Full Abstracts
for Poster Session

Wednesday January 21st, 2015

Session 1: 1:00-1:50pm
Session 2: 1:50-2:45pm
Brief Communications: 3:00-4:30pm
**Title:** Prolonged Impairment Of Sexual Function Associated with Anabolic-Androgenic Steroid Abuse: an Underrecognized Problem

**Keywords:** anabolic steroids, testosterone, substance abuse, erectile function, libido

**Background and Aims:** Anabolic-androgenic steroid (AAS) abuse has become a major substance-use disorder worldwide, but few reports have as yet documented the extent and consequences of AAS-induced hypogonadism. We sought to augment this limited literature with data from two ongoing studies of AAS users at our center.

**Methods:** We compared 24 male former long-term AAS users and 36 non-AAS-using weightlifters recruited by advertisement in Massachusetts, USA. Participants were administered structured psychiatric interviews, detailed questions regarding history of use of AAS and other drugs, tests of urine and hair for drugs of abuse, physiological measurements, laboratory determinations of serum hormone levels, and the International Index of Erectile Function (IIEF).

**Findings:** Compared to non-AAS-using weightlifters, former AAS users displayed significantly smaller testicular volumes ($p = 0.047$) and lower serum testosterone levels ($p = 0.004$), with five users showing testosterone levels below 200 ng/dL despite abstinence from AAS for 3-26 months. Former users also displayed significantly lower scores on the Sexual Desire subscale of the IIEF ($p < 0.001$) and on self-rated confidence that they could maintain an erection ($p = 0.011$). Seven (29%) users had experienced major depressive episodes during AAS withdrawal. Two men had failed to regain normal libidinal or erectile function despite seemingly adequate treatment with physiologic replacement doses of testosterone.

**Conclusions:** AAS-induced hypogonadism is common, frequently prolonged, and associated with substantial morbidity. Some cases appear unresponsive even to replacement testosterone therapy and might possibly be irreversible. Substance-abuse professionals should be alert for this emerging and probably underrecognized problem.
Title: Relapse Risk in Major Depression vs. Duration of Initial Antidepressant Treatment

Keywords: depression, treatment-discontinuation, antidepressants, stabilization, trial-design

Background: The efficacy, limitations, and methods of studying antidepressant treatment beyond the initial weeks of acute major depression remain incompletely resolved. There is growing reliance on treatment-discontinuation trial-designs which risk artifacts associated with treatment-discontinuation, as documented in our earlier studies.

Aims: For subjects in controlled, continuation trials for acute major depression, to clarify the relationship of relapse-risk within 12 months of re-randomizing to placebo vs. duration of initial treatment and putative stabilization.

Methods: Data from placebo arms of 45 relevant controlled trials identified in recent reports were pooled and analyzed by regression modeling.

Results: There was a strong, inverse, correlation of shorter initial treatment and greater relapse risk after re-randomizing to placebo-treatment (p=0.003); risk declined by >10-fold as initial treatment continued for >4 months.

Conclusions: Discontinuation of antidepressant treatment before 6 months was associated with rising relapse risks after re-randomization to placebo. This manifestation of treatment-discontinuation risk requires critical consideration in both clinical management of depressed patients and the design and interpretation of treatment-discontinuation trials.
**Title:** Gender Differences in Substance Abuse Treatment and Medical Services Use in the Stage II Women’s Recovery Group Trial

**Keywords:** Treatment services, Women, Addiction

**Aims:** In a Stage II trial of the single-gender Women’s Recovery Group (WRG), women randomized to the WRG (n = 52) or mixed-gender Group Drug Counseling (GDC; n = 48), and men assigned to GDC (n = 58) had significant reductions in mean days of substance use at the end of treatment and 6 month follow-up. Groups were implemented in a rolling format consistent with community practice and participants could engage in treatment as usual (excluding other substance abuse group therapy during the 12-week group treatment). There were no significant gender differences in group therapy treatment outcomes. In a secondary data analysis, we investigated gender differences in substance abuse (SA) and medical treatment services use at baseline, end of group treatment, and 6 months post-treatment. We hypothesized that at the 6 month follow-up compared with baseline: (1) women and men would increase use of SA treatment (including self-help); (2) medical services use would decrease.

**Methods:** Participants ≥18 years were included if they were substance dependent and used substances in the past 60 days. SA and medical treatment use was assessed using the Treatment Services Review and Monthly Self-Help Questionnaire.

**Results:** Compared to men, women had a later age of first alcohol use and regular alcohol use, but there was no gender difference in age of first SA treatment. Few participants reported use of other SA treatment services at baseline, end of group therapy, and at the 6 month follow-up with the exception of self-help. There were no gender differences in mean days/month of self-help use or the proportion of men and women attending self-help groups. Almost half of men used individual psychotherapy at all measured time points, but significantly more women than men used individual therapy at baseline, end of treatment, and 6 month follow-up. Women were more likely to have a physical exam or visit a medical specialist at baseline but no gender differences were observed at the 6 month follow-up.

**Conclusions:** Women initiated and first regularly used alcohol at an older age but had their first SA treatment at the same age as men. There were few gender differences in SA or medical services use. Individual psychotherapy and self-help were the most frequently used treatment modalities with significantly more women using psychotherapy than men. Otherwise, participants used few additional substance abuse treatment services, and use of self-help significantly declined over the course of the study. Compared with men, women had more medical specialty and physical exam service use at baseline but not at the end of group treatment or 6 months post-treatment. ASI medical composite scores significantly increased (worsened) over time for both men and women, indicating that SA treatment may need to address medical problems and services during and after treatment.
Original Research - Clinical

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Title: Relations Between Non-Suicidal Self-Injury and Physical Activity in Psychiatric Adults

Keywords: Non-suicidal self-injury, Physical activity, Exercise, Treatment-seeking adults

Non-suicidal self-injury (NSSI) is highly prevalent in adult psychiatric inpatients, with as many as 45% reporting lifetime NSSI (Andover & Gibb, 2010). To date, no gold standard treatment exists for NSSI (Washburn et al., 2012). However, a fairly large literature has examined the preventative and therapeutic effects of regular exercise/physical activity on both physical (DHHS, 1999; Pate et al., 1995) and mental health outcomes (Deslandes et al., 2009; Stein et al., 2007). For example, clinical evidence suggests that exercise positively impacts depression (Deslandes et al., 2009) and emotional distress/disorders (Smith, 2006). A small body of research suggests that physical activity/exercise may have clinical utility in reducing urges to engage in NSSI (Klonsky & Glenn, 2008; Wallenstein & Nock, 2007). Whether regular exercise is related to NSSI, and/or whether exercise may be used for prevention and intervention efforts for NSSI, is largely unknown. This research examines the relations between physical activity and NSSI in an adult psychiatric sample attending a partial hospitalization program (PHP). Ninety-eight adults attending treatment for acute psychiatric concerns (e.g., major depression, bipolar disorder) completed the Inventory of Statements about Self-Injury – Behavioral Scale (e.g., minor NSSI such as skin picking, to moderate/severe NSSI such as cutting; ISAS; Klonsky & Olino, 2008), the International Physical Activity Questionnaire (IPAQ; Hagstromer, Oja, & Sjostrom, 2006), the Center for Epidemiologic Studies Depression Scale (CES-D-10; Andresen et al., 1994), and the GAD-7 (a brief measure for generalized anxiety disorder; Spitzer et al., 2006). Rates of NSSI were comparable to those reported in previous psychiatric samples; 47 (48%) participants endorsed a lifetime history of NSSI behavior(s). Of these, 5 (11%) had done so in the past year, 10 (23%) in the past 30 days, and 7 (16%) in the past week. On average, participants with a history of NSSI engaged in marginally significantly less physical activity than those without (t = 1.90, p = .06) with a medium effect size (Cohen’s d = .39, r = .19). Follow-up ANCOVA analyses controlling for self-reported depression and anxiety demonstrated persistent between-group significance to marginal significance (p = .05, partial eta squared = .04; p = .07, partial eta squared = .04, respectively). These results indicate that individuals with a history of NSSI may engage in less physical activity. This is concerning given the evidence of the mental health benefits of physical exercise (Yeung, 1996) and the preliminary evidence that supports the impact physical activity may have on reducing and/or eliminating urges to engage in NSSI (e.g., Washburn et al., 2012). Data collection for the current study is ongoing and within approximately one month the sample should be sufficiently powered to fully investigate the relations between NSSI, IPAQ scores, and distress (e.g., potential moderating effects). Thus far, results suggest that targeting increases in regular physical activity in short-term treatment settings may serve as a promising adjunctive treatment for patients with a history of and/or current NSSI.
**Original Research - Pre-Clinical | Division: Division of Basic Neuroscience**

**Presenting Author:** Glenn Konopaske, Research Psychiatrist, Instructor in Psychiatry, McLean Hospital, Laboratory for Psychiatric and Molecular Neuroscience

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**Title:** Altered prefrontal cortical MARCKS and PPP1R9A mRNA expression in schizophrenia and bipolar disorder

**Keywords:** dorsolateral prefrontal cortex, quantitative real time PCR, postmortem, schizophrenia, bipolar disorder

**Background:** We previously observed dendritic spine loss in the dorsolateral prefrontal cortex (DLPFC) from schizophrenia and bipolar disorder subjects. In the current study, we sought to determine if the mRNA expression of genes known to regulate the actin cytoskeleton and spines correlated with spine loss.

**Methods:** Five candidate genes were identified using previously obtained microarray data from the DLPFC from schizophrenia and control subjects. The relative mRNA expression of the genes linked to dendritic spine growth and function, i.e. IGF1R, MARCKS, PPP1R9A (neurabin I), PTPRF, and ARHGEF2, were assessed using quantitative real-time PCR (qRT-PCR) in the DLPFC from a second cohort including schizophrenia, bipolar disorder, and control subjects. Functional pathway analysis was conducted to determine if the genes of interest interact with NMDA receptor signaling pathways that regulate the actin cytoskeleton.

**Results:** MARCKS mRNA expression was increased in both schizophrenia and bipolar disorder subjects. PPP1R9A mRNA expression was increased in bipolar disorder subjects. For IGF1R, mRNA expression did not differ significantly among groups; however, it did show a significant, negative correlation with dendrite length. MARCKS and PPP1R9A mRNA expression did not correlate with spine loss, but interact with NMDA receptor signaling pathways that regulate the actin cytoskeleton and spines.

**Conclusions:** MARCKS and PPP1R9A might contribute to spine loss in schizophrenia and bipolar disorder through their interactions, possibly indirect ones, with NMDA signaling pathways that regulate spine structure and function.
Craving is a risk factor for relapse in individuals with opioid dependence. Previous research has shown that substance-related cues, such as images of drugs and of drug paraphernalia, induce strong craving responses and that such cue-induced craving increases risk for use. Understanding how types of drug cues trigger craving can help to inform treatment strategies; for example, clinicians may be better able to identify particularly situations that could be considered risky for this population. The aim of this study was to determine whether particular cue types elicit greater craving responses than other cue types among individuals with opioid dependence. We hypothesized that participants would report more craving in response to cues including paraphernalia relative to drug cues alone. Participants receiving inpatient treatment at the McLean Hospital Alcohol and Drug Abuse Treatment Program were recruited for a single session research study. This sample (N=52) included participants who were dependent on heroin, prescription opioids, or a combination thereof. Participants completed a battery of self-report measures in addition to a task that assessed cue-induced craving in response to various stimuli. These stimuli included images of opioids (drug stimuli) or drug use paraphernalia (paraphernalia stimuli); participants reported on dimensions of craving after the presentation of each image. Collapsing across all groups, there was significantly higher craving in response to paraphernalia stimuli than to drug stimuli for the primary opioid of abuse (i.e., prescription opioid images in the prescription opioid users, and heroin images in the heroin users) (mean difference = -0.89, t[49] = -3.74, p < .001). This within-subjects effect was significant even when controlling for presence of injection use (F[1,48]=20.34, p < .001). For the heroin group, craving in response to heroin paraphernalia was significantly higher than to drug images (mean difference = -1.39, t[29]=-4.01, p <.001). However, this was not the case for prescription opioids (mean difference = -0.01, t[29]=-0.03, p = .98). In this treatment-seeking sample of participants with opioid dependence, drug paraphernalia cues elicited greater craving responses than images of the drug alone. This finding was qualified by the primary opioid of abuse, with a strong difference in heroin users, and no difference among prescription opioid users. These findings highlight the importance of context in cue-induced craving and further suggest important clinical differences between those dependent upon heroin relative to those dependent on prescription opioids.
Title: Axon guidance molecules in Parkinson’s Disease

Keywords: Parkinson’s disease, axon guidance cues, human iPS cell-derived dopaminergic neurons

Recently important evidence came to light implicating axonal degeneration as an early hallmark of developing pathology in Parkinson disease (PD). More importantly, gene expression studies, genome wide association studies (GWAS) of single-nucleotide polymorphism variations and pathway analysis studies identified axon guidance signaling pathways to be associated with PD development (Edwards et al., 2011, Plos One;6(2):e16917, Bossers et al, 2009, Brain Path;19(1):91-107, Lin et al., 2009, Trends Neurosci;32(3):142-9, Srinivasan et al., 2009, Hum. Mutat;30(2):228-38, Lesnick et al., 2007, Plos Genet;3(6):e98, Maraganore et al., 2005, Am J Hum Genet;77(5):685-93). Based on GWAS and pathway analysis Lin et al. (2009, Trends Neurosci;32(3):142-9) identified five axon guidance genes associated and predictive of PD outcome: DCC, EPHB1, NTNG1, SEMA5A and SLIT3. Axon guidance cues persist to be expressed in the adult CNS maintaining the structural plasticity of the neuronal circuits (Mironova and Giger, 2013, Trends Neurosci;36(6):363-73). It is thought that through this maintained expression of guidance cues in the adult host brain neuronal transplants reconnect their dopaminergic (DA) axons to their specific target—the dorsal lateral striatum (Isacson & Deacon 1996, Neuroscience;75(3):827-37). Mouse ventral midbrain (VM) primary cultures and DA neurons derived form embryonic stem cells are sensitive to Slit and Netrin signaling (Lin et al., 2005, Mol Cell Neurosci;28(3):547-55, 2006, Stem Cells;24(11):2504-13). For the first time we show that human iPS-cell derived DA neurons may also be sensitive to known DA axon guidance regulators by expressing Ephrin and DDC receptors. Preliminary data from human iPS cell-derived dopaminergic neurons indicate that LRRK2 may play a role in neurite outgrowth regulation. IPS cell-derived DA neurons carrying LRRK2 mutations showed increased neurite collapse and lack of recovery after thapsigargin stress in vitro. These data indicate that axon growth and maintenance is potentially aberrant in PD. We hypothesize that these changes can either take place in the years preceding the clinical diagnosis, or are already present during the development of CNS hindering the functionality of the neuronal circuitry.
Title: Glucocerebrosidase deficiency and glycolipid accumulation occurs in both normal aging and sporadic Parkinson’s disease

