial cells, using human pluripotent stem cell technology. We validated molecular, cellular and functional properties of the derived cells using microarray profiling and cell-based assays. Co-culture of human periventricular endothelial cells with human interneurons showed a significant increase in rate of interneuron migration in vitro. Co-transplantation of human periventricular endothelial cells with human interneurons in adult mouse brain led to faster migration and wider distribution of grafted interneurons, compared to neuron-only transplants. These results establish that human periventricular endothelial cells are critical for long distance migration of human GABAergic interneurons, and pave the way for a novel strategy for effective interneuron transplantation. Co-delivery of human periventricular endothelial cells with human interneurons will accelerate the migration of grafted neurons in diseased brain, leading to faster and effective brain repair. This strategy will facilitate the advancement of interneuron-based cell therapy into a clinical setting and open new avenues for cure of serious neuro-psychiatric disorders.

Topic areas:
Neurology
Quality/Outcomes
Schizophrenia
McLean Research Day 2019

Original Research - Clinical

Poster # 22

Time: 1:50-2:45pm

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

Co-Authors: Heejong Sung, Charity J. Morgan, Michael J. Coleman, Deborah L. Levy

Title: Heritability of Thought Disorder in Schizophrenia and Bipolar Patients and their Clinically unaffected First-Degree Biological Relatives

Key words: Thought disorder, schizophrenia, bipolar disorder, endophenotypes, heritability

Cognitive dysfunction is a fundamental component of serious mental illness (SMI). One key feature of cognitive dysfunction is thought disorder (TD). Although TD is a transdiagnostic feature of SMI, certain TD profiles are strongly associated with individual disorders. The TD phenotypes in clinically unaffected relatives of schizophrenia patients (RelSZ) and relatives of bipolar disorder patients (RelBPD) are qualitatively similar to (but milder than) that found in the respective proband groups. Among RelSZ, 34% (91/268) show the same distinct form of TD seen in schizophrenia (SZ) probands. Among RelBPD, 37% (14/38) show the same distinct form of TD seen in bipolar disorder (BPD) probands. Here we examine the heritability, as measured by relative risk, of TD in the largest patient and relatives' samples studied to date. We report significant heritability of schizophrenia-related TD in SZ and RelSZ (but not in BPD and RelBPD) and of BPD-related TD in BPD and RelBPD (but not in RelSZ). These results are consistent with the relative specificity of each TD phenotype and meet the heritability criterion for an endophenotype. The significant heritability and high recurrence rate of TD in unaffected relatives strengthen the rationale for incorporating TD in genetic studies of SMI.

Topic areas:

- Bipolar Disorder
- Psychotic Disorders
- Schizophrenia
Presenting Author: Devin Dattolico, Research Student

Co-Authors: Andrew D. Peckham Ph.D., R. Kathryn McHugh Ph.D., Thröstur Björgvinsson, Ph.D., A.B.P.P., Courtney Beard Ph.D.

Title: How Does Urgency Overlap with Craving in A Transdiagnostic, Acute Psychiatric Sample?

Key words: Urgency, Craving

Background: Urgency is a facet of impulsivity involving impulsive actions in response to strong positive or negative emotions. Impulsive action triggered by negative affect is known as negative urgency, while impulsive action due to positive emotion is called positive urgency. Substance craving may also be triggered by strong negative or positive emotion, yet little research has investigated potential overlap between craving and urgency. Some research has demonstrated links between negative urgency and substance craving in community and student samples, but little research has tested the connection between craving and urgency in psychiatric treatment-seeking samples. The present study examined the overlap between substance craving and urgency in a transdiagnostic, acute psychiatric sample. We hypothesized that craving would correlate with both negative and positive urgency. In addition, we plan to test whether high levels of urgency at admission are predictive of higher levels of daily craving measured during treatment.

Method: Data were obtained from 141 adults attending McLean Hospital’s Behavioral Health Partial Hospital program, which provides intensive, transdiagnostic CBT-based treatment. Participants were selected for analysis if they indicated problematic substance use patterns at admission, as defined by positive screens self-report measures of alcohol use (the AUDIT) or drug abuse (DAST). The average age of participants was 29.9 (SD = 13.85), and was 56% female, 41.1% male, and 2.8% transgender/non-binary. Patients completed the negative and positive urgency scales from the short form of the Urgency, Premeditation, Perseverance, Sensation Seeking, and Positive Urgency scale (UPPS-P) on admission day. On admission day and on each consecutive treatment day participants also completed a 3-item self-report measure of state alcohol and drug craving. Upon discharge a subset of participants completed a modified 6-item Obsessive Compulsive Drinking Scale (n = 63), which measures intrusive drug and alcohol craving over the past week.

Results: On average, self-report scores of craving were relatively low (3.0/10) and moderately right-skewed. We found that craving correlated (using Spearman’s rho) with positive urgency, r = .19, p = .03 and negative urgency r = .25, p < .01. Past week intrusive cravings measured at discharge correlated with positive urgency, r = .36, p < .001, however not with negative urgency, r = .14, p = .27. We also plan to test if day-to-day trajectories of craving levels during treatment are influenced by baseline (admission) level of negative and positive urgency; data collection supporting this question is ongoing and will be presented as well.

Conclusion: Our results found craving to have small to moderate correlations with urgency. Although craving and urgency are two different processes, it seems that there could be some overlap between them. Future research could test this relationship in a sample of individuals with substance use disorders, since our sample had relatively low overall substance craving. Additionally, future studies could investigate if treatment-related changes in impulsivity yield reductions in craving. Research on reducing urgency could have many clinical implications across diagnoses, including substance abuse and self-harm.

Topic areas:
Anxiety
Depression
McLean Research Day 2019

Original Research - Clinical

Poster # 24
Time: 1:50-2:45pm

Presenting Author: Devon Brunner, Clinical Research Assistant II
Co-Authors: Ironside, M.A., Kang, M.S., Rutherford, A.V., Boyden, S.D., Olson, D.P., Cusin, C., & Pizzagalli, D.A.

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

Key words: Depression, Stress, Reinforcement Learning, fMRI

Background: Stress has been implicated in the etiology of major depressive disorder (MDD), but the neural mechanisms underlying such risk remain largely unknown. Prior studies in healthy controls (HC) have shown negative effects of stress on reinforcement learning (RL), but the putative effects of stress on RL in MDD have not been tested. Using fMRI and a two-step RL task, we probed neurobiological changes in model-based (MB) and model-free (MF) RL after exposure to acute stress in MDD.

Methods: During fMRI acquisition, 43 unmedicated adults (17 with current MDD) completed a sequential two-step RL task both before and after a well-established psychosocial stressor, which involved a combination of hand immersions in cold water and difficult arithmetic under social evaluation. During the RL task, participants were given a choice between two options, which transitioned to a subsequent common (70%) or rare (30%) state, where choices were rewarded randomly.

Results: The contrast testing the Group (MDD vs HC) x Stress (pre vs post) x Learning (MF vs MB) interaction revealed increased activation in the left dorsolateral prefrontal cortex during MB decisions post-stress in the MDD group versus HC (p=.002). Uncorrected analyses (p=.005, k>20) revealed a cluster in the right caudate with increased activation during MF decisions post-stress in the MDD group versus HC.

Conclusions: These initial results reveal aberrant patterns of activation during MB decisions after stress in MDD and raise the possibility that the MDD group exerted additional cognitive control to make MB decisions.

Topic areas:
Depression
Imaging
Abnormalities of brain connectivity and signal transduction are consistently observed in individuals with schizophrenias (SZ). Underlying these anomalies, convergent in vivo, post mortem, and genomic evidence suggest abnormal oligodendrocyte (OL) development and function and lower myelination in SZ. Our primary hypothesis was that there would be abnormalities in the number of induced pluripotent stem (iPS) cell-derived OLs from subjects with SZ. Our secondary hypothesis was that these in vitro abnormalities would correlate with measures of white matter (WM) integrity and myelination in the same subjects in vivo, estimated from magnetic resonance imaging. Six healthy control (HC) and six SZ iPS cell lines, derived from skin fibroblasts from well-characterized subjects, were differentiated into OLs. FACS analysis of the oligodendrocyte-specific surface, glycoprotein O4, was performed at three time points of development (days 65, 75, and 85) to quantify the number of late oligodendrocyte progenitor cells (OPCs) and OLs in each line. Significantly fewer O4-positive cells developed from SZ versus HC lines (95% CI 1.0: 8.6, F 1,10 = 8.06, p = 0.02). The difference was greater when corrected for age (95% CI 5.4:10.4, F 1,8 = 53.6, p < 0.001). A correlation between myelin content in WM in vivo, estimated by magnetization transfer ratio (MTR) and number of O4-positive cells in vitro was also observed across all time points (F 1,9 = 4.3, p = 0.07), reaching significance for mature OLs at day 85 in culture (r = 0.70, p < 0.02). Low production of OPCs may be a contributing mechanism underlying WM reduction in SZ.
Presenting Author: Eben Holderness, Research Data Analyst

Co-Authors: James Pustejovsky, Marie Meteer

Title: Evaluating the Role of Pretraining in Natural Language Processing of Clinical Narratives

Key words: Natural Language Processing, EHR, Embeddings, Machine Learning

Background: Electronic health records (EHRs) contain detailed descriptions and longitudinal history about a patient’s illness presentation, prior course, and treatment plans. Recently, researchers have begun implementing natural language processing (NLP) models (e.g. models for topic classification, information extraction, sentiment analysis, etc.) to systematically analyze large volumes of EHR data to reveal patterns of clinical importance. Most state-of-the-art NLP models have adopted deep learning approaches where analysis is performed on an n-dimensional vector embedding of the input as opposed to the surface word level. These distributed semantic representations rely on the theory that words that are similar will cluster together in vector space. There are many approaches to generating embeddings, with a wide variance in performance on downstream tasks depending on what is being analyzed. In general, embedding models that have been pretrained on very large amounts of general-domain textual data scraped from internet resources have been shown to achieve the highest performance. Due to accessibility issues, however, there is little research on the performance of these models when applied to psychiatric EHR data. In this work we undertook a comparative analysis of several state-of-the-art embedding models for use in a topic extraction task. Specifically, we compared relative performances of the same embedding models when trained on a smaller corpus of institutional EHRs versus a much larger public domain corpus.

Methods: We evaluated numerous embedding models at the word and sentence level. At the word level we used the FastText and Embeddings from Language Models (ELMo) algorithms and at the sentence level we used the Doc2Vec and Universal Sentence Encoder (USE) algorithms. We trained each embedding algorithm (with the exception of USE) on the same set of 5M preprocessed EHR documents of patients diagnosed with a psychotic disorder and treated at any non-McLean Partners institution. We then compared these models trained on EHR data with those trained on much larger amounts of general-domain data. The strength of a given model is based on the performance of a downstream feedforward neural network that identifies EHR paragraphs involving specific ‘risk factor domains’ for readmission in a cohort of OnTrack patients, which we established precision, recall, and F1 baselines for in earlier work using Term Frequency – Inverse Document Frequency (TF-IDF) embeddings.

Results: The clustering behavior of EHR data differed across embedding models, with the strongest, most spatially distinct clustering and highest downstream performance occurring with USE embeddings (F1=0.73) due to their context-sensitive and length-insensitive nature, in addition to the large (~1000GB) general-domain corpus it is trained on. The least distinct clustering occurring with the EHR-trained Doc2Vec embeddings (F1=0.52). Preliminary results show that our baseline TF-IDF scores performed well against the other embeddings (F1=0.7) with significantly less pretraining involved.

Conclusion: Our analysis showed that our baseline TF-IDF embeddings performed well against the other embedding models. Performances varied widely, suggesting that specific algorithms are better at capturing the structure of psychiatric EHR data. Overall, results indicate that training embedding models on more data, even out-of-domain data, leads to higher performance on downstream EHR analysis tasks.

Topic areas: Bipolar Disorder, Psychotic Disorders, Schizophrenia
Introduction: Art therapy is effective for older adults by stimulating cognitive processes, helping to externalize and express emotions, and creating the potential for meaningful activity. Mindfulness has been shown to improve working memory and focus, and enhance integration of verbal and nonverbal processing. Phototherapy involves taking, viewing, manipulating, and interpreting photographs as a therapeutic process. Because of its relatively easy accessibility, spontaneity, and the ability to easily correct errors, phototherapy is an especially approachable form of art therapy compared to painting or drawing. The explosion of digital tools for phototherapy in the past 5 years offers the capability to maximize the potential of this modality by facilitating combination of both mindfulness and phototherapy for exponential treatment impact. In this study we report preliminary findings from a digital phototherapy-based mindfulness group in the SAGE program within the Division of Geriatric Psychiatry at McLean.

Objectives: The primary objective of this study was to assess the feasibility and qualitative effectiveness of a mindfulness-based phototherapy group for older adults experiencing anxiety and depression.

Methods: This was an observational pilot study of a 13-week group of 4 older women. Each session was 60 minutes long, which was later expanded to 75 minutes to allow times for mindfulness exercises and group sharing. Each participant learned how to take pictures and use the MyMoments, Union, Fuse, & Collage apps on their iPhone and iPad. Effectiveness was evaluated both qualitatively and quantitatively, by collecting unstructured participant feedback at Week 13 and administering the Rosenberg Self-Esteem Scale (RSES) and the Day to Day Experiences Scale at baseline and Week 13.

Results: We demonstrated that an approach combining digital phototherapy with mindfulness is feasible and possible to implement in a group of older adults. We also demonstrated the feasibility of teaching this cohort the use of apps for phototherapy in a group setting. While we did not conduct quantitative analysis of intervention efficacy, we noted 3 out of 4 patients scored higher on the Day to Day Experiences Scale at Week 13 compared to baseline; in addition, on the RSES at Week 13, participants endorsed statements indicative of higher self-esteem compared to baseline. Qualitative feedback indicated that participants felt a sense of mastery and continued interest in both mindfulness and phototherapy practices.

Conclusion: Our preliminary study points to the vast potential of incorporating technologies to accelerate and expand the process of art therapies such as phototherapy. Our findings bear replication and quantitative validation but point to the possibility of improving self-esteem and mindfulness skills in older adults. They may also serve as a model of how to incorporate digital tools into the process of clinical care in group and individual settings.

Topic areas:
Anxiety, Depression, Geriatric Psychiatry, Technology
Background: In a highly cited ecological momentary assessment (EMA) study, Killingsworth & Gilbert (2010) reported that healthy adults spend approximately half (46.9%) of their waking hours thinking about something other than what they are doing (i.e., mind-wandering). Importantly, mind-wandering was found to be a stronger predictor of lower mood than the activities in which participants were engaged in at the time of the EMA surveys. Research has yet to examine the role of mind-wandering within adolescent populations experiencing higher levels of low mood. The present study used EMA to investigate the affective correlates and consequences of mind-wandering in adolescents with low mood (LM) and healthy controls (HC). In addition, we examined the association between mind-wandering and resting state functional connectivity within brain networks linked to self-referential thinking (default mode network; DMN) and attentional control (dorsal attention network; DAN; frontoparietal network; FN).

Methods: The study included 55 adolescents aged 12-18 years (33 HC and 22 with LM). Participants completed a six-minute resting state fMRI scan and subsequently downloaded a smartphone application for EMA data collection (2-3 times/day for a week). Each survey prompted adolescents to report on their current positive and negative affect (PA & NA), cognitions, and activity. Functional connectivity results were corrected for multiple comparisons at the whole-brain level (height threshold p<0.005; FWE, p.13). Greater levels of mind-wandering to unpleasant content were associated with decreased connectivity between the lateral prefrontal cortex of the FN and the frontal pole (voxel size=364), angular gyrus (voxel size=176) and middle temporal gyrus (voxel size=139), as well as between the intraparietal sulcus of the DAN and the precuneus (voxel size=364), middle temporal gyrus (voxel size=310) and frontal pole (voxel size=102).

Conclusion: Rates of mind wandering among adolescents were high, especially among those endorsing elevated low mood. Results suggest that mind wandering may contribute to decreased PA and increased NA. Furthermore, elevated levels of mind-wandering to unpleasant content were linked to decreased connectivity in brain networks related to attentional control. In contrast to traditional laboratory-based paper-and-pencil questionnaires, the sampling density of repeated, daily smartphone-delivered EMA surveys allow for a more fine-grained and ecologically valid assessment of the temporal relationship between cognition and affect in real-time and in the real world.

Topic areas:
Child/Adolescent
Depression
Imaging
Effort-cost decision making is linked to individual differences in reward processing in affective but not non-affective psychosis

Background: Effort-cost decision making (ECDM) deficits are well-documented in both psychotic and affective conditions. However, recent theories posit that dissociable factors may drive these deficits in psychotic disorders with and without mood pathology; impairments in reward processing may be more strongly associated with effort deficits in individuals with mood pathology, whereas deficits in working memory may be more strongly associated with poor effort expenditure in psychotic disorders without mood symptoms.

Goals and Hypotheses: We examined associations between ECDM, reward processing and working memory in controls and a sample of individuals with psychosis spectrum disorders. We hypothesized that 1) individuals with psychosis would show deficits in ECDM compared to controls, and 2) ECDM performance would be associated with working memory in psychotic individuals without mood pathology, but with reward processing in psychotic individuals with mood pathology.

Methods: Participants with schizophrenia (SZ; n=17), schizoaffective disorder (SZA; n=25), mood with psychosis including bipolar disorder (BD; n=44) and major depressive disorder (MDD; n=1), and healthy controls (HC, n=48) were assessed for state clinical symptoms, cognitive functioning—Brief Assessment of Cognition Scale (BACS), and reward and motivational processes—Effort Expenditure for Reward Task (EEfRT) and Probabilistic Reward Task (PRT). ECDM was measured by number of hard task choices at different probabilities of winning the reward. Reward processing was measured as response bias to the more frequently rewarded (“rich”) stimulus, and “rich misses,” the rate of switching to the less rewarded stimulus after non-rewarded rich trials. The strength of this response bias was used to reflect the individual’s reward sensitivity. Working memory was measured using the Digit Span Task on the BACS.

Results: No group differences emerged for ECDM or PRT. However, when the psychosis sample was split as a function of depression status, we found that better ECDM was linked to working memory in controls (r=0.55, p<0.001) and psychosis patients without depression (r=0.57, p=0.008), but was associated with better reward learning in psychosis patients with depression (r=0.40, p=0.005).

Discussion: These findings are consistent with recent models proposing that similar deficits in ECDM across depression and SZ may arise as a result of different processes, and adds that these processes may be a result of state symptoms rather than of diagnosis.

Topic areas:
Depression
Psychotic Disorders
Schizophrenia
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Title: Altered Expression of Perineuronal Nets after Chronic Electroconvulsive Stimulation: A Pilot Study

Key words: ECT, microglia, neuroplasticity, schizophrenia, depression

Background: Perineuronal nets (PNN) are extracellular matrix structures that envelop neurons in the adult brain and modulate synaptic plasticity. PNNs have been implicated in a wide array of psychiatric disorders, most relevant in this study, major depressive disorder and schizophrenia. Electroconvulsive therapy (ECT) is an effective and fast-acting treatment for refractory depression. Despite the effectiveness of ECT, the mechanisms behind its therapeutic effects remain unknown. Recent brain imaging studies suggest that ECT may contribute to increased brain connectivity between cortical areas, particularly the anterior cingulate cortex (ACC), a region consistently implicated in major depression. Extracellular matrix molecules are broadly involved in regulating synaptic plasticity and brain connectivity. Rodent studies on epilepsy suggest that heightened electrical activity causes widespread alterations in extracellular matrix molecules, including molecules that compose PNNs, suggesting that ECT may also impact these structures and in turn contribute to changes in synaptic plasticity. We tested the hypothesis that PNN numbers are altered in brain regions involved in mood regulation, following chronic electroconvulsive stimulation (ECS) in rodents, using a model that is closely aligned with current human clinical ECT practice.

Methods: A cohort of 12-15 male mice was split into separate groups that received ECS treatment, or sham (control) treatment for 12 sessions over a course of 4 weeks. Mice were sacrificed at the two separate timepoints following the last ECS session at zeitgeber time (ZT)4 or ZT10. Total numbers and numerical densities of PNNs labeled with wisteria floribunda agglutinin lectin (WFA) were quantified in the hippocampus and ACC.

Results: We observed a significant (p=0.001) decrease in the density of WFA positive PNNs in the dorsal ACC of mice given ECS and sacrificed at ZT10. Furthermore, a moderate, non-significant (p<0.1) decrease was observed in the dentate gyrus and CA4 regions of the hippocampus in the ECS 10 hour group. No changes in PNN densities were detected in the 4 hour group.

Conclusion: Our data suggests that PNNs are affected by ECS in a region-specific manner, with the strongest effects in the dorsal ACC. Decreases of PNNs following ECS in this region may contribute to changes of connectivity reported by brain imaging studies following ECT, perhaps allowing for windows of increased synaptic plasticity. Interestingly these data also challenge the widespread notion of global and nonspecific synaptic plasticity alterations that accompany ECT and instead suggest a specificity previously unsuspected. Ongoing studies using a larger sample size and additional timepoints following ECS, along with quantification of additional brain regions and synaptic markers will provide more information into the selectivity and functional implications of PNN alterations following ECS.

Topic areas:
Depression, Neurology, Schizophrenia, Technology
Title: The involvement of SKA2, a novel GR interaction partner, in stress-related psychiatric disorders

Key words: GR, HPA axis, PTSD, Suicide, bipolar disorder

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

Methods: We conducted Immunohistochemistry (IHC) to study the expression pattern of Ska2 in human postmortem hippocampus and amygdala samples and in the mouse brain. Additional co-immunoprecipitation (co-IP) assays addressed whether SKA2 physically interacts with the GR in the mouse brain and in human postmortem brain samples. Moreover we performed GR reporter gene activity (MMTV-Luc) assays and qPCR following Ska2 perturbation to investigate the receptors activity and downstream effects in neuronal cell culture. Western blot analysis were performed to examine SKA2 protein expression in basolateral amygdala (BLA) samples of individuals with bipolar depression and matched controls. Stress-induced changes in Ska2 mRNA expression in mice were investigated via qPCR following fear conditioning.

Results: IHC analyses in human postmortem hippocampus and amygdala samples revealed a prominent expression of SKA2 in Vglut1-positive, glutamatergic neurons. Moreover, co-IPs revealed a physical interaction between SKA2 and GR in the mouse brain and human postmortem brain samples. In addition, Ska2 knockdown in mouse neuroblastoma (N2a) cells led to significantly reduced GR reporter gene assay activity, while Ska2 overexpression resulted in the opposite effect (2-Way ANOVA, interaction: F(14,42) = 16.38, p < 0.0001). Along these lines, Ska2 knockdown led to significantly altered mRNA expression of GR target genes Fkbp5 (t-test, T(21) = 2.683, p<0.05) and Id3 (t-test, T(22) = 5.762, p < 0.001). Interestingly, we detected significantly increased SKA2 protein levels in the BLA of individuals with bipolar depression compared to matched controls (ANCOVA, F = 5.83, p < 0.025, n=14 per group). Detailed mapping and co-labeling studies in mice also revealed a distinct pattern of Ska2 expression in neurons of the BLA, as well as in the hippocampus (HC), medio-dorsal thalamus, the paraventricular nucleus of the hypothalamus and throughout the cortex. Most of the Ska2-positive neurons also expressed the GR. Consequently, we assessed whether acute stress is able to modulate Ska2 gene expression. Using qPCR, we found dynamic changes of Ska2 mRNA expression four hours after stress (fear conditioning, 5 tone/foot shock pairings). Stressed mice showed significantly decreased Ska2 mRNA levels in the HC (T(18) = 2.446, p < 0.05, n = 8 (ctrl), n = 12 (stress)) and increased levels in whole amygdala punches (T(15) = 2.693, p < 0.05, n = 5 (ctrl), n = 12 (stress)) compared to baseline controls (home cage group).

Conclusions: Our findings reveal Ska2 as a novel GR interaction partner in brain regions associated with emotion processing and cognition. Further experiments showed that Ska2 gene expression is dynamically regulated by stress exposure and that Ska2 is able to positively modulate GR signaling and its downstream targets, providing a mechanistic link to its association with stress-related psychopathologies. Collectively, our data point to an important, and thus far unappreciated, role of Ska2 in stress-related psychiatric disorders, which is relevant to our understanding of the molecular mechanisms underlying such diseases.

Topic areas: Bipolar Disorder, Depression, PTSD
As cognitive impairment progresses, people with neurodegenerative diseases increasingly rely on surrogate decision-makers in all aspects of life. Thus, it is an ethical imperative for surrogate decision-makers to understand the preferences for people with clinically significant cognitive impairment (PCSCI). This study uses the Preferences for Everyday Living Inventory (PELI) to assess everyday preferences regarded as most important for PCSCI (Clinical Dementia Rating Scale ≥ 0.5). The PELI is a validated preferences assessment tool for older adults with 55 items across five domains: growth activities, enlisting others in care, diversionary activities, social contact, and self-dominion. Care partners, acting as surrogate decision-makers, also complete the PELI from the perspectives of PCSCI. Participants were community-dwelling members of a longitudinal cohort study on memory and aging. Data from 43 dyads (PCSCI and care partner; 53% female; mean age=80 years, SD=7.7) indicated that the top everyday preferences for PCSCI include “regular contact with family”, “taking care of the place you live”, and “spending time outside”; the top everyday preferences, as rated by care partners for PCSCI, include “regular contact with family”, “keeping up with the news”, and “learning about interesting topics”. The largest discrepancy in preferences assessment was in the domain of self-dominion: care partners significantly overestimated the importance of these preferences for PCSCI (paired-sample t-test, corrected p=0.032). This study yields new insights regarding the most important preferences for PCSCI and clarifies a path to optimize surrogate decision-making for PCSCI by highlighting areas of apparent disagreement in everyday preferences.
Title: Reduced stimulus evaluation of ambiguous faces in aggressive individuals

Key words: aggression, intermittent explosive disorder, face processing, EEG

Background: Social information processing theories posit that biases in encoding social cues and attributing intent contribute to aggressive behavior. Aggressive individuals show biased perception of facial affect and interpret neutral faces and ambiguous social cues as more hostile. In EEG research, the P3/late positive potential (LPP) component of the event-related potential has been shown to be enhanced in response to salient stimuli. P3/LPP is also enhanced by stimulus relevance and modulated by individual differences. The purpose of this study was to evaluate the psychophysiological response to unambiguous angry face expressions and ambiguous neutral face expressions in healthy and aggressive research participants.

Methods: Non-aggressive healthy adults (HC; n=27) and aggressive adults (n=27) who met criteria for current intermittent explosive disorder (IED) completed two facial emotion recognition tasks that presented frequent happy targets and infrequent angry and neutral targets, respectively. Participants categorized all stimuli using a button press while EEG was recorded on 128 channels. Grand average event-related potentials (ERPs) were averaged for happy, angry, and neutral faces. Permutation testing was used to test for within- and between-groups differences in ERP amplitudes (a=0.05). A dipole source model was developed based on a series of distributed source models. Source waveforms were compared between facial expressions and groups using permutation testing (a=0.05).

Results: HC subjects showed larger P3/LPP ERPs over fronto-central electrodes between 400-500 ms post-stimulus, in response to neutral compared to angry faces (p<.013). IED subjects showed no differences in ERPs in response to angry compared to neutral faces. The dipole source model yielded a residual variance (RV) of 1.7%, compared to a best fit of RV=0.6%. The model included the following sources: ventromedial prefrontal cortex (vmPFC); left dorsolateral prefrontal cortex (L DLPFC); posterior cingulate cortex (PCC); right and left insula; right and left amygdala; and right and left fusiform. Permutation testing showed that healthy subjects showed greater dipole strength in the PCC for neutral versus angry faces between 400 and 600 ms (p=.041); IED subjects show no differences in PCC dipole strength between the conditions. HC subjects showed greater dipole strength in the amygdala dipole for angry versus neutral faces between 500-700 ms (p=.011); IED subjects showed no difference. IED subjects showed greater dipole strength in L DLPFC (p=.001) and vmPFC (p=.048) during late-stage processing (600-1000 ms) in response to angry versus neutral face expressions.

Discussion: Relative to healthy (non-aggressive) subjects, aggressive subjects show reduced effects of facial expression on stimulus evaluation as indexed by the P3/LPP ERP component. Healthy subjects showed evidence of greater stimulus evaluation of ambiguous neutral facial expressions compared to unambiguous angry expressions as indexed by P3/LPP. In contrast to IED subjects, healthy subjects show differentiated responses to angry versus neutral faces in brain regions implicated in processing emotionally salient stimuli. IED subjects show evidence of greater prefrontal cortex activity in response to angry versus neutral faces, in contrast to healthy subjects. Overall, the findings are consistent with evidence from behavioral studies that aggressive individuals show biases relative to non-aggressive individuals in interpreting ambiguous social stimuli, including faces.

Topic areas:
Imaging
Probing the Adolescent Prefrontal Cortex and Hippocampus: Functional MRI Activation during Virtual Watermaze Performance and in vivo Brain GABA

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Background: During adolescence, the frontal cortex undergoes the most substantial structural and functional changes, although significant developmental changes also occur in hippocampus. Neurodevelopmentally, dynamic integration of hippocampal and prefrontal circuitry is necessary to incorporate experience into behaviors that can be risky, but adaptive for successful developmental transitions. The inhibitory neurotransmitter gamma-amino-butyric-acid (GABA) also matures during this developmental period, providing important inhibitory control over behavior. While significant age-related increases in frontal lobe GABA have been reported, less is known about age-related changes in hippocampal GABA.

Methods: In the current study, multimodal neuroimaging methods were applied at 3 Tesla, including MEGAPRESS to acquire in vivo brain GABA, from single voxels placed in dorsal anterior cingulate cortex (ACC) and in a region with strong functional and anatomical connections to hippocampus, the medial temporal lobe (MTL). Metabolites were quantified using LCModel, normalized to creatine (Cr) and corrected for relative gray matter content in each voxel type. Multiband blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired during performance of a virtual translation of the classic Morris Water Maze task using a block design and analyzed using FSL. Participants included 33 healthy adolescents, aged 13-14 years who were alcohol and drug naïve, and who exhibited no psychiatric symptoms or conditions, recruited locally to participate in a three-year longitudinal study.

Results: Spectral data acquired in year 1 demonstrated significantly lower GABA/Cr in ACC compared to MTL (p<.0001). Significant BOLD activation (cluster-based thresholding, z=3.1, p<.05) was observed in hippocampus and PFC in the memory retrieval/motor contrast [in regions that overlapped with both MRS voxels]. In an exploratory analysis combining data from these imaging modalities, during memory retrieval, ACC GABA negatively predicted activation in ventral medial PFC, whereas both ACC and MTL GABA positively predicted thalamic activation. While GABA levels in the selected voxels of interest were not correlated, functional imaging data provide evidence of both hippocampal and prefrontal activation, that in future functional connectivity analyses may be used to probe the coupling between these regions.

Conclusion: Lower ACC GABA likely reflects a later maturation of this neurochemical in PFC, which will be examined in longitudinal analyses. Furthermore, while MTL GABA did not predict PFC activation, GABA levels across both regions predicted thalamic activity, which may be an important neuronal relay between these regions. Coupling between hippocampal and prefrontal regions, as described by the Experience-Driven Adaptive Cognitive Model, may shed light on the role of memory in risk-related behaviors that are developmentally adaptive, but that can become maladaptive, particularly as adolescents initiate alcohol and drug use.

Topic areas:
Child/Adolescent, Imaging
Introduction: A major cause of motor vehicle related deaths is alcohol-impaired driving. It continues to be a significant problem in the United States and claims approximately 10,000 lives each year. In an effort to reduce drunk driving and ameliorate this problem, the National Highway Traffic Safety Administration (NHTSA) and the Automotive Coalition for Traffic Safety (ACTS) commenced research leading to the development of several passive alcohol sensing prototype devices aimed for installation into motor vehicles. This research led to the development of the Driver Alcohol Detection System for Safety (DADSS), which uses two passive technologies: a breath-based system (SenseAir™) and a touch (tissue)-based system that measures alcohol through the skin (TruTouch™). We tested both devices against a commercially available hand-held breathalyzer (Intoximeter™, Alco-Sensor FST) and venous blood. The aim of the experiments was to test whether the alcohol concentrations measured by the two prototype devices correlate with venous blood, since blood alcohol concentration (BAC) is the “gold standard” for measuring ethanol in the body.

Methods: The population for this study consisted of healthy social drinkers ages 21 to 40. Each participant received a 0.9 g/kg dose of 80-proof Absolut vodka; the dose was consumed over a two-minute period. We obtained blood samples in 5-minute intervals using an indwelling catheter in an antecubital vein. Gas chromatography with flame ionization detection (GC/FID) was utilized to quantify whole blood alcohol concentrations, and breath alcohol (BrAC) was measured every 5 minutes with a hand-held breathalyzer (Intoximeter Alco-Sensor FST). Additionally, the SenseAir™ (Generation 3.0) and TruTouch™ devices were employed every 5 minutes to collect breath and touch samples. Samples were collected for two hours. A visual analogue scale (VAS) questionnaire was utilized throughout the study to assess self-reports of how drunk they are and whether they would currently drive.

Results: To determine the accuracy of breath and tissue alcohol concentration as compared to BAC, we looked at the R^2 values for each device used. The R^2 values are as follows: 0.72649, 0.74431, and 0.8321 for tissue (TruTouch™), breath (SenseAir™), and breath (FST Breathalyzer), respectively. To correct for buccal alcohol contributing to erroneously high readings after consuming alcohol, the BrAC data for the first 20 minutes of both the SenseAir™ and FST measurements were removed. The experiment revealed that alcohol appears first in the breath, followed by blood, and then tissue. However, early breath samples are skewed because of buccal alcohol. The concentration-time curves for both prototypes paralleled that of blood.

Conclusions: We confirmed that there is a strong correlation among BrAC, BAC, and tissue alcohol concentrations. Since the successful operation and implementation of alcohol sensing devices, such as the TruTouch™ and SenseAir™, into automobiles is contingent on alcohol appearing in both the breath and the tissue at similar concentrations and time course as in blood, these findings are an important step towards validating their use in automobiles. These devices, if proven to be reliable and reproducible with additional human testing, could reduce the number of alcohol-impaired drivers on the road, which will save lives.

Topic areas:
Addiction, Pharmacology, Technology
Dissociative symptoms occur in trauma-spectrum, dissociative, anxiety, personality, and psychotic disorders and therefore are “transdiagnostic.” Despite decades of research aimed at understanding and defining dissociation, researchers and clinicians have failed to reach consensus (Braude, 1995, 2009; Dell, 2009; Van der Hart & Dorahy, 2009). While various groups such as the American Psychiatric Association (APA) and World Health Organization (WHO) put forth definitions for dissociation (APA, 2000, 2013; WHO, 1992, 2016), many researchers and clinicians have identified numerous shortcomings of these descriptions further fueling disagreement and confusion regarding diagnosis (Braude, 2009; Dell, 2006, 2009; Van der Hart & Dorahy, 2009). Dell (2009) posits that a primary shortcoming of most widely used definitions of dissociation is that they do not clearly identify the domain of explanation that is being used. Dell identifies that at least three domains are pertinent to the description and understanding of dissociation including a neuroanatomical-neurophysiological explanation, a psychological explanation, and phenomenological description (Dell, 2009). The need for accurate, scientifically supported definitions and descriptions of mental disorders across multiple domains (e.g. neurobiological, genetic, psychological) is consistent with the National Institute for Mental Health’s (NIMH) Research Domain Criteria (RDoC) initiative (Sanislow et al., 2010). While the APA (2013) Diagnostic and Statistical Manual, 5th Edition (DSM-5) and WHO (2016) International Classification of Diseases, 10th Edition (ICD-10) have continued a long-standing tradition of defining mental disorders as unique, narrowly defined, separate classifications based on “…clinical observation, clustering of symptoms, the course of the disorder, and other related indices”, the RDoC takes a different approach (Sanislow et al., 2010, p.631). The RDoC aims to create and validate “dimensional constructs” that are informed by interdisciplinary data (e.g., psychological, neurobiological, etc.) and are theoretically informed, narrowly defined, clinically significant psychiatric difficulties (Kozak & Cuthbert, 2016). A growing body of literature highlights the absence of clear-cut separation of diagnoses and the significant prevalence of co-occurring disorders when using DSM-5/ICD-10 classification (e.g., Howland et al., 2009; Kendall & Jablensky, 2003; Lowe et al., 2008; Regier, Narrow, Kuhl, & Kupper, 2009). This problem of diagnostic validity is particularly challenging when faced with co-occurring and/or inter-related transdiagnostic symptoms as is often the case with traumatic dissociation. Traumatic dissociation is associated with chronic exposure to traumatic stress, as is often the case in childhood abuse and neglect (Carlson, Yates, & Sroufe, 2009; Dalenberg et al., 2012). Traumatic dissociative symptoms are included in DSM diagnostic criteria for PTSD as well as severe dissociative disorders (APA, 2000, 2013). The ability to accurately assess and diagnose PTSD and dissociative disorders is essential for the successful treatment of these disorders and also for advancing our understanding of these disorders through research. Diagnostic assessment results (CAPS-5, SCID-D-R, MID) as well as clinical interview data collected from women with histories of childhood abuse and neglect were examined and compared. The current study aims to examine the clinical utility of the gold standard diagnostic assessments for traumatic dissociation by comparing the consistency of results across measures.

**Topic areas:**
Dissociative Disorders, PTSD, Women
Growing evidence from neuroimaging studies has reported deficits in circuit connectivity between several regions involved in emotional processing, including the prefrontal cortex, amygdala, and midline thalamus in people with schizophrenia and bipolar disorder. Connectivity deficits are postulated to contribute to mood dysregulation, poor sleep hygiene, and anhedonia experienced by people living with these conditions. Brain imaging and human postmortem studies consistently indicate microstructural white matter abnormalities in the thalamus. The present studies focus on the paraventricular thalamic nucleus (PVTn), a small dorsal subnucleus containing numerous thalamic outputs to the prefrontal cortex, amygdala, and nucleus accumbens. The PVTn has been shown to play a role in circadian food timing cues, wakefulness and motivation and to be dysregulated in anxiety disorder, substance use disorder, and eating disorders. As a first step in efforts to identify specific cells and molecular pathways behind connectivity deficits, we focus on oligodendrocytes using high resolution quantitative microscopy on human postmortem brain samples. Our hypothesis is that mature oligodendrocytes are decreased in the PVTn of donors with schizophrenia and bipolar disorder. Oligodendrocytes play a fundamental role in sustaining myelin integrity throughout adulthood, and alterations in oligodendrocyte populations could critically impact thalamocortical connectivity in schizophrenia and bipolar disorder. In order to determine whether mature oligodendrocytes are decreased in the PVTn in schizophrenia and bipolar disorder we are in the process of quantifying myelin oligodendrocyte specific protein immunoreactive (MOSP-IR) oligodendrocytes in post-mortem human tissue using immunohistochemical staining and quantitative stereology-based sampling with light microscopy. We collected whole thalamic specimens of control (n=15), subjects with schizophrenia (n=15), and bipolar disorder (n=15), and performed immunohistochemistry to quantify the number of MOSP-positive oligodendrocytes in the paraventricular thalamic nucleus. Quantitative stereological sampling is being employed to estimate total numbers and numerical densities of MOSP-IR oligodendrocytes in the human PVTn. Information from donors’ health records, including exposure to medication, smoking and alcohol use history, as well as information such as post-mortem interval, age, sex, and brain weight have been collected and will be used for statistical analyses to control for confounding factors. Our pilot data thus far shows decreased MOSP-IR oligodendrocytes in the PVT of subjects with SZ (p<0.05) and subjects with BD (p<0.05). We expect that the numbers of MOSP positive oligodendrocytes in the PVTn of people with schizophrenia and bipolar disorder will be significantly reduced. If so, these changes would contribute to decreased myelination and impact the PVTn connectivity with key cortical and subcortical regions involved in psychiatric disorders. These findings would raise questions on the mechanisms leading to mature oligodendrocyte decreases. Ongoing studies will examine the relationship of mature oligodendrocyte cell numbers with immature oligodendrocytes expressing NG2 to determine if myelin deficits are associated with glial cell maturation.
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**Title:** Social Support as a Protective Factor Against Suicidal Ideation After Childhood Trauma

**Key words:** suicidal ideation, perceived social support, trauma

**Objective:** Previous literature has suggested that childhood trauma is a risk factor for suicidality, and that social support can be protective against suicidality. Research also suggests that social support may serve as a moderator in the relationship between childhood trauma and suicidal ideation and behavior, there is little literature examining the differential effects of different subtypes of childhood trauma on suicidality later in life, and on various dimensions of social support as moderators in this relationship. The present study examines: (a) the severity of abuse (sexual, physical and emotional subtypes), and neglect (physical and emotional subtypes) within a transdiagnostic sample of adult psychiatric patients; (b) the effect of trauma subtypes on suicidality over a lifetime; and (c) the moderating effect of perceived social support (from friends, family, or significant others individually) on the relationship between childhood trauma and suicidality.

**Methods:** We performed secondary analysis of data collected April 2017 through February 2018 at the Behavioral Health Partial Program—a skills-based, transdiagnostic day treatment program for adults with psychiatric disorders. Data was provided at admission by 420 patients through clinical interviews and questionnaires. Childhood trauma was assessed using the Childhood Trauma Questionnaire (CTQ), measuring emotional abuse and neglect, physical abuse and neglect, and sexual abuse amongst patients who chose to provide answers to questions upon admission. We used the Columbia Suicide Severity Rating Scale (C-SSRS), a structured clinical interview, to measure lifetime history of active suicidal ideation. Perceived social support by friends, family, and significant others was investigated using the Multidimensional Scale of Perceived Social Support (MSPSS). We then analyzed descriptive statistics, correlations, linear regression and tested for moderation.

**Results-Discussion:** When controlling for age and gender, experiencing childhood trauma increased the probabilities of having suicidal ideation by 1.024 times. Moderate or high levels of total perceived social support were protective against suicidality (b= -.839, p = .001) and altered the effects of childhood trauma on suicidality (b= -.052, p = .049). This effect on suicidality was significant for those who had been emotionally abused or neglected but received support from friends, family, and significant others, and for those who experienced sexual abuse but were supported by family and significant others. Accordingly, social support was protective only against emotional abuse, sexual abuse and emotional neglect, but not for physical types of trauma (abuse or neglect). Implications of these findings suggest that not only is social support important for those who have experienced childhood trauma, but that clinical settings ought to consider the specific type of support and trauma of patients when involving patient supports in treatment.

**Topic areas:**
Quality/Outcomes
Borderline personality disorder (BPD) is a prevalent disorder associated with substantial morbidity, mortality, and healthcare costs. With the emergence of evidence-based specialist treatment packages, such as dialectical behavior therapy (DBT) and mentalization-based treatment (MBT), BPD is now widely considered treatable. However, the resource-intensiveness of these treatments is such that they might not be available in all cases. Generalist treatments such as Good/General Psychiatric Management (GPM), Structured Clinical Management (SCM), Guideline-Informed Treatment for Personality Disorders (GIT-PD), and Good Clinical Care (GCC) offer a pared-down, principle-driven approach to the treatment of BPD. Their resource-efficiency in terms of both training and administration, and their effectiveness—some able to match outcomes of specialist models in several randomized controlled trials (RCTs)—render them of interest to those clinicians who clinically manage patients with BPD, but do not have the time, resources or interest to pursue an intensive training in a specialist treatment for BPD. The aim of the following review is to illustrate the similarities shared by the ever-increasing number of generalist treatments for BPD so as to define their core shared features. Although each treatment differs in its structure, framework, and aims (e.g., comparator in RCT vs. standalone treatment), similarities emerge, including an emphasis on diagnostic disclosure, psychoeducation, the therapeutic relationship, crisis management, and goal-setting also seen in specialist treatments. Differences between the treatments can be viewed as differing instantiations of common underlying principles, adapted to the patient population and treatment environment. It is therefore possible that a common generalist approach, even applied outside of the aforementioned frameworks, could be helpful to persons with BPD.

**Topic areas:**

Borderline Personality Disorder
Application of behavioral economic principles to the characterization of drugs of abuse has yielded compelling evidence for a relationship between price (P) and consumption (Q). In turn, a quantitative assessment of this relationship provides a metric for comparing the reinforcing effectiveness (alpha) of various drugs, and demand analysis may provide a screening mechanism to evaluate candidate medications for the management of substance abuse. However, discordance between the \( \alpha \) values for some drugs in nonhuman subjects and their reinforcing effectiveness in humans (e.g., high alpha values and high rates of abuse of nicotine) suggests that previous demand equations may require further refinement. In the present work, demand equations were derived to try to more accurately reflect the contribution of behavioral momentum- evident in resistance to vehicle extinction- to the calculation of reinforcing effectiveness. Resistance to extinction conceivably may influence demand curve elasticity, especially at higher prices. Here, demand curves were derived from intravenous self-administration data obtained with four psychomotor stimulant drugs using a logarithmic model modified from the Hursh-Silberberg (2008) exponential equation with a two-parameter fitting algorithm for consumption versus price. The new algorithm reduces the three free parameter model to a two free parameter model by interpolating data at the minimum fixed ratio (FR) and at the breakpoint \( p_B \) (i.e., the FR where \( Q=0 \)). The augmented model takes the form:

\[
\log(Q) = \log(Q_{FRL}) - a(P-FRL) - a\log(P/FRL) + \log\left(\frac{1-P/p_B}{1-FRL/p_B}\right)
\]

where \( Q_{FRL} \) denotes consumption at the lowest evaluated FR and \( p_B \) denotes the breakpoint price. A strategy was tested for developing a single parameter classification scheme for fitted models using the parameter \( \alpha \) as a measure of elasticity of the demand curves. The strategy normalizes behavioral momentum as measured by data for vehicle self-administration. More specifically, if \( Q(P) \) denotes the demand curve for a particular drug, the discounted demand curve, \( Qd(P) \), is defined by: \( Qd(P) = \max\{Q(P) - Qs(P), 0\} \) where \( Qs(P) \) denotes the demand curve generated by vehicle. To test this approach, two doses of cocaine, 3,4-methylenedioxymethamphetamine (MDMA), methylenedioxypyrovalerone (MDPV), and methcathinone (MCAT) were examined in rhesus monkeys (\( N=4 \)). Using the Hursh-Silberberg (2008) exponential formula, a rank-order of reinforcing effectiveness of cocaine>MDPV>MCAT>>MDMA was established, and reinforcing effectiveness did not vary as a function of dose. However, in the Two-Parameter Exponential-Demand formula, a rank-order of cocaine (large dose)>MDMA=MCAT>MDPV (large dose)>MDPV (small dose)>cocaine (small dose) was established. These results suggest that behavioral momentum may influence demand elasticity in a dose-dependent manner, and a values derived in the augmented model may differentiate drug effects that contribute to price-consumption relationships in a pharmacologically sensitive manner.
Epidemiological evidence indicates that immune activation during pregnancy via infection or autoimmune disease is a risk factor for neuropsychiatric illness. Work from our lab and others has demonstrated that prenatal immune can cause long-lasting behavioral and neurophysiological alterations in offspring. Previous prenatal immune activation protocols have primarily involved administration of agents to mimic infection that target subtypes of the toll-like receptor (TLR) family, a class of receptor proteins that regulate innate immune responses. As examples, TLR3 recognizes Poly I:C and TLR4 recognizes lipopolysaccharide (LPS). In this study we examined the role of TLR7 in prenatal immune activation, considering evidence that this receptor subtype is implicated in the etiology of autoimmune diseases. We administered subcutaneous injections of the selective TLR7 agonist imiquimod (IMQ, 5.0 mg/kg) or vehicle to timed-pregnant dams (C57BL/6J mice) on embryonic days (E) 12, 14, and 16. Over the first 13 weeks of postnatal development, we assessed the offspring on a battery of behavioral tests that include ultrasonic vocalizations (USVs), open field, social approach, reciprocal social interaction, as well as on measures of circadian activity and temperature. In a parallel set of experiments, we collected whole brain sections for microglia histology and tissue punches of the dorsal striatum for RNA-sequencing. Mice exposed to prenatal IMQ exhibit a behavioral phenotype characterized by decreases in anxiety-like behavior, a fragmentation of social behavior, and an alteration in USV production. This phenotype is readily distinguishable from those seen following prenatal activation of TLR3 and/or TLR4. On many of these measures there are significant sex differences. Additionally, mice exposed to prenatal IMQ have normal baseline locomotor activity, but are hyperactive in response to various types of stimuli including the presence of a social partner, circadian cues, or gonadal hormone fluctuations. Prenatal IMQ exposure causes a decrease in microglia density and an increase in the number of microglia ramifications in numerous brain areas, with particularly strong effects in striatum. RNA-sequencing of the dorsal striatum revealed that prenatal IMQ exposure induces differential expression of hundreds of genes, especially those encoding synaptic components, cell adhesion molecules, and glial markers. However, there are dramatic sex differences, with virtually no overlap in differentially expressed genes between males and females. Prenatal immune activation with a TLR7 agonist produces a behavioral phenotype and changes in microglia that are distinct from previous models using other TLR ligands. Underlying this phenotype is a propensity for “conditional hyperactivity”, reflected by an exaggerated response to some types of internal and external stimuli. Further, genome-wide analysis of mRNA identified numerous molecular pathways affected by prenatal IMQ exposure, but demonstrated profound sex differences in the directions and patterns of expression. Considered with the existing literature, our findings suggest that early immune system activation can promote various—and sometimes even opposite—developmental trajectories, depending on the type and/or pattern of TLRs activated.
The onset of borderline personality disorder (BPD) is typically between puberty and young adulthood and its prevalence is higher in younger samples. Yet diagnosis and treatment are usually delayed, potentially exacerbating functional impairment and contributing to therapeutic nihilism. Since BPD can be reliably diagnosed in early stages, has shown to be responsive to early intervention, and involves traits that are considerably more malleable in youth, it is an ideal target for early detection and intervention. Thus, prevention efforts have included the adaptation of evidence-based treatments (EBTs) for BPD to younger populations. This poster will review adaptations of EBTs for BPD in adolescents, which include Mentalization-Based Treatment for Adolescents (MBT-A), Dialectical Behavior Therapy for Adolescents (DBT-A), Cognitive Analytic Therapy (CAT), and Emotion Regulation Training (ERT). While these treatments are well-designed and shown to be effective in randomized-control trials, their implementation is sparse, and a less intensive, generalist approach to treating adolescents with BPD – Youth Mental Health (YMH) – has shown to match outcomes of CAT. To help address the public health need, we investigated how these treatments have been modified to suit emerging adult populations in order to inform the adaptation of another generalist treatment, Good/General Psychiatric Management, to adolescents (GPM-A). GPM-A revises the overall principles originally outlined in the GPM manual, and considers how the theory of interpersonal hypersensitivity applies to an adolescent versus an adult population. It identifies the risk factors and core features of BPD early in life, and addresses the questions clinicians may have when seeking to diagnose BPD before the age of 18. Finally, we will provide suggestions for clinical practice based on our revisions, and future directions for GPM-A.
Presenting Author: Gabriele Chelini, Postdoctoral Fellow

Co-Authors: Cristina Berciu  Anne Boyer Boiteau  Kailine Polanco  Kathy Huang  Pantazopoulos Harry  Kerry Ressler  Sabina Berretta

Title: **CS-6 clusters: a novel form of segregated microenvironments modulating synaptic plasticity**

Key words: Synaptic Plasticity, Microcircuitry, Chondroitin sulfate proteoglycans, Memory engram, Synaptic Clusters

Growing evidence show that experience-dependent plasticity depends on coordinated structural changes affecting segregated groups of synapses. This process of synaptic remodeling is limited by time and space boundaries that allow local synapses to cluster together in response to specific external inputs. Visualization of coordinated synapses clusters represents a challenge, likely due to the highly cell-specific molecular signature underlying synaptic machinery. We report of a potentially new form of synaptic clusters, formed by sustained astrocyte-derived 6-sulfated chondroitin sulfate (CS-6) proteoglycans accumulation in the postsynaptic density (CS-6 clusters). We tested the hypothesis that these clusters may represent segregated microenvironments modulating synaptic plasticity. First, in mice, we quantified the number of dendritic spines within and outside the CS-6 clusters in the Auditory Cortex of mice expressing green fluorescent protein in a subset of cortical pyramidal neurons. Our findings show significantly increased spine density within clusters microenvironments with respect to the outside (p=0.04). In a second group of animals we tested the hypothesis that expression of Arc, an activity-dependent neuroplastic protein, may correlate with number of CS-6 clusters in the barrel cortex. Our results show Arc-positive dendrites localized within CS-6 clusters with a relatively consistent pattern. We also show a significant positive correlation between Arc-positive dendrites and CS-6 clusters (r= 0.79, p=0.02, n=8). In two new sets of experiments, we tested the hypothesis that CS-6 clusters may be associated with learning. In a group of mice (n=8) 4 hours following fear conditioning we observed a trend toward altered numbers of clusters in the lateral amygdala. Lack of strong/clear changes may be due to the timeframe chosen, as results from Arc experiments suggest that CS-6 clusters may be expressed at earlier time. Follow-up experiments using a time course are being planned. In a second group of mice, we applied 1 week of whisker deprivation to test the hypothesis that CS-6 clusters are formed in response to experience. Results from this pilot study (N=3 per group) suggest a marked decrease of CS-6 clusters in sensory deprived mice. Taken together, our results show that CS-6 clusters are associated with neuroplastic protein Arc and that their formation is dynamically modulated by experience. These findings suggest that CS-6 synaptic clusters are segregated areas of enhanced experience-dependent synaptogenesis, potentially corresponding to transient memory engrams across the mammalian brain.

Topic areas:
Bipolar Disorder
Cognitive Sciences
Schizophrenia
Technology
Background: The Partners Healthcare Biobank (Biobank) is a multi-institutional research initiative that provides researchers within the Partners Healthcare network access to data on over 90,000 consented participants. Participants provide genetic materials (DNA, plasma, and serum), complete a lifestyle questionnaire and allow researchers to access electronic health records (EHR). At McLean Hospital, we aim to collect one of the largest hospital-based psychiatry biobanks and to utilize this tool across the whole of Partners to understand rate and impact of Depression in a large community sample.

Methods: Using curated disease populations – phenotypes developed by the Biobank portal team using both structured and unstructured EHR data and clinical, computational and statistical methods – we analyzed demographic data for individuals with a history of depression (N=9,466) and controls without a history of depression (N=63,484). For further analyses, we examined health questionnaires on a subset of those with depression (N=3,307) or healthy controls with no evidence of psychiatric history (based on the Biobank curated disease populations N=4,246). Statistical analyses included chi-squared tests for proportional differences.

Results: 1) Of the overall Partners Biobank population (N=73,257), we find that 12.9% met the curated definition of Major Depressive Disorder. 2) Of those patients with MDD (N=9,466), 67.4% were female whereas in the overall non-depression cohort (N=63,484), only 52.5% were female, supporting a preponderance of MDD prevalence in females (x²=737, P<0.0001). Within the subset of patients who completed health questionnaires, 3) we found more unemployment in those with depression (40.9%) compared to those with no history of psychiatric disorder (21.1%) (x²=349, P<0.0001). 4) We also found greater incidence of heavy alcohol usage (>3 drinks per day) in those with depression (4.9%) compared to those without psychiatric history (2.7%) (x²=25.5, P<0.0001). 5) Finally, those with a history of depression had lower attainment of higher education (4 or more years of college or advanced degree) (66.1%) compared to those without a psychiatric history (78.8%) (x²=152, P<0.0001).

Conclusions: These data show that a large hospital system-based sample of convenience provides important epidemiological data on the frequency of Major Depressive Disorder and its sequelae. We see MDD rates of at least 12.9%, with higher rates among females and with higher rates of unemployment, alcohol usage, and lower rates of educational attainment, further demonstrating the negative impact of depression. Additional analyses will utilize these large datasets to understand the biology, genetics, and risk factors for Major Depression within a hospital system.

Topic areas:
Depression
Examination of the Co-morbidity of Hypothyroidism and Major Depressive Disorder

Background: With longstanding appreciation of thyroid dysfunction overlapping with many psychiatric illnesses, there has been evidence of hypothyroidism (Hypo) sharing many behavioral and cognitive manifestations such as lethargy, cognitive impairment, anhedonia, and anxiety, that are similar to those seen in Major Depressive Disorder (MDD); however, the extent to which these diagnoses are co-morbid or present risk factors for one another remains unknown. Using medical record data from the Partners Healthcare Biobank, a large healthcare system in the greater Boston area we examine the contribution of Hypo to potential risk of developing MDD.

Methods: Utilizing data from 84,606 subjects from the Partners Biobank, we generated cohorts of individuals having MDD and hypothyroidism independent and co-occurring diagnoses. Using the clinical definition of Hypo, defined by Thyroid Stimulating Hormone (TSH) levels exceeding 10uU/ml, and excluding Hypo due to medications, we obtained a cohort consisting of 2,939 subjects (Age: 62.22 ± 15.09 years, 3.75 % of total Biobank participants). The MDD cohort (N=8282, Age: 58.16 ±15.49, 9.79 % of Biobank participants) was defined using a curated disease validated phenotype algorithm for MDD with positive predicted value set at (0.90). Additional, control medical conditions: Coronary Artery Disease (CAD) and Asthma which occur at similar rates to Hypo were used to examine the specific relationship of Hypo to the risk of MDD.

Results: Nonparametric Kruskal-Wallis tests for the frequency of TSH labs (TSH ≥10uU/ml) revealed significance H(2)= 1868.256, P <0.001 between different groups (Hypothyroidism, Asthma, and CAD) with MDD, stepwise comparisons also suggested that the number of tests for MDD+Hypo was significantly different than MDD+CAD, and MDD+Asthma. The frequency of elevated TSH lab tests (≥10ug/ml) was found to be higher for MDD+Hypo than MDD without, Hypo alone (H(2)7817.813, P <0.001; stepwise comparisons P <0.058 trends towards significance and MDD with any other control condition (all p>0.05).

Conclusion: Our preliminary data suggest an association between elevated TSH lab tests in MDD even in the absence of officially diagnosed clinical hypothyroidism. Additional analyses will examine the temporal relationship between these events and the extent to which elevated TSH may contribute to risk for development of MDD.

Topic areas:
Depression
There is a paucity of effective, evidence-based treatment for older adults with bipolar disorder (OABD) who are currently depressed. Most commonly-used pharmacotherapies have not been extensively studied for use specifically in older adults, and many patients do not respond to first-line therapies. Low Field Magnetic Stimulation (LFMS), a novel experimental treatment for depression, is currently being studied for clinical effects in OABD, but its mechanism of action is still unclear. LFMS operates at low electric field strengths (< 1 V/m), high frequencies (1kHz) and is administered remotely through induced electric fields which provide relatively uniform field strength over the whole head. These characteristics differ from the typical response, field strengths, timing, and target regions observed and utilized in other electromagnetic treatments such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). This suggests that a different mechanism of action is present for LFMS. A previous proof-of-concept study used fMRI and EEG to observe changes in brain function associated with LFMS treatment in healthy controls. Notable findings from this study include changes in seed-based connectivity in the rostral Anterior Cingulate Cortex (rACC) and the bilateral Dorso-Lateral Prefrontal Cortex (DLPFC). Additional research is warranted to ascertain whether these changes are associated with symptoms seen in mood disorders. To further investigate these findings, we developed a protocol to study the effects of LFMS treatment using fMRI and magnetic resonance spectroscopy (MRS) in older adults (ages 50 and older) with bipolar depression. Subjects in this protocol complete two study visits in which they undergo fMRI and MRS imaging immediately before and after 20 minutes of LFMS treatment. Based on the initial findings in healthy controls, we expect to see changes in the rACC and DLPFC. Results of this study will help us understand the neurobiological processes that underlie the antidepressant effects of LFMS, and inform future research investigating the clinical utility of this treatment.
Title: Chronic intermittent nicotine exposure attenuates conditioned fear: a therapeutic model of the nicotine patch

Key words: chronic, nicotine, fear, context, startle

The use of nicotine products such as cigarettes and smokeless (chewing) tobacco in the military is highly prevalent, but it is not known how nicotine affects vulnerability to stress and stress-related conditions including post-traumatic stress disorder (PTSD). Previous work has demonstrated that nicotine can relieve stress while also enhancing cognitive function. These two broad actions may have opposing effects on vulnerability to stress-related illness such as PTSD, which is thought to involve learning and memory components. Preliminary studies from our lab suggest that intravenous self-administration (IVSA) of nicotine in rats can reduce the impact of a traumatic event, as reflected by decreased responsivity to a context previously associated with footshock in the fear-potentiated startle (FPS) paradigm. These findings suggest that nicotine use in soldiers might reduce pathological responses that occur in contexts that have similarities with those in which a trauma was experienced, whether in combat settings or after returning home. Here we examined if the putative beneficial effects of nicotine IVSA on contextual fear learning are retained when the drug is given by a different (safer) route of administration, using a model of the nicotine patch. Male Long-Evans rats were implanted with a subcutaneous iPRECIOTM programmable minipump. After 7 days of recovery, rats received 1, 10, or 21-day exposure to either 0.3 mg/kg (low) or 1.0 mg/kg (high) of nicotine or saline for a 12-hr on/12-hr off period; doses were based on previous work showing that rats self-administer ~1.0 mg/kg in 12-hr sessions. Following exposure, rats were trained in the FPS paradigm, which provides an index trauma and enables quantification of exaggerated startle response, a characteristic observed in humans with PTSD. Context-potentiated startle (CPS) and FPS were determined in each subject in a test session 10 days after training. We found that a 10-day exposure to the high dose of nicotine leads to decreased responsiveness to trauma (footshock)-associated cues and contexts, similar to findings after nicotine IVSA. Notably, a 1-day exposure produces the opposite effect on CPS, suggesting that chronic exposure is an important factor for the potential therapeutic benefits of nicotine. We are currently evaluating the effects on fear conditioning when nicotine exposure is maintained during the 10 days between training and testing. Our findings suggest that passive administration of nicotine can impact physiological responses trauma-associated stimuli and contexts, raising the possibility that medical application of nicotine could reduce the psychological impact of trauma.

Topic areas:
Addiction
PTSD
**Title:** Exposure to Conversion Therapy for Gender Identity Is Associated with Poor Adult Mental Health Outcomes among Transgender People in the U.S.

**Key words:** Gender Identity, Conversion Therapy, Suicide, Transgender, Gender Dysphoria

**Background:** Gender identity conversion therapy has been widely debated as a potential treatment approach for transgender people; however, its relationship to mental health outcomes has been understudied. As 0.6% of people in the U.S. identify as transgender, this topic is relevant to practitioners and has been an active area of policy debate. However, there is a paucity of data on the associations between exposure to gender identity conversion therapy and mental health outcomes. This study aimed to evaluate if lifetime and childhood exposure to gender identity conversion therapy are associated with higher levels of past-month severe psychological distress, suicidal ideation, and suicide attempts among transgender adults in the U.S.

**Methods:** Using data from the National Transgender Discrimination Survey, a cross-sectional survey of 27,715 transgender adults in the U.S., we examined the prevalence of self-reported lifetime exposure to conversion therapy for gender identity and this exposure’s association with adult mental health outcomes (last-month severe psychological distress, defined as a K6 score > 12; lifetime suicidal ideation; lifetime suicide attempt). We employed multivariable logistic regression, adjusting for demographic variables significantly different between groups.

**Results:** Of the 27,715 transgender adults in the study, 19,917 (71.9%) had discussed their gender identity with a therapist. Of these, 19.6% had been exposed to gender identity conversion therapy. Those exposed were more likely to be birth-assigned males, unemployed, and to have a lower total household income. After adjustment, lifetime exposure to gender identity conversion therapy was associated with last-month severe psychological distress (aOR 1.74, 99.7% CI 1.21-2.51) and a lifetime history of suicide attempt (aOR 2.14, 99.7% CI 1.47-3.10). Exposure to gender identity conversion therapy before age ten was also associated with a lifetime history of suicide attempt (aOR 4.98, 99.7% CI 2.39-10.42).

**Conclusions:** There are strong associations between both lifetime and childhood exposure to conversion therapy for gender identity and adverse mental health outcomes in adulthood.

**Topic areas:**
- Child/Adolescent
- Depression
- Gender/Sex Differences
Presenting Author: Gordana Vitaliano, Assistant Professor of Psychiatry, Director

Co-Authors: Jae Kim, Dionyssios Mintzopoulos, Christopher Adam, Franco Vitaliano, Scott Lukas, Marc Kaufman

Title: Novel Targeted Clathrin-Based Superparamagnetic Iron Oxide Nanoparticles for CNS Magnetic Resonance Imaging of Dopamine Transporters

Key words: Magnetic Resonance Imaging, Dopamine transporter imaging, Clathrin nanoparticles, Superparamagnetic iron oxide (SPIO), Dopamine transporter antibody

Background: Magnetic Resonance Imaging (MRI) offers high spatial resolution, but has poor sensitivity for visualization of molecular targets. Superparamagnetic iron oxide (SPIO) contrast agents along with antibodies are used to improve MRI sensitivity and molecular targeting, but they cannot cross an intact blood-brain-barrier (BBB), limiting their use. Our goal was to enable MR molecular imaging of dopamine transporters (DAT) using novel clathrin-based nanoprobes carrying SPIO and anti-DAT-antibodies, which noninvasively pass an intact BBB.

Methods: Clathrin triskelia (CT)-nanoprobes were synthesized by conjugating anti-DAT-antibody and SPIO to CT using polyethylene glycol at 1:1:1 molar ratio. Adult male mice were given saline or CT-nanoprobes intranasally (68 pmol, 50 μL). 4 hours later, their brains were perfused, fixed, and collected for immunohistochemistry or ex vivo MRI. Voxel-wise R2* relaxation rates were obtained using a series of gradient-echo images, and estimated in the striatum (STR), substantia nigra (SN) and visual cortex (vCTX, a control region).

Results: The iron stained brain slices showed an accumulation of CT-nanoprobes in brain regions rich in DAT (e.g., STR). MRI studies revealed that R2* values were significantly higher in the STR (p=0.0010) and SN (p=0.0007) compared to vCTX in animals that received CT-nanoprobes, but not in saline treated animals. CT-nanoprobes significantly increased R2* in the STR (p<0.0001) and SN (p=0.0002) compared to saline without significantly altering R2* in vCTX.