Keywords: AGING, ALPHA-SYNUCLEIN, AUTOPHAGY

Clinical and neuropathological evidence links GBA1, which encodes for the lysosomal hydrolase glucocerebrosidase (GCase) with sporadic PD. GCase is responsible for the conversion of the undegraded lipid substrates glucosylceramide (GluCer) and glucosylsphingosine (GluSph) into ceramide and sphingosine, respectively. A subset of sporadic PD-patients (~4-7%) has been identified as GBA1-mutation carriers, causing diminished activity (~30-40%) of GCase. PD-patients that carry a GBA1 mutation are often diagnosed younger and the symptoms are usually reported as more severe than PD-patients lacking a mutation. Identifying reliable biomarkers that closely associate with the pathogenic changes that occur during the early stages of PD may help increase the accuracy of early diagnosis. Diminished levels of GCase activity have been reported in the brains and CSF of sporadic PD patients, irrespective of whether they harbor GBA1 mutations. Therefore, we hypothesize that GCase activity and its associated glycolipids may be useful biomarkers to predict early stages of sporadic PD. We found widespread GluSph up-regulation in the putamen, cerebellum, hippocampus and frontal cortex, which coincided with reductions in GCase activity of non-GBA mutation carrying sporadic PD-patients in comparison to age-matched control patients. In addition to these changes, we also found age-dependent increases in GluSph, which correspond to a reduction in GCase activity. Moreover, we found age-dependent increases in GluCer and GluSph in wildtype and transgenic mice that overexpress human wildtype α-synuclein. Therefore, we hypothesize that age-dependent dysregulation in GCase activity and accumulation of glycolipids occurs with normal aging, which is further exacerbated with sporadic PD-patients.
Title: Characterization of iPSC-derived neuronal preparations and bioassays for use in transplantation in Parkinson’s disease

Keywords: iPSC, Transplantation, Parkinson’s disease

Patients with Parkinson’s disease can gain improved motor function upon fetal ventral midbrain cell transplantations (Mendez et al. Nat Med. 2008 May;14(5):507-9). Fetal cell sources are however limited and patients receiving transplantations require immunosuppression. Induced pluripotent stem cells (iPSCs) present opportunities for autologous transplantations, provided that the cells are safely and effectively differentiated toward a midbrain dopaminergic fate. We have derived iPSCs from cynomolgus monkeys for future and ongoing autologous transplantations. 6-OHDA lesioned hemi-parkinsonian rats have been transplanted with these iPSCs differentiated using previously published floor-plate-based protocols for midbrain dopaminergic fate (Cooper et al., 2010, Mol Cell Neurosci;45(3):258-66, Sundberg et al., 2013 Stem Cells;31(8):1548-62) in order to determine long-term (6 months) graft characteristics. Midbrain dopaminergic survival, presence or absence of proliferating cells and neural precursors, blood vessel growth in grafts, graft morphology and behavioral recovery has been documented in preparation for clinical IND applications. Furthermore, we have optimized our midbrain dopaminergic differentiation protocol to be feeder-free and xeno-free and to generate TH/FoxA2 expressing neurons at a similar level as previously described protocols (Cooper et al., 2010, Mol Cell Neurosci;45(3):258-66, Sundberg et al., 2013 Stem Cells;31(8):1548-62). Cells generated using these protocols are being characterized using qPCR and ICC at the end of the protocol and after long-term culturing in vitro. Together the ongoing autologous transplantations into non-human primates, the long-term xenogeneic transplantations and in vitro characterizations evaluate the safety and efficacy of iPSC therapy for Parkinson’s disease at a pre-clinical level. The collected data will be used when establishing GMP-grade midbrain dopaminergic neurons from patient derived iPSCs for future clinical applications.
One of the main hurdles in developing novel therapeutics for age-related disorders is the still limited understanding of both the biology of normal aging and the mechanisms of disease pathology. Aging and age-related disorders are characterized by slow progressive deterioration or death of neurons, and are influenced by age- and disease-specific factors, including genetic predisposition, dysfunctional proteins, and compensatory mechanisms and molecules that are important in cell survival. If the cellular defense mechanisms are compromised, the penetrance of disease-specific mechanisms becomes higher and cell survival less likely. Among the regulatory factors that govern gene and protein networks and, consequently, influence neuronal health and function are small molecules such as miRNAs. It is increasingly appreciated that even small disturbances of these regulatory factors can have profound effects on cell survival in response to stress. We have identified a novel mechanism in neurons, mediated by miR-126, which regulates the effects of numerous neurotrophic and neuroprotective growth factors (GF). Specifically, we found that elevated levels of this miRNA are neurotoxic and increase the vulnerability of neurons to a variety of non-specific and disease-specific toxic factors, including Staurosporine (STS), Alzheimer’s disease (AD)-associated amyloid beta 1-42 oligomers (Aβ1-42), and 6-OHDA which induces oxidative stress in dopamine (DA) neurons mimicking Parkinson’s disease (PD) pathology. Mechanistically, miR-126 targets a series of factors in PI3K/AKT/GSK-3β and MAPK/ERK signaling pathways and small increases of this miRNA cause a downregulation of these signaling cascades, impairing the effects of neurotrophic and neuroprotective GF, such as IGF-1, NGF, BDNF, and soluble amyloid precursor protein α (sAPPα). In turn, inhibiting miR-126 enhances the actions of GF without disturbing normal neuronal cell function. Our data indicate that miR-126 may play a profound role in neuronal cell survival, at least in part by regulating GF/PI3K/AKT and MAPK/ERK signaling. While its elevation is neurotoxic, its inhibition is neuroprotective, suggesting that targeting this miRNA may have therapeutic potential for neurological and age-related disorders.
**Title:** Hippocampal GABA Levels Vary as a Function of Menstrual Cycle Phase in Healthy Adults

**Keywords:** GABA, Hippocampus, MRS, menstrual cycle, memory

**Background:** Magnetic resonance spectroscopy has been used to examine cellular health, integrity and metabolism, although few studies investigate sex differences. Given prior research demonstrating sex differences in hippocampal-dependent memory functioning and occipital GABA, the objective of this study was to examine hippocampus GABA in relation to sex differences and memory performance in healthy adults.

**Methods:** Proton metabolite data were acquired at 4T from left and right hippocampus (LH, RH) and compared between healthy adult men (n=10) and women (tested in follicular and luteal menstrual cycle phases, n=7). Verbal and spatial learning and memory ability were also assessed.

**Results:** Women in the luteal phase exhibited significantly lower RH GABA than both women in the follicular phase and men (p=.028). GABA was lower in the LH of men and women in the follicular phase, than women in the luteal phase, however differences were not statistically significant. Lower LH GABA was associated with better verbal recall (p=.012), whereas higher RH GABA was associated with better semantic clustering (p=.008). Lower LH GABA also correlated significantly with better spatial memory (p=.046).

**Conclusion:** These preliminary data indicate that hippocampal GABA varies with menstrual cycle phase in women, and that GABA levels correlate with verbal and spatial memory performance in male and female subjects. Given that low brain GABA has been implicated in depression and anxiety, conditions that disproportionately affect women compared to men, menstrual cycle phase may play an important role in the course of illness and responsiveness to pharmacological interventions that target GABA.
Original Research - Clinical

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Title: The Effect of Nursing Interventions Aimed at Reducing Metabolic Syndrome Risks in Persons with Serious Mental Illness

Keywords: Metabolic Syndrome, Serious Mental Illness, Nursing Interventions, Motivational Interviewing

PROBLEM: The aim of this study was to determine if metabolic risk factors can be stabilized or improved with motivational interviewing/coaching and routine medical follow-up care in subjects who have been hospitalized for serious mental illness, and are at risk for metabolic syndrome.

FRAMEWORK: Motivational Interviewing is a directive, client-centered approach to the nurse-patient interaction focusing on willingness to change, identifying ambivalence, assisting in identification of realistic goals and encouraging change behaviors. Aspects of Integrative Theory of Health Behavior Change were also utilized to design patient-centered education to affect behavior change to impact health.

METHODS: This study enrolled 38 subjects during their inpatient stay and followed them for 18 weeks post discharge. Interventions included: lifestyle modification education, weekly telephone motivational interviewing by psychiatric nurses and medical follow up visits with NP.

RESULTS: This pilot study demonstrated no significant patterns of change in physiological markers. Some individuals showed improvement, others showed deterioration. In general, individuals reported a positive response to weekly contact and developed strong relationships with the clinician-researchers.

IMPLICATIONS: The integration of care is critical as the care of individuals with SMI can become very complex. Nurses are in a strategic position to assure that transitions of care across all levels are seamless and to develop long term lifestyle modification programs for individuals with SMI. Health status maintenance may be a realistic goal.

FUTURE RESEARCH: This small pilot study needs replication with a larger sample to determine whether these nursing interventions can be effective in improving or maintaining the health of individuals with SMI.

Topics areas: Psychotic disorders
Autism Spectrum Disorders (ASDs) are thought to result from brain synapse dysfunction. Emerging evidence indicates that rare, deleterious mutations increase the risk for developing autism, and many of these identified genes have known functions in the formation, pruning or plasticity of brain synapses. The myocyte enhancer factor 2 (MEF2) family of transcription factors regulates a gene expression program involved in activity-dependent synapse elimination in the developing brain. We found that MEF2 promotes synapse elimination through a process involving the RNA-binding protein, Fragile X Mental Retardation Protein (FMRP), the causal gene in the ASD, Fragile X Syndrome. More recently, mutations in MEF2C have been identified in patients with severe intellectual disability, epilepsy and autism, further supporting the critical link between MEF2 and normal brain development and function.

To examine the role of MEF2 in brain development and autism-related phenotypes, we generated a conditional knockout (cKO) of the MEF2C gene within excitatory neurons of the forebrain in early brain development of mice. The MEF2C cKO mice are viable and healthy, but they display significant autism-like behavioral phenotypes, including reductions in social behaviors, restricted and repetitive motor behaviors, and deficits in social communication (ultrasonic vocalizations). Moreover, the mice are hyperactive, and they display robust deficits in reward-related behaviors. Ongoing studies are exploring the cellular, synaptic, and forebrain circuit abnormalities that accompany these behavioral abnormalities. Taken together, our findings reveal that genetic deletion of MEF2C in excitatory forebrain neurons in the mouse brain results in behaviors reminiscent of the three core diagnostic criteria for autism in humans, and as such, provide a new mouse model for studying potential brain dysfunctions that underlie autism-like behaviors.
The role and regulation of Histone Deacetylase 4 (HDAC4) in cocaine-related behaviors

Repeated exposure to drugs of abuse alters the function of the nervous system and produces states that encourage continued drug use. Changes to chromatin landscape and transcriptional accessibility, mediated in part by nuclear enzymes such as histone deacetylases (HDACs), are thought to play important roles in the development and persistence of addiction-related behaviors. HDAC4, a member of the Class IIa HDAC family, shuttles between the nucleus and cytoplasm in response to neuronal activity, and overexpression studies have implicated it in drug-related behaviors in the nucleus accumbens (NAc). As such, we sought to determine whether and how HDAC4 is regulated by cocaine, and whether this regulation is important for its suspected role(s) in addiction-related behavioral plasticity. Our findings indicate that acute and chronic cocaine differentially regulates HDAC4’s phosphorylation state and nuclear/cytoplasmic localization, suggesting that the change in cellular localization might contribute to changes in cocaine-induced behaviors. We find that nuclear HDAC4 strongly suppresses MEF-2 dependent transcription activity and may reduce cocaine conditioned place preference. As a complementary approach to mutant expression within the NAc, we generated conditional gene deletion of HDAC4 from the adult nucleus accumbens using viral-mediated expression of Cre recombinase. Our preliminary findings indicate that HDAC4 may regulate initial sensitivity to cocaine but not the development of locomotor sensitization nor the expression of conditioned place preference.
**Title:** Altered CREB binding to activity-dependent genes in serine racemase deficient mice, a mouse model of schizophrenia

**Keywords:** D-serine, NMDA receptor, Arc, BDNF

**Background:** cAMP-response-element-binding protein (CREB) is a ubiquitously expressed transcription factor in the brain that regulates neuroplasticity by modulating gene expression. There are numerous signaling pathways by which information is transmitted from the cell membrane to the nucleus that in turn affects CREB binding to DNA. The influx of calcium through N-methyl-D-aspartate receptors (NMDARs) is a well-defined mechanism that leads to the increased expression of CREB-dependent genes, including brain derived neurotrophic factor (BDNF), microRNA-132 (miR132), and activity-regulated cytoskeleton-associated protein (Arc). We have previously demonstrated that serine racemase knockout (SR-/-) mice, which exhibit NMDAR hypofunction, also have reduced mRNA and protein levels of the aforementioned CREB-dependent genes in the hippocampus. In addition, these molecules are reduced in schizophrenia.

**Methods:** Wild-type (WT; n = 5-6) and SR-/- (n = 5) mice were killed and their hippocampi were flash frozen on dry ice. Tissue samples were dissociated and then fixed with 1.5% paraformaldehyde. Chromatin was digested using the SimpleChIP Plus Enzymatic Chromatin IP kit (Cell Signaling Technologies). The chromatin was incubated with a rabbit anti-CREB antibody (1:50; Cell Signaling Technologies) overnight at 4°C on a rotisserie. The crosslinks were reversed and the DNA was purified for analysis using qPCR (Sybr Green). To determine the levels of CREB bound at each gene of interest, PCR primers were directed near the CRE sequence of each promoter. All of the primers were validated in previous publications. Melting temperature analysis was performed after every PCR to ensure accuracy.

**Results:** We first validated the ChIP kit for brain tissue using a positive control antibody and primers to ensure proper chromatin shearing. SR-/- mice have approximately 50% less CREB binding at the miR-132 gene than WT mice. Using BDNF exon-specific primers, SR-/- mice have significantly less CREB binding at the BDNF I promoter, but not at the BDNF IV promoter. Finally, SR-/- mice have 80% less CREB binding to the synaptic activity response element (SARE) region of the Arc gene.

**Discussion:** These data demonstrate that in vivo, NMDAR hypofunction caused by the selective removal of the NMDAR coagonist, D-serine, leads to altered CREB binding on known activity-dependent genes. The ChIP results suggest that reduced CREB binding contributes to the lower levels of BDNF, miR-132, and Arc that we previously observed in SR-/- mice. Future studies will determine whether D-serine administration, which reverses these abnormalities at the RNA and protein level, also normalizes the epigenetic perturbations. Serine racemase knockout (SR-/-) mice recapitulate many of the molecular and cellular abnormalities associated with impaired neuroplasticity that are observed in schizophrenia, including reduced levels of miR-132, BDNF, and Arc. These chromatin immunoprecipitation data suggest that impaired binding of the transcription factor CREB to the promoter regions of several activity-dependent genes in SR-/- mice could contribute to their reduced expression.
Adolescent suicide is a serious public health concern. Approximately 4% of adolescents make a suicide attempt by age 18 (Nock et al., 2013), and depressed individuals are at 6 fold greater risk (Nock et al., 2008). However, depression severity predicts suicide ideation and plans, but not attempts (Nock, Hwang, Sampson, & Kessler, 2010). Consequently, there is a pressing need to identify factors that differentiate attempters from non-attempters. Both childhood sexual abuse (CSA) (see Miller, Esposito-Smythers, Weismoore, & Renshaw, 2013 for a review) and impulsiveness (e.g., Auerbach et al., 2014; Brent et al., 2003) have been consistently associated with adolescent self-injurious and suicidal behaviors, and these effects are robust after controlling for psychopathology. Further, CSA and impulsiveness are strongly associated (e.g., Brodsky et al., 2001) and may interact to predict suicide risk. Specifically, impulsiveness may be an inherited trait that only predicts suicidal behaviors when it is exacerbated by early trauma (e.g., CSA). In order to test the unique and interactive effects of CSA and impulsiveness in predicting suicidal behaviors, we recruited a sample of 163 depressed adolescents (38 boys, 125 girls) aged 13 to 18 (M = 15.60, SD = 1.27) from the McLean Hospital Academic Center. All participants completed the Self-Injurious Thoughts and Behaviors Interview (SITBI; Nock, Holmberg, Photos, & Michel, 2007) to assess suicidality and provided self-reports of depressive symptom severity and past sexual abuse. Finally, participants were categorized into “high” and “low” disinhibition (a subdomain of impulsiveness) groups based on their rate of commission errors on a gradual onset Continuous Performance Task (Esterman, Noonan, Rosenberg, & Degutis, 2013). Consistent with previous research, CSA was associated with past suicide attempts, controlling for suicidal ideation, suicide plans and depressive symptoms. As hypothesized, CSA moderated the effect of disinhibition in all analyses. For example, high disinhibition was strongly associated with making at least one lifetime attempt for adolescents reporting CSA, B = 1.99, SE = .73, Wald(1) = 7.39, p = .007, OR = 7.33, but had a non-significant effect among adolescents without CSA, B = -.50, SE = .45, Wald(1) = 1.26, p = .26, OR = .61. Our results support diathesis-stress models of suicidality implicating childhood maltreatment and impulsivity (e.g., Braquehais, Oquendo, Baca-Garcia, & Sher, 2010) and may inform clinical efforts towards enhanced early identification of youth most at risk for suicide.
Title: Psychometrics of the short grit scale among inpatients with alcohol use disorders

Keywords: Grit, Alcohol, Substance use disorder, Psychometrics

Purpose: The purpose of this study was to examine the psychometric properties of the Short Grit Scale (Grit-S) in patients with a primary alcohol use disorder. The Grit-S is a trait-level, 8-item measure that assesses grit as perseverance and passion in attaining long-term goals, with a total score and two subscales, consistency of interest and perseverance of effort. The Grit-S has previously been validated in both high-achieving and general populations (Duckworth et al. 2009); however, to our knowledge, this is the first study to examine the psychometric properties of the Grit-S in a sample with alcohol use disorder. Grit may be a relevant construct in alcohol use disorders given the importance of goal-related perseverance in the completion of treatment and maintenance of abstinence.

Methods: Data were collected as part of a survey study on an inpatient detoxification unit. Consecutively admitted inpatients were offered the opportunity to participate. The Grit-S was administered as part of a battery of self-administered questionnaires, which also included the Anxiety Sensitivity Index, the Overall Anxiety Severity and Impairment Scale, the Motivation to Change Scale, and a Craving Scale. Participants with a primary diagnosis of alcohol use disorder are the focus of this analysis.

Results: The sample consisted of 72 participants (35% women) with a mean age of 42.6 years (sd=12.2). Internal consistency was good for the total score (Cronbach’s α=0.73) and the consistency of interest subscale (α=0.81), and lower for the perseverance of effort subscale (α=0.62), consistent with findings for the Grit-S in other populations. The Grit-S demonstrated good discriminant validity as assessed by Pearson’s r, with nonsignificant or low associations when compared to the anxiety sensitivity (r=-.21, ns), craving (r=-.13, ns), anxiety symptom severity (r=-.31, p<.01), and motivation to change measures (r=.25, p<.04).

Conclusion: The Grit-S demonstrated good internal consistency and strong discriminant validity relative to distinct affective and motivational constructs in a sample of inpatients with primary alcohol use disorders. These initial data provide support for the use of the Grit-S among those with alcohol use disorders.
Grit among inpatients with alcohol use disorders

Introduction: Grit is a trait-level construct defined as perseverance and passion for long-term goals. Individuals with higher grit demonstrate greater success and achievement in several domains, such as educational attainment among adults and retention among West Point cadets (Duckworth et al., 2007). Although grit has been studied in a range of populations, grit has not been examined in a substance use disorder (SUD) population. If grit is associated with greater success in achieving recovery among those with SUDs, it could assist in treatment.

Purpose: The aim of the study was to examine grit in inpatients with a primary diagnosis of alcohol use disorder (AUD), using the Short Grit Scale (Grit-S; Duckworth & Quinn, 2009). We hypothesized that those with AUDs would report lower grit than the general population.

Methods: Consecutively admitted SUD inpatients were invited to complete a battery of assessments. The Grit-S has 8 items, with 2 subscales: Consistency of Interest and Perseverance of Effort. Total scores range from 1 (low grit) to 5 (high grit). Grit-S scores of those with AUD (N=72) were compared to published scores from a general population and to our sample of inpatients with an opioid use disorder (N=64). Among those with AUD, associations between Grit-S scores and patient characteristics were examined.

Results: Participants’ age ranged from 19-70 years (M=42.6, SD=12.2; 65% male). Scores for the Consistency of Interest subscale ranged from 1.0-4.8 (M=2.8, SD=0.9; scores for the Perseverance of Effort subscale ranged from 1.5-5.0 (M=3.6, SD=0.7). These subscale means did not differ from the previously reported means of 2.9 and 3.7 in the general population. However, total Grit-S scores for the AUD participants (M=3.2, SD=0.6; range 2.0-4.6) was lower than the general population mean of 3.4 (t(71)=-2.52, p<0.02) but higher than participants with opioid use disorder (M=3.0, t(134)=-2.38, p<0.02). AUD participants with a co-occurring psychiatric disorder had lower Grit-S scores compared to those without a psychiatric disorder (M=3.1 versus 3.4, t(70)=2.08, p<0.05). Gender and age were not associated with Grit-S scores.

Conclusion: Inpatients with alcohol use disorders reported low levels of grit relative to population estimates. Given the importance of perseverance to the achievement and maintenance of abstinence, low grit may be a marker of risk for poor treatment outcomes.
Keywords: P3 event-related potential (ERP), gamma oscillations, proton magnetic resonance spectroscopy (1H MRS)

Background: The auditory P3 event-related potential (ERP) and the evoked auditory steady-state response (ASSR) at 40 Hz are thought to index cognitive processing. Glutamate neurotransmission plays an important role in modulating P3 ERP and gamma oscillations depend on the interplay between the excitatory actions of glutamate and inhibitory actions of γ-aminobutyric acid (GABA). We investigated here the relationships between P3 ERP, evoked 40 Hz ASSR, and indices of glutamate, and GABA function measured in vivo with proton magnetic resonance spectroscopy (1H MRS).

Methods: Frontal P3a (Fz) and parietal P3b (Pz) were collected from 32 healthy participants who performed an auditory oddball task. ASSR phase-locking responses at Fz were collected using trains of clicks presented at 40 Hz. Resting GABA and GlN/Glu (an index of glutamate function) measures were obtained on a 4 Tesla MR scanner using MEGAPRESS and J-resolved MR spectroscopy, respectively. Linear regression and partial correlations were used for statistical analysis.

Results: A significant positive correlation was found between frontal P3a amplitude and GlN/Glu ratio in the anterior cingulate cortex (ACC) (partial R=0.52; P=0.004). Relationships between parietal P3b and the GlN/Glu ratio in the parietal-occipital cortex (POC) and between 40 Hz ASSR phase-locking and GABA level were not significant.

Conclusions: These results indicate a specific connection between an index of glutamate neurotransmitter function in ACC and frontal P3a and gamma responses, providing a novel insight into the neurochemistry underlying normal cognition. Abnormalities in glutamate neurotransmission have been observed in schizophrenia and other psychiatric conditions and may underlie illness related deficits of P3 and ASSR.
**Original Research - Pre-Clinical | Division: Division of Basic Neuroscience**

**Presenting Author:** Rebecca Benham, Post-doctoral fellow, LGN

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**Title:** GABA and depression: Examining the role of alpha2-containing GABA-A receptors in depression-like behavior and antidepressant action

**Keywords:** GABA-A receptors, depression, stress, antidepressants

Major depressive disorder affects millions worldwide, yet a slow onset of clinical improvement and a lack of efficacy in 25-35% of patients highlights the need to identify novel targets for the development of more efficacious antidepressants (ADs). The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and its type A receptor have shown promise as clinical studies report decreases in GABA levels in the plasma of depressed patients, while AD-induced increases in GABA have been implicated in the therapeutic effects of standard ADs.

Studies have begun to elucidate the role of individual GABA-A receptor (GABAAR) subunits in depressive-like behaviors using genetically modified mice. In particular, others have demonstrated that alpha2 heterozygous knockout (KO/WT) mice exhibit depressive-like behavior, which is reversed with chronic desipramine (DMI), but not fluoxetine (FLX) treatment. Such findings suggest that GABAARs may be necessary for the therapeutic effects of FLX.

Our laboratory reported depressive-like behavior in alpha2 homozygous knockout (KO/KO) mice in preclinical tests of behavioral despair. We sought to determine whether this behavior could be reversed by chronic AD treatment. Wild-type (WT/WT), KO/WT, and KO/KO mice received 4 mg/kg FLX or 53 mg/kg DMI in their drinking water for four weeks, and then underwent behavioral testing. While DMI had an antidepressant-like action, i.e. increasing latency to immobility in the forced swim test (WT/WT, trend in KO/WT and KO/KO) and decreasing total immobility in the tail suspension test (KO/KO), FLX had no significant effect. These results suggest that chronic DMI but not FLX treatment has antidepressant-like actions in alpha2 knockout mice. As monoamine-based ADs can have acute treatment effects (not seen in humans) in these behavioral tasks, we examined the role of alpha2-containing GABAARs in coping with chronic stress using the conflict-based chronic social defeat stress (CSDS) paradigm. CSDS produces persistent behavioral changes associated with depression which are reversed only following chronic standard AD treatment. KO/KO control mice spent less time interacting with an aggressive mouse as compared to WT/WT controls. Interestingly, CSDS did not further exacerbate this reduction in social interaction. Current studies are further examining this social avoidance behavior, as well as the effects of chronic DMI and FLX treatment in alpha2 KO/KO mice, to begin to understand the molecular mechanisms behind these behavioral alterations. Taken together our findings suggest a role for alpha2-containing GABAARs in depression and potentially other stress-related psychiatric disorders, as well as their treatment.
Original Research - Clinical | Division: Psychotic Disorders Division

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Title: Visual and cognitive processing of face and non-face signals in schizophrenia

Keywords: Schizophrenia, Psychophysics, Perception, Face, Cognition

Face perception is impaired in schizophrenia. The processing of face signals involves both specific and general visual and cognitive domains. Given the visual and cognitive problems implicated in this psychiatric disorder, it is critical to probe these information processing domains in order to understand the mechanisms underlying the face perception impairment. In this study, we examined a series of visual and cognitive factors that contribute to face perception in schizophrenia patients (n=40) and healthy controls (n=39), based on their performances on relevant tasks. These tasks include 1) face detection (identifying the presence of a face), 2) tree detection (identifying the presence of a non-face visual object), 3) contour detection (identifying the presence of configural visual signals important for face perception), and 4) contrast detection (identifying the presence of basic visual signal). Performance accuracies of patients were significantly lower than those of controls for face detection (p=0.048) and contour detection (p=0.02) but not tree detection or contrast detection. In patients, averaged face detection was significantly correlated with averaged tree detection (r=.76), averaged contour detection (r=0.58) and average contrast detection (r=0.63). The poor face detection was moderately but not significantly correlated with PANSS negative subscale scores (r=-0.31). This pattern of results highlights the contributions of basic visual signal and spatial integration to impaired face processing in schizophrenia. These results also suggest a potential association of face perception impairment with negative psychotic symptom status.
Title: Subchronic Pharmacologic NMDA Receptor Antagonism with MK801 Activates Akt Signaling Pathways.

Keywords: Schizophrenia, Akt, Mk801, D-serine

NMDA receptor (NMDAR) hypofunction is a powerful hypothesis for the pathophysiology of schizophrenia, because in part, NMDAR antagonists like phencyclidine and MK801 cause symptoms in healthy subjects that are similar to schizophrenia. Therefore, NMDAR antagonists have been used as a tool to induce NMDAR hypofunction in animals as a pharmacologic model of schizophrenia. Our laboratory has previously generated serine racemase-null mutant (SR-/-) mice, which display constitutive NMDAR hypofunction due to the lack of the NMDAR co-agonist, D-serine. SR-/- mice have deficits in multiple pathways, including V-akt murine thymoma viral oncogene (Akt) signaling and glycogen synthase 3 kinase (GS3K), which parallel what is observed in schizophrenia. Although some pharmacological NMDAR hypofunction models utilize sub-chronic NMDAR antagonist administration (5-7 days), our SR-/- mice have life-long NMDAR hypofunction. Thus, we analyzed intracellular signaling pathways in MK801 sub-chronically (0.15 mg/kg; o.d; 5 days) treated adult wild-type mice that are reduced in SR-/- mice and schizophrenia. We found that in contrast to SR-/- mice, the phosphorylation (activated) states of Akt1, GS3K, and mammalian target of rapamycin (mTOR) were increased in MK801 treated mice. Furthermore, there is a notable age-dependent change in the behavioral reaction of people to NMDAR antagonists. We therefore administered the same dosing regimen of MK801 to juvenile mice (3-4 weeks old) and compared them to juvenile SR-/- mice. Our findings demonstrate that sub-chronic, pharmacologic NMDAR antagonism has different effects on Akt/GS3K/mTOR signaling than constitutive NMDAR hypofunction caused by a deficit in D-serine. Considering the concordance with schizophrenia, our results suggest that SR-/- mice are a more accurate NMDAR hypofunction model of schizophrenia.
Title: Seeing the Future? Marijuana Use Predicts Functional and Structural Brain Changes

Keywords: marijuana, executive function, white matter, diffusion tensor imaging (DTI)

Background: As legalization of medical and recreational marijuana (MJ) continues to spread, conversations about MJ often highlight potential benefits. Further, the perception of risk and harm related to MJ is at an all-time low. This view persists despite research highlighting cognitive and neural alterations in MJ smokers. Given the rise in MJ use, specifically among youth, it is critical to determine if MJ use patterns can predict cognitive impairment and white matter alterations.

Results: Analyses of 44 chronic MJ smokers revealed that more smoking episodes and higher grams of MJ per week predicted worse performance on cognitive tasks, particularly those of executive function, including the Stroop Color Word Task and the Wisconsin Card Sorting Test (WCST). Specifically, more smoking episodes and grams per week predicted increased errors and lower accuracy. Higher urinary cannabinoid levels predicted fewer WCST categories and increased perseverative errors. MJ use patterns also predicted white matter alterations; higher amounts and more frequent MJ use predicted increased fractional anisotropy (FA), a measure of white matter coherence. Interestingly, once divided into early (MJ prior to age 16) and late (MJ after age 16) onset groups, results indicated the relationship between FA and MJ use was driven entirely by the early onset group, suggesting a differential impact of MJ based on initiation of use.