Conclusions: CT-nanoprobes noninvasively delivered SPIO contrast agents along with anti-DAT-antibody to the mouse brain, enabling detection of DAT using MRI. These preliminary results merit further investigation into the use of clathrin as a new theranostic for noninvasive molecular brain imaging and targeted drug delivery.

Topic areas:
Addiction
Depression
Imaging
Technology
McLean Research Day 2019

Title: Clinical and Demographic Correlates of Past Month Suicidal Thoughts and Behaviors and Non-suicidal Self-injury in an Acute Psychiatric Sample

Key words: suicidal thoughts, suicide attempts, non-suicidal self-injury, partial hospital program

Aims: Partial hospitalization programs (PHPs) are intensive, non-residential, psychiatric treatment programs designed to provide an alternative to inpatient care or bridge the transition from inpatient to outpatient care. Given that PHPs serve patients during a high-risk time period (i.e., first week following inpatient) without the safeguards of inpatient hospitalization, the suicide risk presentation of PHP patients is of interest. While a number of studies have characterized suicidality in inpatient samples, little is known about the presentation of suicidal thoughts and behaviors (STBs) and non-suicidal self-injury (NSSI) among acute patients in PHPs. Furthermore, there remains a need to better understand differences in correlates of suicidal thoughts versus suicidal behaviors, including differentiating suicide attempts, interrupted attempts, and aborted attempts. This study examined the prevalence and correlates of past month STBs and NSSI among patients seeking treatment at a PHP.

Methods: Participants were 950 patients admitted to the Behavioral Health Partial Hospital Program. Participants completed self-report measures of demographic (e.g., age, gender) and clinical variables (e.g., symptom severity, number of prior hospitalizations), as well as clinical interviews assessing diagnostic and suicidal symptom histories (Mini International Neuropsychiatric Interview, Columbia-Suicide Severity Rating Scale). Medical chart data was also collected (e.g., referral source [inpatient vs. community] and disposition [home vs. inpatient]). Chi-square tests, ANOVAs, and logistic regressions will be used to examine correlates of past month suicidal thoughts, plans, and attempts, and NSSI. Data collection for the full sample (N = 950) has recently been completed and is being prepared for analysis. Full sample analyses will examine demographic and clinical correlates of past month STBs and NSSI in our PHP sample.

Results: With regards to prevalence, 45.2% reported past month suicidal thoughts, 13.1% reported a suicide plan with intent, and 7.3% reported at least one attempt in the past month. Furthermore, 5.9% reported an aborted attempt, and 2.5% reported an interrupted attempt. Additionally, 15.5% reported past month NSSI. We will also present the remaining analyses involving demographic and clinical correlates of each category of suicidality and NSSI.

Conclusions: Results showed high rates of STBs and NSSI among patients in a PHP. Results also suggest rates of past month suicide attempts in our sample are similar to that of suicide attempts in the week before admission for individuals in inpatient care. However, rates of recent suicide attempts were lower in our sample than the rates of suicide attempts in a sample of adolescents in the two weeks before admission to an inpatient unit. Our complete analyses will help clarify whether rates of STBs and NSSI differ based on referral source (inpatient vs. community). Our data also provide an in depth understanding of different types of attempts (e.g., interrupted, aborted) which may help clarify their relevance in an acute care setting such as a PHP. Data on the clinical and demographic correlates of self-injurious thoughts and behaviors in this sample have implications for clinicians seeking to identify patients at partial hospital level of care who may be at highest risk for suicide and in need of additional support.

Topic areas:
Anxiety, Bipolar Disorder, Borderline Personality Disorder, Depression, Psychotic Disorders
Presenting Author: Kristin Javaras, Assistant Psychologist and Assistant Professor

Co-Authors: Kristin N. Javaras, Erin M. LaFlamme, Meghan E. Reilly, Chris Perriello, Lauren C. Porter, Harrison G. Pope, Jr., James I. Hudson, Staci A. Gruber, Shelly F. Greenfield

Title: A Novel, Behavioral Task for Measuring Social-Stressor-Induced Changes in Consumption of Palatable Food

Key words: Negative Emotions, Stressors, Eating Behavior, Emotional Eating, Eating Behavior

Stressful events ("stressors") can predict a variety of eating-related behaviors, from extreme restriction to objective binge-eating episodes. Valid, within-person measures are needed to advance understanding of how stressors differentially affect eating behavior across individuals. Thus, we describe a novel behavioral task for objectively assessing stressor-induced changes in food intake, and we present preliminary results for the task. The laboratory-based task is designed to measure how social exclusion, a clinically-relevant interpersonal stressor, affects consumption of palatable food. Participants engage in a computerized throwing game involving an equal number of inclusion and exclusion rounds, and consume a participant-determined amount of milkshake during breaks between rounds. Affective responses during the game are assessed via repeated self-report measures and continuously recorded facial expressions. Participants in the validation sample (n = 20 to date) are women aged 18-30 years, selected on the basis of high or low levels of self-reported emotional eating on the Dutch Eating Behaviour Questionnaire. Exclusion (vs. inclusion) rounds produced the expected changes in both implicit and explicit affect, and milkshake intake varied during initial rounds, although it was generally minimal thereafter. Condition (exclusion vs. inclusion) and self-reported emotional eating did not interact significantly in their effect on milkshake consumption during initial rounds, except for self-reported emotional eating in response to anxiety (b = 3.3; 95% CI = [0.2, 6.5]). Individuals reporting a moderate urge to eat when anxious consumed more milkshake after exclusion (vs. inclusion), whereas individuals reporting an urge NOT to eat when anxious consumed less milkshake after exclusions (vs. inclusion). These findings could suggest that (most) self-report measures of emotional eating have limited validity with respect to actual behavior. Alternatively, laboratory tasks may tap only specific negative emotions, which are well captured only by specific self-report measures.

Topic areas:
Eating Disorders
Technology
Women
Title: The role of interactions between ventral hippocampus and basolateral amygdala in control of fear extinction memory

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

In Pavlovian fear conditioning, fear memory is formed after pairing the conditioned stimulus (CS) with the unconditioned stimulus (US), so that a presentation of the CS, after the CS-US association is formed, evokes stereotypic physiological responses of escape or avoidance. Fear responses are gradually diminished when the CS is repeatedly presented without the US in a process reflecting new learning termed extinction. Neurobiological studies of fear extinction mechanisms could potentially provide the mechanistic background in the development of remedies against fear-related mental disorders, such as PTSD, panic disorder, and generalized anxiety disorder. One of the interesting features of fear extinction is its context-dependence, so that fear memory is renewed in a novel non-extinguished context, but the underlying mechanisms of fear renewal are still poorly understood. To explore these mechanisms, we focused on connections between the ventral hippocampus (vHPC), important for relaying context-associated information, and basolateral amygdala (BLA). Using optogenetic tools, we found in experiments on male mice that vHPC sends monosynaptic glutamatergic (excitatory) projections to the BLA which form synapses on both principal neurons and local circuit GABAergic interneurons. Activation of the latter by hippocampal excitatory inputs mediate feed-forward inhibition in the BLA. In our experiments, a comparison of input-output curves for the vHPC-BLA excitatory postsynaptic currents (EPSCs) showed that synaptic efficacy in glutamatergic inputs to the BLA was enhanced after fear conditioning and this potentiation was eliminated in mice which were subjected to extinction training (CS-only group, n = 11 BLA neurons from 8 mice; CS-US group, n = 13 neurons from 8 mice; Extinction group, n = 17 neurons from 9 mice; two-way ANOVA, F2,429 = 46.18 between groups, p<0.0001; F10,429 = 22.51 for light power density, p < 0.0001; p < 0.001 for CS-US group versus CS only or Extinction groups, Bonferroni post-hoc test). The inhibitory feed-forward synaptic responses in vHPC-BLA projections were also potentiated in mice from the CS-US group compared to the CS-only control group, and they remained enhanced following fear extinction. Thus, the EPSC/IPSC ratio was suppressed in the Extinction group, resulting in suppressed BLA excitability in fear extinguished mice and, therefore, diminished fear responses. Our findings indicate that synaptic plasticity in both excitatory and inhibitory hippocampal inputs to the BLA may contribute to the mechanisms of fear learning and fear extinction. Presently, we perform chemogenetic experiments in order to provide direct evidence for the role of these projections in fear control, expressing inhibitory DREADD in the vHPC in a cell type-specific manner in order to assay the consequences of inactivation of this pathway for the acquisition and extinction of fear memory and memory retrieval.

Topic areas:
Anxiety
PTSD
Presenting Author: Laura Patriarca, Clinical Research Assistant II

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

Title: Assessing the Impact of Medical Marijuana on Clinical State: Improvements After Three Months of Treatment

Key words: medical marijuana, clinical state

Background: Increasing numbers of individuals are exploring the therapeutic use of marijuana (MJ), with estimates of registered medical marijuana (MMJ) consumers exceeding 2.1 million in the US alone. Considerable differences in both the goal of use and constituent profiles of MJ products typically used medicinally versus recreationally support the study of MMJ as distinct from recreational MJ. Despite the growing popularity of MMJ, the existing research on its clinical impact is limited primarily to acute efficacy studies that are specific to a particular indication. We recently analyzed data from an ongoing, longitudinal observational study of MMJ patients in order to assess the potential impact of MMJ treatment on clinical outcome.

Methods: Patients interested in exploring MMJ treatment for various indications were recruited from MMJ certifications centers and via local flyers and online postings. Additionally, a group of treatment as usual (TAU) patients comprised of individuals not interested in using MMJ but presenting with similar chronic conditions as the MMJ group were also included. Clinical state was assessed via self-report questionnaires at baseline and after 3 months of MMJ treatment or TAU. Measures of clinical state included the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI), Profile of Mood States (POMS), the abbreviated version of the World Health Organization Quality of Life (WHOQOL), and RAND 36-Item Short Form Medical Outcomes Survey (SF-36).

Results: MMJ patients showed significant improvement in several measures of clinical state after 3 months. Relative to baseline scores, MMJ patients demonstrated significant improvements on measures of depression (BDI), sleep disturbance (PSQI), and fatigue (POMS); no change was detected for measures of anxiety (BAI). Additionally, MMJ patients reported improvements on some aspects of quality of life; specifically, improved ratings were noted on measures of vitality (SF-36), general health (SF-36), and physical health (WHOQOL). TAU patients, who were well-matched with MMJ patients for indication and clinical state at baseline, did not exhibit any significant changes on these assessments between baseline and 3 months.

Conclusions: Following 3 months of treatment, MMJ patients reported significant improvements in several measures of clinical state, including depression, sleep, energy/fatigue, and general and physical health. In contrast, TAU patients did not exhibit any significant changes in clinical state after 3 months, suggesting that improvements seen in MMJ patients are likely related to MMJ treatment. Future research should continue to investigate the clinical efficacy of MMJ treatment over a more extended time course and study the impact of specific cannabinoids on measures of clinical state.

Topic areas: Quality/Outcomes
Background: Sleep disruption may be a crucial factor mediating the association between childhood maltreatment (MAL), brain changes and psychopathology. We have recently reported that MAL was the critical determinant of sleep continuity and that neither depression nor anxiety accounted for a significant portion of the variance once MAL was taken into account. This finding raises concern that previous associations between psychiatric disorders and sleep may be specific to individuals with histories of childhood maltreatment.

Objective: To further assess the role of type and timing of MAL on sleep disruption and associated brain changes.

Methods: Actigraph, Ecological Momentary Assessment (EMA) and neuroimaging data was collected on 18-19 year old, healthy, unmedicated participants recruited from the community. n=15 had no exposure to MAL and n= 22 had moderate to high exposure (mean 4.8 +/- 2.2 types of MAL). Type and timing of Maltreatment were assessed using the Maltreatment and Abuse Chronology of Exposure (MACE) scale.

Results: The most important predictors of impaired sleep were exposure to parental non-verbal emotional abuse at 9-10 years of age. Reduced sleep efficiency correlated with reduced gray matter volume in hippocampus including CA1 subfield, molecular layer and dentate gyrus as well as inferior frontal gyrus and insula. Furthermore, sleep disruption (reduced sleep efficiency) mediated 39-46% of the effects of MAL on volume of hippocampal structures and inferior frontal gyrus.

Conclusion: This study provides further evidence that maltreated individuals show persistent disturbance in sleep continuity, manifest most clearly by decreased sleep efficiency and that there are significant associations between sleep efficiency and gray matter volume in hippocampal subfields CA1, CA3, molecular layer and dentate gyrus as well as insula.

Topic areas:
Anxiety
Child/Adolescent
Depression
Imaging
Neurology
McLean Research Day 2019

Original Research - Clinical

Poster # 55
Time: 1:00-1:50pm

Presenting Author: Laurel Meyer, Clinical Research Assistant II

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

Title: Women’s and Men’s Experiences in Group Therapy for Substance Use Disorders: A Mixed-Methods Analysis

Key words: Gender, Therapy, Substance use disorders

Aim: There are gender differences in the antecedents, course, and consequences of substance use disorders (SUDs). Gender-responsive SUD treatment is effective in addressing the unique concerns of women and may also be salient for men’s recovery. We used a mixed methods approach to compare women’s experiences in single-versus mixed-gender groups as well as to examine women’s and men’s experiences in mixed-gender group treatment for SUDs.

Methods: In a Stage II clinical trial, women (n=100) were randomized to one of two group therapies for SUDs – the Women’s Recovery Group (WRG) or mixed-gender Group Drug Counseling (GDC); men (n=58) were assigned to GDC. At end of treatment, participants completed questionnaires and exit interviews regarding their experiences. Tapes of exit interviews were transcribed and coded for themes using NVIVO.

Results: Participants rated both groups highly (M=3.7, SD=0.6; Likert scale 0-4; 4=Liked a lot) with no significant differences in ratings between groups. Women assigned to mixed-gender GDC rated the gender composition as less helpful than those assigned to WRG (t=2.15, df=72, p<.05). Qualitative interviews demonstrated that the major themes discussed by participants differed by gender. Women overall valued feelings of comfort, safety, and feeling understood compared with men. Women in the WRG were more likely to emphasize gender composition of the group than women in the GDC. Men overall expressed the importance of having opposite gender feedback and perspective.

Conclusions: Gender composition of group treatment of SUDs is a significant factor in women’s experiences of treatment. The results also demonstrated several gender differences in the group attributes most valued by men and women.

Topic areas:
Addiction
Gender/Sex Differences
Women
Presenting Author: Lauren Moran, Psychiatrist-in-charge, Research psychiatrist, Instructor, HMS

Co-Authors: Dost Ongur, John Hsu, MSCE, Victor M. Castro, Roy H. Perlis, Sebastian Schneeweiss

Title: Risk of psychosis with amphetamine versus methylphenidate in adolescents and young adults with attention deficit hyperactivity disorder

Key words: stimulant, psychosis, amphetamine, methylphenidate, ADHD

Background: The prescription use of the stimulants amphetamine and methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) is increasing. In 2007, the US Food and Drug Administration mandated changes to stimulant prescribing labels based on findings of new-onset psychosis in patients without pre-existing disease. We sought to compare the risk of psychosis in adolescents and young adults with ADHD who initiated stimulants.

Methods: We studied a cohort of patients 13 – 25 years old with a diagnosis of ADHD who started taking amphetamine or methylphenidate between January 1, 2004 and September 30, 2015 based on two commercial insurance claims databases. We defined the outcome as patients with a new diagnosis of psychosis requiring treatment with an antipsychotic medication within 60 days of the date of diagnosis. This outcome definition was validated in a study using an external electronic health record database (Partners HealthCare System Research Patient Data Registry). We estimated hazard ratios (HR) for psychosis using propensity score matching and pooled results across databases.

Results: Among a total of 337,919 patients, the propensity score matched subset consisted of 221,846 participants with 143,286 person-years of follow-up who experienced 343 psychotic events (2.4 per 1,000 person-years). There were 237 psychotic events in amphetamine users (0.21%) and 106 in methylphenidate users (0.10%). Use of amphetamine was associated with a higher risk of psychosis than with methylphenidate (HR 1.65, 95% CI 1.31 to 2.09).

Conclusions: Amphetamine use is associated with an increased risk of treatment-emergent psychosis compared to methylphenidate among adolescents and young adults with ADHD.

Topic areas:
Child/Adolescent
Psychotic Disorders
Cognitive control across the lifespan

Cognitive control is involved in processes such as goal selection, response inhibition/suppression, and performance monitoring (RDoC, 2013). Many psychiatric disorders experience deficits in cognitive control including schizophrenia (Lesh et al., 2011), posttraumatic stress disorder (Banich et al., 2009), anxiety (Hallion et al., 2017), depression (Fales et al., 2008), and more obvious disorders of impaired cognition such as dementia (Braver et al., 2002). Reaction time variability within an individual, also known as the intraindividual coefficient of variation (ICV), is a metric used to evaluate cognitive control. We aimed to examine intraindividual variability across the lifespan to establish updated population-based norms. Using a choice RT test and a large, diverse, web-based sample, we calculated trial-by-trial variations in performance with standard deviation in mean RT divided by mean RT across trials. Participants were 11,867 visitors to TestMyBrain.org. Segmented regression analyses demonstrated that the relationship between age and ICV was best fit by a three segment (two breakpoint) linear function, $R^2 = .03$, $F(2, 11855) = 11.58$, $p < .001$ compared to a two segment (one breakpoint) linear function, $R^2 = .02$, $F(2, 11857) = 91.69$, $p < .001$. Age of peak cognitive control was 36.20. Clinical implications will be discussed.
Family Accommodation as a Predictive Measure for Obsessive-Compulsive Disorder Treatment Outcome

Background: Obsessive-compulsive disorder (OCD) is characterized by distressing, intrusive obsessive thoughts and/or repetitive compulsive physical or mental acts to alleviate distress triggered by perceived threats (DSM-5). Previous studies have found that individuals with severe OCD commonly receive family accommodation (FA) entailing involvement of a family member in completing rituals (Amir et al., 2000). Higher levels of FA have been correlated with greater OCD symptom severity (Stewart et al., 2008). This study will examine how levels and frequency of FA at admission predict treatment progression for adults with severe OCD receiving Intensive Residential Treatment (IRT) at the McLean Hospital Obsessive Compulsive Disorder Institute (OCDI).

Methods: The sample consisted of 131 participants (49.4% female) ranging in age from 18-57 years (mean age: 29 years, SD: 9.9) receiving IRT at the McLean Hospital OCDI. Participants completed the Family Accommodation Scale (FAS) patient-report questionnaire to identify levels of family accommodations and the Yale-Brown Obsessive-Compulsive Scale (YBOCS) to identify OCD symptom severity. YBOCS was additionally obtained at weekly intervals throughout treatment and at discharge.

Results: Preliminary findings suggested correlation (r = .396, p = 0.01) of symptom severity determined by YBOCS score at admission to levels of family accommodation determined by FAS questionnaire upon admission. There was a positive correlation of YBOCS at week one to FASa (r = .189, p= 0.05); week two (r= .227, p=0.05); week three (r= 0.231, p=0.05); week four (r= 0.236, p=0.05). There was no significant correlation found between YBOCS at discharge and FASa.

Conclusion: Preliminary results demonstrated that from admission to week four of treatment, family accommodation at admission was correlated with symptom severity. This correlation was not present at discharge. FA predicted symptom severity at admission, but was not predictive of symptom severity at discharge. This implicates that treatment outcome is independent of FA levels at admission. Future research should examine how change in YBOCS scores throughout treatment relates to FAS scores throughout admission. Future research should aim to identify how FA impacts participants living in residence at the OCDI as opposed to participating in the partial, day program and returning to their home environment each evening. Future direction should also aim to identify how levels of FA change throughout treatment as psycho-education is provided to families and how this impacts treatment outcome.

Topic areas:
Anxiety
Presenting Author: Julia Cohen-Gilbert, Assistant Neuroscientist, Instructor

Co-Authors: Nickerson, Lisa D.  Sneider, Jennifer T.  Oot, Emily N.  Seraikas, Anna M.  Rieselbach, Maya R.  Caine, Carolyn E.  Stein, Elena R.  Harris, Sion K.  Silveri, Marisa, M.

Title: Neurobiological underpinnings of the intersection between emotion and impulse control in adolescents

Key words: Emotion, Inhibitory control, fMRI, Adolescence

Adolescence features heightened emotionality and limited impulse control. Development of prefrontal cortex (PFC) and related circuitry during this period enables gradual improvements in inhibitory control. However, emotional information frequently disrupts adolescents’ efforts to control impulsive responses. The current study used functional magnetic resonance imaging (fMRI) to record brain activity during a task requiring participants to ignore positive, negative, neutral or scrambled background images, while performing an inhibitory control task (Go-NoGo). Subjects were 30 healthy 13-14 year-olds (15 male). Brain activation on inhibitory (NoGo) versus non-inhibitory (Go) trials was contrasted between negative and neutral, and positive and neutral conditions. Results showed increased recruitment of multiple PFC regions during emotional versus non-emotional conditions, including inferior frontal gyrus, orbital frontal cortex and ventral medial PFC (VMPFC). VMPFC activation from the negative>neutral contrast was correlated with increased NoGo errors on negative (r=.49, p=.007) and neutral (r=.40, p=.039) trials, as well as parent-reported attention problems on the Child Behavior Checklist (r=.50, p=.005), while activation from the positive>neutral contrast predicted positive NoGo errors (r=.38, p=.041). Contrasts of NoGo>Go for neutral and scrambled backgrounds revealed extensive deactivation in the default mode network (DMN), including VMPFC, amygdala and hippocampus. Deactivation during response inhibition was not evident in emotional background conditions. This suggests that emotional images reduce inhibitory control, in part, by eliciting self-referential emotional processing and reducing DMN deactivation, with VMPFC deactivation supporting inhibitory control across emotional conditions. These findings elucidate neural mechanisms underlying increased impulsive, often risky, behaviors that can occur under emotional conditions during adolescence.

Topic areas:
Child/Adolescent
Imaging
**Background:** A critically important consequence of early childhood trauma is reflected in the way individuals inhabit and experience their bodies. Trauma-related abnormal body perceptions can take a number of forms, including body shape and weight dissatisfaction, body avoidance and shame, and depersonalization. Although psychometric assessments of body image and perception have been used to contrast the bodily experiences of control vs. childhood trauma-exposed individuals, the mechanisms underlying this relationship remain unclear.

**Aim:** The aim of this study was to examine how childhood maltreatment type, Post-traumatic Stress Disorder (PTSD) symptom severity, and distorted trauma-related cognitions contribute to the experience of abnormal body perceptions in individuals with histories of childhood trauma.

**Methods:** Participants were treatment-seeking women (ages 28-63) receiving in-patient, partial, or residential treatment at a psychiatric care facility. All participants had histories of early childhood trauma and a diagnosis of PTSD, with varying levels of trauma-related dissociation (N = 24). As part of a larger study on the biological mechanisms of PTSD, participants completed a battery of self-report measures, including the Body Uneasiness Test (BUT) to measure body perceptions, the Childhood Trauma Questionnaire (CTQ) to measure childhood maltreatment (i.e. sexual abuse, physical abuse, emotional abuse, and neglect), the PTSD Checklist (PCL-5) to measure total PTSD symptom severity, and the Posttraumatic Cognitions Inventory (PTCI) to measure trauma-related, distorted cognitions about oneself, the world, and attribution of blame for the traumatic experience.

**Results:** In our first regression model, childhood trauma alone predicted 46% of the variance in abnormal body perceptions (R² = .46, F(5,17) = 2.88, p = .046), with sexual abuse driving this effect (β = .42, p = .044). We found in our second model (R² = .66, F(1,19) = 13.02, p = .002) that over and above sexual abuse (β = .49, p = .006), post-traumatic distorted cognitions (β = .58, p = .002) significantly predicted abnormal body perceptions, whereas total PTSD symptom severity did not (β = .02, p = .925).

**Conclusions:** In a treatment-seeking sample of women with PTSD, early childhood sexual trauma and cognitive distortions about the self, world, and blame were significantly predictive of abnormal body perceptions, whereas PTSD symptom severity was not. Given that women with histories of childhood sexual trauma and subsequent distorted trauma-related cognitions are disproportionately likely to develop abnormal body perceptions, this suggests that distorted cognitions are a key target for therapeutic intervention.

**Topic areas:**
- PTSD
- Women
Alcohol is the most commonly abused substance in individuals seeking treatment for post-traumatic stress disorder (PTSD). Clinical and epidemiological studies have consistently reported that PTSD is associated with a 3-fold higher risk for developing alcohol use disorder (AUD), and the lifetime prevalence of AUD was estimated at 40% in individuals with PTSD. Despite the high rates of comorbidity between PTSD and AUD, there is a substantial gap in understanding how traumatic experiences lead to a transition from initially controlled alcohol consumption to the development of alcohol seeking and dependence. The amygdala, a critical neural substrate of both aversive and appetitive behaviors, is directly affected by a variety of acute and chronic stressors, as well as addictive substances, which can lead to sensitization. It has been shown that individuals with comorbid AUD and PTSD exhibit hyper-reactivity of the amygdala upon presentation of both aversive/distressing stimuli as well as alcohol cues. These intriguing findings suggest that the amygdala is a key structure mediating interactions between AUD and PTSD; however, molecular, cellular and circuit mechanisms underlying amygdala dysfunction in AUD and PTSD comorbidity are not well understood. Recently, studies in mice have indicated that distinct subpopulations of neurons within the amygdala are differentially responsible for the activation and inhibition of fear memory. In addition, divergent ensemble activity from these subpopulations seems to mediate positive or negative valence coding. Specifically, we have found that a specific excitatory neuronal population in the basolateral amygdala (BLA), marked by a combination of Thy1 expression (Thy1+), serve as ‘Fear-Off’ neurons. They also heavily project to the nucleus accumbens (NAcc), a core structure for reward-based learning and substance addiction, instead of the central amygdala (CeA), suggesting that these neurons directly inhibit fear and may support appetitive behavior. Understanding this molecularly identified population in stress and alcohol related behaviors is central to our study. To establish a procedure combining a stress paradigm with a reliable behavioral measurement of associative Pavlovian learning, we first employed a well-established immobilization stress (IMO) and conditioned place preference (CPP) paradigm with systemic injection of alcohol (EtOH, 2g/kg BW) in mice. Second, to investigate roles of BLA Thy1+ neurons and their projections to the NAcc, we performed inhibitory optogenetic manipulation in Thy1+ neurons using Thy1-Cre driver mice and AAV encoding Cre-dependent halorhodopsin (eNpHR). We found that unstressed mice formed a preference for the chamber associated with EtOH, but then rapidly extinguished their CPP behavior. Notably, mice with prior IMO stress showed enhanced alcohol-chamber association and reduced CPP extinction. In contrast, mice injected with saline in both chambers did not display a preference (N=2; saline n=8, EtOH n=8, EtOH+IMO n=7). In addition, the preference formation of EtOH-associated compartment was disrupted when optogenetic inhibition was performed at Thy1+ cell bodies in the BLA (N=2; eYFP n=7, eNpHR n=8) or Thy1+ projections in the NAcc (N=2; eYFP n=8, eNpHR n=7). The findings suggest that alcohol exposure alters the firing activity of subpopulations of amygdala neurons and the functional interactions between the BLA and NAcc via its projections. A prior traumatic experience may augment these changes and lead to enhanced alcohol seeking behavior.
McLean Research Day 2019

Original Research - Clinical

Poster # 62
Time: 1:50-2:45pm

Presenting Author: Kara Kelley, Research Assistant

Co-Authors: Kelley, K., Falkenstein, M., Potluri, S., Geagea, A., and Krompinger, J.

Title: Family Accommodation and Symptom Dimensions in OCD

Key words: family, accommodation, obsessive-compulsive disorder

Background: Family accommodation (FA), a phenomenon characterized by participation in rituals and modification of family routine, has been linked to increased symptom severity and attenuated treatment response in individuals with obsessive-compulsive disorder (Lebowitz, Panza, Su & Bloch, 2012; Ferrao et al., 2006). More specifically, previous research has suggested that FA is more likely to occur in the families of patients with contamination and cleaning symptoms (Stewart et al., 2008). While much of the literature utilizes family member reports of FA, the current study will evaluate the discrepancies between patient and family reports of FA in adults with severe OCD. We aim to compare the discrepancies among various dimensions of OCD: contamination, responsibility of harm, incompleteness, and unacceptable thoughts. We hypothesized that greater discrepancy will occur among patients with unacceptable thoughts, as these symptoms may be less overt than other symptom dimensions.

Methods: The total sample included 146 individuals. The sample included 73 patients receiving IRT for OCD (N=73; 52.1% male, 47.9% female) and their respective family members (N=73; 72.6% female, 27.4% male). Of the family members, 72.6% were the patient’s parent, 11% a spouse, 4.1% a partner, 8.2% a sibling, and 4.1% reported other. Family accommodation was measured using the Family Accommodation Scale (FAS). The Dimensional Obsessive-Compulsive Scale (DOCS) was used to assess the following symptom dimensions: contamination (DOCS1), responsibility of harm (DOCS2), unacceptable thoughts (DOCS3), and incompleteness (DOCS4). OCD symptom severity was measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

Results: A linear regression was calculated to predict Y-BOCS symptom severity based on FA. A significant regression equation was found (F (1, 71)=21.279, p<.01) with an R2 of .231. Linear regression analyses indicated that patient-reported FA was significantly associated with increased symptom severity of DOCS1 (β=.542, p<.01), DOCS2 (β=.579, p<.01), and DOCS4 (β=.365, p<.05); however, family-reported FA was not significant. Neither patient-reported nor family-reported FA was significantly associated with symptom severity of DOCS3.

Conclusion: In line with previous research, greater FA was linked to increased symptom severity, and contamination symptoms was linked to greater FA. Our hypothesis that greater discrepancy would occur among those with unacceptable thoughts was not supported. Those who endorsed DOCS3 items reported lower FA overall. However, results do suggest that discrepancies among patient and family reported FA occur in those with contamination, responsibility of harm, and incompleteness, and that patient-reported FA is significantly linked to increased dimension-specific symptom severity. These findings provide evidence for the clinical relevance of the patient-reported FAS, as well as the potential treatment target of family psychoeducation.

Topic areas:

OCD
Recent research suggests a narrowing of the “digital divide” of smartphone and social media availability between the general population and individuals with serious mental illness (Torous and Roberts, 2017). The availability of smartphone applications (“apps”) designed to enhance wellness or support mental health has also grown exponentially, with over 10 thousand available (Torous and Friedman, 2014). However, there is very little data available characterizing smartphone use in psychiatric populations. We aimed to fill this gap in knowledge, first, by assessing general smartphone app and social media usage in a partial hospital population, and second, by examining current engagement and interest in the use of smartphone apps to support mental health. A transdiagnostic sample of all adult hospital patients (N = 322) enrolled in a partial hospitalization day program completed self-report measures of smartphone app (Smartphone Use Survey) and social media use (Mobile Technology Engagement Questionnaire). Participants also completed self-report measures of symptoms of anxiety (Generalized Anxiety Disorder Scale - 7 item) and depression (Patient Health Questionnaire-9) and overall improvement as part of standard clinical care. The most frequently used app functions were texting, email, and social media. Younger individuals reported more frequent use across most types of apps. Baseline depression and anxiety symptoms were not associated with frequency of app use. Facebook was the most commonly used social media app. Participants reported healthcare, calendar, and texting apps as most supportive of their mental health, and social media apps as negatively affecting their mental health. Most patients reported interest in (74%) and willingness to use (81%) a smartphone app to monitor their mental health condition. Less than half (44%) of patients currently had a mental health app downloaded on their smartphone, with mindfulness and meditation apps being the most common type. The high interest in and willingness to use mental health apps, paired with the only moderate current reported usage, indicate a potential unmet treatment need in psychiatric populations. The high rate of phone-checking and low rate of social media posting may suggest that social media is experienced as a platform for rumination and social comparison. The naturalistic use of calendar and texting apps may suggest the usefulness of these functions in mental wellness focused apps. More implications for future development and use of mental health apps are discussed.

**Topic areas:**
Depression
Technology
It has been well documented that assessing behavioral symptoms of depression, anxiety, insomnia, and agitation in Alzheimer’s Disease trials exclusively through self- or observer– report scales has its limitations. A wireless sensor device developed at MIT may provide a solution to some of these issues. This device, Emerald, is mounted to the wall and maps behavioral data, such as an individual’s motion, respiratory rate, location, and sleep through low power radio signals, without requiring the individual to wear or regularly recharge the device. In this study, the device was installed in the rooms of four patients who had been diagnosed with dementia in a residential care setting. The device collected behavioral data on the patients over the course of four months and we were able to map out the behavioral information of these patients. Analysis of this data in combination with various socio-environmental factors allowed us to detect behavioral changes in order to facilitate preventative intervention. Furthermore, this study establishes the safety and feasibility of the Emerald device in a residential care setting for dementia.
Background: Post-Traumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder with profound social burden and few effective treatments. Fear extinction deficits are thought to contribute to PTSD pathogenesis. Research from animal models and from human neuroimaging studies implicate medial prefrontal cortex (mPFC), among other structures, as playing a crucial role in fear extinction memory formation. In rodent models of fear conditioning and fear extinction, driving activity of neurons within infralimbic cortex (IL) within the mPFC has been shown to be sufficient to extinguish previously encoded fear memories. The IL is a heterogeneous cortical structure, however, which contains many cell-types. The molecular signature of the cell-types which are necessary and sufficient for forming and consolidating fear extinction memories remain unknown.