Conclusions: Findings suggest that early exposure to MJ may result in a potential failure to prune unnecessary connections during neuromaturation. These data have implications for more efficient treatment options, as strategies may be individualized based on age of onset and current patterns of MJ use.
**Title:** Epigenetic factors can dysregulate the GABA cell phenotype in schizophrenia

**Keywords:** RNAi, GABA, HDAC1, Daxx, Translational

GABAergic dysfunction in schizophrenia (SZ) is associated with a marked decrease in the expression of GAD67 in interneurons found in the stratum oriens (SO) of sector CA3/2 of the hippocampus (HIPP). A microarray-based gene expression analysis of laser microdissected (LMD) human hippocampus has suggested that GABA neurons in the SO of CA3/2 may contain a network of differentially regulated genes that are involved in GAD67 regulation. Several of these genes may contribute to the highly significant decrease of GABAergic activity at the SO-CA3/2 locus in SZ. To validate the role of this network in GAD67 regulation, both in vitro and in vivo studies in which shRNAi and lentiviral vectors have been used to explore how changes in the expression of GAD67 may be influenced by two other genes, HDAC1 and DAXX, that have been specifically implicated in the proposed network could potentially influence the expression of GAD67. Toward this end, knockdowns of HDAC1 and DAXX expression were induced both in vitro (in HiB5 cells with a GABAergic phenotype) and in vivo (in GABA cells of the SO of CA3/2 following selective stereotaxic infusions of the vectors). Suppression of HDAC1 and DAXX expression was associated with a highly significant increase of GAD67 expression; however, neither gene was associated with changes in the expression of its respective co-repressor (i.e. DAXX or HDAC1, respectively). Viral vector knockdowns of both HDAC1 and DAXX did, however, induce significant changes in the expression of other putative GAD67 regulatory genes, such as Runx2 and PAX5. Taken together, these findings suggest that both HDAC1 and DAXX are components of a complex network of genes identified in GABAergic neurons at a key locus of the trisynaptic pathway where significant abnormalities have been observed in patients with SZ. HDAC1 and DAXX are known co-repressors of methylation reactions at CpG islands and may be contributing to transcriptional regulation of GAD67 expression. In summary, these experiments have provided validatory information suggesting that there is a complex network of interactive genes that play a complex role in both normal and abnormal GABA cell function in the hippocampus. Supported by MH MH077175, The Brain and Behavior Research Foundation (NARSAD), Takeda Pharmaceuticals and the William P. and Henry B. Test Endowment.

**Topics areas:** Bipolar, Psychotic disorders, Schizophrenia
**Original Research - Clinical**

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**Title:** Transdiagnostic Mediation: The Association Between Attentional Control, Rumination, And Clinical Symptomatology

**Keywords:** Attentional Control, Rumination, Depression, Anxiety, Mediation

**Background:** The National Institute of Mental Health’s (NIMH) Research Domain Criteria (RDoC) approach aims to delineate important transdiagnostic mechanisms underlying symptomatology across various clinical disorders. In the study of depression and anxiety, attentional control and rumination are two transdiagnostic constructs of note and furthermore, have been well connected in extant literature. Deficits in attentional control have been hypothesized to underlie rumination, suggesting that the relationships between attentional control and depression or anxiety symptoms may be mediated in part by rumination. However, no study to our knowledge has attempted to examine these constructs transdiagnostically in a mediational model. Clarification of how attentional control and rumination may give rise to anxiety or depression symptoms can improve our understanding of these disorders of emotion regulation and inform existing/future interventions (e.g., neurocognitive/neurotranslational interventions).

**Methods:** Forty-two adults presenting for treatment at a psychiatric hospital completed measures of self-reported attentional control, rumination, and depression and anxiety symptoms. An ordinary least squares (OLS) path analysis-based approach using 95% bias-corrected bootstrap confidence intervals was employed to test whether indirect (i.e., mediating) effects were significantly associated with these outcomes. Separate mediation models for depression and anxiety symptoms were tested along with a reverse mediation model using attentional control as a proposed mediator.

**Results:** The relationship between attentional control and clinical symptomatology (i.e., both depression and anxiety symptoms) was mediated by rumination. Lower attentional control was associated with more rumination and consequently more severe symptoms of depression and anxiety. Attentional control did not, however, mediate the relationship between rumination and depression or anxiety symptoms.

**Conclusion:** Attentional control appears to impact depression and anxiety symptoms through rumination. These results suggest two possible pathways for intervention: attempting to improve attentional control in order to reduce the ruminative processes that contribute to depression and anxiety symptoms or more directly intervene with rumination. If deficits in attentional control do play a causal role in ruminative processes though, interventions solely targeting rumination may be insufficient. Examining the stability of this mediational relationship over time (and in the face of targeted interventions) can improve our understanding of how attentional control, rumination, and clinical symptomatology are connected.

**Topics areas:** Anxiety, Depression
Title: Spirituality and religiosity among individuals receiving substance abuse treatment.

Keywords: spirituality, religion, addiction, substance, abuse

Background Numerous studies suggest that spiritual and religious (S/R) involvement has a generally protective impact on the incidence and severity of substance use disorders (SUD). We conducted this cross-sectional study of inpatients on a substance abuse treatment unit in order to examine associations between S/R and core features of addiction and to assess level of interest among patients for the integration of S/R principles in their substance abuse treatment and recovery.

Methods Among individuals admitted to McLean Hospital for acute inpatient detoxification, we conducted a survey on the importance of S/R using validated self-report measures. Data collection is ongoing, with 101 surveys completed to date. Participants were asked questions about the importance of S/R in their lives, the degree to which they would like S/R incorporated in their treatment, and the frequency of using S/R to cope with stress.

Results Forty-two percent of the sample reported that spirituality is at least moderately important in their life; however, only 26% reported that religion is moderately or very important in their life. Forty-five percent of respondents indicated they would like to include spirituality in their treatment at least moderately. Results of a linear regression model indicated that importance of religion was the weakest predictor of self-reported importance of spirituality in mental health treatment relative to the importance of spirituality, belief in God, and engagement in a religious community. Positive religious coping (i.e., the use of religion to cope with distress in psychologically adaptive ways) was associated with less craving ($r=-.25$, $p<.05$), more self-help meetings attended ($r=.21$, $p<.05$), and greater engagement in self-help activities ($r=.24$, $p<.05$).

Conclusion S/R may modify the course of substance abuse treatment through its potential impact on craving and engagement in self-help activities. Although almost half of participants reported that it is important to them to include S/R in their treatment, many did not report that religion was important in their life. Providers should consider the relevance of spirituality in treating individuals with SUD who may not necessarily identify with a particular religion.
Marijuana (MJ) is predicted to become a multi-billion dollar industry in the United States within the next five years. Currently twenty-three states and the District of Columbia have legalized medical MJ, while four of these (Colorado, Washington, Oregon, and Alaska) have also approved recreational use. Recent statistics also show that MJ use is on the rise, particularly amongst the nation’s teens and emerging adults, raising serious public health concerns given the potential deleterious effects of MJ on the developing brain.

In order to study the impact of early onset MJ use on the frontal/executive system of the brain, we examined 50 chronic, heavy MJ smokers divided into early onset (regular MJ use prior to age 16; n=24) and late onset (regular use at age 16 or later n=26). We also examined 34 healthy, non-MJ smoking control participants who were well matched for age and IQ. All participants completed a modified Stroop Color Word task while undergoing functional magnetic resonance imaging (fMRI) and completed the Barratt Impulsiveness Scale (BIS-11).

Results showed that relative the control group, MJ smokers exhibited significantly poorer performance on the Interference subtest of the Stroop, reported significantly higher levels of impulsivity on the BIS-11, and demonstrated altered patterns of brain activation in the anterior cingulate cortex (ACC). Further analyses suggested these alterations were primarily attributable to those with early onset, as this group exhibited poorer performance (lower percent accuracy and higher omission and commission errors) relative to both controls and late onset smokers. No significant differences, however, were noted between the late onset smokers and controls. Interestingly, early onset smokers also reported using MJ nearly twice as often (smokes/week) and over 2.5 times as much (grams/week) as their late onset counterparts. Further, regression analyses indicated that earlier age of MJ onset, as well as increased frequency and magnitude of MJ use were predictive of poorer Stroop performance. fMRI results extended these findings, revealing that the while the late onset smokers exhibited a pattern of activation similar to the control subjects’ in the posterior ACC, a markedly different pattern of activation localized to the anterior cingulate was evident in the early onset group.

Taken together, results suggest that individuals with earlier MJ onset may collectively have an “additive vulnerability” – a relatively immature brain that is neurodevelopmentally susceptible to the impact of MJ exposure compounded with an increased likelihood of using MJ in higher amounts and with greater frequency than those with later exposure. These findings underscore the importance of assessing age of onset of MJ use as well as patterns of MJ use in future research, and highlight the need for early identification and intervention among our nation’s youth, as early exposure to MJ may result in enduring neurocognitive and neurobiologic alterations.
Title: Lack of face selectivity for putative neural markers of face processing in schizophrenia: Converging evidence from ERP and fMRI responses during face detection

Keywords: schizophrenia, face detection, fusiform face area, fMRI, ERP

Faces are a sui generis stimulus class that conveys key information for social interaction. Face detection, an ability to identify a visual stimulus as a face, is impaired in patients with schizophrenia. While this perceptual deficit may contribute to patients’ poor social functioning, its underlying brain mechanisms are not well understood. Previous MRI studies have shown that patients have altered structure of brain regions subserving face perception such as fusiform gyrus, but functional responses of these regions to face images appeared to be normal. Previous event-related potential (ERP) studies showed lower amplitudes of face-evoked responses such as N170 in patients. The face processing system possesses a key functional property - face selectivity - that has seldom been examined in schizophrenia.

In this study, we examined temporal dynamics (using ERP) and spatial locus (using fMRI) of face selectivity in medicated schizophrenia patients (n=19) and healthy controls (n=18). Specifically, we measured and compared N170 responses, a putative temporal neural marker of face processing, with BOLD responses in fusiform face area (FFA), a putative spatial neural marker of face processing, during face detection and tree detection.

For controls, N170 amplitudes were significantly greater for faces than trees across all three visual salience levels tested (manipulated using contrast at perceptual threshold, two times perceptual threshold and 100%). For patients, however, N170 amplitudes did not differ between faces and trees. This pattern of result indicates reduced face selectivity (indexed by the difference in response to face vs. non-face stimuli) on the N170, mirroring a finding of our recent fMRI study (to be also presented in this conference). In controls, significant correlations between N170 and BOLD signal in FFA were found for faces, but not for trees. In patients, no significant correlations between N170 and FFA activation were found for either faces or trees.

These ERP and fMRI results provide converging evidence for a lack of face-selectivity in spatial and temporal responses of putative brain machinery for face processing in patients with schizophrenia. This neuroimaging finding suggests that face processing should be specifically targeted during the remediation of social functioning in schizophrenia.
**Identifying Neural Predictors of Adolescent Depression**

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Adolescent major depressive disorder (MDD) is a major public health concern (Birmaher et al., 2002; Greden, 2001), and despite the increasing prevalence of depression in youth (Merikangas et al., 2010), the neurobiological mechanisms underlying adolescent MDD remain largely unknown.

Previous research indicates that depressed adolescents may be characterized by blunted neural responsiveness to reward (Forbes et al., 2009; Gotlib et al., 2010), and consistent with the diathesis-stress perspective, it is believed that stress may elicit reward-related deficits (Auerbach et al., 2014). While the majority of research has examined currently depressed adolescents, this approach is unable to determine whether reward dysfunction is a cause or effect of depression. Thus, research is needed to identify whether these reward-related deficits, particularly in the context of stress, prospectively predicts depression onset.

In the current study, healthy low- and high-risk (i.e., with a maternal history of MDD) female adolescents aged 12-14 years, completed a reward task (i.e., monetary gain vs. loss) under stress- and no-stress conditions while fMRI data were collected (target sample: low-risk = 20 and high-risk = 20). Preliminary findings in the post-stress paradigm demonstrate that compared to high-risk adolescents (n = 7), low-risk adolescents (n = 17) exhibit increased activation in the right putamen in response to monetary rewards (x = 26, y = -4, z = -2; cluster size = 31; p < 0.05 small volume correction – sphere diameter of 8mm – voxel threshold = 15). These findings suggest potential differences in reward valuation, which may have important implications for the onset of depressive symptoms. Results from the current study are expected to advance our understanding of neurobiological mechanisms that prospectively predict depressive disorders in youth.
Previous studies provide significant experimental evidence for the role of pituitary adenylate cyclase-activating polypeptide (PACAP)-mediated signaling in regulation of anxiety in both experimental animals and human subjects. It has been demonstrated that PACAP may regulate anxiety-related behaviors through its actions in two interacting brain regions, the amygdala and BNST. However, synaptic and network mechanisms of PACAP-mediated effects in the brain are poorly understood. Recently, we started addressing specific questions about the nature of PACAP-induced synaptic and network-level modifications in BLA-BNST circuits, possibly contributing to control of anxiety states. We expressed the photosensitive protein, channelrhodopsin-2 (ChR2), under control of the neuron-specific promoter CaMKIIα in BLA neurons and photostimulated corresponding fibers synapsing on neurons in two BNST subdivisions, ovBNST and adBNST, known to regulate anxiety in opposite directions—activation of ovBNST was shown to induce anxiety, whereas activation of adBNST is anxiolytic. Consistent with our finding that PACAP is expressed in ovBNST only, we found that PACAP potentiated excitatory synaptic responses at inputs to ovBNST but not at inputs to adBNST, selectively increasing the synaptically-driven spike output of ovBNST neurons in response to activation of projections from the BLA. The enhanced firing of ovBNST neurons would result in inhibition of adBSNT, since ovBNST neurons, projecting to adBNST, are GABAergic. We hypothesize that neuropeptide PACAP may contribute to regulation of anxiety states by differentially affecting synaptic efficacy at BLA projections to different BNST subdivisions, and, therefore, modifying the signal flow in BLA-ovBNST-adBNST circuits in such a way that adBNST is inhibited. This would explain the ability of PACAP in BNST to trigger anxiety, as direct optogenetic inhibition of adBNST was shown to be anxiogenic.
The role of nuclear HDAC5 in cocaine addiction behavior