Methods: We used single-cell nuclear sequencing (InDrops) to identify clusters of neurons in the mouse mPFC that exhibit immediate early gene (IEG) expression two hours post fear extinction (n=9) when compared with home cage (n=7) and fear conditioned (n=7) animals. We have used fluorescent in situ hybridization (FISH) and immunohistochemical techniques to confirm markers for cell clusters found with single-cell nuclear sequencing. Retrograde viruses expressing Rpl10a-eGFP were also used to identify molecular signatures of projection neuron populations using translating ribosomal affinity purification (TRAP).

Results: We have identified over 20 distinct cell-type populations within the mPFC, including populations of glutamatergic neurons, GABAergic interneurons, astrocytes, microglia, and endothelial cells. Many of these clusters express known cell-type specific markers. We have also identified populations of neurons with previously undescribed molecular signatures. Several neuronal clusters exhibit IEG expression (including Fos, Junb, Npas4, Egr1, Egr4, and Nr4a1). One of the clusters with strongest IEG expression after fear extinction upregulates plasticity-master regulator BDNF and also Ptgs2, a potential pharmacologic target for PTSD.

Conclusions: We provide pilot data to begin construction of a comprehensive map of cell-types within the mouse mPFC. We have identified both known and uncharacterized cell-types. Some of these cell-types possess transcriptional signatures suggestive of activity during fear extinction. Follow-up studies will assess the functional role of these cell-types in the process of fear extinction formation and consolidation.

Topic areas:
- PTSD
Presenting Author: Woori Kim, Postdoctoral Research Fellow

Co-Authors: Galen Missig, Beate C. Finger, Samantha M. Landino, Abigail J. Alexander, Emery L. Mokler, James O. Robbins, Yan Li, Vadim Y. Bolshakov, Christopher J. McDougle, William A. Carlezon Jr and Kwang-Soo Kim

Title: Sex- and region-specific regulation of immune-related genes by maternal and early postnatal immune activation

Key words: Development, Infection, Pro-inflammatory, Anti-inflammatory, Sex-difference

Autism spectrum disorders (ASDs) are neurodevelopmental syndrome with significantly higher prevalence in males. Recent emerging clinical and preclinical data suggest that the immune system plays a critical role for etiology of ASDs, as evidenced by its association with autoimmune disorders and maternal infection during pregnancy. To address the hypothesis that ASD’s male prevalence is linked to sex-different regulation of immune-related genes, we investigated molecular changes of three categories of inflammatory genes (i.e., pro- and anti-inflammatory genes and neuroinflammation-related marker genes) in male and female mouse brains following treatment of timed-pregnant mice with polyinosinic:polycytidylic acid (Poly I:C) on gestational day 12.5 to produce maternal immune activation (MIA) and/or with lipopolysaccharide (LPS) on postnatal day 9 to produce postnatal immune activation (PIA). Our molecular studies revealed that early immune activation produced prominent sex-specific changes in inflammation-related gene expression in the brain. Both sexes showed increases in pro-inflammatory factors (such as TNFα, iNOS, IL-6 and IL-1β) and neuroinflammation markers (such as Iba-1, GFAP and TSPO) but their increases were in general much higher in male mouse brains, as reflected by levels of mRNA and corresponding proteins. Strikingly, however, we found that expression of anti-inflammatory factors was decreased in male mouse brain regions but increased in female mouse brain regions. Thus, our findings demonstrate that early developmental immune activation can produce sex-specific effects on the function of factors that regulate inflammatory responses in the brain, which may contribute to sex differences in the prevalence of ASD-like behaviors.

Topic areas:
Child/Adolescent
Gender/Sex Differences
Acceptability and Feasibility of a Computer-Based Cognitive Control Training for Impulsivity in an Acute Psychiatric Setting

Introduction- Positive and negative urgency, or impulsive responses to positive and negative mood, are transdiagnostic aspects of impulsivity. Urgency predicts worse treatment outcome in partial hospital settings, and it is associated with deficits in cognitive control. A previous study has shown cognitive control training to be effective in decreasing urgency in a non-clinical population (Peckham & Johnson, 2018), but studies have not yet explored if this type of training is feasible in psychiatric settings. In the present study, cognitive control training targeting working memory and response inhibition was administered to patients with significant levels of impulsivity. Implementing a cognitive control training in a partial hospital raises questions about the compatibility of this intervention with such intensive treatment due to scheduling constraints, patient’s possible lack of interest, and comfortability. In this study, we tested the feasibility and acceptability of an adjunctive daily computer-based cognitive control training intervention in patients with clinically significant levels of impulsivity who are seeking treatment at McLean’s Behavioral Health Partial Hospital (BHP).

Methods- Patients seeking treatment at the McLean BHP, an intensive CBT-based day program, reporting high scores (average of 3 out of 4) on the urgency scales of the UPPS-P short were invited to participate. Eligible participants completed a daily 15-minute training session where the PASAT, a working memory task, and the Go/NoGo, a response inhibition task, were alternately administered. On their last day in the study, participants completed a debriefing questionnaire which asked about their perceptions, comfortability, and understanding of the PASAT and Go/NoGo tasks on a 7-point scale in addition to qualitative feedback.

Results- Of the 20 participants enrolled in the study, 17 (85%) completed the training, attending an average of 5.71 (SD= 1.31) training sessions. Participant’s average age was 28.6 (SD= 11.75), and 50% were female. Of participants who completed the training, 11 completed a debriefing questionnaire during their last session. Overall, participants rated the PASAT lower on average than the Go/NoGo on all measures of acceptability. Specifically, participants rated the Go/NoGo as significantly more helpful than the PASAT, t(10)= -2.75 p = 0.02) and significantly easier to see how the task relates to impulsivity than the PASAT, t(9)= -2.94 p =0.016). Qualitative feedback showed that some participants found the session to be too long and frustrating, while others found the training to be helpful and useful for practicing the skills they were learning in treatment.

Conclusion- Overall, the majority of participants enrolled completed the intervention in full. These findings suggest that a cognitive control training for clinically significant impulsivity is feasible and at least partially acceptable in an acute psychiatric population in a partial hospital setting. The differences in acceptability between the PASAT and Go/NoGo task exemplify the need to increase participant’s understanding of how the tasks relate to impulsivity.

Topic areas:
Technology
McLean Research Day 2019

Original Research - Pre-Clinical

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

Presenting Author: Kenneth Mccullough, Postdoctoral Research Fellow

Co-Authors: Kenneth M McCullough, Galen Missig, Mykel Robbel, William A. Carlezon

Title: Chronic cell-type specific modulation of nucleus accumbens medium spiny neuron activity precipitates stress-like effects on sleep architecture.

Key words:

Background: Changes in sleep (insomnia, hypersomnia) are well known to accompany stress-related psychiatric conditions including Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD), both of which are defined by depressive-like features. Research from our lab and others has demonstrated that the NAc is important for the development of stress-related psychiatric conditions. Specifically, changes in CREB, ΔfosB and other genes within the NAc dramatically affect susceptibility to chronic stress related behavioral phenotypes. Chronic stress leads to elevations in CREB and over expression of CREB leads to anxiogenic, depressive-like behavior while suppression of CREB function causes anxiolysis. Within the NAc, enhanced CREB activity leads to increases in the expression of dynorphin, an endogenous kappa opioid receptor (KOR) ligand that is expressed in dopamine D1 receptor-expressing medium spiny neurons. Molecular or activity-related changes in D1- and D2-expressing neurons have been shown to modulate core features of depressive illness, such as anhedonia (reduced ability to experience pleasure) or social avoidance following stress. Specifically, changes in the molecular and firing properties of D1 MSN’s have been observed following and correlated with susceptibility to chronic social defeat stress (CSDS). Our lab recently demonstrated that CSDS, a chronic stress regimen not only produces many depression-like behaviors, but also causes increases in paradoxical sleep (called REM sleep in humans). Remarkably, this effect is blocked by the administration of JDTic, a KOR antagonist, further implicating D1 MSN’s in observed stress-precipitated enhancements of paradoxical sleep.

Results: Chronic inhibition of D1 MSNs through Gi DREADD lead to increases in the time spent in paradoxical sleep without affecting time spent in slow wave sleep or wake. Chronic activation of D1 MSNs through Gq DREADD lead to moderate decreases in paradoxical sleep without affecting time in slow wave sleep or wake. Theses effects were maintained five days later following washout suggesting that activation or inhibition of D1 MSNs leads to persistent effects on sleep architecture.

Conclusions: Changes in sleep architecture are an important component of stress-related disorders. Specific changes to D1 MSNs have been implicated in susceptibility to stress-precipitated dysfunction and here we suggest they may be crucial for production of stress-precipitated changes in sleep. Chronic inhibition of D1 MSNs leads to increases in paradoxical sleep while chronic activation leads to decreases in paradoxical sleep. Importantly, this recapitulates effects of CSDS on paradoxical sleep without changing slow wave sleep or wake. These data contribute a circuit based model where chronic stress may change D1 MSN activity leading to alterations in sleep architecture similar to those seen in humans with stress-related illnesses.

Topic areas:
Depression
Presenting Author: Maria Kristina Schwartz, Student

Co-Authors: Hilary Connery, MD, PhD

Title: The Cannabis Health Harms Questionnaire: pilot data to inform cannabis prevention during mental health and substance use treatment

Key words: Cannabis, Health-harms, Risks, Perceived, Treatment-seeking

Rationale: Expanding access to medical marijuana and recreational legalization appears to be reducing cannabis use perceptions of harm. Prevention in this environmental context is important yet understudied.

Methods: The Cannabis Health Harms Questionnaire (CHHQ) was developed for exploratory quality improvement in prevention. CHHQ assesses demographics, patterns and types of cannabis use, and asks patients to rate perceived risk among a comprehensive list of evidence-based cannabis-related health harms, and to identify the item of greatest individual concern.

Results: Forty-two patients admitted for treatment of a non-cannabis substance use disorder and 25 patients admitted for severe mood/anxiety disorder without substance use disorder voluntarily completed CHHQ during treatment. Long-term risks were more frequently ranked (n=43) than short-term risks (n=16), with a smaller number perceiving no harm (n=4), total harm (n=1), or unsure (n=3). The most frequently concerning long-term risks were adolescent exposure, progression to other drug use, and bronchitis; short-term risks were driving impairment and acute psychosis. Young adults age 18-25 years (n = 13) ranked driving impairment and child exposure as primary harms, 35-44 year-olds (n = 17) most frequently ranked progression to other drug use, and adults age 55-64 years (n = 10) ranked adolescent exposure and impact on co-occurring psychiatric disorders as primary harms. Those without substance use disorders were not concerned about progression to other substance use, and among substance users women were twice as likely as men to be concerned about progression to other drug use. Adolescent exposure and driving impairment were top harm perceptions regardless of substance use disorder status.

Conclusions: Health harm perceptions of cannabis use vary by demograph. Long-term effects of cannabis exposure during youth and short-term effects of cannabis on driving impairment dominate. Preliminary findings suggest that those with substance use disorder have greater risk perception regarding progression to other drug use.

Topic areas:
Addiction
Presenting Author: Katherine Davis, Clinical Research Assistant II

Co-Authors: Madeline K. Kuppe, Staci A. Gruber, Scott E. Lukas, Chun S. Zuo

Title: Metabolic profiling of mood and craving behavior during initial phase of marijuana abstinence

Key words: Marijuana, Mood, Cannabis, Withdrawal, Relapse

Objective: To non-invasively monitor regional GABA and glutamate (glu) in conjunction with assessing clinical state, craving, withdrawal signs, and cognitive performance during initial phase of a verified marijuana (MJ) abstinence.

Methods: Subjects: Recreational MJ users (n=21) who met DSM-5 criteria for cannabis use disorder only were recruited under a McLean Hospital/Partners IRB approved protocol. Five participants discontinued after baseline visit and sixteen completed a verified three-week MJ abstinence. Using proton magnetic resonance spectroscopy (MRS), GABA and glu of dACC and striatal (str) regions were measured at baseline, weeks 1 and 3 during abstinence. MRS data were analyzed with LC model spectral fittings. Clinical measures: A battery of mood and behavior measures including PANAS, POMS, CWS, MCQ, HAM-A, HAM-D, BAI, BDI, and BIS were administered weekly. Subscales of the behavioral measures were also examined. Sleep was also assessed weekly with PSQI and monitored daily with a Fitbit device. Levels of GABA and glutamate and scores of clinical measures were examined across the time duration of the abstinence. Pearson correlations between CWS and craving, mood, and other measures as well as GABA and glu concentrations were evaluated at baseline and other time points during the abstinence. P-values of the correlation were calculated in and correlations were considered significant if p-values were less than 0.05.

Results: Group averages of dACC GABA and glu in the marijuana users showed a mild decrease at week 1 into abstinence and returned towards baseline levels at week 3. Those of str GABA and glu exhibited a mild increase at week 1 and, similarly, returned towards baseline at week 3. Group averages of CWS and MCQ showed a mild trend up and down respectively at week 1 before turning lower but remained at elevated levels at week 3. Portion of the mood scales (e.g. BAI, BDI, PANAS_negative) was generally on a down-trend while others (e.g. PSQI, POMS_tension, PANAS_positive) fluctuated at week 1 and persisted near baseline levels at week 3. Trajectories of GABA and glu across abstinence was negatively correlated with that of MCQ (R2 = 0.99) and that of POMS_tension (R2=0.98). At week 3, POMS_tension was positively and significantly correlated with MCQ (R2=0.71). Examination of dACC GABA changes from baseline to week 1 revealed the insignificance was, in part, resulted from two subgroups: GABA increased (GABA+, n=6) from baseline to week one and GABA decreased (GABA-, n=10) during this period. Although the subgroups were demographically very similar, they appeared to have distinct difference in several mood and behavioral parameters as well as cognitive function.

Discussion: Elevated craving, CWS, mood, and POMS_tension during the abstinence demonstrated that they were the apparent barriers for MJ users to remain in abstinence. Our data of the neurochemical changes across the abstinence process have intrinsic relationship with mood, craving, and withdrawal signs during the abstinence and support the notion that brain neurochemicals correlate with behaviors that parallel MJ withdrawal.

Topic areas:
Addiction, Imaging, Pharmacology
Intro/Background: Recovery-orientated practice (ROP) is an approach to patient care emphasizing unique individual processes of change in context of recovery. This includes aspects such as offering empowerment to the patient, supportive attitudes, protecting patient rights, providing care with dignity and respect, facilitating partnership and communication, and evaluating the recovery process (Australian Government, 2010). On many inpatient psychiatric units, a large portion of staff are Mental Health Specialists (MHS) and Registered Nurses (RN). While many staff have some awareness and personal perceptions about recovery, trainings can promote additional knowledge of recovery principles and improve patient involvement in treatment decisions and outcomes (Farkas et al., 2005; Majumder, Walls, & Fullmer, 1998). ROP training can foster staffs’ self-awareness/views on recovery and help identify areas for improvement. This study evaluated differences in ROP knowledge between MHS/RN staff pre-training and evaluated the impact of a brief ROP training.

Methods: ROP trainings of six modules were conducted over two months on two inpatient units at a psychiatric hospital in the United States. ROP knowledge was measured with the Recovery Knowledge Inventory (RKI; Bedregal et al., 2006), evaluating recovery perceptions/knowledge across four subfactors on a five-point scale. The RKI was administered pre/post-training to 94 mental health staff: MHSs (n = 40), RNs (n = 54). The RKI assesses four factors in recovery: Role and Responsibility (Factor 1), Non-linearity of Recovery Process (Factor 2), Roles of Self-definition and Peers (Factor 3), and Expectations (Factor 4).

Results: Data was compared pre/post-training within RNs, MHSs, and the total sample. At pre-training the sample had a mean RKI score of 3.75 out of 5 (SD=.33). RNs were observed to have relatively higher scores (M=3.79, SD=.32) compared to MHSs (M=3.67, SD=.33). Post-training, RKI scores increased significantly (t (29)= -2.13, p=.042), indicating improvement in overall knowledge. MHSs and RNs did not significantly differ in the amount their knowledge increased across the training (F (34, 1)=.226, p=.638), suggesting all staff improved their understanding of ROP to similar extents regardless of education/occupation. Factor 1 was the only domain significantly different between groups at pre-training (F (79, 1)=12.32, p=.001).

Discussion: Our aim was to evaluate staffs’ baseline ROP knowledge and impact of a brief ROP training. Compared to previous literature, our sample demonstrated pre-training scores commensurate or higher than similar samples (Bedregal et al., 2006; Okamoto and Tanigaki, 2018). Our psychiatric hospital’s general culture/treatment approach and ROP inclusion during employee orientation may have caused elevated scores. Factor 1 baseline RKI scores were elevated in RNs versus MHSs. RNs’ focus on symptom management/objective outcomes (i.e. pain/anxiety scales, detox symptoms), which may result in greater understanding of various roles/responsibilities for managing wellbeing. Factors 3 and 4 were slightly higher in MHSs. While not significant the cause might be related to MHS duties; high level of milieu involvement allows for direct observation of patients’ treatment participation. Overall, our brief ROP training was effective. Future research could seek to control for work/educational experience and length of employment to identify potential confounding factors and improve training for various staff.

Topic areas:
Quality/Outcomes
The mental health and well-being of first responders has received growing attention in recent years. The term first responder has commonly included police officers, firefighters, and emergency medical technicians (EMTs)/paramedics (Haugen et al., 2017; McCaslin et al., 2006; Take et al., 2007; Weiss et al., 1995). A few studies have demonstrated high rates of PTSD, stress, depression, and substance use among first responders as well as limited service utilization (Fox et al., 2012; Haugen et al., 2012; Kleim & Westphal, 2011). While services for first responders have become more available (i.e., McLean Hospital's LEADER Program), there is still reticence to use these services (Lewis-Schroeder et al., in press). The way mental health stigma and barriers to mental health care affect first responders remains largely unclear (Haugen et al., 2017). First responders frequently witness and experience traumatic events (Heffren & Hausdorf, 2016; Karrafa & Koch, 2016). Additionally, first responders work in environments where they experience high levels of psychological and physical stress (Galloucis et al., 1999; McCaslin et al., 2006). One study found rates of PTSD between 8-32% and slightly lower rates of depression among first responders (Kleim & Westphal, 2001). In addition to struggling with symptoms of PTSD, depression, and stress, untreated mental health difficulty among first responders is associated with increased distress and impairment as well as work productivity loss, early retirement, physical health consequences, substance abuse, and suicide (Bloodgood, 2006; Fox et al., 2012; Haugen et al., 2017). Friendships, family, and intimate relationships also suffer and in some cases untreated mental health problems can lead to domestic violence (Sheehan, 2000; Wester et al., 2010). Work stress and untreated mental health problems contribute to burnout (Chatzea et al., 2017) resulting in diminished job performance (Cocker & Joss, 2016), putting the public and first responders at greater risk. Despite the numerous consequences of untreated mental health difficulty, a large number of first responders refrain from seeking help (Karaffa & Koch, 2016). Researchers have begun exploring barriers to seeking help among first responders including fears about confidentiality, negative evaluations/treatment by colleagues and supervisors, being assigned to less desirable job duties, and scheduling difficulty due to shift work (Fox et al., 2012; Haugen et al., 2017). However, in most cases the primary identified barriers have been attributed to modifiable factors, especially stigma (Fox et al., 2012). Chapman and colleagues (2012) found that stigma was the strongest barrier to seeking mental health treatment among a sample of U.S. Army personnel and found that both public- and self-stigma were associated with negative attitudes toward seeking mental health treatment. The current study aims to fill a gap in the research by gathering data on mental health variables, stigma, and barriers to care for first responders. This will be the first study to date that includes firefighters and emergency medical personnel along with police in exploring both mental health stigma and mental health outcomes using validated measures.

**Topic areas:**

PTSD
Cognitive biases, such as attention and interpretation, play a causal role in emotional disorders. However, few studies have tested the theoretical role of these cognitive vulnerabilities in suicidal ideation. One exception is a recent study which found that interpretation bias was the best predictor of suicidal ideation out of numerous demographic and clinical variables (Beard, Rifkin, & Bjorgvinsson, 2017). However, there is a dearth of research investigating attention and interpretation biases simultaneously in psychiatric samples. The goal of the current study was to replicate and extend prior work by testing whether cognitive biases predict suicidality and other symptoms of depression and anxiety. Participants in this study were adults (N = 100) attending the Behavioral Health Partial Hospital Program. Participants completed objective measures of attention bias (free viewing of emotional facial expressions eye tracking task) and interpretation bias (the Word Sentence Association Paradigm (WSAP), which assesses the endorsement, or lack thereof, of negative and positive interpretations of ambiguous sentences). Suicidal thoughts and behaviors were assessed by a structured interview (Columbia Suicide Severity Rating Scale) and self-report measures administered at admission and discharge as part of routine clinical care. Data collection is complete, and we will present results of analyses predicting suicidal thoughts and behaviors from cognitive biases and other relevant demographic and clinical variables. We hypothesize that interpretation bias will be a robust predictor of suicidality, and we will explore whether attention bias also contributes meaningfully to suicide outcomes. Results will have theoretical implications regarding the specific role of cognitive biases in suicidal ideation and may inform future efforts to identifying those at risk for suicide using more implicit measures.
Voice-hearing is highly prevalent in PTSD, and how an individual is asked about voice hearing matters.

**Topic areas:**
Dissociative Disorders
Psychotic Disorders
PTSD
Comparing Two Methods of Calculating Post-Error Slowing: A Neurobehavioral Investigation

**Background:** Deficits in cognitive control have been implicated in psychiatric illnesses, including major depressive disorder. An important domain of cognitive control is error monitoring, or the ability to detect and respond adaptively to mistakes. This study examined two ways of measuring post-error slowing (PES), which refers to the tendency to increase response times after errors. Although PES has been used as a marker for cognitive control in clinical populations, recent studies suggest alternative methods of calculation. The recently proposed “robust” method compares response times (RTs) on post-error trials with RTs on trials that both come after correct responses and precede errors. The robust method may be superior to the “traditional” method because it considers the sequence of events that surrounds errors to more accurately capture dynamics specific to errors.

Here, we compared traditional and robust methods and examined convergent correlations with event-related potential (ERP) indices of error monitoring.

**Method:** Forty-six healthy participants completed a modified Eriksen Flanker task while continuous 96-channel electroencephalogram (EEG) was collected. We examined PES, comparing the traditional method (calculated as average post-error RT minus average post-correct RT for all post-correct trials) and the robust method (calculated as average post-error RT minus average for post-correct RT only for trials that precede errors). We also measured two event-related potential (ERP) components that have been consistently linked to error processing: the error-related negativity (ERN) and error positivity (Pe). The ERN and Pe were measured 0-100ms and 200-400 ms following errors, respectively. Compared to the ERN, the Pe is more explicitly linked with error-specific processing, such as attention allocation and evidence accumulation of having made a mistake.

**Results:** As hypothesized, PES was significantly larger in magnitude when calculated with the robust method (M difference = 38ms, d = 0.96) compared to the traditional method (M difference = 10ms, d = .28; t(45) = 7.73, p < .001). Moreover, the Pe was correlated with both the robust (r = .38, p = .009) and traditional (r = .33, p = .03) measures of PES. Accordingly, participants with larger Pe responses showed larger post-error slowing. However, after controlling for overall RT, Pe was only significantly related to robust PES (p = .031) and not traditional PES (p = .083). The ERN was unrelated to either measure of PES.

**Conclusion:** The robust method provided an estimate of PES that was significantly larger in magnitude than the traditional method. We also found that Pe was correlated with robust PES even after controlling for general response time. This correlation to the Pe shows that the robust method captures error-specific processing, instead of general processes common to all types of responses. Together, the data suggest that the robust method can more accurately capture the full range of behavioral changes after an error. As we continue to use PES in clinical contexts, we should investigate the most optimal way to measure PES and consider using the robust method exclusively.
Capturing longitudinal fluctuations in behavior, mood, and cognition in patients with obsessive compulsive disorder

Standard procedures for symptom assessments fail to capture subtle fluctuations in thought and behavior in a way that is both precise and reproducible. We aim to enhance the temporal and spatial precision of behavioral readout by recording objective, continuous behavioral signals over long periods of time using temporally dense assessments tailored to the individual study participants. In particular, deep longitudinal data is being collected from 30 OCD patients, with a subset of these patients undergoing deep brain stimulation (DBS). Our analysis of behavioral data will work to capture the natural course of changes in mood and cognition, quantifying relevant behavior both during and between study visits, including detection of ritualized behaviors. This in itself enables improved diagnosis and the development of personalized therapeutics. Additionally, neural recording data from the deep brain implants will allow us to link neural activity with rich behavioral measurements, which could both elucidate neural underpinnings of OCD symptoms, and contribute to the development of improved closed-loop DBS technology.

Topic areas:
Neurology
OCD
Quality/Outcomes
Technology
Presenting Author: Monica Dawes, Technical Research Assistant

Co-Authors: Chandrashekhar Honrao, Xiaoyu Ma, Alexandros Makriyannis, Elena Chartoff, Rajeev Desai

Title: An in vivo microdialysis study of oxycodone and fentanyl: changes in neurochemical activity and detection of drug levels in the nucleus accumbens of male and female rats.

Key words: Opioid Addiction, Sex Differences, Neurochemistry, Microdialysis

Opioid abuse is the nation’s fastest-growing drug problem and represents a public health concern of epidemic proportion. Thus, there is an urgent need to elucidate the underlying mechanisms that may be involved in the abuse-related effects of opioids. The present in vivo microdialysis studies were undertaken to: a) determine the neurochemical profiles of cumulatively administered oxycodone (0.3–3.0 mg/kg, i.p.) and fentanyl (0.0032–0.056 mg/kg, i.p.) on neurotransmitter flux in the nucleus accumbens (nAcc) of male and female Sprague-Dawley rats (n=9-11/group); and b) determine whether neurochemical changes induced by oxycodone and fentanyl can be related to their concentrations within the nAcc. Dialysate samples were analyzed using Liquid Chromatography Mass Spectroscopy following derivatization with benzoyl chloride. Results from ongoing studies in female rats indicate that oxycodone (0.3–3.0 mg/kg, i.p.) produced a dose- and time-dependent increase of dopamine (DA) (~250% of basal values) and glutamate (GLU) (~300% of basal values) efflux, whereas extracellular levels of γ-aminobutyric acid (GABA) were unchanged. In contrast, cumulatively administered oxycodone did not produce any changes in extracellular levels of DA, GLU, or GABA in the nAcc of male rats. As with oxycodone, preliminary results indicate that fentanyl produces a dose-and time-dependent increase in DA efflux (~350% basal values) in the nAcc of female rats. In addition, analysis and quantification of oxycodone and fentanyl levels was performed in dialysate sampled from the nAcc. Results show that levels of opioids increased in a dose- and time-dependent manner in both sexes after i.p. administration of oxycodone and in female rats after i.p. injections of fentanyl. Peak levels of oxycodone and fentanyl were observed following the highest cumulative dose (3.0 and 0.056 mg/kg respectively) and seem to correspond with increases in DA efflux in female subjects. These results suggest important roles for DA and GLU in abuse-related neurochemical effects of opioids in females but not in males. Furthermore, sex differences in the neurochemical profiles of opioids may provide a possible explanation for observed differences in opioid addictive behavior between males and females, primarily increased addiction vulnerability in females.

Topic areas:
Addiction
Pharmacology
Development of a touchscreen-based Flanker Task in rats for translational studies of cognitive control

Background: Deficits in cognitive function, such as reward sensitivity and cognitive control, are a common feature of virtually all neuropsychiatric disorders. While perturbations in cognitive control have been studied extensively in humans, it has been challenging to develop rodent-based tasks to assess these complex processes and, consequently, to identify and advance innovative treatments for neuropsychiatric disorders. As part of a larger effort to create reliable and valid cross-species assays of cognitive function, we have developed a rodent version of the Eriksen Flanker Task to assess behavioral and neurophysiological indices of cognitive control.

Methods: Using fading and correction procedures combined with touch-sensitive response technology, we trained male and female Long Evans rats to discriminate between several distinct pairs of visual stimuli. Rats were trained in daily sessions with 100 trials in which each correct response resulted in a 30% sweetened condensed milk reward (0.1 ml). Discrimination was deemed successful when the criterion of 70% response accuracy was observed on two consecutive days in the final stage of the fading procedure. The results of validation studies indicated that detailed photographic stimuli (green leaf/violet flower) yielded appropriate stimulus control and were suitable stimuli for use in the Flanker Task. Following training under these final conditions, rats were surgically implanted with skull surface and depth electrodes, and neurophysiological data were collected during Flanker Task testing. In parallel studies, EEG data were collected from human subjects using the stimuli validated in the rodent task.

Results: All human subjects showed the expected Flanker interference effects of reduced accuracy (p < 0.001) and increased response latency (p < 0.001) on incongruent trial types. In addition, robust N200 components (p < 0.001) as well as increased theta power (p < 0.001) were noted when comparing incongruent and congruent trial types as well as increased error-related negativity (ERN; p < 0.001) and theta power (p < 0.001) for incorrect vs. correct responses. These results indicate that the stimuli chosen for the rodent Flanker Task elicit the expected effects in humans. All rodents tested show the Flanker interference effect of reduced accuracy on incongruent trial types (p < 0.01). Preliminary electrophysiological recordings in rodents suggest ERP and spectral findings were qualitatively similar to those observed in humans. The evaluation of the effects of systemic modafinil treatment on Flanker Task performance is ongoing in both species.

Conclusion: We have developed a touchscreen-based rodent flanker task that shows cross-species similarity in behavioral performance. Initial electrophysiological analysis in rodents indicates that ERP and spectral findings are similar to their well-characterized effects in human subjects. Ultimately, cross-species comparisons of behavioral and neurophysiological indices of cognitive control will afford new opportunities to evaluate potential therapeutics for a range of neuropsychiatric disorders.

Topic areas:
Cognitive Sciences
Presenting Author: Leila Guller, Post-doctoral fellow (Ph.D.)

Co-Authors: Lois Choi-Kain, M.D., Gregory T. Smith, Ph.D.

Title: Reciprocal Relationships Between Impulsivity and Depression in the Prediction of Adolescent Problem Drinking

Key words: Adolescence, Impulsivity, Depression, Alcohol, Longitudinal

Separate externalizing and internalizing pathways to problem drinking have been described. However, there is good reason to believe that internalizing and externalizing behaviors do not operate independently. We tested an integrative developmental model of transactions among internalizing symptomatology, externalizing personality, and psychosocial learning in the prediction of both drinking problems and future internalizing symptoms. To do so, we studied a large sample (n = 1910, 49.9% female) of children over a critical developmental period, from the last year elementary school through the first year of high school. Using a battery of self-report questionnaires, we assessed demographics, pubertal status, negative urgency, depressive symptoms, positive drinking expectancies, and drinking behavior. Structural equation modeling yielded significant findings for hypothesized direct and indirect pathways, with overall good model fit (CFI = .94; SRMR = .05; RMSEA = .05, 90% CI .04-.05): elementary school depressive symptomatology predicted middle school drinking problems (mediated by urgency and psychosocial learning) and middle school drinking problems predicted increased risk for depressive symptoms in high school, pointing to a reciprocal relationship between internalizing and externalizing dysfunction. These findings highlight the need to integrate both internalizing and externalizing forms of dysfunction into models of adolescent risky behavior.

Topic areas:
Addiction
Child/Adolescent
Depression
Title: Impact of conscious related factors on intensive/residential treatment for obsessive-compulsive disorder: Implications for targeted treatment approaches

Key words: OCD, Scrupulosity, Treatment, Guilt

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

Methods: The overall objective of this study was to evaluate the impact of unaddressed conscience-related factors (C-RFs; e.g. guilt, scrupulosity symptoms, locus of control) impact intensive/residential treatment. 125 patients receiving IRT for severe OCD completed the Interpersonal Guilt Questionnaire, Pennsylvania Inventory of Scrupulosity-Revised Questionnaire (PIOS-R), Dimensional Obsessive-Compulsive Scale (DOCS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), at admission/discharge.

Results: Omnipotent guilt ($\beta=.257, t(115)=2.850, p=.005$) and survivor guilt ($\beta=.196, t(114)=2.129, p=.035$) were found to be significantly associated with overall symptom severity at admission. Further, one-way ANOVA found significant differences in overall OCD symptom severity between those who endorsed elevated scores on the PIOS ($F(1,114) = 4.547, p = .035$) However, significant differences on measures of guilt were not seen between groups. Furthermore, the DOCS2 (concerning responsibility for harm/injury/bad luck) and DOCS3 (unacceptable obsessive sexual/violent/religious) domains were significantly correlated with levels of omnipotent and survivor guilt. Additionally, the impact of these factors on treatment response will be presented. For example, those who were in the high scrupulosity group at admission evidenced significant differences on their discharge DOCS2 ($F(1,97) = 5.681, p = .019$) and DOCS3 ($F(1,97) = 12.775 p = .001$) severity scores. The impact of augmenting IRT with a scrupulosity-focused treatment group on symptom reduction across treatment will also be presented.

Discussion: Results suggest elevated feelings of guilt and the presence of significant scrupulosity symptoms were both related to greater overall OCD severity at admission and variations in treatment response based on discharge severity scores. This may suggest that individuals with increased scrupulosity and conscious related factors may differ on their response to intensive/residential OCD treatment. Following from this finding, the impact of attending a scrupulosity-focused treatment groups to the IRT program will be discussed, along with implications for tailoring future OCD treatment to address CR-Fs.

Topic areas:
Anxiety
OCD
McLean Research Day 2019

Original Research - Pre-Clinical

Poster # 81
Time: 1:00-1:50pm

Presenting Author: Lia Hocke, Research Fellow

Co-Authors: K. Cayetano, B. deB. Frederick

Title: Systemic Low frequency oscillations in fNIRS

Key words: functional Near-Infrared Spectroscopy, systemic signals, global low frequency oscillations, functional Magnetic Resonance Imaging

Functional Near-Infrared Spectroscopy (fNIRS) has become increasingly popular for the study of brain function. fNIRS is a non-invasive imaging method, which uses changes in the optical properties of haemoglobin as an indirect measure of neuronal activity. Low frequency oscillations (LFOs) mostly around 0.01-0.15Hz, are prominent in functional imaging data. Part of the signal is due to neuronal activity, but a substantial part is not. Evidence shows that even in blood oxygen level dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) voxels, systemic non-neuronal LFOs highly contaminate the signal; the problem fNIRS faces is significantly worse, as brain signals also contain contamination from the intervening layers of the head. This problem becomes even more pronounced in resting state fNIRS, because no stimulation protocol can be used to guide analyses and distinguish neuronal from non-neuronal systemic signals. A common practice is to use additional shallow measurements of the upper layers of the head to reduce the systemic noise signal in the deeper measurements. In this study we evaluate the influence of these systemic influences with a specifically designed multimodal probe. We evaluated the temporal overlap between the systemic signal from the vasculature (with vessel-maps) as well as the spatial profile of the fNIRS signal. A multimodal, simultaneous resting state measurement was performed on 10 subjects using a purpose-built multimodal probe on the Siemens Trio 3T (fMRI) and ISS Imagent (fNIRS). The 3D printed probe features 3 overlapping circular receive only RF-coils, closely formed to the right frontal area of approximately 8x4.5cm with depth sensitivity of ~5cm. Directly integrated fNIRS (6.25Hz) probes featured 2, 3 and 4cm source-detector distance (SD) measurements. fMRI acquisition was performed with multi-band acquisition (1.8mm isotropic voxels, TR=0.72). In addition, vessel maps were acquired with Time Of Flight (TOF) MRI. The mean low-frequency fMRI BOLD signal from the vessel maps was extracted (fslmeants) to acquire a signal in the vicinity of the fNIRS probes, which only contains the systemic LFOs from the vasculature. The vascular time-course was then cross-correlated with the fNIRS total hemoglobin LFOs from all channels. Data analysis was conducted in MATLAB for fNIRS and FSL and in-house Python software (RapidTiDe)6 for fMRI. The contribution of known low frequency systemic signals in fMRI could be isolated and their influence on fNIRS could be evaluated. Correlation varied between the fNIRS signal and the systemic LFOs varied between r=0.3 to 0.8. fNIRS LFOs were not only highly correlated to vessels in the vicinity, but also remain highly correlated to vessels farther away from the area as well, supporting its non-neuronal component influence. Surprisingly, the 2cm source-detector distance (and therefore the most shallow measurement), was slightly less affected by the systemic signal from vessels maps in comparison to deeper measurements (3cm). This suggests that short-source separation denoising, commonly used, might not suffice to remove the systemic noise from vessels within the brain.

Topic areas:
Imaging
McLean Research Day 2019

Program Description

Poster # 82
Time: 1:50-2:45pm

Presenting Author: Liana Mathias, Clinical Research Assistant

Co-Authors: Rose May Katherine Hobbs Emily Mellen Hannah Heintz Praise Owoyemi David Harper Regan Patrick David Olson

Title: Anti-amyloid and anti-tau monoclonal antibodies for treatment in Mild Cognitive Impairment and mild Alzheimer’s Disease

Key words: Alzheimer’s, MCI, Amyloid, Tau, Treatment

Alzheimer’s Disease (AD) is a progressive dementia caused by neurodegeneration. This epidemic currently effects 5.7 million people in the United States alone, and this figure is estimated to grow to 13.8 million people by 2050. Alzheimer’s rapidly escalating prevalence, along with significant caregiver burden, makes Alzheimer’s a global health issue that demands the development of new treatments. The Geriatric Psychiatry Research Program (GPRP) at McLean Hospital engages in innovative, global clinical trials that investigate new disease-modifying treatments. These treatments target Amyloid-β plaques and tau neurofibrillary tangles, the two proteinaceous hallmarks of AD, hoping to slow the progression of the disease. These hallmarks of AD contribute to the neurodegenerative process, as well as problems with memory and thinking. The Biogen Emerge study, Biogen TANGO study, and Eli Lilly Trailblazer study examine the effects of monoclonal antibody therapies on the progression of early AD. Emerge and Trailblazer both study the effect of anti-amyloidal therapies, Aducanumab and LY3002813, respectively. TANGO studies the effects of an anti-tau compound, BIIB092. All are industry-sponsored, randomized, double-blind, placebo-controlled, outpatient clinical trials assessing the efficacy and safety of investigational medications. Emerge is in Phase III while Trailblazer and TANGO are in Phase II. All three of these drugs differ in antibody structure, safety profile, and plaque/tau removal mechanism. Participation in the Emerge, TANGO, and Trailblazer studies aligns with the GPRP’s research goals of engaging in meaningful research to help understand neurodegenerative diseases and thus better the lives of the ever-growing geriatric population.

Topic areas:
Alzheimer’s/Dementia
Geriatric Psychiatry
Depression is one of the most common psychiatric disorders in the United States, with an estimated 16.2 million American adults suffering at least one depressive episode in 2016. Antidepressant pharmacotherapies primarily target the biogenic amine neurotransmitter systems, but characteristically exhibit a slow onset and fail to satisfactorily treat up to 30% of patients. A growing body of evidence, however, implicates cholinergic neurotransmission in the pathophysiology of depression. Indeed, emerging clinical findings show that scopolamine, a muscarinic acetylcholine receptor antagonist, rapidly relieves symptoms of depression and, importantly, may be effective in treating refractory depression. Unfortunately, scopolamine also has well known cognition-impairing effects, including deficits in both attention and memory, which may limit its clinical utility. Previous work has demonstrated that another muscarinic antagonist, L-687-306 (at doses of 0.32-1.0 mg/kg) is as effective at decreasing depression-relevant behavior in the rat Forced Swim Test as scopolamine (0.1-0.32 mg/kg), but the cognitive effects of this antagonist have not been characterized. In the present studies, we compared the effects of these two antagonists on cognitive abilities in rats to determine whether L-687-306 might offer an improved safety profile compared to scopolamine at equivalent antidepressant doses. Male and female Long-Evans rats (n=6/sex) were trained in touchscreen operant chambers under either a sustained attention task, the Titrating Vigilance task, or in a spatial short-term memory task, the Titrating Delay Matching-to-Position task. Once stable baseline performance was established, subjects were exposed to doses of scopolamine and L-687-306 no more than twice per week prior to cognitive assessments. Scopolamine dose-dependently impaired performance in both the attention task (0.1-3.2 mg/kg) and in the memory task (0.1-0.32 mg/kg). Scopolamine’s effects were more potent in the memory task than in the attention task – the maximally effective antidepressant dose of scopolamine in the Forced Swim Test (0.32 mg/kg) nearly completely abolished performance in the memory task, but produced only moderate impairment in the attention task. L-687-306, however, was equipotent at producing impairment in the two tasks – the maximally effective antidepressant dose of L-687-306 (1 mg/kg) produced moderate impairment in each cognitive task. No dose of L-687-306 tested, up to 3.2 mg/kg, abolished performance in either task. Additionally, while the smallest effective antidepressant dose of scopolamine (0.1 mg/kg) produced impairment in both attention and memory task performance, the lowest effective antidepressant dose of L-687-306 (0.32 mg/kg) did not impair performance in either task. Taken together, the present findings suggest that L-687-306 may induce fewer cognition-impairing effects at effective antidepressant doses relative to scopolamine, and position this compound as a superior antimuscarinic candidate for antidepressant use.
Presenting Author: Luke Scheuer, Clinical Research Assistant II

Co-Authors: Naomi Chaytor, Laura Germine

Title: Assessing subtle cognitive dysfunction using self-administered online cognitive tests

Key words: Technology, Online, Diabetes, Depression

Our objective for this study was to analyze the validity of remote self-administered cognitive assessment in adults with chronic diseases that show high comorbidity with depression and anxiety, specifically Type 1 and Type 2 diabetes. Diabetes is associated with a two to three fold increased risk of development depression and anxiety. Likewise, people with depression are also more likely to develop Type 2 diabetes. Given these comorbidities, and the link with both diabetes, depression, and the development of dementia in older age, we wanted to look at methods for assessing cognitive functioning in both these conditions. Specifically, we wanted to see if (1) whether such scores are similar to scores from standard neuropsychological batteries, and (2) whether remote self-administered cognitive assessments are able to detect subtle impairments in cognition associated with diabetes and depression. Using our online research laboratory, TestMyBrain.org, we examined the validity of the TestMyBrain Digit Symbol Matching Test (DSMT), a test that measures processing speed and short term memory. Based on sample of participants with Type 1 Diabetes, convergent validity between the DSST and the WAIS Coding subtest was excellent ($r = .74$), and divergent validity with the Vocabulary subtest was as expected ($r = .31$). Additionally, 79% of the sample indicated they would be likely or almost certain to participate in a research study if cognitive testing was done remotely, compared with 57% for in-person testing. Participants with diabetes (Type 1 and Type 2) had poorer performance relative to normative samples ($Z = -0.43, p < 0.001$). They also had greater within-test performance variability ($Z = 0.34, p < 0.01$), a metric that is associated with accelerated aging and poorer brain health and is not possible to ascertain from standard in-person assessments. Performance on the same test was also lower in people with more depression symptoms ($B = 0.09, p < 0.0001$) and anxiety ($B = 0.17, p < 0.01$) symptoms. Overall, these data strongly indicate that self-administered online cognitive tests are a valid method of assessing cognitive status and processing speed in adults with chronic diseases, including conditions like diabetes and depression.

Topic areas:
Cognitive Sciences
Technology
**Title:** It All Matters: Improved White Matter Integrity After Three and Six Months of Medical Marijuana Treatment

**Key words:** medical marijuana (MMJ), diffusion tensor imaging (DTI), white matter, fractional anisotropy, mean diffusivity

**Background:** Diffusion tensor imaging (DTI) assesses brain microstructure and provides a quantitative measurement of the integrity of white matter fiber tracts in the brain. Fractional anisotropy (FA) measures white matter integrity by measuring direction-dependent diffusion of water along axon bundles. Mean diffusivity (MD) measures overall isotropic water diffusivity in all directions and is usually inversely related to FA. Previous studies of recreational marijuana (MJ) users demonstrated decreased FA and increased MD in MJ users relative to controls, with earlier age of onset of MJ use associated with reduced white matter integrity. To date, however, no studies have examined the impact of medical marijuana (MMJ) use on white matter integrity despite that fact that 33 states and Washington D.C. have fully legalized MMJ and an additional 14 states allow limited access to some MMJ products. Given recent interest regarding medical applications for MJ as well as increased access to MMJ products, it is important to examine the effect of MMJ use on white matter integrity.

**Methods:** As part of a larger, longitudinal study, patients were recruited from local MMJ certification centers, assessed before initiating MMJ treatment (baseline), and returned for follow-up assessments after 3 and 6 months of MMJ treatment. DTI data were acquired on a Siemens Trio 3T magnet using a 12-channel phased array head coil in 30 noncollinear directions and 3 b-value diffusion weights of 0, 1000, and 2500 s/mm². Region of interest (ROI) analyses were used to determine FA and MD values of fiber tracts in the corpus callosum, and included bilateral assessment of the genu, anterior corona radiata, anterior limb of the internal capsule, and the external capsule.

**Results:** Following 3 months of MMJ treatment, patients demonstrated significantly increased FA values bilaterally in the genu, anterior corona radiata, and external capsule as well as in the left anterior limb of the internal capsule relative to their baseline values. After 6 months of MMJ treatment, patients continued to demonstrate increased FA values bilaterally in the genu, anterior limb of the internal capsule, and external capsule as well as in the right anterior corona radiata relative to their baseline values. Although MD values were not significantly different between baseline and 3 months of MMJ treatment, after 6 months of MMJ treatment, patients demonstrated significantly decreased MD values bilaterally across all ROIs relative to baseline.

**Conclusions:** Current findings suggest that MMJ patients demonstrate significant increases in white matter integrity following MMJ treatment. Specifically, FA values were significantly increased after 3 months of MMJ treatment relative to baseline measures, and these increases were sustained at 6 months of MMJ treatment. Additionally, after 6 months of MMJ treatment, overall diffusivity (measured by MD) was significantly reduced in patients relative to baseline. Given previous findings of decreased white matter integrity among recreational MJ users, these data suggest a differential impact of MJ use on brain microstructure in MMJ patients, which may be related to differences between recreational and medical MJ-using populations including age of onset of use, product choice, and frequency/magnitude of use.

**Topic areas:**
Imaging, Quality/Outcomes
McLean Research Day 2019

Original Research - Clinical  
Poster # 86
Time: 1:50-2:45pm

Presenting Author: Madeline Kuppe, Clinical Research Assistant II

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

Title: Distinct Patterns of Change on Measures of Executive Function, Verbal Learning and Memory across 6-months of Medicinal Marijuana Treatment

Key words: medical marijuana, executive function, verbal learning, verbal memory,

Background: Although previous studies of recreational marijuana (MJ) use generally report cognitive decrements among heavy users, studies examining cognition in medical marijuana (MMJ) patients are limited. However, access to MMJ is growing; currently 33 states and DC have full MMJ programs while an additional 14 allow limited access. MMJ patients often differ from recreational users in their motives for use, age of onset of MJ use, and product choice. Given these important distinctions between medical and recreational users, it is crucial to specifically assess the impact of MMJ use on cognition over the course of treatment.

Methods: As part of a larger observational, longitudinal study, patients interested in MMJ treatment for a variety of indications completed a baseline study visit prior to starting MMJ treatment. Follow-up visits occurred at regular intervals over the next 24 months; cognitive data from baseline, 3 and 6 months of treatment have been analyzed thus far. At each visit, patients completed a neurocognitive battery consisting of several frontal/executive measures including the Stroop Color Word Test, Letter-Number Sequencing (LNS), Digit Symbol Substitution Test (DSST), and the Controlled Oral Word Association Test (COWAT). In addition, patients also completed the Rey Auditory Verbal Learning Task (RAVLT), a measure of verbal learning and memory.

Results: After three months of MMJ treatment, patients demonstrated significant improvements on several tasks of executive function relative to baseline, specifically faster completion of the Stroop Interference condition, and improved performance on both the LNS and DSST; these improvements were either sustained or continued to improve after 6 months of MMJ treatment. Although patients did not demonstrate improvements in verbal fluency after three months of MMJ treatment, significant improvements were detected after 6 months of MMJ treatment. Interestingly, on the RAVLT, patients demonstrated significant but temporary impairments in verbal learning and memory over the course of MMJ treatment; decrements observed after 3 months of treatment improved after 6 months, in some cases reflecting similar or better performance relative to baseline.

Conclusions: MMJ patients demonstrated distinct patterns of change on measures of executive function and verbal learning and memory across 3 and 6 months of MMJ treatment, indicating that cognitive domains may be differentially impacted over the course of treatment. Executive function notably improved following 3 months of MMJ treatment, which may be due to symptom alleviation or a reduction in use of conventional medications. Importantly, improvements in executive function were either sustained or further improved after 6 months of MMJ treatment. In contrast, after 3 months of MMJ treatment, verbally mediated tasks did not improve or appeared worse relative to baseline. However after 6 months of MMJ treatment, improvement was noted across these measures, suggesting that patients may need time to habituate to having MJ “on board”. Future studies should examine cognition over a longer course of MMJ treatment as findings will help inform patients, physicians and policy makers.

Topic areas:
Cognitive Sciences
Quality/Outcomes
Presenting Author: Marc Copersino, Associate Psychologist/Assistant Professor of Psychology, HMS

Co-Authors: Elspeth Slayter, PhD  R. Kathryn McHugh, PhD  Scott E. Lukas, PhD  Roger D. Weiss, MD

Title: Clinical Utility of Delivering Alcohol and Other Drug Refusal Skills Training to Developmental Disabilities Services Clients with Borderline-to-Mild Intellectual Disability

Key words: Substance Use Disorders, Neurodevelopmental Disabilities, Intellectual Disability, Cognitive Behavioral Therapy, Refusal Skills Training

People with intellectual and other developmental disabilities (I/DD) face barriers to accessing appropriate substance abuse treatment services for two main reasons. First, receiving these services traditionally requires going to agencies that are unfamiliar with I/DD clients and their needs. Second, standard substance abuse treatment is not developmentally appropriate because it requires cognitive, language and social skills that I/DD clients do not have. This study examined the feasibility and utility of delivering a 10-session alcohol and other drug refusal skills group to clients enrolled in developmental disabilities services (DDS) agencies. The aim of the refusal skills group is to increase attendees’ awareness of risk and teach them well-rehearsed and assertive responses to people who try to pressure or manipulate them to use, hold, or obtain alcohol and other drugs. Thirty subjects with borderline-to-mild intellectual disability were enrolled in the study: 20 from CLASS, Inc./Arc of Greater Lawrence, and 10 from Bay Cove Human Services, Inc. Subjects from the two locations differed significantly with regard to age (36+/-9 versus 45+/-9 years respectively), but not sex (80% versus 60% male), race (90% versus 60% white), or previous receipt of formal addiction treatment services (60% versus 70%). The primary outcome measure, refusal skill acquisition, was measured using a modified version of the situational competence test (SCT; Chaney et al., 1978) and collected pre-and-post-delivery of the two-week refusal skills group. There was no difference in refusal skill acquisition between recruitment locations, so data were pooled across 30 subjects. Results showed a significant pre- versus post-group improvement in refusal skill competency (p<.001). Furthermore, the improvement rate was more strongly predicted by group attendance (p<.001) than by performance on a standardized verbal learning test (p=0.69). Clinical utility of the refusal skills group was demonstrated in that individuals with global cognitive and functional disabilities can learn and demonstrate skills to cope with the social pressure and manipulation that frequently accompany alcohol and other drugs; and that the rate of learning is predicted more strongly by repeated exposure to the intervention than by individual differences in learning characteristics. Furthermore, delivering refusal skills in DDS settings in a location and with other attendees already familiar to clients increased their access to and willingness to receive services, and minimized disruption to their usual routines and schedules.

Topic areas:
Addiction
Quality/Outcomes
McLean Research Day 2019

Original Research - Pre-Clinical

Poster # 88
Time: 1:50-2:45pm

Presenting Author: Margaret Branham, Technical Research Assistant

Co-Authors: Margaret Branham, Fernando Moura, Jack Bergman

Title: The Effects of Nicotinic Drugs as an Adjuvant for μ-Opioids: Tail Withdrawal Latency and Disruptions in Operant Responding

Key words: Opioids, Operant Conditioning, Antinociceptive Effects

Prescription opioids are the most commonly used pharmacotherapeutics for pain management. However, their use is limited by the occurrence of adverse effects that occur at clinically effective doses (e.g., respiratory depression, addiction, and behavioral impairment). Thus, there is a clear clinical need for the development of new pain management strategies to limit adverse effects. Previous preclinical studies have demonstrated that nicotine has antinociceptive effects and, more recently, that nicotine can enhance the antinociceptive effects of some prescription opioids at doses that do not otherwise greatly disrupt behavior. However, the extent to which differences in efficacy at, and selectivity for, subtypes of nicotinic receptors impacts the capacity of nicotinic ligands to augment the antinociceptive effects of prescription opioids is unclear. In the present experiments, nicotinic drugs (e.g., epibatidine and varenicline) that differ in efficacy (epibatidine > varenicline) and selectivity for α4β2 nicotinic receptors were combined with the μ-opioid receptor agonists oxycodone and nalbuphine, which also differ in efficacy (oxycodone > nalbuphine), to address this question. Male squirrel monkeys (Saimiri sciureus; N=4) were trained to press a lever for the delivery of sweetened condensed milk under a fixed-ratio 10-response; timeout 30-s schedule of reinforcement. During the 30-s timeout, the distal portion of the subject’s tail could be submerged in warmed water to measure the latency for the withdrawal of their tail as a measure of nociception. During daily training sessions, latencies for withdrawal from 50, 52, or 55 ºC water were determined to establish baseline values for nociception at varying temperatures. In studies with varenicline, 0.032 mg/kg, i.m., of the nicotinic partial agonist had no significant effect on response rate or tail-withdrawal latency but increased the potency of nalbuphine to disrupt operant behavior and, at low and moderate water temperatures (50 and 52°C), shifted the nalbuphine dose-response functions approximately 10-fold leftward. Varenicline also increased the apparent efficacy of nalbuphine at 55°C, evident as a 3-s increase in tail-withdrawal latency. Varenicline did not modify the behaviorally disruptive, i.e., rate-decreasing, effects of oxycodone or, regardless of water temperature, its antinociceptive effects. Studies with epibatidine are ongoing: the relatively low i.m. dose of epibatidine, 0.00032 mg/kg, has had no effect on the rate-decreasing and antinociceptive effects of oxycodone, and experiments with higher doses of epibatidine are under way. Taken together, results thus far suggest that the ability of nicotinic ligands to augment opioid antinociception may vary with both nicotinic and opioid efficacy: both varenicline and nicotine enhanced the effects of low efficacy prescription opioids such as nalbuphine; however, only the higher-efficacy nicotinic agonist, nicotine, has been effective with the higher-efficacy opioids such as oxycodone.

Topic areas: Pharmacology
The transition between intensive partial day treatment (a highly structured and supportive environment) and outpatient treatment is a critical period that can feel abrupt and scary. Indeed, the first 30-day period following acute psychiatric care poses the greatest risk of relapse, re-hospitalization, and suicide (Durbin et al., 2007; Qin & Nordenstoft, 2005; Vigod et al., 2013; Woo et al., 2006). Scalable interventions that facilitate this transition are needed, and ideally such interventions should help patients implement the skills learned during acute care into their daily lives. The current pilot study examined the feasibility and acceptability of smartphone apps to promote the practice of Behavioral Activation (BA) skills during the first month following discharge from a partial hospital program. Data was obtained from 30 patients attending a partial hospitalization program. All participants were given the same orientation session and had the same access to the 2 BA smartphone applications, Moribus and Moodmission, as well as daily goal setting and outpatient adherence monitoring delivered via MetricWire App. No attempt at increasing retention was made other than an email on their second day after discharge if the Research Coordinator noted no activity on the MetricWire app up to that point. 36 partial hospital patients were approached for participation, of whom 2 declined the study, 4 were excluded, and 30 consented. 26 participants completed the study (3 dropouts at discharge, only 1 dropout after discharge). During the first week following discharge participants reported daily usage of Moodmission 2.27 times per day (SD=2.89) and Moribus 2.54 times per day (SD=3.63). However by week 4 participants reported daily usage of Moodmission 0.69 times per day (SD=1.85) and Moribus 0.50 times per day (SD=1.79). Participants clearly preferred Moodmission over Moribus. They rated MoodMission higher on user-friendliness and satisfaction (ps < .01). Additionally, there was a trend for patients to use MoodMission more frequently by the end of the month post-discharge, t(25) = 2.00, p = .056. This study was well received by the patient population and easily implemented in this setting, which supports the feasibility and acceptability of this post-acute treatment intervention. Specifically, we found that Moodmission was preferred over Moribus. These results suggest that a randomized, controlled trial comparing this BA post-acute intervention to a control is warranted.

**Topic areas:**
Quality/Outcomes
Technology
Presenting Author: Ria Thomas, Post doctoral research fellow

Co-Authors: Joanna A Korecka, Dan P Christensen, Michelle Hastings, Penelope Hallett, Ole Isacson

Title: Familial LRRK2 G2019S Parkinson’s disease patient fibroblasts have reduced mitochondrial clearance

Key words: Mitophagy, LRRK2, Parkinson’s disease

Human induced pluripotent stem cells (iPSCs)-derived neurons from LRRK2 G2019S mutation carriers exhibit disrupted mitochondrial movement and increased vulnerability to chemical stressors of mitochondrial function (Cooper, Seo et al. 2012). We and others have also uncovered changes in mitochondrial phenotypes in fibroblasts derived from LRRK2 G2019S carrying PD patients. Utilizing a static co-localization based assay we have shown that LRRK2 inhibition with IN-1 normalizes LRRK2 mutation-mediated changes in mitophagy (Smith, Jansson et al. 2015) but the dynamics of mitophagy are largely unknown in patient fibroblasts harboring the LRRK2 G2019S mutation.

To study the temporal changes in mitophagy, we performed live cell imaging of mitophagic flux with a pH sensitive dual fluorescence reporter containing a mitochondrial target sequence (a variant of the Rosella bioprobe) in human fibroblasts. There was a decreased rate of mitophagy at baseline and upon treatment with valinomycin (mitochondrial complex I inhibitor) in human fibroblasts derived from PD patients carrying the LRRK2 G2019S mutation compared to fibroblasts from healthy subject controls. Pharmacological (using IN-1 LRRK2 inhibitor) and genetic (using antisense oligonucleotides) inhibition of the LRRK2 kinase activity normalized this phenotype. For further investigation of the stage of mitophagy (initiation, transport, autophagosome maturation, and degradation by the lysosome) caused by the LRRK2 G2019S mutation, we analyzed expression levels of various proteins that regulate each phase, in control and LRRK2 G2019S cells, at baseline and upon treatment with valinomycin and bafilomycinA1. There was a significant increase in the mitochondrial marker Tom20, mitophagy initiator Optineurin, lysosomal content regulators TFEB and non-glycosylated LAMP1, and a decrease in the autophagosomal load associated LC3 (A & B) I/II ratio. The increased expression of proteins associated with initiation of mitophagy and lysosomal load, coupled with decreased mature autophagosome load in LRRK2 G2019S cells, indicate that the reduced rate of mitophagy could be due to defective vesicular transport. These data show that the LRRK2 G2019S mutation alters mitophagy rates, which may have important implications for understanding the cell biology leading to pathology in vulnerable cells carrying the mutation.

Topic areas:
Neurology
Title: Atopic-allergic-inflammatory-autoimmune comorbidity and suicide in antecedent phases of first-psychotic episodes among 263 bipolar-I disorder patients

Key words: atopic-allergic-inflammatory-autoimmune comorbidity, affective psychosis, bipolar-I disorder, first-psychotic episode antecedents, suicide attempt

Background: Bipolar-I Disorder (BD-I) with its high prevalence, early onset, multiple recurrences and chronic components carries an extraordinarily severe risk of suicide and greater medical morbidity and mortality than in the general population. Both medical comorbidity, particularly with allergic-atopic-inflammatory-autoimmune (AAIA) diseases, and suicide vulnerability often antecede BD-I first-lifetime syndromal onset by several years. In this regard, higher levels of systemic inflammatory marker interleukin 6 (IL-6) in childhood were associated with hypomanic symptoms in young adulthood, suggesting that inflammation might play a role in mania pathophysiology. Also, BD-I incidence was found higher among patients with rheumatoid arthritis (RA) than in control subjects without RA, and multivariate models indicated that asthma, liver cirrhosis, and alcohol use disorders were independent risk factors for subsequent BD-I development among RA sufferers. Moreover, adolescents with attention-deficit-hyperactivity disorder (ADHD) showed an increased risk of developing bipolar depression later in life with comorbid asthma causing a synergistic effect and enhancing this risk further. The long hypothesized role of innate immunity in BD-I pathophysiology was corroborated by Genome-wide association studies encompassing the major histocompatibility locus (MHC) region implicating the MHC complex class II immune genes (HLA-DPA1 and HLA-DRB1) and an MHC II messenger-RNA (mRNA), CD74, interacting within the same immune complex. Gene expression methods performed in different brain areas and lymphoblastic cell lines showed that both HLA-DPA1 and CD74 were significantly decreased in BD-I vs. healthy control-subjects. Clinical data also pointed to a potentially crucial link between comorbid AAIA diseases and BD-I core psychopathological dimensions including mood reactivity and psychomotor-affective instability as well as suicide proneness. In particular, one study using English national record linkage showed that asthma, psoriasis, eczema and inflammatory polyarthropathies were associated with an increased risk of self-injury and suicidal behaviors. Biological findings were also reported as to the involvement of innate immunity responses in suicide pathophysiology including abnormalities of innate immune receptors, Toll-like receptors (TLRs) in the brain of suicide victims, and alterations of proinflammatory cytokines related to an abnormal TLR3/TLR4 over-expression. Analysis of cerebrospinal fluid (CSF) cytokines and growth factors in medication-free suicide attempters vs. healthy volunteers showed that CSF vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) levels were significantly lower in suicide attempters. Preliminary findings: Recently, we found a highly significant association between antecedent medical comorbidity with AAIA diseases and an increased risk of suicide, violence, and emotional-motor instability in BD-I vs. unipolar depressive disorder (MDD) and nonaffective psychoses among 516 patients with first-psychotic affective and nonaffective episodes in the McLean First-Psychotic Episode Study. BD-I diagnosis with an antecedent comorbidity of AAIA diathesis was a greatly significant predictor of suicide attempts and aggressive behaviors as well as mood-psychomotor instability during antecedent and prodromal phases of first-lifetime psychotic syndromal-presentations. Conclusion: If the link between suicidality and AAIA diathesis will be confirmed by further studies on the interactions of innate-immunity responses and psychopathology, the results could provide interesting new insights into the "systemic" nature of mood disorders physiopathology as well as a promising target for future treatment strategies and early identification approaches.

Topic areas:
Bipolar Disorder, Psychotic Disorders, Quality/Outcomes
Title: Hypnotic Susceptibility and Placebo Responders: An Unknown Threat to the Integrity of Randomized Clinical Trials?

Key words: placebo, clinical trials, hypnotic susceptibility, responder analysis, self-report

The placebo effect is a vexing problem in randomized clinical trials (RCTs). This mind-body response dynamic is associated with an inexplicable amelioration of symptoms and can call the efficacy of supposedly potent medical and psychological interventions into question, thereby undermining clinical trials that actually demonstrated intervention efficacy in the treatment group. However, without knowing what mediates the placebo effect would a decision to eliminate what has been shown to be an effective intervention/treatment be justified or clinically prudent? In cases in which intervention efficacy is established in both the treatment and placebo group, should the latter carry more empirical weight in outcome determinations than the former? Or, should positive outcome in the treatment group, whose mechanisms, when biomarker verifiable and directly attributable to manipulative interventional procedures (e.g., psychotherapy) or a drug, have higher evidentiary value than non-specific placebo effects that may not be real, replicable, enduring or only evident in subjects who happen to possess psychological traits, behaviors or genes that increase the probability of a placebo response occurring? One trait in particular, hypnotic susceptibility (HS) may play a key mediating role in the placebo response equation, not only potentiating this phenomenon, but being overrepresented in RCT subjects. High HS is hypothesized to be associated with placebo proneness that can be explained on the basis of this measure's unique cognitive-perceptual style. Clinical anecdotal data also suggests that people who are high in HS are more likely to present for, are more amenable to and believe in the efficacy of medical and psychological treatment. This theoretical paper advances and will discuss the following hypotheses: 1. High HS will be significantly correlated with placebo responses in RCT. 2. RCT subject pools will contain significantly more individuals who are high in HS than would be expected by chance alone. 3. RCT in which the placebo-group outperforms the treatment group will consist of significantly more individuals who are high in HS than in RCT in which the treatment group outperformed the placebo group. 4. Subjects who are high in HS and assigned to an RCT treatment group will exhibit stronger responses than treatment group subjects who are low in HS. 5. The preemptive or retrospective removal of individuals who are high in HS from a placebo control group in an RCT that outperformed the treatment group will increase the probability that intervention efficacy will demonstrated (a methodological adjustment that can be justified without compromising the integrity of an RCT).

The Dual-Pseudo-Placebo-Effect hypothesis in psychotherapy will also be introduced. It proposes that clinician-patient belief that psychotherapy is working can be mediated by mutually high levels of hypnotic susceptibility (HS) a measure that may positively bias outcome perceptions. Unfortunately, mere belief in treatment efficacy can be misleading and mask negative subliminal psychophysiological response tendencies, that if not recognized and addressed can adversely impact health. This phenomenon can be especially insidious for clinical psychotherapy trials where outcome measures are often self-report and not biomarker-based.

Topic areas: Cognitive Sciences, Education, Pharmacology, Quality/Outcomes, Technology
Presenting Author: Katherine Hein, Clinical Research Assistant

Co-Authors: Christina M. Temes, PhD, Frances R. Frankenburg, MD, Mary C. Zanarini, EdD

Title: The Relationship Between Family Medical History and Key Medical Illnesses in Prospectively Followed Borderline Patients

Key words: Borderline Personality Disorder, Medical Comorbidity, Family History

Objective: Previous research has established a link between psychiatric disorders and physical health problems, and to a lesser extent, the connection between borderline personality disorder (BPD) and medical comorbidities. In the present study, we described the prevalence of common medical conditions in a sample of BPD patients and their family members. We also determined risk factors for each condition within patients with BPD.