The transition from cocaine use to abuse is a poorly understood phenomenon. Extensive evidence in the literature suggests that this transition to abuse may be mediated by changes in nervous system structure and function, including chromatin remodeling and epigenetic mechanisms. Recently, we reported that cocaine administration induces transient nuclear accumulation of the class IIa histone deacetylase, HDAC5, which functions to limit the development of cocaine reward behavior. Furthermore, the nuclear accumulation of HDAC5 in a key reward region, the nucleus accumbens (NAc), was sufficient to attenuate cocaine reward. We sought to explore the role of nuclear HDAC5 on the NAc in a model with high face validity for cocaine addiction, the self-administration model. For this purpose, we have developed adeno-associated virus (AAV) that express either the wild type (WT) form of the protein or a nuclear mutant full-length HDAC5. Targeted over-expression into the NAc revealed an attenuating role for nuclear HDAC5 in cocaine prime-dependent reinstatement behavior. This effect appears to be unique to primed-reinstatement as cue-dependent and stress-dependent reinstatement remains unchanged from controls. Furthermore, we observe no differences across groups during extinction of lever pressing in the absence of cocaine. These findings suggest that nuclear HDAC5 acts by reducing the rewarding properties of cocaine, and ongoing studies are testing whether the nuclear, dephosphorylated HDAC5 reduces sensitivity to cocaine. The downstream mechanisms by which HDAC5 suppresses cocaine reward and prime reinstatement is not yet clear, but we observe that nuclear, dephosphorylated HDAC5 dramatically suppresses MEF2-dependent gene expression, and our HDAC5 ChIP-seq findings indicate that HDAC5 associates with genomic DNA predominantly in regions containing MEF2 consensus binding sites. Together, our findings begin to elucidate the key roles and regulation of HDAC5 in cocaine addiction-relevant behaviors.
Most people experience unwanted intrusive thoughts, often in the form of an image (Clark & Rhyno, 2005). These images usually interrupt the flow of thoughts, and trigger emotions such as anxiety or shame. The clinical significance of these intrusive images depends on how they are appraised (for example, if the person believes that the image carries some negative meaning about himself or other people) (Clark & O’Connor, 2005). The person may then resort to compulsive and/or neutralizing strategies, such as repeating words mentally and suppressing the image. Over time, such reactions may actually maintain the intrusive images, which can develop into clinical obsessions (e.g., Clark & Beck, 2010). This process has mostly been researched in the context of how obsessive compulsive disorder (OCD) develops and is maintained. However, intrusive images are common across mental disorders (see e.g., Brewin et al., 2010). Interestingly, reactions to these images have not yet been systematically researched outside of the obsessive compulsive spectrum. We hypothesize that the same general process applies across mental disorders; some individuals will appraise intrusive images in a negative way (e.g., as threatening), which will lead to neutralizing and compulsive strategies. These compulsive strategies may then maintain the intrusive images, leading them to develop into clinical obsessions, similar in form (although different in content) to OCD-specific obsessions. In the current project, we first assess the frequency of intrusive images among patients suffering from a variety of psychopathology. Next, we take initial steps toward determining whether the patients respond to their most current intrusive image with compulsive and neutralizing strategies. The current ongoing research study is being conducted among patients of the McLean Behavioral Health Partial Program. Advanced clinical graduate students assessed patients with structured clinical interviews (Mini International Neuropsychiatric Interview (MINI); Body Dysmorphic Disorder Diagnostic Module (BDD-DM)), and conducted an Imagery Interview; which is based on earlier clinical interviews assessing imagery (see e.g., Hackmann et al., 2000), but adapted to the present study by focusing more specifically on appraisal and reactions to intrusive images. Fifteen patients consented to the study and were assessed with the Imagery Interview, and twelve completed the MINI. Eight out of twelve patients had current major depressive disorder (MDD), two had bipolar I disorder and one had bipolar II disorder, four had social anxiety disorder (SAD), one had obsessive-compulsive disorder (OCD), two had post-traumatic stress disorder (PTSD), one had panic disorder and one panic disorder with agoraphobia. Eleven out of fifteen patients (73.3%) reported having recurrent intrusive images in the past six months. Those eleven patients all reported appraising the images as having some negative meaning about themselves, other people, or the future. Of those eleven patients, six (54.5%) reported one or more compulsive behaviors (e.g., comparing oneself to others) and ten (90.0%) reported one or more neutralizing behaviors (e.g., thought suppression) in response to the image. These preliminary findings indicate that intrusive images along with compulsive behaviors and/or neutralization strategies are common among partial hospital patients with a variety of psychiatric diagnoses.
Program Description | Division: Psychotic Disorders Division

Presenting Author: Kirsten Bolton, Program Director for McLean OnTrack, LICSW, McLean Hospital

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Title: Program Description: McLean OnTrack

Keywords: Psychosis, First episode, Schizophrenia, Bipolar psychosis, Recovery

OnTrack specializes in the early recognition and treatment of both affective and non-affective psychosis for adults ages 18-30 and is one of the few clinics in the United States to address the unique needs of people experiencing a first episode of bipolar disorder. We build trusting and collaborative relationships with patients and family members in a caring and supportive environment in order to achieve the best possible outcomes. We believe that the years immediately following the first episode of psychosis represent a critical period, and that early intervention is important to minimize risk of future episodes, to provide coping skills and to change the overall trajectory of participants’ lives. We seek to empower program participants to acquire the stability, resources, and skills necessary to live fully and productively. We formulate treatment plans around the needs of each individual and family, while incorporating methods of best practice in the area of first-episode psychosis. We strive to integrate the latest technological advances into our clinical care and to use technology to help us stay engaged with our young adult demographic. Our clinical team is interdisciplinary, and comprises social workers, nurse practitioners, psychiatrists, and psychologists. We offer individual psychotherapy and psychopharmacology, family counseling, group therapy for patients and their family members, nutritional counseling, peer support and in-home therapy and case management. We invite every patient in the clinic to participate in research where we study brain abnormalities in early psychosis using clinical, MRI, EEG, cognition, genetics and related approaches. The long term goal is to identify abnormalities which we can correct through novel interventions, leading to better outcomes for our patients. In the end, we believe that our approach will help de-stigmatize mental illness by empowering those afflicted to not fall off track and to lead successful lives.
Original Research - Clinical

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Title: Social Trauma Among Patients in a Partial Hospital Program

Keywords: Social trauma, appraisal, social anxiety disorder

Trauma has mostly been researched in the context of post-traumatic stress disorder (PTSD) and is currently defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2013) as: “Exposure to actual or threatened death, serious injury, or sexual violence” (p. 270). However, trauma may be too narrowly defined in the DSM-5, and there may be other kinds of clinically significant trauma, such as social trauma (see e.g., Carleton et al., 2011). Erwin et al. (2006) found that more than one third of individuals with social anxiety disorder (SAD) met diagnostic criteria for PTSD in relation to a negative social event. Research suggests that the perception and appraisal of the negative social event (but not the event itself) increases the subsequent risk of SAD (Levinson et al., 2013). These findings are consistent with cognitive models of PTSD, which posit that appraisals of traumatic events are more influential in PTSD development than the events themselves (Ehlers & Clark, 2000).

The present ongoing study examines social trauma among patients of the McLean Behavioral Health Partial Program. Advanced clinical graduate students performed structured clinical interviews (Mini International Neuropsychiatric Interview (MINI); Body Dysmorphic Disorder Diagnostic Module (BDD-DM)) and conducted an Imagery Interview which is based on clinical interviews assessing imagery (Hackmann et al., 2000), but adapted to focus specifically on social trauma. Patients also completed the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999), which measures appraisal of traumatic experiences (in this study: of the socially traumatic event).

The MINI was administered to ten out of the twelve patients who were assessed for a history of social trauma. Out of the ten participants, seven had current major depressive disorder, one had bipolar I disorder, one had bipolar II disorder, four had SAD, one had obsessive-compulsive disorder, two had PTSD, one had panic disorder, and one had panic disorder with agoraphobia. Eleven out of twelve patients (91.7%) reported having experienced social trauma (e.g., severe bullying). PTCI scores for patients with a history of social trauma in the present study are similar to those that have been reported by PTSD patients in response to traumatic events (Foa et al., 1999), especially on the subscales of Negative Cognitions about the Self (e.g., “My life has been destroyed by the trauma”) and Self-Blame (e.g., “The event happened because of the way I acted”). Ten out of eleven patients (90.9%) reported appraising the event as having some negative meaning about themselves, other people, or the future. Logistic regression analyses indicate that higher scores on the subscales of Negative Cognitions about the Self and Negative Cognitions about the World (e.g., “People can’t be trusted”) increased the likelihood of a SAD diagnosis.

These preliminary findings indicate that social trauma is common among patients in a partial hospital program and that most patients appraise the events negatively, similar to the appraisal process that occurs in the development of PTSD. Finally, negative cognitions about the self and about the world following a socially traumatic event may predict the development of SAD.
Title: Associations between childhood trauma and grit among inpatients with substance use disorders

Keywords: Addiction, Trauma, Childhood, Grit

Background: Adverse childhood experiences involving traumatic physical and sexual abuse have been associated with posttraumatic stress disorder, substance abuse, depression, poor impulse control, and anxiety sensitivity (Anda et al. 2006, Heim et al. 2008, Martin et al. 2014, Nader et al. 1994, Roesler et al. 1994, Yehuda et al. 2001). Because of trauma’s well-documented effects on anxiety sensitivity and impulse control-factors that can impede the sustained pursuit of long-term goals—we hypothesized that childhood trauma impairs grit, which is defined as perseverance and sustained interest in the pursuit of long-term goals (Duckworth et al. 2007). However, the association between childhood trauma and grit has not yet been examined.

Aims: The aims of this study are (1) to determine whether childhood trauma is associated with grit and (2) to identify additional patient characteristics associated with grit.

Methods: This study was conducted in a 17-bed inpatient detoxification unit. 335 participants completed self-administered questionnaires, including the Short Grit Scale (Duckworth & Quinn 2009). Predictor variables included age, gender, race, primary substance of abuse (alcohol vs. opioid), and responses to the Childhood Trauma Questionnaire (CTQ; Bernstein et al. 1994). Scores on the CTQ were scored dichotomously based on clinical cutoff scores (as defined by Walker et al. 1999). Differences in clinical and demographic characteristics were determined through t-tests and chi-square tests. The association between CTQ and grit was tested through linear regression analyses.

Results: 40.8% of the sample reported experiencing childhood physical abuse, and 20.6% of the sample reported experiencing childhood sexual abuse. CTQ physical abuse was associated with grit when controlling for gender, age, race, and primary drug of abuse (b=-0.12, t(5)=-2.09, p<.05; adjusted R2=0.06, F(5)=4.71, p<.001), however sexual abuse was not associated with grit. Age, race, gender, and primary substance of abuse were not associated with childhood physical or sexual abuse. While grit scores did not vary by race (95.7% white), some patient characteristics in addition to childhood trauma were significant and associated with grit. Older age was correlated with higher total grit score (r=0.20, p<0.001). Participants with alcohol as their primary substance of abuse had higher grit scores on average than participants with opioids as their primary substances of abuse (means=3.2 versus 3.0, t(315)=-3.07, p<0.01). Among women, childhood trauma was not associated with grit; however, among men, those who reported physical abuse had significantly lower grit scores than those who did not (means=3.2 versus 3.1, t(223)=2.04, p<0.05).

Conclusions: There is a modest association between physical abuse during childhood and grit, which suggests that childhood trauma may be a risk factor for lower grit. Given important recent findings suggesting that the association between childhood trauma and later adverse outcomes (e.g., high risk behaviors, depression) is modulated by the age at which the trauma occurs, future studies including the age of the traumatic event will be important to better understanding the association between childhood trauma and grit.
Title: Predictors of Suicidality among Patients with Psychotic Disorders in a Partial Hospital Treatment Program

Keywords: Psychotic Disorders, Suicidality

Introduction: Individuals with psychotic disorders are at increased risk for suicidality. It is estimated that 9.2% of psychiatric suicides are related to psychotic disorders (Arsenault-Lapierre, Kim, & Turecki, 2004). With such a high prevalence, predicting who is most at risk among patients with psychotic disorders is a pressing issue. The current study investigated predictors of suicide risk among patients diagnosed with psychotic disorders who were attending a partial hospital program.

Methods: Demographic and clinical characteristics were compared in partial hospital patients with psychotic disorders (n=259) reporting either high or low suicidality. Suicidality was assessed using the suicide section of the Mini Neuropsychiatric Interview. Patients who scored in the “moderate” or “high” range on the MINI suicidality module were considered to have significant suicidality. Clinical and demographic characteristics were assessed with self-report questionnaires. The questionnaires included a demographics form to collect information on gender, age, ethnicity, race, employment status, and education. The Center for the Epidemiological Studies of Depression-10 (CES-D-10), a brief instrument for measuring symptoms of depression, and the Behavior and Symptom Identification Scale (BASIS-24), a 24-item survey measuring symptoms experienced within the last week, were also administered. Potential predictors included gender, age, race, married, employment, education, prior hospitalization in the last six months, baseline levels of depression severity, relationship functioning, substance abuse, emotional stability, and psychotic symptoms.

Results: Among participants, 116 (44.8%) were classified as high risk on the suicidality section of the Mini Neuropsychiatric Interview, and 143 (55.2%) were considered low risk. Bivariate analyses revealed that patients classified as high risk demonstrated greater depression severity, more relationship difficulties, greater emotional lability, and more substance use problems. A logistic regression model indicated that substance use was the most powerful predictor of higher levels of suicidality.

Conclusion: Monitoring and intervention for substance use should be targeted as a particularly important aspect of treatment for acutely ill patients diagnosed with psychotic disorders. Future studies should extend this work to look longitudinally at the effects of suicidality predictors on actual suicide attempts and gestures as well as examine a more ethno-racially diverse sample.
Reward processing plays a major role in the development and maintenance of addictive disorders (Blum et al., 2000; Versace et al., 2001). Specifically, chronic drug users simultaneously overvalue drugs of abuse while undervaluing more natural rewards such as food, money, and sex (Volkow et al., 2010). While this is a well-known phenomenon, it is unclear whether there is a direct link between the desire to use a drug and blunted reward responsivity for other reinforcers. Such a link may suggest a more nuanced relationship between the subjective experience of craving and disrupted reward processing in addiction.

To test this relationship, 30 nicotine-dependent smokers and 25 age and sex matched non-smokers completed study procedures at McLean Hospital. All smokers met DSM-IV criteria for current nicotine dependence, verified by the Fagerström Test for Nicotine Dependence (FTND). Smokers reported smoking > 10 cigarettes daily in the past 6 months, and had an expired air carbon monoxide (CO) of > 10ppm at screening. Non-smokers reported smoking <5 cigarettes in their lifetime. All participants were otherwise healthy and met no other current or lifetime DSM diagnoses. Study measures included the probabilistic reward task (PRT: Pizzagalli et al., 2005), which assesses participants’ ability to modulate behavior as a function of monetary rewards through a differential reinforcement schedule, and the Questionnaire of Smoking Urges-brief (QSU; Cox, Tiffany & Christen, 2001) to measure cigarette craving. For the smoking group, all measures were completed 4 hours since they had smoked a cigarette. Independent samples t-tests were used to compare PRT task performance between nicotine-dependent individuals. Further, correlations between PRT task performance and QSU scores were examined within the smoking group.

There were no significant differences between smoking and non-smoking groups on reward responsivity during the PRT, indicating that, on average, sated smokers and controls have equivalent sensitivity to monetary rewards. Within the nicotine-dependent group, however, reward responsivity was negatively correlated with craving (r= -.397, p= .03, two tailed). There were no relationships between reward responsivity or craving and variables associated with smoking history including expired CO and lifetime smoking use.