Methods: A total of 264 adult inpatients recruited from McLean Hospital, who at baseline met rigorous criteria for BPD, were included in this study. In addition to follow-up assessments to assess psychopathology, patients reported on past two-year history of serious medical conditions for themselves and their first-degree biological relatives. Collection of medical history data began six years after patients’ initial participation in a larger study of the longitudinal course of BPD and was aggregated to include information from six-year to twenty-year follow-up assessments.

Results: The prevalence of the examined medical conditions ranged from 14.0% to 65.9% in patients, and from 35.6% to 85.6% in their family members. A family history of autoimmune diseases, cardiovascular illnesses, COPD, diabetes, obesity, and syndrome-like conditions were significant predictors of each of these conditions in patients with BPD. Family history of each condition remained as a significant risk factor even after accounting for other disease-specific risk factors (i.e., obesity for cardiovascular illness and diabetes, smoking for COPD, and female gender for syndromes).

Conclusions: These findings suggest that family history is a significant risk factor for common physical illnesses in patients with BPD, which is independent of other known risk factors.

Topic areas:
Borderline Personality Disorder
Quality/Outcomes
Title: What’s in Your Weed? Effects of THC and CBD on Pain Symptoms, Conventional Medication Use, and Clinical State in Medical Marijuana Patients with Chronic Pain

Key words: medical marijuana, THC, CBD, pain, opioids

Background: Marijuana (MJ) contains over 100 phytocannabinoids that modulate activity of the body’s endocannabinoid system, involved in regulating various physiological and cognitive processes. The two most common phytocannabinoids are Δ9-tetrahydrocannabinol (THC), the main psychoactive constituent in MJ, and cannabidiol (CBD), the primary non-intoxicating constituent often touted for its therapeutic potential. Previous studies have demonstrated improvements in pain tolerance and sensitivity following treatment with MJ, suggesting that long-term treatment with medical marijuana (MMJ) may alleviate symptoms associated with chronic pain conditions. Thus far, no studies have evaluated the differential impact of THC and CBD on pain symptoms, conventional medication use and clinical state in medical marijuana (MMJ) patients with chronic pain over the course of treatment.

Methods: As part of a larger observational, longitudinal study, patients with chronic pain were assessed before initiating MMJ treatment and after three months of MMJ use on measures of pain, clinical state, and conventional medication use, including opioids and non-steroidal anti-inflammatory drugs (NSAIDS). In order to analyze the differential impact of THC versus CBD on these domains, patients were divided into those with primarily THC-dominant (THC-Dom) or CBD-dominant (CBD-Dom) treatment regimens. Outside laboratory analyses were completed on patients’ most commonly used products, which provided quantitative values for ten major cannabinoids, including THC and CBD.

Results: Following three months of treatment, both groups reported significant improvement in pain symptoms. Interestingly, while both groups reported a reduction in total opioid tablets taken per week as well as reductions in total opioid dose per week, these changes approached statistical significance only in the CBD-Dom group. In contrast, while both groups demonstrated a reduction in the use of NSAIDS, only the THC-Dom group approached statistical significance. Further, both groups reported a trend toward statistically significant reduction in the use of benzodiazepines. It is of note that both groups also demonstrated concurrent improvement in depressive symptoms, but only the CBD-Dom group reported improvements on measures of anxiety.

Conclusions: These preliminary data suggest that improvements in pain following MMJ treatment may not be specific to THC or CBD, but that other clinical variables such as anxiety may be more sensitive to different cannabinoid regimens. These data also indicate that “what’s in your weed” may be of critical importance in determining the impact of MMJ on conventional medication use, and could be related to the different mechanisms of action of THC and CBD. THC acts as a CB1 agonist, while CBD has low affinity for CB receptors and instead interacts with a variety of different receptor types, including the 5HT-1A pathway. Interestingly, both cannabinoids may act as allosteric modulators of μ-opioid receptors, potentially resulting in alleviation of pain or substitution of cannabinoids for traditional opioid-based medications. Clinical trial models may be ideally suited to address the impact of individual cannabinoids on variables related to pain, conventional medication use, and clinical state.
McLean Research Day 2019

Original Research - Clinical

Poster # 95
Time: 1:00-1:50pm

Presenting Author: Sara Atlas, Clinical Research Assistant II

Co-Authors: Marie Forgeard, PhD  Jeffrey Winer, PhD  Lauren Wadsworth, PhD  Thröstur Björgvinsson, PhD, ABPP  Courtney Beard, PhD

Title: Concealment of Stigmatized Identities in an Acute Psychiatric Population

Key words: identity concealment, stress, stigma, outcomes

Background: People with stigmatized identities often experience disproportionate stress and mental health difficulties. This is particularly true for individuals who hold multiple marginalized social and cultural identities (Meyer, 2003; Seng et al., 2012). People often conceal a stigmatized identity to escape prejudice or discrimination; however, this coping strategy can lead to additional stress including preoccupation about being discovered, feeling isolated from similar others, and feeling detached from one’s true self (Pachankis, 2007). The present study seeks to further illuminate the potential negative effects of marginalized identity concealment within an acute transdiagnostic psychiatric population at baseline (T1) and after (T2) treatment in a partial hospitalization program.

Methods: Participants (n = 699) were patients receiving treatment at the Behavioral Health Partial Hospital Program at McLean Hospital between September 2017 and October 2018. The program delivers CBT-based group therapy, individual therapy, case management, and pharmacological treatment. Patients typically attend the program for 1 to 2 weeks (M = 8 days). Participants completed a questionnaire designed for the purpose of this study, in which they reported which sociocultural identities they attempt to conceal from others. Participants also reported on psychiatric symptoms and functioning (i.e., BASIS-24, PHQ-9, GAD-7) as part of routine clinical care (Cameron et al., 2007; Kroenke et al., 2001; Spitzer et al., 2006).

Results: Overall, 366 participants (52.4%) reported that they conceal a psychiatric diagnosis, from which 276 (75.4%) consider this to be the most stressful identity to conceal. This proportion was much higher than other concealed identities of those who (a) concealed SES, disability/physical health problem, or sexual orientation, and (b) considered it to be the most stressful (40.9%, 33.0%, and 35.3% respectively). Average scores on all three symptom measures were higher at baseline (T1) and discharge (T2) for people who concealed any identity compared to those who did not Cohen’s d: BASIS-24: T1=0.328, T2=0.209; PHQ-9: T1=0.423, T2=0.347; GAD-7: T1=0.201, T2=0.307.) We found similar results for those who reported that they conceal their psychiatric diagnosis, both at baseline and discharge (Cohen’s d: BASIS-24: T1=0.287, T2=0.194; PHQ-9: T1=0.351, T2=0.217; GAD-7: T1=0.155, T2=0.130).

Conclusion: The present study found that in a partial hospital program, a large number of individuals conceal stigmatized identities from others, and reported that concealing a psychiatric diagnosis to be the most stressful identity to keep from others. Concealing an identity (vs. disclosing) was associated with higher clinical symptom severity and poorer functioning at baseline and discharge from the program. This suggests that clinicians should make further efforts to help individuals navigate the challenges of stigma and discrimination related to their psychiatric diagnosis and/or other concealed identities, while weighing both the benefits and drawbacks of concealment. Increased efforts toward directly reducing societal stigma are also necessary, and that treatment providers should be sure to attend to and affirm their patients’ social and cultural identities.

Topic areas:
Anxiety
Depression
Quality/Outcomes
McLean Research Day 2019

Original Research - Clinical

Poster # 96
Time: 1:50-2:45pm

Presenting Author: Sarah Perlo, Clinical Research Assistant II

Co-Authors: Christine E. Richards  Amelia D. Moser  Nara F. Nascimento  Laura M. Holsen  Maria Ironside  Madhusmita Misra  Jill M. Goldstein*  Diego A. Pizzagalli*  *equal senior contributor

Title: Neural correlates of stress circuitry in major depressive disorder in young adults

Key words: depression, fMRI, stress

Background: Major life events are estimated to precede upwards of 80% of major depressive episodes (Monroe et al., 2014). Stress plays a crucial role in the onset and recurrence of these episodes, and disrupted stress circuitry has been implicated as a key contributor to major depressive disorder (MDD). This project aimed to clarify the pathophysiology of depression by investigating neural mechanisms in response to stress in young adults with current (cMDD) and remitted (rMDD) MDD during an acute stressor. To examine trait measures of MDD and increase power for preliminary analyses, cMDD and rMDD functional magnetic resonance imaging (fMRI) data were pooled.

Methods: fMRI data were acquired from participants with cMDD (n=11), rMDD (n=12), and psychiatrically healthy controls (HC; n=34) aged 18-25. Participants completed a combined stressor, involving a baseline block of easy (untimed) arithmetic problems in accordance with the Montreal Imaging Stress Task (MIST) during fMRI data acquisition, followed by the Maastricht Acute Stress Test (MAST) out of the scanner, consisting of hand immersions in ice-cold water and difficult arithmetic problems under social evaluation. After returning into the scanner, subjects completed easy and hard (timed with performance bar) blocks of the MIST followed by negative evaluator feedback and a final hard block of the MIST. Data were preprocessed and analyzed using SPM12.

Results: Whole-brain corrected cluster-level statistics revealed greater left insula activation in the HC group compared to the combined MDD (cMDD/rMDD) group post-stress (p<0.005). Uncorrected analyses (p=.001, k>20) revealed a cluster in the right thalamus with the combined MDD group showing decreased activation compared to the HC group pre-stress. Further uncorrected analyses (p=.005, k>20) suggested a group (HC vs. cMDD/rMDD) X stress (pre vs. post) interaction, with increased activation in the right amygdala (AMYG) and bilateral anterior cingulate cortex (ACC) post-stress compared to pre-stress in the MDD group but decreased activation in HCs in these regions. Conversely, the MDD group had decreased activation in the left hippocampus (HIPP) and right thalamus following stress, while the HC group showed increased activations.

Conclusion: The MDD group showed decreased right thalamic activation pre-stress compared to the HC group. Additionally, relative to the HC group, the MDD group was characterized by lower insular, right thalamic, and left HIPP activation post-stress but increased AMYG and ACC activation post-stress compared. The increased AMYG activation post-stress suggests a neural marker of stress sensitivity seen in MDD, while the decreased hippocampal activation echoes prior structural findings of volumetric HIPP reductions in MDD. While these preliminary findings suggest several potential neural biomarkers of trait depression, a larger sample size, allowing for further analyses, is necessary to elucidate state-dependent neural underpinnings of stress reactivity in cMDD versus rMDD.

Topic areas:
Depression
Imaging
McLean Research Day 2019

Original Research - Clinical

Poster # 97
Time: 1:00-1:50pm

Presenting Author: Sarah Salcone, Clinical Research Assistant II

Co-Authors: Michael Rohan  David G. Harper  Brent Forester  David H. Rosmarin

Title: Spiritual struggles and depression predict neural activation at resting state among geriatric mood disordered patients

Key words: spirituality, depression, geriatrics, imaging

A growing body of literature suggests that spiritual struggles are strongly associated with greater levels of depression (Exline, Yali & Sanderson, 2000) and that such associations are particularly strong among geriatric mood disordered patients (Rosmarin, Malloy & Forester, 2014). However, neural correlates of spiritual life in this population have not been studied. As greater functional connectivity at resting state in the default mode, central executive, and salience networks is a known biomarker for depression and anxiety (Sheline et al., 2009; Hamilton, Farmer, Fogelman & Gotlib, 2015; Yuen et al., 2014; Menon, 2011), we propose that spiritual struggles may be associated with greater neural connectivity within and between these networks. We have collected resting-state functional magnetic resonance imaging (fMRI) with 23 geriatric mood disordered patients and 19 matched control subjects and will examine these hypotheses with two analyses. First, a hypothesis driven analysis that will test the connectivity within and between the brain networks discussed above, and second by an exploratory analysis of connectivity to three standard networks associated with affective disorders. All analyses will be conducted using the FMRIB Software Library (FSL; Woolrich et al., 2009; Jenkinson et al., 2012; Smith et al., 2004), In both analyses Independent Component Analysis (ICA) methods will be employed to identify the networks of interest, and dual regression methods (Beckmann 2005) will be used to assess the strength of connectivity within a given network and between networks. In the first analysis we compare the strength (internal connectivity) of the Default Mode Network (DMN) between groups and its association with spirituality, and the strength of the inverse connectivity between the DMN (which contains the lateral parietal and precuneus regions) and the Central Executive Network (CEN) (containing the bilateral DLPFC) between depressed and control groups, and its association with measures of spirituality. In the second analysis we explore the connectivity and strength of the whole brain to the DMN, CEN and Salience (containing insulae) Networks in an exploratory analysis. Results will be discussed in terms of the relevance of spiritual cognitions and behaviors to affective symptoms, and neural mediators of effect.

Topic areas:
Bipolar Disorder
Depression
Geriatric Psychiatry
Imaging
Marijuana is the most commonly used illicit substance in the United States, and its use is expected to increase with recent and pending changes in its legal and medical status. Adolescent marijuana use is of particular concern because of its association with cognitive impairments during a critical stage of neurodevelopment. The two most common psychoactive components of marijuana are Δ9-tetrahydrocanabinol (THC) and cannabidiol (CBD), and higher CBD:THC ratios are reportedly associated with lesser marijuana-induced cognitive impairment in humans. Recent preclinical evidence from our laboratory suggests that repeated administration of THC combined with CBD attenuates maladaptive molecular changes elicited by THC alone. However, the attenuating effects of CBD on THC-induced cognitive impairments have not been directly investigated in pharmacological studies. The current study investigates the effects of chronic exposure to THC or THC combined with CBD (1:3) on a measure of cognitive function (i.e. discrimination learning) in adolescent squirrel monkeys (2.3-2.5 years; n=4; three treatment groups). Subjects were treated daily with vehicle, THC (1 mg/kg) or THC (1 mg/kg) + CBD (3 mg/kg). In behavioral studies conducted one hour after treatment, we examined the effects of treatment conditions on learning, using a touch-based stimulus-discrimination task. Briefly, each touchscreen session began with concurrent presentation of two 7 x 7 cm digital photographs, each in a different randomly selected quadrant of the screen. A touch response on one stimulus (S+) initiated delivery of a food reward (30% sweetened milk), followed by a 10-second blackout. A touch response on the other “incorrect” stimulus (S-) initiated the 10-sec blackout without food reward. The same two stimuli were presented for 200 trials each day until S+ responses were produced in 9 of 10 consecutive trials (mastery). Once the subject achieved mastery a new S+/S- pair was introduced on the subsequent session. Preliminary data from the first 6 S+/S- stimulus pairs indicates a significant effect of treatment (THC or THC+CBD vs vehicle control). The average number of trials to master the first discrimination (S+/S- pair) was 88.8 ± 32.8 (vehicle), 302.8 ± 123.0 (THC) and 362.3 ± 170.4 (THC+CBD). The number of trials to mastery decreased across consecutive S+/S- pairs for all groups. By stimulus pair 6, the average trials to mastery were 28.5 ± 7.2 (vehicle), 112 ± 76.3 (THC) and 125.5 ± 86.7 (THC+CBD), indicative of a persistent drug effect. In contrast to vehicle controls, some subjects treated with THC or THC+CBD did not engage in the cognitive task for the first 2-17 days following initiation of daily treatment. In summary, ongoing studies suggest that daily treatment with either THC or THC + CBD disrupts mastery of a cognitive task requiring the development of a learning set to facilitate stimulus discrimination.

**Topic areas:**
Adoption
Child/Adolescent
Cognitive Sciences
Pharmacology
Technology
In 2017, over 11 million Americans misused an opioid and more than 49,000 individuals died by opioid overdose. Suicide and overdose are both common among people with opioid use disorder (OUD); however, little is known about the role of suicidal motivation in overdose. Our aims are to characterize correlates of opioid overdose and the frequency of suicidal motivation prior to overdose in people with OUD. Treatment-seeking adults with OUD completed a battery of self-report measures, including a question about degree of desire to die (i.e. suicidal motivation) prior to their last overdose (rated from 0-10). Among the total sample, 45% (54/120) of individuals had overdosed at least once. Those who had overdosed were more likely to have co-occurring psychiatric disorders (72% vs. 50%) and endorsed higher levels of craving. On average, participants endorsed a low to moderate desire to die (mean = 3.79, SD = 4.1) before their most recent overdose. At least some (minimum of 1) desire to die was reported by 58% of participants and 36% reported a high desire to die (7 or greater). Suicidal motivation is common prior to opioid overdose and may be an important target for treatments to reduce this risk.
CRF neurons in control of learned and innate fear: role of the basolateral amygdala

Corticotropin-releasing factor (CRF) is a neuropeptide acting as a neuromodulator or neurotransmitter regulating neuronal activity in the brain. CRF receptors are expressed in several brain regions, including the basolateral amygdala (BLA), an area important for both innate and learned fear, and their activation in BLA exacerbates fear and anxiety. However, the CRF source and its actions within BLA remain opaque. To fill this knowledge gap, we perform extensive in vivo and ex vivo analysis in order to identify the cellular, synaptic and circuit-level bases of CRF actions within the BLA. We identified a population of CRF cells in the BLA (constituting ~3% of all BLA Nissl+ cells) by crossing Crh-IRES-Cre mice with a reporter Ai14(tdTomato) mouse line and performing corresponding immunostainings. CRF-BLA neurons demonstrated unique electrophysiological properties, distinguishing them from neighboring non-CRF-BLA cells. First, CRF-BLA neurons showed higher firing rates and input resistance. Second, CRF neurons did not display spike-frequency adaptation, in contrast to a profound reduction in the firing frequency in non-CRF cells during depolarizing current injections. Third, CRF-BLA cells were much more excitable, as indicated by a lower rheobase (i.e., the minimum current needed to trigger spiking). Taken together, CRF-BLA neurons represent a distinct population of BLA neurons based on their electrophysiological characteristics, most likely a subgroup of BLA inhibitory neurons. Accordingly, a major fraction of CRF-BLA neurons expressed glutamate decarboxylase (GAD67), GABA producing enzyme, as confirmed by immunostaining. As medial prefrontal cortex (mPFC) to amygdala projections control both fear and anxiety, we asked whether mPFC influences the activity of amygdala via projections to CRF-BLA cells. To address this possibility, we transduced neurons in the mPFC of CRF-reporter mice with a virus vector coding ChR2(H134R)-eYFP fusion gene driven by a CaMKIIα promoter, and, about 9 weeks later, performed ex vivo electrophysiology in slices from these animals. We determined that mPFC fibers make functional synapses on CRF-BLA neurons by examining the light-induced excitatory postsynaptic currents (EPSCs) in these cells. The EPSCs were glutamatergic, as demonstrated by their sensitivity to AMPA/kainate and NMDA receptor antagonists. Furthermore, optogenetically activated EPSCs in CRF cells were monosynaptic in nature, as evidenced by their rescue with 4-aminopyridine following tetrodotoxin blockade. Consistent with the observed higher excitability of CRF-BLA cells, input-output curves for EPSC peak amplitudes were significantly different between CRF-BLA and non-CRF-BLA neurons, with much larger currents observed in non-CRF cells. To test the hypothesis that CRF-BLA cells and, more specifically, mPFC projections to these cells, play a role in control of anxiety, we presently use DREADD-based methodologies to selectively manipulate the function of CRF-BLA cells and mPFC inputs to them. For this, we inject viral constructs to the BLA of Crh-IRES-Cre mice, thus expressing an engineered mCherry-tagged Gi(Gq)-coupled receptor hM4D(hM3D) in a Cre-dependent manner. Subsequently, we suppress or promote the activity of CRF-BLA neurons by treating mice with clozapine-N-oxide (CNO), the agonist of hM4D/hM3Dq, prior to fear conditioning/fear extinction and assays of anxiety-related behaviors (ongoing experiments). With these experiments, we expect to potentially identify new targets and new pathways controlling fear-related behaviors.
Childhood emotional neglect has been shown to be a major risk factor for problems with emotion dysregulation, as defined in part by an impaired ability to regulate or tolerate negative emotional states. As presence of an alcohol use disorder (AUD) during adolescence also is associated with increased risk for emotion regulation difficulties, the current study sought to examine the impact of these co-occurring conditions on emotion dysregulation difficulty. Participants included 370 patients (196 female, age = 16.92 ± 1.13) from the McLean Hospital Acute Residential Treatment (ART) two-week program for adolescents with co-occurring psychiatric disorders. As part of a clinical quality assurance initiative, patients underwent a structured clinical interview (MINI-KID) to establish psychiatric diagnoses, including presence of a DSM-5 AUD diagnosis. Patients also completed the Childhood Trauma Questionnaire (CTQ) and the Difficulties with Emotion Regulation Scale (DERS), both upon admission and discharge. Based on the CTQ emotional neglect domain, patients were stratified into high- (H-CEN, N=179) and low-emotional neglect (L-CEN, N= 191) using a mean split approach, and into AUD+ and AUD- groups. Individuals in the H-CEN group had significantly worse emotion dysregulation (higher scores on the DERS) than the L-CEN group (p<.001) at treatment entry. The AUD+ group also had significantly worse emotion dysregulation than the AUD- group (p=.009). The interaction between CEN and AUD, however, was not significant at treatment entry (p=.90). Emotion dysregulation improved significantly over treatment for all groups (p<.001). Within the H-CEN group, a significant interaction with AUD status was observed (p=.035), with the greatest magnitude of improvement observed in the H-CEN/AUD+ group by treatment discharge. These findings demonstrate that adolescent patients with both a history of emotional neglect and with an AUD are able to successfully improve emotion regulation during residential treatment. While both conditions contribute to higher initials difficulties with emotion regulation, those with co-occurring higher levels of CEN and the presence of an AUD demonstrate the greatest benefit of treatment. While co-occurring substance use and psychiatric disorders complicate understanding of neglect-related risk for emotional dysregulation, further studies are necessary to determine specific factors within the residential treatment setting that are most effective for this comorbid population.
McLean Research Day 2019

Original Research - Pre-Clinical

Poster # 102
Time: 1:50-2:45pm

Presenting Author: Nicholas L. Mirin, Program Coordinator

Co-Authors: Nicholas Mirin, Justin T. Baker, Daniel G. Dillon, Sarah C. Vogel, Lauren A. Rutter, Diego A. Pizzagalli, Laura Germine

Title: Development of an RDoC Field Test Battery for Capturing Neurocognition and Digital Phenotypes

Key words: RDoC, Neurocognition, Digital, Phenotyping

Here we report on work conducted with the NIMH to define priorities for an RDoC (Research Domain Criteria) field test battery adaptable to web or mobile devices. Twenty-one performance-based cognitive measures were selected for evaluation, supplemented by next-generation measures derived from (1) passive smartphone data sources, including 15 GPS-related variables and 16 text/call-related variables, (2) wearable devices, including 16 measures of actigraphy, 13 measures of sleep, seven circadian/environmental features, and three measures of physiological arousal, as well as (3) six dimensions of facial/bodily expression features of speech captured by smartphone embedded cameras and microphones. Where possible, we evaluated each measure in terms of its reliability and validity for measuring RDoC constructs, as well as their ease of administration and adaptability for use in a field setting. Other considerations include avoidance of measurement redundancy, availability of normative data, and cost of test development and administration. The tasks selected for final inclusion will be described along with areas for further potential development of measures, where no existing tasks satisfy all criteria.

Topic areas:
Cognitive Sciences
Quality/Outcomes
Technology
Presenting Author: Oeystein Roed Brekk, Postdoctoral Research Fellow

Co-Authors: Alyssa Moskites, Ole Isacson, Penelope J. Hallett

Title: Alpha-synuclein and Tau abnormalities caused by lipids in neurodegenerative aging.

Key words: Neurodegeneration, Glycosphingolipids, Glucocerebrosidase, Tau, Alpha-synuclein

Aging is the most significant risk factor for developing genetic and sporadic neurodegenerative disorders, including Parkinson’s disease (PD) and Alzheimer’s disease (AD). The connections between aging and disease-associated gene products, for example GBA1, alpha-synuclein (aSYN), or Tau, are not fully understood. We have previously observed age-dependent reductions in glucocerebrosidase (GCase) activity (encoded by GBA1) in normal aging in the human (Rocha et al., 2015, Ann. Clin. Trans. Neurol.) and mouse (Hallett & Huebecker et al., 2018, Neurobiol. Aging) brain, with concurrent accumulation of a variety of glycosphingolipids (GSLs) including glucosylceramide and glucosylsphingosine. As glucosylceramide has recently been shown to induce aSYN aggregation and attenuate neurotoxicity in vitro (Zunke et al., 2018, Neuron), we wish to investigate the impact of age-related lipid impairments on disease-associated proteins aSYN and Tau. In wildtype (WT) mice aged 2-24 months of age, presenting with elevated GSL content, we investigated lipid modifications of aSYN and Tau through biochemical lipid-extraction assays of whole-brain homogenates and assessed how these modifications affect protein structure and posttranslational state. Using fluorescent labeling and automated colocalization analysis, we determined the localization of these proteins within the neuronal lipid membrane compartment with known lipid membrane markers including vesicular membranes, to identify likely binding partners. Lastly, we will assess any correlation between GCase function and lipid homeostasis on aSYN burden in human sporadic PD. As an alternative to the classic view of proteinopathy, these findings illuminate the interplay between age-associated changes in lipid homeostasis and the risk for neurodegenerative disease.

Topic areas:
Alzheimer's/Dementia
Imaging
Neurology
Obtaining collateral information from a patient is an essential component of providing effective psychiatric and psychotherapeutic care. Increasing evidence indicates that patients' social and electronic media posts contain information relevant to their psychotherapy and clinical care. However, the mental health field has not yet developed or implemented evidence-based, standardized guidelines for clinicians seeking to incorporate this content into therapeutic care. We developed a survey to characterize the current attitudes and behaviors of outpatient clinicians regarding the monitoring and accessing of patients' social and electronic media as part of psychotherapy. 115 outpatient psychotherapists associated with McLean Hospital in Belmont, MA completed the online survey that consisted of 17 total questions. The majority of respondents (72%) indicated having accessed this content with their patients and 92% of those endorsed being able to provide more effective treatment as a result of this information. Moreover, analysis of survey responses found patterns of use associated with clinician and patient demographics. The results of this survey informed the development of a hospital-wide research study which will assess whether reviewing social and electronic media as part of psychotherapy has an impact on the quality and efficacy of clinical care, as well as on the clinician-patient relationship.

**Topic areas:**
Quality/Outcomes
Technology
Presenting Author: Poopak Hafezi, Research Fellow in Psychiatry

Co-Authors: Alaptagin Khan Laura Hernandez Garcia Elizabeth Bolger Cynthia McGreenery Martin H.Teicher

Title: Type and Timing of Childhood Maltreatment and Risk for Lifetime Substance Use Disorders

Key words: Childhood Maltreatment, Substance Use, Time predictor

Background: Although many studies have reported that childhood maltreatment (MAL) is a major risk factor for drug use and abuse, there is a considerable gap in our knowledge regarding type and timing of exposure that may be the most important predictors. A key finding from the ACE study was that risk increased with exposure to more types of adversity, and led to the belief that cumulative burden was the determining factor.

Objective: To ascertain that most important predictor of risk for psychopathology (substance use disorders) is severity of exposure to particular types of MAL during specific stages of development.

Methods: Self report measures of childhood maltreatment (Maltreatment and Abuse Chronology of Exposure) and drug use were collected on a community sample of young adults (n=2092, ages 18-25).

Results: Sensitive period analyses revealed that most important type/time predictor in males for lifetime polysubstance use, and for lifetime use of stimulants, opioids and sedatives was exposure to peer emotional abuse at 15 years of age. Furthermore, for each class of drugs, this was a much more important predictor than duration, multiplicity or severity of MAL across childhood. For females, the most important type/time predictor for lifetime polysubstance use, and for lifetime use of stimulants, cocaine and hallucinogens was sexual abuse at age 15.

Conclusion: Our findings provide further evidence that increased risk observed with exposure to more types of MAL is not a consequence of cumulative burden but a predictable result of exposure to more types of MAL increasing odds of experiencing a critical type of MAL at a critical age. Developmental sensitive periods mediate the effect of childhood maltreatment on psychopathology. Gender, timing and type specific differences in exposure to maltreatment may influence sensitive periods and the overall risk to develop substance use and other psychiatric disorders.

Topic areas:
Addiction
Child/Adolescent
Title: Effects of Chronic Oral Methadone in Squirrel Monkeys

Key words: Methadone, Opioids, Antinociception, Operant Responding

Background: Opioid abuse is a major public health issue, currently affecting 2 million Americans. Methadone, a μ-opioid agonist commonly prescribed in the treatment of opioid addiction, has proven difficult to examine in preclinical studies because it can produce tissue damage when given repeatedly by intramuscular (i.m) or subcutaneous administration. Therefore, the current study aimed to evaluate the effects of oral (p.o.) administered methadone.

Aims: Since little is known about oral administration of methadone in squirrel monkeys, the current experiments examined the time course of effects of p.o vs. i.m. methadone in preparation for studies involving chronic administration.

Methods: A modified warm water tail withdrawal assay was used to determine concurrently the effects of methadone on tail withdrawal latencies (antinociception) and food-maintained behavior (response rate disruption). Squirrel monkeys (n=4) were trained to respond under an FR10 schedule of reinforcement. Stimulus lights were illuminated to signal the beginning of a test component in which completion of the response requirement within a 20 second period resulted in delivery of a 30% sweetened condensed milk reinforcer and a 30-second short time out. During the short time out, the subject’s tail was dipped in water at 50°, 52°, or 55° C and latency to remove the tail was recorded. A test component consisted of 6-10 tail dips, with a 35° C tail dip occurring prior to each test at a warmer temperature. The effects of a single dose of either 1.8 mg/kg p.o (in a fruit punch flavored gatorade solution) or 0.56 mg/kg i.m. methadone were assessed 10 and 30 min, and 1, 2, 4, 8, and 24 hr following administration.

Results: Peak antinociceptive (10 s, 6.7 s, and 5.0 s tail withdrawal latencies at 50°, 52°, and 55° respectively) and behaviorally disruptive effects (0.35 resp/sec) were observed 30 min after i.m. methadone administration. Tail withdrawal latencies and response rates returned to baseline values at 4 hours (1.5 s, 1.3 s, and 1.3 s at 50°, 52°, and 55°C, respectively, 2.7 resp/sec). In contrast, peak antinociceptive effects (6.8 s, 5.3 s and 3.7s tail withdrawal latencies at 50°, 52°, and 55°C, respectively) and behaviorally disruptive effects (0.92 resp/sec) were observed 2 hours after p.o. administration. Tail withdrawal latencies and response rates returned to baseline values at 8 hours (3.7 s, 1.9 s and 1.3 s tail withdrawal latencies at 50°, 52°, and 55° C, respectively, 3.0 resp/sec).

Conclusions: These findings demonstrate that (1) p.o. methadone has a slower onset and longer duration of action than i.m. methadone, and (2) p.o. methadone can be reliably administered to squirrel monkeys to avoid tissue damage induced by repeated i.m. administration. Future studies will investigate the effects of chronic oral methadone treatment on the ability of other opioids to induce antinociception.

Topic areas:
Addiction
Pharmacology
Title: The Misuse of Benzodiazepines: Key Findings from a Comprehensive Review

Key words: benzodiazepines, prescription drug misuse, epidemiology, literature review

Introduction: Benzodiazepines are a class of medications indicated for the treatment of conditions such as anxiety, alcohol withdrawal, seizures, and insomnia. They are also the 3rd most commonly misused illicit or prescription drug in both adults and adolescents in the U.S. However, much remains unknown about their misuse. In this review, we systematically examined epidemiological studies on benzodiazepine misuse to identify key findings, limitations, and future directions for consideration.

Methods: PubMed and PsychINFO Databases were searched through July 2018 for peer-reviewed publications on benzodiazepine misuse (e.g., use without a prescription; at a higher frequency or dose than prescribed). Only studies with human participants were reviewed; eligibility criteria included studies on prevalence, trends, correlates, motives, patterns, sources, and consequences that explicitly referenced misuse. Finally, references of included publications from the initial search were assessed to identify additional articles.

Results: The search identified 1,947 publications, and 355 articles were eligible for data extraction and inclusion. In 2016, 2.2% of the U.S. population (> 6 million people) misused benzodiazepines and other tranquilizers. Comparatively, 43% of people with opioid use disorder and 7.6% of people with alcohol use disorder reported past-year benzodiazepine misuse. Factors correlated with misuse include identifying as Non-Hispanic White, other substance use, receipt of a benzodiazepine prescription, and having a mood, anxiety, or personality disorder. Benzodiazepine misuse was associated with greater odds of mortality, more HIV/HCV risk-taking behaviors, poorer self-reported quality of life, criminal involvement, and continued primary substance use during treatment. The most common reason for past-year misuse was to cope (e.g., to help manage negative emotions, tension, or sleep difficulty).