Collectively, these results confirm a relationship between heightened craving and blunted reward responsivity to an additional class of non-drug reinforcer. These findings support the hypothesis that the desire for drugs occurs at the expense of other rewards. Thus, drug cessation treatments may benefit from attending to these processes simultaneously, instead of focusing solely on craving amelioration.
Background: Transgender and gender non-conforming individuals face many disparities in the delivery of healthcare. This population faces a disproportionate rate of psychiatric comorbidity, including suicide attempts, that can necessitate inpatient psychiatric care. At the same time, many transgender people are apprehensive about receiving mental health care due to psychiatry’s complicated, and not always supportive, position with regards to gender identity.

Clinical Challenge: The inpatient care of transgender patients presents challenges related to varying levels of staff cultural competence, complex team dynamics, and unforeseen practical considerations in accommodating unit and patient needs. A paucity of research exists to help guide inpatient clinicians and administrators in providing care for this vulnerable and underserved population.

Discussion: This poster reviews key vocabulary and major concepts in transgender mental health. It describes common challenges that arise in the inpatient care of this population. We propose recommendations for the inpatient management of transgender patients based on current treatment guidelines. These will include suggestions for initial assessment, addressing administrative challenges, and ways in which interdisciplinary staff can be united in their approach to care. We identify areas for potential research that would guide the care of this patient population.
Identifying effective pharmacological treatments for polydrug (cocaine/heroin) abusers has proven to be a challenging goal. Noradrenergic alpha-2 agonists may provide one approach for managing polydrug addiction. Two alpha-2 agonists, lofexidine and clonidine, currently are used for alleviating symptoms of opioid withdrawal in humans; other studies suggest that these agonists may prevent drug-cued relapse in animal models. Here we evaluated the ability of three noradrenergic alpha-2 agonists—clonidine, lofexidine and guanfacine—to counter the effects of cocaine/heroin mixtures using drug discrimination and self-administration procedures in squirrel monkeys. Results of drug discrimination studies show that acute treatment with lofexidine, but not clonidine or guanfacine, moderately attenuated discriminative-stimulus effects of a cocaine/heroin mixture. Subsequent ‘choice’ self-administration studies (food vs. drug) indicate that daily treatment with relatively high doses of clonidine (0.1-0.18 mg/kg) can reduce the number of self-administered drug injections but does not consistently alter the reinforcing strength of the cocaine/heroin mixture. In preliminary experiments, acute lofexidine pretreatments (0.18-1.8 mg/kg) also produce a dose-dependent decrease in polydrug intake that, based on time course studies, is evident for up to four hours after treatment. Studies of how chronic treatment with lofexidine modifies the self-administration of a cocaine/heroin mixture are ongoing. The present results suggest that clonidine and lofexidine can decrease the intake of a polydrug mixture without altering its reinforcing strength, perhaps reflecting the sedative properties associated with alpha-2 agonists. The translational value of these actions for the clinical management of polydrug abuse remains to be determined.
**Original Research - Clinical**

**Presenting Author:** Jennifer Buchholz, Clinical Research Assistant II, Anxiety and Traumatic Stress Disorders Lab (CDASR)

**Co-Author(s):** Demers LA, Crowley DJ, Fukunaga R, Rosso IM

**Title:** Anxiety Sensitivity Correlates with Left Anterior Insula Volume in Posttraumatic Stress Disorder

**Keywords:** Posttraumatic stress disorder, Insula, Anxiety Sensitivity, Magnetic Resonance Imaging

**Introduction:** The Anxiety Sensitivity Index (ASI) measures a dispositional trait involving fear of anxiety-related sensations, a vulnerability factor for anxiety disorders including posttraumatic stress disorder (PTSD). Functional imaging studies have found ASI scores to be positively associated with activity in the anterior insula, a region known to play a critical role in conscious interoceptive awareness. Moreover, morphology findings specifically implicate anterior insula abnormalities among various anxiety disorders. Despite such reports, there is little research examining insula morphology as a potential neural correlate of anxiety sensitivity (AS) in PTSD. To better understand this relationship, we investigated whether ASI scores were correlated with insula volume among adults with PTSD and healthy participants.

**Methods:** Twenty-three right-handed adults with PTSD (8 male) and 26 healthy control subjects (11 male) ranging in age from 20-60 years completed structured clinical interviews and the ASI, and underwent 3T magnetic resonance imaging. Correlation and regression analyses examined ASI scores relative to anterior and posterior insular cortex volumes between and within subject groups.

**Results:** Groups did not differ significantly in ASI scores, intracranial volume, or insula volumes (p > .05). Total ASI scores were significantly correlated with left anterior insula volume in the combined sample (r(42) = .5, p = .001) and the PTSD group specifically (r(18) = .62, p = .004), but not in the control group (p > .05).

**Conclusions:** These findings are consistent with a role of the anterior insula as a neural correlate of AS in PTSD. They add to evidence of transdiagnostic commonalities in the neurobiology of AS, and motivate future research exploring the relationship of AS with the anterior insula in anxiety- and stress-related disorders.
A number of traits associated with schizophrenia aggregate in relatives of schizophrenia patients at rates much higher than that of the clinical disorder. These traits, considered candidate endophenotypes, may be alternative, more penetrant manifestations of schizophrenia risk genes than schizophrenia itself. Performance on the antisaccade task, a measure of ability to inhibit prepotent responses, is one of the most widely studied candidate endophenotypes. However, there is little consensus on whether poor antisaccade performance is a true endophenotype for schizophrenia. Some studies comparing the performance of healthy relatives of schizophrenia patients (RelSZ) to that of normal controls (NC) report that RelSZ show significantly more errors, while others find no statistically significant differences between the two groups. A recent meta-analysis of these studies noted that some studies used stricter exclusion criteria for NC than RelSZ and found that these studies were more likely to find significant effect sizes (Levy et al. 2004). Specifically, NC in these studies with a personal or family history of psychopathology were excluded, whereas all RelSZ, including those with psychotic conditions, were included. In order to determine whether a difference in antisaccade performance between NC and RelSZ remains after controlling for differences in psychopathology, we fit a binomial regression model to data from an antisaccade task. Linear contrasts were used to carry out “symmetric” (RelSZ compared to NC with similar personal histories of psychopathology) and “asymmetric” (RelSZ compared to NC with no personal history of psychopathology) comparisons. Only asymmetric comparisons yielded statistically significant differences in antisaccade error rates. We demonstrate that both personal psychopathology and familial history affect antisaccade performance.
Drug addiction is a chronic relapsing brain disease characterized by compulsive drug seeking and taking despite negative consequences to the individual. Over the past few decades, several key brain regions and potential molecular & cellular mechanisms that contribute to the synaptic and behavioral plasticity associated with drug-related behaviors have been discovered. However, further molecular and cellular mechanisms that mediate the development and persistence of drug dependence remain needed to be understood. Many studies report that epigenetic changes in gene expression are critical mechanisms that underlie several aspects of drug induced behaviors, including drug reward, behavioral sensitization, drug memory persistence and relapse-like behaviors. We, and others, have shown that the class IIa histone deacetylase, HDAC5, regulates multiple cocaine-related behaviors, including its ability to antagonize the development of cocaine reward behavior. In addition, HDAC5’s nuclear/cytoplasmic distribution in striatal neurons is regulated dynamically by cocaine administration. However the target genes or molecules by which HDAC5 regulates cocaine behaviors is not clear. To identify HDAC5 target genes in striatal neurons, we performed an unbiased genome-wide screen using the chromatin IP with deep sequencing (ChIP-seq). We found that HDAC5 associates significantly with ~900 genomic DNA regions, and the binding to these sites was regulated differentially by cAMP signaling. Putative target genes included transcription factors, ion channels, membrane/synaptic proteins, kinases and protein signaling molecules. Analysis of consensus transcription factor binding sites with in the HDAC5 binding peaks revealed that the majority contains consensus sequences for binding of MEF2 transcription factors, known binding partners of class IIa HDACs and the some for AP-1 transcriptional factor, a novel binding partner. ChIP-seq analysis identified an activity-dependent neuronal transcription factor, Npas4, as a HDAC5 target gene. Npas4 mRNA expression is induced by the depolarization in the cultured striatal neuron. Nuclear accumulated form of HDAC5 mutant limits Npas4-luciferase activity. The mice lacking HDAC5 exhibit higher Npas4 mRNA expression in the NAc in vivo. Cocaine exposure induces transient Npas4 mRNA expression in the NAc and delayed enrichment of HDAC5 on the Npas4 enhancer region in the mouse striatum in vivo. The mice lacking and knock-down Npas4 expression in the NAc exhibit deficit in the development of cocaine reward. Taken together, our finding reveal that Npas4 is a novel HDAC5 target gene and its role in development of cocaine reward.
Program Description
Presenting Author: Nicholas Yale, McL Research IS Site Manager, ERIS
Co-Author(s): Brent Richter, ERIS Director  Lisa Horton, Research Communications, Outreach & Education Coordinator
Title: Enterprise Research Infrastructure & Services (ERIS)
Keywords: technology, data, computing, software, computational

ERIS is the key division of Research Information Services & Computing (RISC) that serves as your partner in technology, data and computing. ERIS provides information services and computing resources to support basic, biomedical and clinical research missions at McLean Hospital. From data collection to data analysis tools, ERIS provides specialized services that fit the researcher's computing needs. Many of the services are shared across Partners HealthCare and available at no cost. To provide flexible and customized solutions, ERIS operates the Research Computing Core Facility. The Core is the fee-for-service division that offers custom systems development and consulting, data storage, data backup, academic software licenses, and security documentation services to researchers at below market rates. ERIS works to bring tools like Syncplicity, the enterprise online file-sharing service that provides secure and automatic file synchronization, mobile access and sharing, to the community. Syncplicity is approved for research and external collaboration at McLean Hospital and across Partners. ERIS supports the Apple and Mac community through the Partners Enterprise Apple Support (PEAS) Program. Once your Mac is enrolled in PEAS, you can download Microsoft Office, other software and resources directly from the Self Service Application. Stop by the ERIS poster to review the resources available, ask questions and meet members of the team.
Growing evidence supports a role for circadian rhythm abnormalities in the pathophysiology of bipolar disorder (BD). Subjects with BD exhibit shorter circadian periods, and the most effective treatments, lithium and valproic acid, modulate expression of core clock proteins and lengthen circadian period. In addition, multiple genetic polymorphisms for core clock molecules have been associated with BD. Despite this evidence, little is known regarding how circadian rhythm abnormalities contribute to mood dysregulation in BD. Recent rodent work has reported that somatostatin (SOM), and neuropeptide-Y (NPY) neuropeptides with strong anxiolytic effects in the amygdala, are rhythmically expressed in the amygdala of mice and regulate anxiety-like behavior in a circadian manner. In human subjects, reports of altered levels of SOM in the cerebrospinal fluid of depressed subjects only in the early morning suggest that altered rhythm of SOM expression may be present in subjects with mood disorders.

We tested the hypothesis that SOM may be rhythmically expressed in the human amygdala, and that this rhythm may be altered in subjects with BD. Serial sections including the entire rostro-caudal extent of the amygdala from 15 BD and 15 control subjects were processed for immunocytochemical detection of SOM. Total numbers (TN) and numerical densities (ND) of immunoreactive (IR) neurons were measured in the lateral (LN), basal (BN), accessory basal (AB), and cortical (CO) nuclei using computer-assisted light microscopy. Time of death for each subject was used to analyze circadian expression of SOM-IR neurons. Stepwise linear regression models were used to test for the main effect of diagnosis together with a broad range of confounding factors. In control subjects, numbers of SOM-IR neurons plotted by time of death displayed a circadian rhythm, with a peak at 9 AM, antiphase to the rhythm reported in the mouse amygdala. In subjects with BD, this rhythm was reversed in comparison to control subjects, with a low point at 9 AM. SOM-IR neurons were found to be decreased selectively in the LN of BD (TN, p= 0.003; ND, p = 0.007), with a significant effect of time of death as a co-variate (p=0.02). This effect was driven by marled decreases of SOM-IR neurons in BD subjects who died in the morning. Our results show, for the first time, that the expression of SOM in the human amygdala changes according to a circadian rhythm, and that this rhythm is abnormal in subjects with BD. Together, these abnormalities may contribute to a disruption of circadian rhythms in BD, accompanied by marked anxiety and vulnerability to stress.
Borderline Personality Disorder (BPD) is characterized by emotional dysregulation, nonsuicidal self-injury, and suicidality (Paris, 2003). However, relative to mood and anxiety disorders, the pathophysiology of this debilitating disorder is not well understood. In the current study, we examined adolescents and young adults (healthy control (HC) = 30 and BPD = 30), aged 13-23 years. During the assessment, all participants were administered a diagnostic interview as well as self-report questionnaires (i.e., symptoms, rumination). Then, participants completed the emotional interrupt task (EIT; Mitchell et al., 2006) while EEG data were recorded. In the EIT, emotional images (pleasant, unpleasant, neutral) were presented for 1000 ms, followed by a target (left vs. right arrow) for 150 ms and then the same emotional image for 400 ms. Participants were instructed that they must correctly indicate the direction of the target over 120 trials. The task was designed to elicit the late positive potential (LPP) – a positive going event-related component (ERP) believed to index sustained encoding of information. The LPP is begins in parietal-occipital regions as early as 200-300 ms post-stimulus, and past research has demonstrated that LPP positivity is influenced by emotional valence (Weinberg and Hajcak, 2011). Preliminary findings across groups found greater LPP positivity for unpleasant stimuli. However, whereas healthy youth exhibited greater positivity for pleasant as compared to neutral stimuli, borderline youth showed no difference for neutral and pleasant stimuli. These results suggest that BPD youth may be differentially attending and encoding unpleasant stimuli, which may contribute to emotion dysregulation and associated self-injurious behaviors.
Emotion Processing Biases and Resting EEG in Depressed Adolescents

Keywords: depression, adolescent, neuroscience, electroencephalography

While theorists have posited that depression in adolescents is characterized by emotion processing biases (greater propensity to identify sad than happy facial expressions), findings have been mixed. Additionally, the neural correlates associated with putative emotion processing biases remain largely unknown. Thus, the aim of the current study was to identify emotion processing biases in depressed adolescents and to explore neural abnormalities related to these biases using resting electroencephalography (EEG).