Conclusions: Benzodiazepines are among the most commonly prescribed medications. Results from our review indicate that they are also commonly misused, particularly among certain subgroups (e.g., people with substance use disorders). Moreover, benzodiazepine misuse is associated with concerning consequences, such as overdose and suicide risk. However, there are several limitations to the current literature, most notably the lack of a clear, consistent definition of misuse. Finally, the many negative consequences of benzodiazepine misuse underscore the need for more studies on preventing and treating nonmedical use.

Topic areas: Addiction
Background: Autophagy is a vesicle and lysosome-mediated degradative pathway that plays a vital role in protein homeostasis and overall cell health. There is evidence that defective autophagy may play a role in the accumulation of toxic proteins and damaged organelles in Alzheimer’s disease (AD). Autophagy is in part regulated by insulin (IN) or insulin-like growth factor 1 (IGF-1) signaling. It has been suggested that apolipoprotein E (APOE), including the APOE4 variant which is a risk factor for AD, interferes in IN or IGF-1 receptor activation and recycling. These mechanisms, however, remain to be explored in context of late-onset AD (LOAD). Our study examined the possible connection of APOE variants with IGF-1 signaling and autophagy as a potential mechanism in LOAD, using LOAD patients’- and non-demented control subjects’-derived fibroblasts.

Methods: Human skin fibroblast from three different groups: young control (n = 10), old control (n = 10), and LOAD patients (n = 10), and the human fibroblast cell lines D551 and HFF1 were used for the experiments. Cells were treated with human recombinant IGF-1 (80 ng/ml). Different variants of APOE (-2, -3, and -4) were expressed from plasmids transfected into D551 and HFF1 cells, or cells were treated with the respective APOE peptides to explore the relation of ApoE with IGF-1R activation, internalization, and recycling. Meso Scale Discovery (MSD) technology or standard ELISA were used to screen IGF-1 signaling (IGF-1R, IR, IRS-1) and AKT pathway activation. H2O2 (50 uM) and starvation were administrated as stressors to induce autophagy. Autophagy and IGF-1R trafficking were examined by immunocytochemistry (ICC) using the autophagy markers, LC3, Proteostat, BNIP3, and LAMP2, and RAB7 or CD71 for endosomes, and IGF-1R. Different combinations of these markers were used to detect phago-/autophagosomes, lyso-/autolysosomes, endosomes, and IGF-1R localization in endosomes, which were then quantified by CellProfiler software.

Results: Both H2O2 and starvation triggered autophagy, and the autophagic response was reduced in the presence of IGF-1, all as expected. Levels of both total and phosphorylated proteins in the IGF-1 signaling cascade were diminished in old and LOAD cells, while pathway activation by IGF-1 was downregulated in LOAD cells, but not in old fibroblasts, when compared to young control samples. In addition, initial data demonstrate that IGF-1R co-localizes with RAB7-positive endosomes, which aggregate in stress-produced conditions. Treatment with IGF-1 appeared to diminish autophagy and endosome aggregation, and this process may be differentially affected by the different APOE variants.

Conclusions: Our data indicate that the IGF-1 signaling pathway is downregulated in fibroblasts from old control and LOAD patients, which could influence the autophagic response to stress in these cells. APOE variants apparently play different roles in these processes, by interfering to various degrees in IGF-1 trafficking and the induction of endosome aggregation.

Topic areas:
Alzheimer’s/Dementia, Cognitive Sciences, Neurology
Title: Topology of prefrontal fibers in the forceps minor: location matters

Key words: forceps minor, neuroanatomy, prefrontal cortex, connectivity

Background: The forceps minor is the part of the corpus callosum (CC) that carries prefrontal cortical (PFC) fibers. Changes in the forceps minor white matter integrity have been demonstrated across several neuropsychiatric diseases. Moreover, damage of forceps minor fibers correlates with the severity and/or extent of related symptoms. In these studies, the forceps minor is treated as one entity, the region that carries PFC fibers. However, due to: 1. the high number of PFC areas that contribute fibers to it, 2. its thickness, and 3. its links to disease, we asked whether the forceps minor could be further segmented into regions that carried specific PFC fibers. The goal of this study was therefore to determine the topology of PFC fibers in the forceps minor to better pinpoint connections that are abnormal in disease.

Methods: Anterograde or bidirectional tracers were injected into 36 sites evenly distributed in the following regions: frontal pole (FP), ventromedial PFC (vmPFC), orbitofrontal cortex (OFC), ACC, ventrolateral PFC (vlPFC), dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC). Fiber bundles traveling through the corpus callosum were outlined under darkfield microscopy in the software Neurolucida (MBF Bioscience) and integrated into a 3D model via IMOD. Diffusion magnetic resonance imaging (dMRI) data of 15 animals and 35 humans were used to reconstruct the callosal pathways with tractography and compare with the tracing result.

Results: In general, fibers in the most ventral part of the forceps minor connect regions of the vmPFC; those in the central part of the bundle connect OFC, vlPFC and ACC regions; fibers in the most dorsal part connect regions of the dorsal PFC. In addition to this general organization, the PFC fibers follow three topological rules. The first rule applies to PFC regions in the dorsal-ventral direction: Axons from dorsal PFC regions occupy a dorsal portion of the forceps minor, while those from ventral regions are located ventrally. The second rule applies to PFC regions in the lateral-medial direction: Fibers from lateral PFC regions occupy a dorsal portion of the forceps minor, while those from medial regions are located ventrally. This rule is secondary to the first rule, i.e. the position of fibers in the forceps minor is primarily determined by the dorsal-ventral position of its originating region. The third rule applies to PFC regions in a rotated rostral-caudal direction: If one follows the longitudinal axis of the genu, fibers located in the same callosal section originate from a set of cortical sites aligning in the radial direction. Such radial arrangement forms a rotated rostral-causal pattern centering at the genu. The same organizational rules are followed by streamlines generated from diffusion tractography, both in NHP and in human.

Conclusion: The PFC fibers passing through the forceps minor follow three organizational rules. Segmentation based on these rules shows how lesions at particular sites throughout the forceps minor will likely impact different PFC areas in disease.

Topic areas:
Cognitive Sciences
Imaging
Neurology
Title: Profiling bioenergetics in iPSC-derived neural precursor cells and astrocytes from Alzheimer’s disease patients and non-demented control individuals

Key words: Bioenergetics, Alzheimer’s disease, neural precursor cells, astrocytes

Alzheimer’s disease (AD) is an age-related degenerative nervous system disorder characterized by neuronal dysfunction and death. While toxic molecules, such as beta amyloid peptides (Aβ) and phosphorylated tau (p-tau) have been suggested as causing AD, they may be more often be the consequences of other processes.

Bioenergetics is energy production through metabolism of organic compounds in living organisms. A major energy product is adenosine triphosphate (ATP) which cells make through several processes, including glycolysis and mitochondrial respiration, the latter consisting of the tricarboxylic acid (TCA) cycle and oxidative phosphorylation.

Changes in bioenergetics have been suggested in brain aging and neurodegenerative diseases. iPSCs are pluripotent stem cells which can be directly derived from adult tissues, including those from patients with neurological diseases. iPSC can differentiate into various neuronal cells, including neural precursor cells (NPCs), which are multipotent progenitors that can be differentiated to neurons and astrocytes. NPCs can also be used in neural mechanism studies and drug investigation. Astrocytes, which constitute a large portion of the central nervous system (CNS) play important roles in brain function, including metabolism, e.g., they produce lactate which is used by neurons as a substrate for mitochondrial respiration. Therefore, the investigation of iPSC-derived astrocytes could be important in understanding the role of altered bioenergetics in neurological diseases.

In our previous study, we investigated bioenergetic changes in skin fibroblasts from late-onset AD (LOAD) patients and non-demented control individuals and showed increased glycolysis and a decrease in oxidative metabolism in the patients’-derived cells. We now continue these studies in brain cells derived from iPSCs, which would be more useful to ultimately adapt therapeutic developments for neurodegenerative diseases. To this end, we characterized iPSC-derived NPCs and astrocytes from n = 5 non-demented control and n = 5 LOAD samples using immunocytochemistry (ICC). The NPC phenotypes were confirmed with SOX1, PAX6, and NESTIN, and astrocytes were characterized with GFAP, S100β, and GLAST. To confirm their bioenergetic profiles, we screened the cells using Seahorse XFp Cell Mito Stress Tests. The tests showed that the oxygen consumption rates (OCR), the extracellular acidification rates (ECAR), and the proton production rates (PPR) were increased in LOAD patients’-derived NPCs and astrocytes, demonstrating that mitochondrial respiration, glycolysis, and ATP production were elevated in LOAD. The growth rates of NPCs, however, were slower in LOAD patients’-derived cells than in cells from non-demented control individuals. Ongoing studies are focused on L-lactate/pyruvate production, IGF-1-induced glucose uptake, and NAD/NADH synthesis and recycling, which are additional critical bioenergetic parameters that have also been implicated as abnormal in LOAD. Altogether, we have developed a cellular platform consisting of “personalized cell systems” to identify changes in key metabolic pathways that are age- or AD-specific, and, thus, can be used to detect core mechanisms in aging and in the pathogenesis of LOAD, the most common form of AD. These models can lead to the development of novel diagnostic and/or therapeutic strategies.

Topic areas:
Alzheimer’s/Dementia, Neurology
**Title**: Motivational Interviewing for Individuals with Schizophrenia to Enhance Medication Adherence

**Key words**: Schizophrenia, Antipsychotic, Adherence, Motivational interviewing, Adherence therapy

**Background**: The absence of motivation and insight influencing medication nonadherence is prevalent in individuals with the diagnosis of schizophrenia. This may be attributed to an assortment of factors including positive and negative symptoms, substance use, treatment discord, stigma, lack of continuity in care, cultural beliefs, and socioeconomic status. Nonadherence with medication therapy may result in decompensation, worsening symptoms, relapse, functional decline, increased utilization of inpatient and emergency services, and increased risk of death. Motivational interviewing or adherence therapy has been demonstrated to be an effective strategy to improve insight and medication adherence when it is included in daily practice.

**Purpose**: The aim of this systematic review was to determine if adjunctive therapy of motivational interviewing for individuals with schizophrenia is an effective intervention to improve symptoms, medication adherence, relapse, and rehospitalization rates. A modified motivational interviewing and adherence therapy packaged toolkit containing a powerpoint, pre- and post-surveys, and video links was created with provider collaboration and distributed to 30 provider-participants who treat individuals with the diagnosis of schizophrenia in a hospital setting. The providers included: 33% mental health specialists, 43% nurses, 10% psychologists, 7% psychiatrists, 3% nurse practitioners, and 3% social workers. The toolkit included current evidence and protocol for motivational interviewing and adherence therapy.

**Method**: An assessment was performed using the self-report version on MITI 4 survey pre- and post-educational toolkit. This assessment tool determined if the clinical knowledge of these clinicians had changed between pre- and post-survey. A two tailed paired t-test was performed with an alpha value of 0.5.

**Results**: The modified motivational interviewing and adherence therapy toolkit met the primary outcome to significantly increase the provider's knowledge and awareness which proved to be statistically significant ($p=0.0001$) with all clinicians.

**Conclusion**: In turn the newfound knowledge may improve their practice and the clinical outcomes of their patients.

**Topic areas**:
- Education
- Psychotic Disorders
- Schizophrenia
Presenting Author: Yan Li, Assistant electrophysiologist, instructor of psychiatry

Co-Authors: Raúl Andero, Natalia V. Luchkina, Junghyup Suh, Rachel A. Ross, Brad B. Lowell, Kerry J. Ressler, and Vadim Y. Bolshakov

Title: Neuropeptide-mediated modulation of anxiety circuits

Key words: neuropeptide, PACAP, amygdala, the bed nucleus of the stria terminalis, anxiety

Previous studies in both experimental animals and human subjects suggest that pituitary adenylate cyclase-activating polypeptide (PACAP)-mediated signaling may regulate anxiety-related behavioral mechanisms through its actions in two interacting brain regions, the amygdala and the bed nucleus of the stria terminalis (BNST). However, synaptic and network mechanisms of PACAP-mediated effects in the brain are poorly understood. In our earlier studies, we found that PACAPergic fibers and PAC1R are expressed in ovBNST (a subdivision of BNST), and we demonstrated that neurons in the parabrachial nucleus (PBN) of the brainstem are the source of PACAPergic innervation of ovBNST. Performing ex vivo optogenetic analysis, we found that PACAP contributes to regulation of anxiety states by differentially affecting synaptic efficacy at BLA projections to different BNST subdivisions, thus modifying the signal flow in BLA-ovBNST-adBNST circuits in such a way that adBNST is inhibited. This could explain the ability of PACAP to trigger anxiety, as direct optogenetic inhibition of adBNST was shown to be anxiogenic. To address this possibility, we assayed the effects of optogenetic stimulation of PBN fibers in the ovBNST on behavioral manifestations of anxiety. In these experiments, we knocked-down the expression of PAC1 receptors in “floxed” PAC1R mice by injecting AAV-Cre into the ovBNST. We found that photostimulation of ChR2-expressing PBN fibers in ovBNST was highly anxiogenic in control animals, as assayed with the open field and elevated plus-maze tests, but anxiogenesis was diminished in mice with suppressed expression of PAC1 receptors in ovBNST. Notably, control mice remained in a heightened anxiety state for minutes after the cessation of photostimulation, suggesting that plastic changes which resulted from activation of PBN-ovBNST projection were long-lasting. We also explored the effects of chronic stress (mice received footshocks for 7 days) on anxiety and neurotransmission in BLA-BNST circuits. We found that repeated stress was associated with a heightened anxiety and increased immunoreactivity for PACAP and PAC1R in ovBNST. Consistent with this, we found that synaptic efficacy at BLA inputs to ovBNST was enhanced in slices from repeatedly-stressed mice but not at BLA inputs to adBNST in same animals. The IPSC/EPSC ratio in BLA-ovBNST-adBNST projection was enhanced, indicating greater inhibition of adBNST by ovBNST inputs after chronic stress. The stress-associated changes in synaptic function provide support to the notion that PACAP-mediated signaling in BLA-BNST circuits contribute to stress-induced anxiogenesis.

Topic areas:
Anxiety
McLean Research Day 2019

Original Research - Pre-Clinical

Poster # 113
Time: 1:00-1:50pm

Presenting Author: Yong Kee Choi, Instructor

Co-Authors: Anju Vasudevan

Title: Mechanistic insights into autocrine and paracrine roles of endothelial GABA in the embryonic forebrain

Key words: Angiogenesis, GABA neuron, Endothelial cell, Differential gene expression, Neurogenesis

The developing cerebral cortex uses a complex developmental plan involving angiogenesis, neurogenesis and neuronal migration. After establishment of the periventricular vascular gradient by embryonic day 11 (E11), neurons and/or neuronal progenitors from ventricular zones navigate along diverse courses, radially and tangentially, to adopt final laminar positions and integrate into specific brain circuits. Our recent studies have shown that the developing periventricular vascular network exquisitely patterned amidst neurons not only acts as a physical substrate for neuronal migration, but also holds the key to several novel developmental mechanisms and pathways. It highlights the importance of endothelial cell secreted GABA signaling in the embryonic forebrain and establishes novel autonomous links between blood vessels and the origin of neuropsychiatric diseases like epilepsy, autism and schizophrenia. Since a common GABA pathway operates in both endothelial cells and GABAergic neurons of the embryonic telencephalon, it is essential to gain further mechanistic insights by segregating this pathway in individual cell types. Our recently generated Vgat DTie2-Cre or Vgat ECKO (endothelial cell knockout; ECKO) mouse model that blocks GABA release from endothelial cells, serves as a new tool to study how endothelial GABA signaling shapes angiogenesis and neurovascular interactions during prenatal development. Here, we isolated individually periventricular endothelial cells and GABAergic neurons from E15 Vgat DTie2-Cre and Vgat fl/fl telencephalon and characterized them further by using molecular (RNA seq) and cellular techniques. Our results reveal that the endothelial GABA signaling pathway influences angiogenesis related genes and specific processes like tight junction formation, vascular sprouting and migration. It also shows how components of the neuronal GABA pathway, for instance receptor mediated signaling and transcription factors are affected in the absence of endothelial GABA release. Taken together, our findings delineate the close relationship between vascular and nervous systems that begin early in embryogenesis establishing their future interactions and interdependence.

Topic areas:
Neurology
Psychotic Disorders
Presenting Author: Young Cha, Assistant Neuroscientist & Instructor

Co-Authors: Kwang-Soo Kim

Title: Distinct functional roles of SIRT1 and SIRT2 on metabolic reprogramming during human induced pluripotency

Key words: Pluripotent stem cells, Induced pluripotency, Metabolic reprogramming, SIRT1, SIRT2

Metabolic reprogramming (known as “Warburg effect”) from OXPHOS toward glycolysis is a hallmark of cancer cells as well as pluripotent stem cells. We recently found that SIRT1 upregulation and SIRT2 downregulation is a molecular signature of human pluripotent stem cells. In addition, we showed that the miR-200c-SIRT2 axis play an important role for metabolic switch from OXPHOS to glycolysis by controlling the acetylation levels of many glycolytic enzymes. To further understand molecular mechanisms underlying metabolic reprogramming, we comparatively investigated specific roles that are coordinated by SIRT1 and SIRT2 on OXPHOS and glycolysis. In addition, we are exploring how various microRNAs can regulate sirtuins, leading to metabolic reprogramming and control pluripotent stem cell fate and function. We will discuss our findings regarding the differential functional roles of SIRT1 and SIRT2 as regulators of metabolic reprogramming during human induced pluripotency and pluripotent stem cell function.

Topic areas:
Neurology
Adaptive functioning relies on the appropriate application of and balance between flexible goal-directed behavior and efficient habitual behavior. Imbalance between these behavioral systems is thought to play a central role in the etiology of substance use disorder (SUD) and several other neuropsychiatric conditions. While prior research has identified distinct corticostriatal neural correlates for each system, it has become increasingly clear that the goal-directed and habitual behavior systems interact with one another. The transfer of repeated behaviors from the goal-directed to the habitual system, the production of hybrid or "mixed system" behaviors, and the need to coordinate and "arbitrate" the degree to which each system controls behavior in a given circumstance, all suggest interaction between these systems. The present study sought to elucidate the neuroanatomical substrates that underlie interfaces between the goal-directed and habitual behavior systems. Using anatomical tract-tracing in non-human primates, we find that the terminal fields of goal-directed and habitual system cortical regions converge with one another in the striatum. We also find that the striatal terminal fields of the ventrolateral prefrontal cortex (vPFC) - which is posited to play a central role in arbitrating control between the two systems - converge with those from both goal-directed and habitual cortical regions in distinct striatal zones. These findings highlight the role of the striatum as a candidate anatomical interface through which the goal-directed and habitual behavior systems interact with one another.
Title: Mediators of childhood abuse on relapse risk in adults with substance use disorders

Key words: Anxiety Sensitivity, Grit, Childhood Trauma, Substance Use Disorder, Relapse

Background: Childhood physical and sexual abuse are known risk factors for substance use disorders. However, few determinants have been identified that explain these effects. Anxiety sensitivity and grit are two psychological variables that have been associated with substance misuse and may be impacted by exposure to trauma. The aim of this study was to determine if anxiety sensitivity and grit mediate the effects of childhood abuse on relapse risk in those with substance use disorders (SUDs).

Method: Treatment-seeking adults with SUDs (N=655) on a detoxification unit who were recruited for an ongoing cross-sectional study completed the Anxiety Sensitivity Index, Short Grit Scale, Childhood Trauma Questionnaire, and Brief Addiction Monitor (BAM). Mediational analyses were conducted to examine the effects of anxiety sensitivity and grit on associations between childhood physical and sexual abuse and relapse risk as assessed by the BAM.

Results: Analyses indicate that childhood physical and sexual abuse were significantly associated with relapse risk scores, and anxiety sensitivity and grit partially mediated these relationships.

Conclusions: Our findings suggest individuals with SUDs and a history of childhood trauma may benefit from treatment that includes a focus on anxiety sensitivity and grit. Study limitations and directions for future research are discussed.
Presenting Author: Brad Ruzicka, Director of the Laboratory for Epigenomics in Human Psychopathology, HMS Assistant Professor of Psychiatry

Co-Authors: Daniel Reed Tso, Makayla Hourihan, Sivan Subburaju

Title: Multiplexed Single-Nucleus RNA Sequencing of Postmortem Human Prefrontal Cortex in Schizophrenia and Bipolar Disorder

Key words: Single-cell genomics, RNA sequencing, Schizophrenia, Bipolar Disorder, Postmortem human brain

Background: Multiple molecular studies of homogenized postmortem human brain tissue have identified disrupted GABA signaling in schizophrenia and bipolar disorder, and downregulation of the GAD1 gene is among the most widely replicated findings in molecular studies of these disorders. Emerging technologies for single-cell transcriptomics now allow for high-throughput assessment of how the GABAergic deficit is partitioned across distinct neuronal circuitry and GABAergic interneuronal subpopulations, advancing our understanding of circuitry-based information processing and its dysfunction in psychotic illness.

Methods: Postmortem human prefrontal cortex Brodmann Area 10 tissue samples were microdissected from a cohort matched for age, gender, and postmortem interval from schizophrenia, bipolar disorder, and control subjects. Cellular nuclei were isolated by gradient centrifugation and nuclei from multiple individuals were pooled and then used for single-nucleus RNA sequencing experiments on the 10X Genomics Chromium platform. Multiple approaches were evaluated for deconvolution of the data including genotype-based and cell-hashing techniques.

Results: Preliminary data analysis identifies multiple distinct cellular populations within Brodmann Area 10, including neuronal and glial subpopulations. While multiplexing has numerous advantages in the study design of single-nucleus RNA sequencing experiments, deconvolution of this data is not trivial, and we find the cell-hashing approach to be more successful than genotype based deconvolution. Comparison between diagnostic groups is ongoing and demonstrates diagnosis-associated transcriptomic shifts in specific cellular subpopulations, suggesting distinct subpopulations of GABAergic interneurons are impacted differently by the pathophysiology of these disorders.

Conclusions: Advances in single-cell genomics technologies promise to revolutionize our knowledge of the “parts list” of the cellular machinery of the human brain, as well as how molecular pathologies are distributed among those functional units in psychiatric illness. This ongoing project demonstrates the power of assessing single-cell transcription in physically microdissected circuit locations within the human brain to elucidate the molecular pathology of psychotic disorders at a resolution not previously possible, offering insights into how this pathology operates within the complex cytoarchitecture of the human brain.

Topic areas:
Bipolar Disorder
Schizophrenia
Title: Deriving cardiac waveforms from fMRI data using slice selective averaging and a deep learning filter.

Key words: deep learning, fMRI, cardiac

Aim: Cardiac waveforms, recorded simultaneously during fMRI scans, can be used for numerous purposes, including noise removal and inferring physiological state. However, cardiac waveforms are often not recorded, and are not present in many shared datasets. In this work, we develop a method to estimate the cardiac signal in the brain from the fMRI data itself. In order to achieve this, we use the following assumptions. While the individual voxel recording time (TR) is too slow to fully sample the cardiac waveform, signal from the individual slices is rapid, on the order of 10-20 Hz. Averaging the cardiac component among the slice voxels is a sufficient approximation. Individual time slice averaging can be combined with proper time delays to obtain an average estimate for the cardiac signal. However, this signal is quite noisy and distorted. In order to de-noise the signal we use deep learning architecture to invert the signal to reconstruct the driving cardiac signal from the noisy fMRI signal estimate.

Methods: We used Human Connectome Project 1200 Subjects Release (HCP). For each HCP subject, there are 4 15 minutes resting state measurements. Data was collected in 2 sessions on subsequent days, in both LR and RL phase encoding direction. We selected the first 100 subjects numerically in order to keep our training dataset manageable. We used the 400 Hz plethysmography data which was recorded simultaneously during the sessions as our ground-truth. The resulting procedure consists of 3 stages. All operations are performed on raw fMRI data prior to any preprocessing. 1. Average the signal over all voxels for every slice (after regressing out motion timecourses and normalizing to percent deviation over time) and combine the slice timecourses with proper time delays to obtain the first raw estimate of the cardiac signal. 2. Resample the raw waveform to 25 Hz (to generalize the processing to work with any input sample rate). 3. Process the raw estimate using a trained, multilayer Convolutional Neural Network (CNN) implemented in Keras to remove noise and jitter from the raw signal, yielding an improved estimate of the cardiac waveform.

The network parameters are detailed in Figure 1. The network was trained on 80% of the subject data, with the resampled fMRI-derived cardiac waveform as the input, and the matching resampled plethysmogram data as the target.  Runs with spikes in the first stage data were excluded from the training set. Results: We did a simple hyper-parameter search and selected a layer depth of 10, with 10 filters of length 5 for each layer. This choice was stable and had high prediction accuracy, and a low training and computation time. We tested the performances in the validation set. Mean square error of Stage 2 output (raw signal) with respect to plethysmography data was 0.6. This is compared to an error of only 0.14 for the deep learning prediction (~77% noise reduction). We also tested the results by including the noisy data. In this case for the Stage 2 it is 0.86, and the deep learning prediction is 0.44. Discussion: The CNN noise removal filter is a nice extension to usual filtering approaches. In contrast to simple spectral filters, the CNN filter better recovers the waveform shape, as it incorporates prior knowledge of the structure of plethysmogram waveforms. We saw substantial improvement after applying multiple layers with multiple filters. Performance was additionally improved by regressing out motion timecourses (the 6 axis timecourses and their time derivatives). It is important to note that the data was not motion corrected, as this would move signal between slices, however the regression removed major motion correlated noise in the signals. Even with motion regression, we noticed failures in some regimes when the raw signal estimate is extremely noisy. In order to overcome this, we will explore alternative, more advanced network architectures which use global time features in the signal. We also plan to explore using phase projection results of the cardiac signals for removing cardiac noise from the fMRI signal.

Conclusion: By combining time corrected multi-slice summation of slice voxel averages with a deep learning reconstruction filter, we have successfully estimated the cardiac signal from resting state fMRI data itself. The model is trained on an existing dataset where plethysmography data was simultaneously recorded. The trained model was then tested on unseen data, and performance was found to be good, with an 77% reduction in mean squared error. The filter also worked well to reduce prediction error in spike data, despite not having been trained on it. The reconstructed cardiac signal can be used for noise removal, physiological state estimation, and analytic phase projection to construct vessel maps, even in cases where no physiological data was recorded during the scan.

Topic areas: Imaging
Presenting Author: Shi Yu Chan, Research Fellow

Co-Authors: Melissa Hwang, Amy Higgins, Kathryn Nielsen, Sophie Brickman, Dost Öngür, Roscoe Brady, Mei Hua Hall

Title: Functional connectivity changes in early-phase psychosis

Key words: Psychosis, Functional connectivity, Resting state fMRI

Introduction: Previous research has shown that while the greatest deterioration occurs in the early phase of psychosis, it may also present the greatest opportunity for therapeutic intervention to alter disease trajectory. However, much of the underlying neural changes that result from both pathology and treatment are not well understood. Resting state functional magnetic resonance imaging (rs-fMRI) has emerged as a useful technique to study functional connectivity between spatially distinct regions to identify networks that are altered under different conditions. In particular, resting state networks (RSNs), such as the default mode network (DMN), have been shown to be disrupted in patients with both early and late phase psychosis. In this study, we investigated how functional connectivity within RSNs were altered by early-phase psychosis at 2 time-points - baseline (within 2 years of the onset of psychosis) and a follow-up scan (within 2 years from the baseline scan) - to explore the longitudinal changes of functional connectivity that arise as psychosis progresses.

Methods: Rs-fMRI data were collected from 40 participants (20 early-phase psychosis patients, 20 healthy controls) at two sessions on 3-T scanners (Siemens). Functional data were acquired in 2 runs of 6.2 minutes (124 time-points) each with a gradient-echo echoplanar imaging sequence sensitive to blood oxygenation level-dependent (BOLD) contrast. Parameters used were 3 seconds repetition time, 30 milliseconds echo time, 85 degree flip angle, and 3mm voxel size. A T1-weighted structural run was also acquired for each session for co-registration with the functional data. Scan images were converted to NIFTI files, and imported into CONN for further pre-processing, denoising, and analysis. The default pre-processing pipeline was used, with parameters for art-based outlier detection set at 3 for the global signal z-value threshold, and 0.5mm for subject-motion threshold. The first 4 scans of each run was also removed. Confounding effects were removed by linear regression in the denoising step, and a band-pass filter of 0.008 to 0.09 Hz was applied. An ROI-to-ROI analysis was conducted with the 4 regions of the DMN used as seeds against 136 target atlas ROIs to obtain a connectivity matrix of 4 x 136.

Results: Preliminary analysis revealed that at baseline, compared to controls, patients have reduced connectivity between the mPFC and cortical regions in the brain [left planum temporale T(38) = -3.65, p-FDR = 0.0465; left parietal operculum T(38) = -3.54, p-FDR = 0.0465; right pre-central gyrus T(38) = -3.45, p-FDR = 0.0469; right central opercular T(38) = -3.39, p-FDR = 0.0469; right planum polare T(38) = -3.37, p-FDR = 0.0469]. Different results were obtained for the follow-up time-point, where reduced connectivity was observed between the PCC and the left anterior medial temporal gyrus [T(35) = -3.80, p-FDR = 0.049]. Further analysis will be done to explore the interactions between group and time-point as well as effects of symptom severity and medication.

Conclusion: Preliminary analysis showed that neural changes underlie the behavioural changes observed in early-phase psychosis. Differences in the results between time-points highlight the dynamic changes of disease progression and the importance of longitudinal analysis.

Topic areas:
Bipolar Disorder, Imaging, Psychotic Disorders, Schizophrenia
Title: Development of high affinity D2 receptor agonists as PET imaging agents for Parkinson’s and schizophrenia: preclinical studies

Key words: Dopamine D2 Receptor, Schizophrenia, Parkinson’s disease, Addiction, Neuroimaging

The D2high receptor is thought to be the functional form of the D2 receptor to which endogenous dopamine (DA) binds. Elevation of D2high receptors has been demonstrated in various neurological disorders in which the dopaminergic system is affected. In Parkinson’s disease (PD), the loss of dopaminergic neurons causes a shift of remaining D2 receptors into the high affinity state. Evidence for this is supported by the fact that medications used to treat PD have been shown specifically to target the D2high receptor. In schizophrenia, a higher proportion of D2 receptors are in the high-affinity state, evidenced by the fact that schizophrenic patients are behaviorally supersensitive to dopamine agonists. We recently reported the synthesis and receptor binding for D1high, D1low, D2high, D2low, and D3high receptors of a series of fluorinated aporphines, and identified two highly promising high affinity D2high ligands as potential tritiated radioligands for applications in in vitro receptor binding assays and autoradiography studies, MCL-524 and MCL-536. These agonists exhibited no affinity or low affinity for other receptors tested, including serotonin, α and β-adrenergic, benzodiazepine, GABAA, muscarinic, sigma, kappa, and mu opioid receptors, as well as dopamine, serotonin, and norepinephrine transporters and translocator protein. We evaluated the radioligands [3H] MCL-524 and [3H] MCL-536 in saturation binding studies and competition binding studies using human D2long expressed in CHO cells. In a competition binding assay with the agonist R-(−)-N-n-propylnorapomorphine (NPA) as the competing ligand, NPA had a Ki binding affinity of 0.16 nM. When [3H] MCL-524 was used, NPA was found to have a Ki value of 0.9 nM. Co-incubation with guanylylimidodiphosphate abolished binding to D2high. We evaluated radioligands [3H] MCL-524 and [3H] MCL-536 for biodistribution in brain and peripheral tissues in rats. Peak radioactivity levels were detected in the striatum vs. cerebellum between 15-30 minutes post-administration. In summary, the radioligands [3H] MCL-524 and [3H] MCL-536 display high binding affinity to human D2long and have proven to be superior radioligands for in vitro evaluation in receptor binding assays. Biodistribution studies indicate both radioligands have rapid uptake and selectivity for the striatum. This unique profile makes radiolabeled MCL-536 a versatile tool for diagnostics and therapeutics, and may quantify D2high sites in schizophrenia and PD patients in vivo.

Topic areas:
- Imaging
- Neurology
- Psychiatric Disorders
- Schizophrenia
Co-occurring attention-deficit/hyperactivity disorder and posttraumatic stress disorder in adults with substance use disorders

Introduction: Attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD) commonly co-occur, and both have been recognized as risk factors for substance use disorder (SUD). Previous research has shown lifetime prevalence of PTSD was greater in adults with ADHD compared to those without ADHD, and those with both ADHD and PTSD had increased risk for other psychiatric comorbidities, higher functional impairment, and lower quality of life. However, no studies to date have examined the prevalence of these two disorders together in an inpatient population seeking treatment for SUD. The present study aims to examine the prevalence and clinical correlates of these two disorders in a sample of adults being treated for SUD.

Methods: A sample of 293 participants were administered the Adult ADHD Self-Report Scale Symptom Checklist (ASRS-v1.1) which includes 18 questions that constitute DSM-IV-TR diagnostic criteria, with the first six questions seen to be the most predictive of the accompanying symptoms of ADHD. PTSD diagnosis was determined through reporting of a criteria A event, and then administration of the PTSD Checklist 5 (PCL-5), a self-report screening tool used to assess symptom severity of PTSD. A linear regression analysis was run to characterize the association between ADHD and PTSD symptom severity and SUD symptom severity, controlling for clinical and demographic factors.