In the present study, we examined depressed (n = 23) and healthy (n = 36) female adolescents aged 13-18 years. During initial assessment, participants completed a semi-structured diagnostic interview assessing Axis I psychopathology. Following initial assessment, participants completed a modified Facial Recognition Task in which participants viewed faces expressing basic emotional expressions (happy, sad, fear) across intensities ranging from 10% (low intensity) to 100% (high intensity). Participants viewed expressions in a pseudorandom order for 500 ms and were asked to identify, as quickly as possible, the correct emotion by pressing the corresponding key. Additionally, resting EEG data were recorded using a 128-channel EGI (Electrical Geodesics Inc.) system during 8 contiguous, 1-minute trials (4 eyes open, 4 eyes closed). Results suggest that relative to healthy youth, depressed adolescents are less accurate in identifying happy and more accurate in identifying sad. Additionally, low-resolution electromagnetic tomography (LORETA) analyses revealed that relative to healthy adolescents, depressed youth showed greater theta activity in areas of the left dorsolateral prefrontal cortex (DLPFC) (i.e., BA9 and BA46). Additionally, resting EEG and LORETA showed greater theta and alpha activity in depressed versus healthy adolescents, particularly in the left DLPFC (BA9 and BA46). Interestingly, theta and alpha activity were positively correlated, and such activity was negatively correlated with happy accuracy. These findings have important implications for identifying behavioral and neural markers associated with depression in adolescents.
**Original Research - Clinical | Division: Division of Alcohol and Drug Abuse, Division of Basic Neuroscience, Psychotic Disorders Division**

**Presenting Author:** Yunjie Tong, Instructor, OMG

**Co-Author(s):** Lia M. Hocke, Carolyn E. Caine, Blaise deB. Frederick, Rosemond A. Villafuete, Oscar G. Morales

**Title:** Monitoring brain activation of repetitive Transcranial Magnetic Stimulation by functional Near Infrared Spectroscopy

**Keywords:** rTMS, Near infrared spectroscopy, Major depression, Blood flow

**Introduction:** Repetitive Transcranial Magnetic Stimulation (rTMS) is used to treat patients with major depression. During treatment, high-frequency rTMS (10Hz) are delivered to the left dorsolateral prefrontal cortex, but the underlying mechanisms of action are unclear. Real-time imaging methods to measure brain responses during treatment are needed to gain insight into how rTMS alleviates depression symptoms. Functional Near-Infrared Spectroscopy (fNIRS) is a noninvasive optical imaging tool that is able to measure both oxy- and deoxyhemoglobin concentration changes (Δ[HbO], Δ[Hb]) at the cortex through the skull. fNIRS is well-suited for rTMS research due to its compatibility, matching spatial and temporal sensitivity, and adaptability. In this pilot study, we tested an fNIRS system for monitoring the brain response to rTMS treatment.

**Methods:** Brain activations have been observed at ipsi- and contra-lateral sites of rTMS treatment. To prevent any interference with the treatment, an rTMS-compatible fNIRS probe was made for the right DLPFC. During each 1-hr treatment session (4 sec of rTMS (10 Hz) followed by 14 sec rest is delivered to the left DLPFC repeatedly at 120% of the motor threshold), the fNIRS measured the Δ[HbO] and Δ[Hb] corresponding to high frequency rTMS at right DLPFC.

**Results:** Increased Δ[HbO] and decreased Δ[Hb] were observed at right DLPFC corresponding to each high frequency rTMS pulse train (i.e. 4s), indicating increased brain activation, blood flow, or both.

**Discussion:** In this pilot study we show that fNIRS can be used to monitor, in real-time, brain responses to rTMS treatment without interference. The results show increased blood oxygenation or blood flow during high frequency rTMS, demonstrating the feasibility of our methodology. These quantitative measurements illustrate the potential of fNIRS to shed light on the mechanisms by which rTMS alters the depressed brain both in the short-term (i.e. each session) and over long-term (i.e. multiple sessions).

**Topics areas:** Depression, Imaging, Psychotic disorders
Title: Anxiety sensitivity and barriers to quitting smoking among inpatients with substance use disorders

Keywords: Substance use disorders, Anxiety sensitivity, Smoking

Background and aims: Anxiety sensitivity, the fear of anxiety-related symptoms, is associated with barriers to quitting smoking in populations seeking treatment for nicotine dependence. However, anxiety sensitivity and barriers to quitting smoking have not been examined in a general substance use disorder population not seeking smoking cessation treatment. Given both the high prevalence of smoking and the presence of significant barriers to smoking cessation in substance use disorder populations, identifying potential contributors to quitting smoking is of particular clinical importance. The first aim of this study was to determine whether greater anxiety sensitivity was associated with barriers to quitting smoking in an inpatient substance use disorder sample. The second aim was to ascertain which of the three anxiety sensitivity subscales might be associated with barriers to quitting smoking, with the hypothesis that there would be an association with the physical and cognitive subscales but not the social subscale.

Methods: Smokers (N=208) receiving inpatient treatment for non-nicotine substance use disorders completed a battery of questionnaires, including the Anxiety Sensitivity Index-3, the Barriers to Quitting Smoking in Substance Abuse Treatment scale, the Fagerstrom Test for Nicotine Dependence, and the Craving Scale. Psychiatric diagnoses were collected from medical records. Linear regression models assessed the association between barriers to quitting smoking and anxiety sensitivity for the Anxiety Sensitivity Index-3 full scale and three subscales. The following characteristics were included as covariates: age, gender, marital status, nicotine dependence severity, presence of co-occurring psychiatric disorder, primary substance of abuse (alcohol vs. opiates), craving for the primary substance of abuse, and days of primary substance use.

Results: Higher scores on the Anxiety Sensitivity Index-3 were associated with more barriers to quitting smoking (B = 0.21, t(9) = 3.46, p<.01; adjusted R2 = 0.41, F(9) = 15.38, p<.001). Nicotine dependence severity (B = 0.48, t(9) = 8.05, p<.001), co-occurring Axis I disorder (B = 0.20, t(9) = 3.48, p<.01), craving for the primary substance (B = 0.17, t(9) = 2.52, p<.05), and age (B = -0.18, t(9) = -2.03, p<.05) were also associated with more barriers to smoking cessation. Contrary to our hypothesis, all three anxiety sensitivity subscales, including social, were associated with barriers to quitting smoking.

Discussion: In an inpatient substance use disorder sample, anxiety sensitivity was associated with barriers to quitting smoking and may be a risk factor for smoking cessation difficulty. Interventions to decrease anxiety sensitivity may be helpful for substance users attempting to quit smoking.
Title: Ultra-high resolution concurrent fMRI/NIRS mapping using a specially designed probe

Keywords: fMRI, NIRS, simultaneous, Ultra-high spatial resolution, Ultra-high temporal resolution

Introduction: Near-infrared spectroscopy (NIRS) has become increasingly popular to study brain functions as it is noninvasive, easy to use, highly adaptable, and low cost. However the spatial resolution is poor and putative neuronal signals are always contaminated by the blood signals from extra-cerebral layer [1,2]. To accurately localize the NIRS signal and understand the anatomical and physiological influences to the signal, we developed a special multimodal NIRS/fMRI probe. NIRS source-detector fibers were integrated into MR coils on a curved surface, enabling close contact between the probe and head. This coil can acquire high spatial resolution fMRI images (1.2x1.2x1.8mm) at ultrafast speed (2.5Hz/0.4TR), while simultaneously recording NIRS signals from the same area. We applied the probe in both resting state and mental task studies to dynamically map the NIRS signal with the fMRI with ultra high spatial and temporal resolution.

Methods: The 3D printed probe features 3 circular RF-coils, formed to the right frontal area of approximately 8x4.5cm with depth sensitivity of ~5cm. Integrated NIRS (6.25Hz) probes for deep (3-4cm source-detector distance) and shallow measurements (1cm source-detector distance) were integrated into the design. For comparison, peripheral measurements were also taken with NIRS. Measurements with the 3T (fMRI) and the ISS Imagent (NIRS) were acquired during resting state as well as 15 mins mental subtraction and rapid semantic task [2]. Two types of fMRI acquisition were performed; a high spatial resolution data on a broad field of view with 1.5s TR, and 5 consecutive stacked data sets (1.8mm x 5 for each stack) with a TR of 0.4s acquired using our previously described technique [3]. Outer volume suppression was used to limit the field of view. Data analysis was conducted in MATLAB (for NIRS) and FSL (for fMRI). FSL (FEAT) and in house Python software (RapidTiDe) [4] were used for localization of the focal activation detected by NIRS as well as fMRI.

Results: The high resolution multimodal acquisition allowed us to differentiate signals from the skin, skull, pial vessels and brain. The probe covered both task activation areas. Clear activation patterns below the probe for NIRS and fMRI were found. Short and long distance measurements of NIRS showed high involvement of the vasculature especially directly below the probes.

Original Research - Clinical  |  Division: Division of Women's Mental Health
Presenting Author: Thomas Weigel, Associate Medical Director, Klarman Eating Disorders Center; Assistant Director of Clinical Measurement, McLean Hospital; Instructor in Psychiatry, Harvard Medical School, McLean Hospital / Klarman Eating Disorders Center

Co-Author(s): Thomas Weigel MD  Jennifer Thomas PhD  Kamryn Eddy PhD  Casey Pierce  Mary Zanarini EdD  Garrett Fitzmaurice ScD  Alisa Busch MD

Title: Differences in eating disorder outcomes associated with co-occurring substance use and borderline personality during residential treatment for eating disorders

Keywords: anorexia, bulimia, eating, borderline, addictions

Background  Borderline personality and substance use disorders are common among individuals with eating disorders. Little research exists on whether these co-occurring conditions are associated with differences in eating disorder residential treatment outcomes. The goal of this study is to examine whether eating disorder outcome trajectories during residential treatment differ for patients who screen positive for these co-occurring disorders compared to those who do not.

Study Population and Methods  The Klarman Eating Disorders Center participates in the McLean Hospital Clinical Measurement Initiative (CMI). Using computerized software (REDCap), patients complete psychometrically validated self-report surveys that screen for alcohol and drug use disorders (AUDIT-C and DAST-10) and borderline personality disorder (MSI-BPD) on admission, and a survey of eating disorder symptoms (EDE-Q) completed on admission, every two-weeks and discharge. The study sample consisted of women admitted to residential treatment at Klarman between November 15, 2010 and September 16, 2014 (N=468), representing 84% of consecutive admissions during this period. Patients in the study cohort are grouped into 4 mutually exclusive categories. Those who screen: 1) positive for substance use disorder (alcohol or drugs) only, 2) positive for borderline personality disorder only, 3) positive for both, and 4) negative for both. Analyses will include longitudinal regression modeling that will examine differences in eating disorder outcome trajectories during 9 weeks of residential treatment for women in each of these groups.

Results  Early analyses find that 106 patients (22%) screened positive for a substance use disorder alone, 68 (14%) screened positive for borderline personality disorder alone, 93 patients (19%) screened positive for both and 219 (45%) screened negative for both.

Conclusion  More than half (51%) of patients in residential eating disorders treatment screened positive for a substance use disorder, borderline personality disorder, or both. Our analyses will identify whether there is an association between screening positive for one or both of these comorbidities and longitudinal residential eating disorder treatment outcomes. The results will be useful in identifying especially high-risk groups in need of specialized intervention.

Topics areas: Eating Disorders
Title: Evaluating the Psychoactive Effects of Endogenous Cannabinoids

Keywords: Anandamide, 2-arachidonoylglycerol, Fatty Acid Amide Hydrolase, Monoacylglycerol Lipase, Drug Discrimination

The discriminative-stimulus (SD) effects of CB1 ligands can be reproduced in mice by non-selective inhibition of the anandamide-(AEA-) and 2-arachidinoyl glycerol-(2-AG-) inactivating enzymes, respectively, fatty-acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL). Additionally, we have shown that nonselective FAAH/MGL inhibitors produce a CB1-like SD effect in squirrel monkeys. The present studies with selective and nonselective ligands [FAAH (URB597; AM2018), MGL (AM2036); and FAAH/MGL-mixed (AM2129)] were conducted to further evaluate the effects of FAAH and MGL inhibition in squirrel monkeys trained to discriminate the CB1 agonist AM4054 from vehicle (n=4). Results indicate that: 1) co-administration of selective FAAH- and MGL-inhibitors, but not FAAH- or MGL-selective inhibitors alone, produces CB1-related SD effects; 2) AEA, but not 2-AG, produces CB1-like SD effects after either FAAH or mixed FAAH/MGL inhibition; and 3) CB1 receptor antagonism effectively and blocks the CB1-like effects of combined FAAH/MGL inhibition; this effect was insurmountable. The present data strengthen the idea that complementary, but not individual, actions of the endocannabinoids AEA and 2-AG produce CB1-related SD, and perhaps subjective, effects in primate species.
**Original Research - Clinical | Division: Division of Basic Neuroscience**

**Presenting Author:** Manon Ironside, Clinical Research Assistant, B.S., McLean Hospital, Laboratory for Affective and Translational Neuroscience

**Co-Author(s):** Alexis E. Whitton, Michael T. Treadway, J. Eric Jensen, Amy Garabaugh, Thilo Deckersbach & Diego A. Pizzagalli

**Title:** Reward learning across the mood disorder spectrum

**Keywords:** Reward learning, Event-Related Potentials, Bipolar disorder, Major depression, Mania

**Background:** Approximately 60% of individuals presenting for treatment of bipolar depression are misdiagnosed with unipolar major depressive disorder (MDD). Given that treatment regimens for MDD can be ineffective for and even exacerbate the symptoms of bipolar disorder, misdiagnosis can increase the overall disease burden for sufferers. The high rate of misdiagnosis is in part due to the current diagnostic system, which is based heavily on the categorical classification of self-reported symptoms, rather than objective measures of underlying neurobiology. In an effort to address this shortcoming, the NIMH’s Research Domain Criteria (RDoC) advocates for classifying symptoms based on abnormality along dimensions of neurobiological functioning. The current study draws on this initiative, focusing on the construct of ‘Reward Learning’ within the RDoC Positive Valence Systems matrix. Previous research has shown that deficits in reward learning exist in MDD and bipolar disorder; these deficits have been specifically related to mood-relevant symptoms of anhedonia, impulsivity, and mania. Anhedonia, or lack of response to pleasurable stimuli, is associated with blunted anticipation and response to reward. Conversely, (hypo)mania can involve a tendency to seek reward excessively. The aim of this study is to identify potential biomarkers related to reward learning that predict symptoms of (hypo)mania, in an effort to more accurately differentiate bipolar from MDD.

**Methods:** Nineteen treatment-seeking individuals with depressive disorders (5 with a history of hypomania) who were symptomatic at the time of screening completed the Probabilistic Reward Task (PRT), along with 6 healthy controls. The PRT measures an individual’s tendency to modify behavior as a function of prior reinforcement, and has been validated as an objective measure of reward learning. At a separate session, the same participants completed the PRT a second time, while we measured the amplitude of feedback-related positivity (FRP) in response to reward feedback. This event-related potential (ERP) component is generated by positive prediction errors, and believed to be indicative of sensitivity to reward. In addition to the FRP, we measured P300 amplitude, an ERP component driven by an individual’s response to salient stimuli.

**Results:** Within the clinical sample, greater severity of depressive symptoms was associated with impaired development of response bias across the PRT. Moreover, within the whole sample, depressive symptom severity ($r = -.44$, $p = .03$) and in particular, anhedonia ($r = -.54$, $p = .006$) was associated with blunted neural responses to reward feedback at frontocentral electrode site FCz. In contrast, severity of (hypo)mania was associated with increased neural response to reward feedback ($r = .48$, $p = .02$), however this was observed at parietal electrode site Pz, where the P300 is maximal.

**Conclusions:** These preliminary results indicate that within a group of individuals seeking treatment for depressive disorders, more severe depression and anhedonia were associated with reduced behavioral reward learning and blunted neural prediction-error signals. In contrast, severity of (hypo)mania was associated with neural responses indicative of heightened reward salience. These findings suggest that individuals at risk for (hypo)mania may show neural responses to rewards that are distinct from individuals with primarily depressive symptomatology.