Results: Results indicated that ADHD and PTSD were highly prevalent in this setting, (39% and 35%, respectively). Diagnosis of one disorder was strongly associated with the likelihood of the other disorder ($\chi^2 = 17.49$, df = 1, $p = .001$), and symptom severity scores for the two disorders were moderately correlated ($r = 0.50$, $p < .001$). In multivariable models controlling for sociodemographic variables and primary substance of abuse, greater PTSD severity was associated with higher overall SUD severity, and while not significant, greater ADHD symptom severity was associated with craving at a trend level ($p = .056$).

Conclusion: The prevalence of co-occurring ADHD and PTSD in this sample was at the high end of what has been previously cited in other settings, with significant associations between ADHD and PTSD symptoms and diagnosis likelihood. In this sample of adults with severe SUD, PTSD symptoms were associated with greater SUD severity. While integrated therapeutic modalities currently exist, additional study is needed to devise appropriate and efficacious behavioral interventions for this constellation of disorders.

Topic areas:
Addiction
PTSD
Title: Aggression in Psychosis: Clinical Characteristics, Associations with Community and Social Functioning, and the Role of Depressive Symptoms

Key words: psychosis, aggression, schizophrenia, bipolar disorder

Background: Aggression is common during an acute episode of psychosis and often leads individuals to be hospitalized. While many studies have used violence as a measure of aggression, fewer studies have included less serious forms of aggression (e.g. verbal aggression, confrontations, throwing things). Previous research in both violent and physically aggressive patients have shown relationships between aggression and positive symptoms, substance use disorders, and lack of insight. The current study compared these characteristics in patients characterized as aggressive or non-aggressive, including both chronic and first episode patients. We also examined associations between aggression and measures of clinical symptoms and functioning.

Methods: 23 patients with a diagnosed psychotic disorder who scored higher than a 4 on the YMRS aggressive/disruptive behavior item were compared with an age, gender, and treatment status (inpatient vs. outpatient) matched non-aggressive group who scored 0 on the same YMRS item.

Results: The aggression group exhibited higher positive symptom scores (t(41)=5.38, p<.001) and worse insight (t(44)=3.33, p=.002) replicating previous research. However, history of a substance use disorder was not significantly different between groups (X2(1, N=46) =.383, p=.536). General community functioning (t(42)=−2.58, p=.012) and social functioning (t(42)=−2.64, p=.011) were significantly lower in the aggression group. Depression (t(44)=.048, p=.962) and anxiety (t(41)=.086, p=.932) scores were not different between groups. In line with previous literature, depression scores were significantly correlated with insight in the non-aggression group (r=−.588, p<.01); however, depression and insight were not significantly correlated in the aggression group (r=−.303, p=.159). Depression was negatively correlated with social functioning in both the aggression (r=−.538, p<.01) and non-aggression groups (r=−.450, p<.05).

Conclusions: Aggressive psychosis has a clinically different presentation than non-aggressive psychosis and presence of aggression has negative implications for community and social functioning. Future research is needed to determine the etiology of aggressive behaviors and the best way to improve functioning in this population.

Topic areas:
Bipolar Disorder
Psychotic Disorders
Schizophrenia
Introduction: The dorsomedial prefrontal cortex (DMPFC) has been implicated in emotional experience and awareness. DMPFC dysfunction may be related to symptoms of decreased intensity of emotional experience, including anhedonia and emotional numbing symptoms of PTSD. DMPFC hypoactivation in response to negative emotional stimuli has been associated with PTSD diagnosis (Etkin et al., 2007) and with emotional numbing symptoms within PTSD (Frewen et al., 2012). Furthermore, a recent study from our lab found that, in a trauma-exposed sample, higher scores on a measure of anhedonia were correlated with higher positive connectivity between the right DMPFC and the nucleus accumbens (Olson et al., 2018). Although some studies have reported lower DMPFC volume in PTSD (Wang et al., 2016; Knight et al., 2017), it is unclear whether anhedonia and emotional numbing are associated with DMPFC anatomy in this population. The current study examined the relationship between DMPFC volume and the severity of anhedonia and emotional numbing in adults with posttraumatic stress symptoms. We hypothesized that decreased DMPFC volume would be related to greater emotional numbing and anhedonia.

Methods: Fifty-nine trauma-exposed adults (29F, 30M) underwent magnetic resonance imaging on a 3T Siemens Trio whole body scanner using a 32-channel head coil. Participants completed an interview using the Clinician-Administered PTSD Scale (CAPS), the Snaith-Hamilton Pleasure Scale (SHPS), and the Beck Depression Inventory (BDI). Measures of left and right DMPFC volume were derived using Freesurfer’s superior frontal volume parcellation unit (Desikan et al 2006), and corrected for total intracranial volume. Separate repeated measures analysis of covariance models examined CAPS emotional numbing score and SHPS total score as predictors of left and right DMPFC volume, with age and gender as covariates. Follow-up analyses examined whether significant results persisted after accounting for total illness severity (total CAPS score) and depression severity (BDI score).

Results: Emotional numbing was associated with larger DMPFC volume ($F(1,54)=7.87, p =.007$), controlling for a significant effect of age ($F(1,55)=5.25, p =.03$), and there was no significant emotional numbing by hemisphere interaction. Similarly, anhedonia was a significant predictor of larger DMPFC volumes ($F(1,55)=11.36, p =.001$), and the interaction of anhedonia by hemisphere was not significant. BDI score and CAPS score did not affect these relationships when entered as covariates, nor was either significantly associated with DMPFC volume.

Conclusion: We found that larger DMPFC volume was associated with more severe emotional numbing and anhedonia in trauma-exposed adults, even after accounting for total PTSD symptom severity or total depression severity. These findings add to evidence that the DMPFC is implicated in reduced interest and positive emotions, and possibly, in a broader range of restricted affective experience in PTSD. Because anhedonia is a component of emotional numbing, it is possible that these findings reflect only a relationship between anhedonia and DMPFC volume. Therefore, in order to more definitively assess the association between DMPFC and emotional numbing, future research should examine a possible relationship between DMPFC volume and other components of emotional numbing (i.e., detachment, restricted range of affect, and sense of foreshortened future).
Predictors and Effects of Treatment Duration in Short-Term Intensive Cognitive Behavioral Therapy for Youth with Anxiety

Background: Short-term intensive cognitive-behavioral therapy (CBT) has been shown to be an effective treatment for anxiety disorders in youth. However, less is known about predictors of outcome for this treatment format, especially when delivered outside of a research context. In particular, we do not know which dosing of treatment predicts optimal symptom improvement. Understanding the effect of treatment duration on outcome, as well as the factors that impact duration, are important next steps in enhancing treatment effectiveness. The present study examined predictors and effects of treatment duration for youth receiving short-term intensive CBT for anxiety disorders in a specialized outpatient clinic.

Methods: Participants were 103 children and adolescents (Mage[SD]=14.41[0.26]; 53.1% female) who enrolled in a short-term intensive CBT program and consented to having their treatment data used for research. Participants attended treatment for 2.5 hours per day, four days per week, for a minimum of four weeks, with the option to extend treatment in full-week increments. At admission and discharge, participants and their parents completed measures of anxiety (Spence Children’s Anxiety Scale; SCAS), depression (Center for Epidemiological Studies Depression Scale for Children), and functional impairment (Child Anxiety Impact Scale). Outcome variables were calculated as change scores from admission to discharge on each clinical measure. Treatment duration was measured in weeks, and a dichotomous variable was created to indicate whether a participant attended more than four weeks of treatment. Independent t-tests were used to compare participants who did and did not extend.

Results: Average treatment duration was 6.31 weeks (SD=0.25; Range=4-12). Approximately 70% of participants extended treatment past the minimum four weeks, with an average extension of 3.31 weeks (SD=0.27). Participants who extended differed in clinical symptom change scores on the child-rated SCAS \( t(88)=2.03, \ p<.05 \), reporting greater decreases in anxiety symptoms (M=-13.02) compared to those who did not extend (M=-7.63). No differences emerged in other clinical symptom change scores. Participants who extended also differed in age \( t(87)=2.18, \ p=.03 \), being younger (M=14.06) than those who did not extend (M=15.37). No differences emerged in gender, household income, or symptom severity at admission.

Conclusion: Our results demonstrated that the majority of participants extended treatment beyond the four-week minimum. Participants who extended experienced greater reductions in anxiety symptoms and were younger than those who did not extend. These findings suggest that children may gain momentum in achieving symptomatic relief when in an intensive treatment environment for an extended period of time, and younger participants may benefit from more time to rehearse learned skills. Future research should investigate the optimal dosing of intensive treatment and its feasibility.

Topic areas:
Anxiety
Stigma and isolation are often experienced by the patient seeking ECT treatment. Peer support groups and group programming for ECT patients and significant others aid in the recovery process. We will describe the program development and explore ways to expand this programming to address the needs of this patient population. A pilot study was held in the spring of 2017 to determine if the use of cognitive training skill development would alleviate the impact of the memory and cognitive effects of ECT. Nurses, in collaboration with a psychiatrist, a cognitive psychologist and a person with lived experience, developed a series of 6 modules designed for cognitive retraining of ECT patients utilizing an educational and support group format. A battery of self-assessments were measured before and after the series of groups. Results are discussed and changes to the curriculum and practice exercises are reviewed. The cognitive effects of ECT can be profound and nurses working with patients having ECT need to develop strategies like these to assist patients manage and lessen the effects. Simple skills development can help.

**Topic areas:**
Anxiety
Bipolar Disorder
Depression
Education
Psychotic Disorders
Title: The Role of Social Support on Psychiatric Symptom Severity and Treatment Outcomes

Key words: Social Support, Symptom Severity, BASIS-24, Outcomes

Background: Social support is a concept that refers to the resources provided by a social network to help individuals cope with psychological distress. Current research is continually expanding our understanding of perceived social support’s influences on mental health, as the lack of social support has been found to be risk factor to mental health.

Objective: Investigate the impact of social support on patient symptom severity at intake and subsequent treatment outcomes.

Method: The data consists of psychiatric patients from 2001 to 2018. Six BASIS-24 composite scales have been used to quantify the severity of psychiatric symptoms and functioning. A multi-level logistic regression model was used to evaluate the impact of social support on the severity of the psychiatric symptoms at intake and subsequent treatment outcomes. The model was adjusted for age, gender, ethnicity, marital status, education, and employment. The model yielded odds ratios of each of the levels of the severity problem vs. no problem for people without any social support compared with those with some social support. The sample included all patients who completed a BASIS-24 assessment at admission (N=357,807). Improvement on a BASIS-24 scale is the reduction of severity score for more than one standard deviation, approximately 1 point for each scale. There was little to be improved for a score of <1 at admission, so patients with these low admission scores were excluded (N=75,539).

Results: The study findings show that risk of depression for those patients without any social support is 380% (OR, 4.8; 95% CI 4.4-5.1) more “likely” to suffer from extremely severe depression when compared to those with some social support, using adjusted OR as a risk index. Furthermore, the study shows similar effects across all BASIS-24 subscales such as Relationship, Psychosis, Substance Abuse, Self-Harm, Emotional Lability, and the overall difficulty. The odds ratio of improvement on depression at discharge by more than one standard deviation for people with some social support vs. those without any social support is (OR, 3.0; 95% CI 2.7-3.3). The results show similar impacts of social support on treatment outcomes across all BASIS-24 subscales.

Conclusion: The results showed that lack of social support had significant effect on risk of psychiatric problem and the effect was higher for more severe problems, which was found across all BASIS-24 subscales. Patients privileged with social support had more chance of improvement for more than one standard deviation when compared to those without social support. This study establishes the positive effect of social support across all BASIS-24 measurement on psychiatric problems. This research provides implications for clinical intervention and practice development. By identifying individuals with little to no social support at admission, patient’s treatment may be altered to account for a deficit in social support, such as allocating more resources to this individual or alter their group interaction. Furthermore, aftercare can center upon developing new communities and networks.

Topic areas:
Depression, Quality/Outcomes
Title: Clinical Profile and Resource Utilization of Pediatric Patients with Autism Spectrum Disorders (ASD) and Subclinical-ASD Symptoms in the Inpatient Setting

Key words: Autism Spectrum Disorder, Pediatric inpatient, Resource utilization, Psychiatric symptoms, Length of stay

Background: Youths with ASD have disproportionately higher rates of medical and psychiatric service utilization. Approximately 11% of youths with ASD are hospitalized psychiatrically before 21 years of age. Youths with ASD tend to have significantly longer length of stay (LOS) in comparison to their peers. There is a dearth of research examining specific clinical characteristics of ASD and subclinical-ASD populations, especially for the pediatric population in the higher acuity of care setting.

Methods: Patient data were obtained through retrospective chart reviews of a pediatric inpatient psychiatry unit in a metropolitan area. Patients were admitted between 01/15/16 – 10/13/16, whose parent or guardian had completed a Social Responsiveness Scale-2 (SRS-2). The SRS-2, including Brief SRS scale, and Brief Psychiatric Rating Scale for Children (BPRS-C). A positive screen cut-off was >65 on the Brief SRS scale; higher scores = more severe symptomatology. 26.77% (n=72) screened positive on the Brief SRS scale.

Results: Clinical Profile: Positive SRS (+SRS) group correlated well with discharge diagnoses of neurodevelopmental disorder, ASD, and ADHD. +SRS group presented with more severe symptoms in thinking disturbances (P= 0.024), psychomotor abnormalities (P= 0.002), and depressed mood (P= 0.053). Safety evaluation: +SRS group was less likely to report SA (P= 0.015) and SI (P= 0.054) upon admission. There was no significant difference between the SRS-screened groups for Self-Injury (P= 0.18). Resource Utilization: +SRS group had a significantly longer LOS (mean 6.1 days, P= 0.0015) in comparison to their peers. Specific subscales associated with longer LOS: Social Cognition (P = 0.0041), Social Communication (P= 0.0082), Social Motivation (P=0.0011), and Restricted Interests and Repetitive Behavior (P= 0.0017). Social Awareness was not associated with longer LOS (P= 0.22). Discussion: +SRS group had several significant differences in their clinical profile and resource utilization pattern. SRS may serve as an appropriate clinical tool for identifying patients with subclinical and clinical ASD symptoms. Understanding the presenting clinical profile of patients with ASD and subclinical symptoms may assist in outpatient treatment plan and monitoring. Despite SRS+ group reporting less safety concerns, inpatient level of care was still recommended. SRS+ group had a much higher level of resource utilization as evidenced by a significant longer LOS, which seemed to corroborate the findings of previous studies. The specific subscales may suggest inherent challenges of ASD and sub-clinical ASD symptoms that may prolong hospitalization and require more extensive disposition resources. Our study demonstrated that patients with ASD and subclinical ASD symptoms not only presented differently but required more inpatient management and resources.

Future Directions: Further studies are needed to comprehensively understand the predictive nature of specific clinical profile in resource utilization and symptom severity in both inpatient and outpatient setting. It will be important to ascertain concrete steps to better tailor the treatment of patients with ASD and subclinical ASD symptoms and reduce the burden of healthcare utilization.

Topic areas:
Child/Adolescent, Cognitive Sciences
Presenting Author: Caitlin Monaghan, Research Fellow; Research Fellow in Psychiatry

Co-Authors: Sophie Brickman, Amy Higgins, Polly Huynh, Kevin Spencer, Dost Ongur, Mei-Hua Hall

Title: Early Sensory Processing Event-Related Potentials Across a Longitudinal Study of First Episode Psychosis

Key words: Event related potentials, Longitudinal, First episode psychosis

Background: Individuals with chronic psychotic disorders have measurable deficits in processing sensory information. Some of these deficits occur early in the processing stream, which compromises the accuracy and interpretation of the original signal’s representation throughout subsequent processing steps. In contrast to chronic patients, less is known about the presence and progression of these deficits in individuals who have recently experienced a psychotic episode for the first time, before irreversible changes have occurred leading to chronicity.

Methods: Three early auditory processing event-related potentials (ERPs): sensory gating (P50), mismatch negativity (MMN), and auditory steady state response (ASSR), were measured in 45 first episode psychosis (FEP) patients (21 schizophrenia (SZ) spectrum diagnoses and 24 bipolar disorder (BD) with psychotic features) and 32 healthy control (HC) subjects. Seventeen FEP patients underwent EEG recordings at the 12-month timepoint.

Results: Correlations between each ERPs were between -0.27 and 0.01 (p values > 0.15). At baseline and 12-month follow-up time points, FEP patients not taking antipsychotics had significantly impaired sensory gating (P50 ERP) while those prescribed antipsychotics had P50 values similar to HCs. No differences in MMN were seen between FEP patients and HCs at baseline. However, there was a trend suggesting a deficit at 12 months, reflecting a longitudinal decrease in MMN amplitude in SZ patients specifically. Furthermore, in SZ but not BD patients, MMN and functioning measures were significantly correlated. Phase locking and evoked power measures of ASSR did not differ between FEP patients and HCs at baseline or follow-up visits.

Conclusion: None of the ERPs were correlated across paradigms, suggesting they index different components of early sensory processing. Sensory gating is impaired at the time of a first episode, though this phenotype can be rescued through use of antipsychotics. MMN in FEP patients is intact at baseline but declines over the progression of the illness, particularly in patients with SZ diagnosis. Contrary to literature reports, we did not observe impairments in either ASSR measure in FEP patients, which warrants further investigation. Our results support the notion that there is a large amount of heterogeneity within the FEP population, likely with distinct clinical trajectories and optimal treatments.

Topic areas:
- Bipolar Disorder
- Psychotic Disorders
- Quality/Outcomes
- Schizophrenia
Title: Quantitative Assessment of Mania and Psychosis During Hospitalization Using Automated Analysis of Face, Voice, and Language

Key words: Schizophrenia, Bipolar disorder, Facial expression, Machine learning, Voice

Background: A major challenge for reliable and effective behavioral and mental health care is the lack of objective markers of illness. Computational approaches to measuring naturalistic behavior in clinical settings could, therefore, provide an objective backstop for mental health assessment and disease monitoring, both of which are extremely costly and often unreliable using currently available methods.

Objectives: This study aimed to train machine-learning (ML) classifiers to estimate conventional clinical measures of severe mental illness using quantitative metrics derived from computational analysis of facial and vocal behaviors.

Methods: Individuals hospitalized for any active psychotic condition, carrying diagnoses of schizophrenia, bipolar disorder, schizoaffective disorder, or related conditions) were recruited to participate in up to ten recorded study visits, comprised of three segments: (1) Participant sitting alone lasting ~2 minutes, (2) a 13-question semi-structured interview performed by a psychiatrist (10-15 min), and (3) a standardized clinical assessment performed and scored by a research fellow or assistant (45-60 min). The MD interview was designed to resemble a typical "clinical rounds" encounter, experienced daily by hospitalized individuals since it is used for clinical record keeping and clinical decision-making. The standardized assessment, performed on a subset of visits, included the Positive and Negative Syndrome Scale (PANSS), the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), and the Brief Psychiatric Rating Scale (BPRS). Each visit was captured using two synchronized HD webcams (Logitech) and cardioid microphones (Sennheiser HSP4), to obtain high-quality audiovisual (AV) data from both patient and interviewer, and then automatically uploaded to HIPAA-compliant cloud storage for encryption and processing. Analysis: We performed automated facial action coding (e.g., facial expression, eye contact, head pose) and vocal analysis (e.g., prosody, pitch, rate, volume), using publicly available software (e.g., openFace, openSmile), binned into 10-sec intervals throughout each interview. Speech samples were transcribed (TranscribeMe, Inc.) for linguistic analysis (e.g., word and sentence-level coherence). Interview-, segment-, and question-level summary statistics were derived for each feature and used to train support vector regressors (SVRs) to estimate conventional assessments, using a leave-one-out cross-validation (LOO-CV) procedure to avoid overfitting.

Results: A total of 34 participants, participated in 66 sessions between 2015 and 2018, resulting in over 40 hours of AV recordings. We found that several features derived from face, voice, and use of language (i.e. eyebrow furrowing, eyebrow flashing, eye widening, smile variability, characteristics of vowels) were both robustly measured using our approach, and allowed us to accurately estimate multiple symptom domains (i.e. mania, depression, psychosis) with R>0.7. In many cases, these effects were specific to the question or experimental epoch.

Conclusion: Automated analysis of face, voice, and speech provides a number of robust behavioral markers sensitive enough to detect changes in psychopathology within individuals over time. Therefore, we conclude that naturalistic, quantitative assessments can yield objective markers of mood and cognition that can be used to optimize both access and quality of treatments for a wide range of psychiatric conditions.

Topic areas:
Bipolar Disorder, Depression, Psychotic Disorders, Schizophrenia, Technology
McLean Research Day 2019

Original Research - Clinical

Presenting Author: Cemre Erkol, Visiting Scholar

Co-Authors: Talia Cohen, Emily Ness, Xiaoying Fan, Fei Du, Dost Öngür

Title: Relationship Between White Matter Abnormalities and Cognition in Schizophrenia

Key words: cognition, neuroimaging, schizophrenia, DTS, MTR

Introduction: White matter abnormalities are one of the most common neuroimaging findings in patients with Schizophrenia. Diffusion Tensor Spectroscopy (DTS) is an MRI modality that provides information on metabolite [e.g. N-acetyl aspartate (NAA)] diffusion within axons and Magnetization Transfer Ratio (MTR) provides information on brain myelin content. We previously reported abnormalities in both measures in the prefrontal white matter in schizophrenia patients. In this study, we examined the impact of these abnormalities on cognitive function. We used the MATRICS Composite score as an index of overall brain function and the Stroop Color-Word test score as an index of prefrontally-dependent function. We hypothesized that prefrontal white matter abnormalities would be more closely correlated with Stroop test scores than MATRICS Composite scores.

Methods: We studied chronic stable patients with Schizophrenia/Schizoaffective disorder (SZ group) (n=35) who were taking medications and a healthy control (HC) group (n=33) between 18-49 years old. Participants completed a scan at our 4T Varian Scanner for NAA apparent diffusion coefficient (NAA ADC) and MTR measures. Participants were administered the Stroop and MATRICS tests on scan day.

Results: We partially replicated our previous findings to show white matter abnormalities in SZ compared with HC, i.e. there was a significant elevation in NAA ADC in the SZ group. MTR was numerically lower in the SZ group, but this difference did not reach statistical significance. Patients performed significantly worse than controls in both MATRICS and Stroop testing. We also observed substantial correlations between MTR and Stroop scores which differed between HC and SZ groups (Pearson’s r = 0.38, -0.164, respectively) and between NAA ADC and Stroop scores (r=0.27, -0.10, respectively). As hypothesized, these results were stronger than those seen with the MATRICS Composite scores (MTR r = 0.28 for HC, 0.159 for SZ; NAA ADC r = 0.09 for HC, -0.003 for SZ).

Conclusions: In this study, we demonstrate that both axon- and myelin-specific white matter abnormalities in SZ patients have functional implications. Using a prefrontal-specific MRI data collection approach, we found that prefrontally-dependent cognitive functions are more closely related to white matter abnormalities than whole-brain dependent cognitive functions.

Topic areas:
Psychotic Disorders
Schizophrenia
Parameters of Reported Childhood Sexual Abuse in Adolescents and Adults with Borderline Personality Disorder

Objective: Prior research has demonstrated a link between childhood sexual abuse and borderline personality disorder (BPD) in adolescents and adults and has indicated that more severe abuse is related to poorer psychosocial functioning. The present study describes the overall severity of sexual abuse in adolescents and adults with BPD and compares both groups on specific parameters of abusive experiences.

Methods: Participants included 104 adolescent (aged 13-17 years) inpatients with BPD, and 290 adult inpatients with BPD. All participants completed two interviews that assessed the presence and severity of sexual abuse.

Results: Of the studied patients with BPD, 26.0% of adolescents and 62.4% of adults reported a childhood history of sexual abuse before the age of 18. Adults had higher scores on an index of sexual abuse severity than adolescents, and a higher proportion of adults reported scores in the severe range. Adults with BPD were also more likely than adolescents to report having experienced sexual abuse that occurred at multiple developmental stages, was frequent (i.e., weekly basis or more), was longer in duration (i.e., a year or more), and was perpetrated by a parent. The groups did not differ on other parameters of abuse.

Conclusions: Taken together, these results suggest that adults with BPD are more likely to report sexual abuse than adolescents with BPD. Additionally, adults report abuse that is more severe than adolescents with BPD, with specific differences observed in timing, frequency, duration, and perpetrator.

Topic areas:
Borderline Personality Disorder
Presenting Author: Christopher King, Research Data Analyst

Co-Authors: Christopher D. King EdM, Blake T. Hilton PsyD, Margaret L. Griffin PhD, R. Kathryn McHugh PhD, Elizabeth Kneeland PhD, Scott Provost MM MSW, Nadine R. Taghian BS, Roger D. Weiss MD, Kerry J. Ressler MD PhD

Title: Childhood Sexual Abuse and Pain Interact to Increase Opioid Use in Adults Treated for Substance Use Disorders

Key words: Childhood Trauma, Pain Interference, Opioid Use Disorder, Alcohol Use Disorder, Chronic Pain

Background: Child abuse increases risk for negative outcomes including substance misuse, and substance use risk factors such as pain interference. In patients with substance use disorders (SUDs), little is known about the childhood trauma experiences influencing primary substance of abuse.

Methods: Adults with chronic pain (N=160) seeking treatment for alcohol or opioid use disorder completed validated surveys assessing childhood trauma, pain interference, and substance use. Hierarchical logistic regression was used to model these measures predicting alcohol use disorder vs. opioid use disorder.

Results: As levels of pain interference increase, the odds of having a primary diagnosis of opioid use disorder increase in patients with higher levels of childhood sexual abuse (CSA), whereas the odds of having a primary diagnosis of alcohol use disorder increase in patients with lower levels of CSA. This interaction effect ($z=-2.18$, $p=.029$) is present even when controlling for severity of childhood physical abuse ($z=2.26$, $p=.024$), substance use risk factors ($z=-4.78$, $p<.001$), substance use prior to treatment ($z=5.72$, $p<.001$), and anxiety sensitivity ($z=4.02$, $p<.001$).

Conclusions: In adults seeking treatment for SUDs, CSA may biologically or behaviorally prime individuals to self-medicate with opioids over alcohol as pain interference increases. Study limitations and directions for future research are discussed.

Topic areas:
Addiction
Title: Thalamus structure and re-experiencing symptoms in PTSD

Key words: posttraumatic stress disorder, thalamus, magnetic resonance imaging, tractography

Introduction: Sensory information flow from the thalamus to the amygdala and prefrontal cortex (PFC) is necessary for fear learning, which is implicated in the pathophysiology of PTSD. Re-experiencing symptoms of PTSD are thought to be an expression of conditioned fear, and they are often relived as predominantly sensory-perceptual impressions of the trauma. These symptoms are associated with increased activation in subcortical limbic regions, as well as decreased activation in the PFC (Rauch et al, 2006; Fenster et al, 2018). As yet there is limited literature addressing the relationship between the thalamus and re-experiencing symptoms. Previously, reduced functional connectivity between the bilateral thalamus and medial PFC has been shown to correlate with re-experiencing symptoms (Kennis et al., 2013). However, little is known about anatomical differences in thalamic volumes that may relate to the occurrence of re-experiencing symptoms.

Hypothesis: We examined the relationship of re-experiencing symptoms with anatomical thalamus measures in a sample of adults with posttraumatic stress symptoms. We predicted that thalamic volumes and white matter integrity of thalamus-PFC pathways would be associated with re-experiencing symptoms in adults with posttraumatic stress disorder.

Methods: Participants were 80 trauma-exposed adults: 43 met criteria for PTSD, and 37 were non-PTSD trauma-exposed controls (TENC). All underwent imaging on a 3T Trio Siemens MR scanner with a 32-channel head coil. PTSD and TENC participants completed the Clinician Administered PTSD Scale (CAPS), from which current re-experiencing symptom scores were obtained. High-resolution anatomical T1 images and diffusion tensor imaging (DTI) data were collected. Freesurfer software was used to derive volumes of the left and right thalamus and total intracranial volume (TIV). TRACULA provided a metric related to white matter integrity (fractional anisotropy [FA]) within the left and right anterior thalamic radiation (ATR).

Results: PTSD participants had significantly higher re-experiencing symptoms than TENC participants. In the combined PTSD and TENC group, re-experiencing symptoms were associated with significantly larger left thalamus/TIV (p = 0.021), with significantly lower FA in right ATR (p = 0.002) and left ATR (p = 0.043), and with non-significantly larger right thalamus/TIV (p = 0.065), all analyses controlling for age and sex. When examining the PTSD group alone, re-experiencing symptoms also were associated with lower left ATR and right ATR FA, and with larger left thalamus volumes.

Conclusion: To our knowledge, this study is the first to examine anatomical measures of the thalamus in relation to re-experiencing symptoms in trauma-exposed adults. Our findings show that more severe re-experiencing symptoms were significantly correlated with larger volume of the left thalamus and lower white matter integrity of bilateral thalamus-to-prefrontal cortex tracts. This encourages further research into the relationship of the thalamus with re-experiencing symptoms of PTSD, including examination of how various thalamic indices (e.g., sub-territory volume, shape and function) may mediate these symptoms.

Topic areas: Imaging, PTSD
Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurodevelopmental disorder with a devastating impact on the quality of life of millions of children, adolescents and adults. While ADHD is thought to be highly heritable, its etiology is largely unknown and likely to involve a combination of environmental factors and the contribution of multiple genes defects. To understand the molecular underpinnings of ADHD, we hypothesize that 3D neuralized structures (organoids) derived from patient-specific induced pluripotent stem cells (iPSCs) can be used as a potential platform. In particular, the Prefrontal Cortex (PFC) is emerging to be of central relevance to the neural pathways of ADHD, as it connects extensively to sensory and motor cortices, as well as to the basal ganglia and cerebellum. These areas are intricately interconnected and modulated by a mesh of neurons that in ADHD display heavy deficits in dopaminergic and noradrenergic transmission. Thus, it is critical to understand the molecular influences modulating PFC’s function in order to develop novel medications for patients afflicted with the disorder. We have started to generate and characterize iPSC-derived cortical organoids from ADHD patients and healthy siblings controls to study the molecular and cellular differences in corticogenesis between diseased and control brains. Particularly, we propose that the root cause of the PFC’s smaller structure involves a limited progenitor pool and impaired radial migration. To achieve these long-term goals, we attempted to use our novel and non-viral reprogramming methods to generate high quality control and ADHD-iPSC lines, to optimize in vitro organoid generation, and then fusion organoid models. Our approach will facilitate examination of how disease risk is translated at the cellular and tissue levels through comparative studies of processes such as progenitor cell proliferation, migration and connectivity during development.

**Topic areas:**
Child/Adolescent
Neurology
Orienting nursing float staff to geropsychiatric care units is a complex process. Despite the growing population of older adults with dementia and escalating costs associated with caring for this cohort, limited attention has been paid to adequately prepare the healthcare workforce (Eden, Maslow, LE, & Blazer, 2012). Massachusetts recently passed legislation requiring hospitals that serve adults have a plan in place to care for individuals with dementia [MA HS, 2018]. Dementia is a clinical syndrome characterized by progressive deterioration in cognitive function and ability to live independently. Cognitive, behavioral and psychological symptoms greatly impact quality of life (Backhouse, Camino, & Mioshi, 2018). Agitation is a troubling symptom that often interrupts care processes (Livingston et al., 2014). Educating and supervising nursing staff to care compassionately and safely for older people suffering with dementia is critical. This orientation curriculum included neurocognitive disorders, team building, interpersonal communication, cultural sensitivity, trauma informed care, activities of daily living, and experiential simulation. The 5-day educational opportunity was offered to float and regular mental health specialists, and included didactic and clinical experiences facilitated by a multidisciplinary team. Direct-care nursing staff and older adults on geropsychiatric units hail from many cultural backgrounds. This workforce must be prepared to engage and communicate with diverse populations (Eden et al., 2012). Overall, the participants in this pilot program expressed feeling better prepared to work with individuals with dementia and demonstrated increased empathy. In conclusion, including principles of trauma informed care and cultural sensitivity in geropsychiatric orientations can improve communication among caregiving teams and delivery of quality care.
Presenting Author: Miles Cunningham, Associate Psychiatrist; Assistant Professor

Co-Authors: Sina Azimi  James Thompson  Aidan Piper  Griffin Van Horne

Title: Holographic Display of Three-Dimensional Data: The Theatre Ghost Projector

Key words: hologram, three-dimensional, neuroanatomy, imaging

Presentations of scientific and clinical information and images have traditionally been represented on a flat screen in two dimensions. However, this imposes certain limitations on the viewer’s conceptualization of the information as it actually exists in three-dimensional (3d) space. We have constructed a novel system allowing presenters to display data holographically. This system is comprised of Pepper’s ghost technology and a corresponding software development pipeline to process and render data. Virtually any still image or animation can be “suspended” in 3d space before an audience. This platform gives the presenter the ability to better communicate complex spatial structures and relationships. Applications are diverse, including confocal z-series constructions, retrograde/anterograde tracing anatomy, active neural circuit labeling, animations, and brain imaging data, such as MRI, Spect, and DTI. The Theatre Ghost Projector prototype will become available at no cost to McLean scientists and clinicians to enhance their presentations.

Topic areas:
Technology
Thank You!

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