**Topics areas:** Bipolar, Depression, Imaging
Title: Importance Of Type And Timing Of Childhood Maltreatment On Development Of Anterior Cingulate And Insula

Keywords: Child abuse, brain development, sensitive periods, cingulate cortex, insula

Background: Childhood maltreatment is associated with increased risk for psychopathology. We recently reported that maltreatment was associated with decreased centrality of the left anterior cingulate and increased centrality of the right anterior insula. Brain regions appear to have sensitive periods when they are most susceptible to stress, and differ in vulnerability based on type of maltreatment. Hence, we sought to delineate sensitive periods when these regions were most susceptible, and to assess whether type of maltreatment mattered.

Methods: MRI scans were obtained on 233 (150F/83M) unmedicated, right-handed 18-25 year olds and analyzed using FreeSurfer. Type and timing of exposure was assessed using the Maltreatment and Abuse Chronology of Exposure scale, which retrospectively assessed degree and timing of exposure to 10 different types of maltreatment. Data were analyzed using boosted regression trees.

Results: Right anterior insula was maximally sensitive to maltreatment at 4 and 11 years of age, and specifically associated with emotional neglect at age 4 and peer emotional abuse at age 11. Left anterior cingulate was maximally sensitive to non-verbal emotional abuse at 15-16 years, and to emotional neglect at 17-18 years. The probability of obtaining these relative importance patterns by chance was extremely low given the null hypothesis that exposure at all ages were of equal importance (both p < 10^-16).

Conclusions: These regions appear maximally susceptible to emotional neglect or abuse during very different stages of development. Periods of vulnerability may turn out to be windows of opportunity when interventions may have the greatest likelihood of success.
McLean Research Day 2015

**Original Research - Clinical**

**Presenting Author:** Shreya Divatia, Clinical Research Assistant II, Anxiety and Traumatic Stress Disorders Lab, CDASR

**Co-Author(s):** Demers, LA; Buchholz JL; Olson EA; Rauch SL; Rosso IM

**Title:** Resilience mediates the association between childhood trauma and current PTSD symptoms

**Keywords:** PTSD, childhood trauma, resilience

**Background:** Resilience refers to the ability to thrive despite adversity. When resilience is considered as a dimensional process rather than as a categorical measure, increased resilience scores have been shown to be associated with a lower instance of posttraumatic stress disorder (PTSD) amongst individuals who have been exposed to extremely traumatic events. In individuals who meet full criteria for PTSD, resilience significantly reduces symptom severity. Traumatic experiences in childhood have been identified as a major risk factor for the development of both child- and adult-onset PTSD. Childhood abuse has also been associated with reduced trait resilience, even in individuals who do not develop PTSD after exposure to severe childhood trauma. In this study, we aimed to examine the predictive value of resilience for the development of PTSD. We hypothesized that the relationship between childhood trauma and current PTSD symptoms would be mediated by resilience in individuals who had been exposed to DSM-IV Criterion A traumatic events.

**Methods:** Subjects were 36 right-handed, trauma-exposed adults (ages 20-50; 21 female). 20 subjects met criteria for PTSD based on the Clinician Administered PTSD Scale (CAPS), and 16 subjects had subthreshold PTSD. All subjects completed the 25-item Connor-Davidson Resilience Scale (CD-RISC) and the Childhood Trauma Questionnaire (CTQ), which assesses childhood abuse and neglect. Three hierarchical multiple regressions were performed to test whether resilience mediated the relationship between childhood trauma and current PTSD symptoms within the entire sample. These regressions tested the effect of childhood trauma on resilience, of resilience on PTSD symptoms and whether the relationship between childhood trauma and current PTSD symptoms was mediated by resilience.

**Results:** There was a significant positive relationship between CTQ scores and CAPS scores ($\beta = .48, t(34)=2.90, p=.006$, $R^2$ change=.18), as well as a significant negative relationship between resilience scores and CAPS scores, ($\beta = -.69, t(34)=-5.55, p<.001$, $R^2$ change=.46). A regression model was estimated with current CAPS scores as the dependent variable and CTQ and CD-RISC scores entered simultaneously as predictors ($R^2$ change=.471, $F$ change (1, 34)=13.214, $p<.001$). Resilience significantly predicted current CAPS scores ($\beta = -.87, t(34)=-4.38, p<.001$), but childhood trauma no longer significantly predicted current PTSD symptoms, ($\beta = .21, t(34)=1.426, p=.164$). A Sobel test showed that the overall indirect effect of childhood trauma on current PTSD scores was significant ($z=2.25, p=.02$).

**Discussion:** These analyses show that individuals who have experienced greater childhood adversity develop more symptoms of PTSD. This relationship exists in individuals who develop symptoms of PTSD in childhood as well as in individuals who develop PTSD symptoms in adulthood. This relationship is mediated by resilience scores such that individuals with greater trait resilience develop fewer PTSD symptoms despite significant childhood trauma. Understanding the relationship of childhood trauma and resilience on the development of PTSD may lead to early identification and intervention for individuals who are likely to develop PTSD following trauma exposure in adulthood.

**Topics areas:** PTSD
Original Research - Pre-Clinical | Division: Psychotic Disorders Division

Presenting Author: Jacqueline Goldbach, Research Assistant, BA, McLean Hospital, Schizophrenia and Bipolar Disorders Program

Co-Author(s): Jacqueline Goldbach, Cagri Yuksel, Fei Du, Pan Lin, Thida Thida, Begum Dora, Jennifer Gelda, Lauren O'Connor, Selma Sehovic, Caitlin Ravichandran, Staci Gruber, Dost Ongur, Bruce M. Cohen

Title: Probing Cerebral Energy Metabolism in Schizophrenia and Bipolar Disorder Using Dynamic 31P Magnetic Resonance Spectroscopy

Keywords:

Background: Several lines of evidence suggest that bioenergetic abnormalities exist in both Bipolar Disorders (BD) and Schizophrenia (SZ). ATP and phosphocreatine (PCr) are the high energy phosphate (HEP) bond containing molecules that are critical for all energy requiring cellular processes. After ATP synthesis, the reversible creatine kinases (CK) transfer HEP from ATP to PCr. PCr acts as reservoir molecule and at times of increased energy demand CK withdraws HEP from PCr to generate ATP again in the cytosol. 31P-magnetization transfer (31P-MT) and functional spectroscopy (31P-fMRS) are dynamic neuroimaging methods that measure the CK reaction rate and HEP molecule levels during a functional task, respectively. In these studies we aimed to investigate bioenergetic abnormalities in BD and SZ by using these methods.

Methods: Two separate studies were carried out in SZ and BD patients. In the first study, the forward (PCr → ATP) chemical exchange constant (kf) of the CK reaction was measured by 31P-MT from a voxel in the frontal lobe in SZ patients and healthy controls (HC). In the second study, 31P-fMRS was used to measure the levels of PCr, ATP and pH in the occipital lobe at baseline and during a visual stimulation task. All measurements were acquired at a 4T scanner.

Results: In the first study, there were significant reductions for CK kf (22%; p=0.003) and pH (p=0.007) in SZ patients. In the second 31P-fMRS study, the BD subjects showed a significantly different pattern for PCr and ATP during stimulation compared to HC (p=0.01). In HC, PCr was reduced (p=0.005) and ATP remained stable, as expected. In BD, the opposite pattern was observed with a decrease in ATP (p=0.02) and no significant change in PCr.

Conclusions: These results suggest that regulation of ATP levels through access to HEP derived from PCr -especially at times of high energy demand- may be disturbed in BD and SZ. This may be due to an abnormality in the CK enzyme(s). The intracellular pH reduction in SZ suggests a potential shift from oxidative phosphorylation to glycolysis due to a possible mitochondrial dysfunction.

Topics areas: Bipolar, Psychotic disorders, Schizophrenia
Title: Descriptive data for the initial patient cohort admitted to an innovative male mental health residential treatment service for law enforcement, active duty military, and emergency responders (LEADER)

**Keywords:** substance, mood, stress, military, trauma

**Introduction:** In 2014 McLean Hospital developed comprehensive mental health services designed to meet needs of law enforcement, active duty military, and emergency responders (LEADER), a population known for high rates of suicide and poor treatment engagement. We report descriptive data for the first 34 patients entering a 6-bed male residential LEADER program between May-November 2014.

**Methods:** Self-report assessments including mood/suicidal ideation, substance use, and acute stress are administered at admission and discharge; completion is voluntary. Perceptions of care are collected at discharge. Retrospective chart review is conducted as a quality improvement initiative.

**Results:** Primary referral sources include peer support and EAPs of LEADER organizations. Average residential length of stay was 13 days. Lifetime alcohol or drug use disorder was present in 29/34 (85%); of these 27/29 (93%) had active substance use as the primary reason for referral. Sexual indiscretion was the referral event for 3/34 men (9%); only 1 of these 3 had co-occurring substance use disorder. Half reported current tobacco use. Twenty-eight patients (82% of all patients) completed admission assessments, with 11/28 (39%) reporting at least moderately severe depressive symptoms and 12/28 (43%) screening positively for posttraumatic stress disorder on the PTSD Checklist 5. Patients rated their perceptions of care (a patient satisfaction measure) with the highest possible score (100 on a scale from 0-100) on 18 out of 21 nationally standardized items, with all clinical care related items rated higher than 90 on average. Substance relapse accounted for 5 of 7 readmissions, and appeared to significantly contribute to one post-discharge suicide. Family conflict was reported as contributing to relapse in 4 of 5 substance readmissions.

**Conclusions:** Patients in the men’s residential LEADER program are receptive to integrated mental health/substance use treatment when provided culturally competent care in a confidential peer setting. Clinical innovations to support abstinence maintenance and positive family relations are needed to reduce suicide risk and further improve clinical outcomes.
Program Description | Division: Division of Alcohol and Drug Abuse
Presenting Author: Rachel Tester, PMHCNS, BC; Program Director, LEADER, Residential Treatment Program, McLean Hospital

Co-Author(s): Patricia Diaferio, LICSW John Rodolico, PhD Joseph Gold, MD Diane Bedell, LICSW Gerald Sweet, PhD Kathryn McHugh, PhD Jennifer Taylor, PhD Lynn Carlson, LICSW Kevin Hill, MD, MHS Nancy Merrill, PMHCNS, BC Roger Weiss, MD Hilary Connery, MD, PhD

Title: Rationale and program design of a male mental health residential treatment service for law enforcement, active duty military, and emergency responders (LEADER)

Keywords: substance, mood, stress, military, trauma

Introduction: In 2014 McLean Hospital developed and implemented comprehensive mental health services designed to meet needs of law enforcement, active duty military, and emergency responders (LEADER). We report rationale, design, and collaborative structure of a 6-bed male residential treatment program for LEADER patients in need of acute psychiatric stabilization and aftercare planning. The residential unit is located on the main hospital campus and all staff were trained to provide culturally competent, integrated mental health/substance use treatment for this population.

Methods: Literature review on health care of LEADER, coupled with consultation expertise in law enforcement and military behavioral health, guided program design. Community resources to support confidential treatment (e.g., police peer support, military behavioral health, and 12-step LEADER groups) were embedded within program structure. Local police and military medical formulary guided psychopharmacological algorithms.

Results: Evidence-based treatment for LEADER is well-studied in the military but no other members; psychopharmacological guidance is clearest in military formularies. A specialized group therapy program, private to LEADER and targeting high incidence LEADER health concerns (depression, substance use, stress, impulsivity, sleep disorders, medical co-morbidities and injury, and family stress), was superimposed on evidence-based mental health/substance use day treatment and supports open to the community. LEADER-exclusive outpatient and 12-step support aftercare and formal/informal peer monitoring assisted discharge transition. Patients, families, and referrers reported high satisfaction in surveys on perceptions of care. Physical training was less well-utilized than anticipated, medication non-adherence post-discharge was common, and a gap in specialized vocational supports was noted for non-military members with job loss.

Conclusions: Quality indicators demonstrate a successful integrated treatment and recovery approach to LEADER men who are in need of intensive mental health stabilization. Concerns that blending occupations within the LEADER residential treatment unit (e.g., co-locating police with firefighters) could present an unintended source of tension or conflict within the treatment milieu have not been supported by experience. Likewise, co-locating men with and without co-occurring SUD did not appear to pose any problems to the treatment milieu; in fact, residents were highly supportive and empathic with each other, overall. Program development includes improving physical training, medication maintenance, and vocational services.
Title: Drug Discrimination in (+)-Epibatidine-Trained Monkeys: Agonists and Antagonists Effects of Nicotinic Drugs

Keywords: drug discrimination, nicotinic agonist, nicotinic antagonist, behavioral pharmacology, squirrel monkeys

The behavioral effects of nicotinic agonists and antagonists were studied in squirrel monkeys using a two-lever drug discrimination procedure. Monkeys (n=4) were trained to discriminate i.m. injections of 0.001 mg/kg (+)-epibatidine (EPI)–a α4β2 selective nicotinic agonist that is pharmacologically similar and structurally distinct from nicotine (NIC)–from saline on a 10-response fixed-ratio schedule of stimulus-termination. Results show that high efficacy nicotinic agonists [(+)-EPI, (-)-EPI, NIC] substituted fully for (+)-EPI, whereas the highest doses of other nicotinic agonists produced intermediate levels of (+)-EPI-like discriminative-stimulus (SD) effects [varenicline (VAR), cytisine (CYT)] or did not substitute for (+)-EPI (lobeline). Minor tobacco alkaloids produced full (nornicotine, anabasine, myosmine, anatabine), intermediate (anabaseine) or no (cotinine) (+)-EPI-like effects. Pretreatment studies with nicotinic antagonists show that: a) mecamylamine (non-selective) unsurmountably antagonized (+)-EPI’s effects; b) dihydro-β-erthroidine (α4β2-selective) surmountably (>3-fold rightward shift) blocked (+)-EPI’s effects; and c) methyllycaconitine (α7 selective) and hexamethonium (peripherally-restrictive) failed to modify the SD effects of (+)-EPI. In further studies, pretreatment with the partial nicotine agonists VAR and CYT did not block the SD effects of (+)-EPI, and in fact, shifted the (+)-EPI dose-effect curve to the left (>3-10-fold). These results suggest that the SD effects of (+)-EPI are mediated through a α4β2 nicotinic receptor subtype at which the partial agonists VAR and CYT do not exert partial antagonist actions.
**Original Research - Clinical**

**Presenting Author:** Jesse Crosby, Assistant Psychologist, OCDI Office of Clinical Assessment and Research

**Co-Authors:** Caitlin A. Chiupka, M.A., Jesse M. Crosby, Ph.D., Jason W. Krompinger, Ph.D., Brittany M. Mathes, B.A., & Jason A. Elias, Ph.D.

**Title:** The Role of Externalizing Blame on Treatment Outcomes in Obsessive-Compulsive Disorder

**Keywords:** OCD, Blame, Externalization, Outcomes, Treatment

Externalizing blame is a cognitive attributional construct in which an individual defensively attributes the cause of negative circumstances to others and the environment, minimizing personal contributions to a given situation. This study examined the relationships between externalization (blaming others for one’s circumstances) and therapeutic outcomes in a longitudinal sample of residential patients with Obsessive-Compulsive Disorder (OCD). Participants (n = 172; 48% female) completed a series of empirically validated measures including the Test of Self-Conscious Affect-3 (TOSCA-3), the Yale–Brown Obsessive Compulsive Scale (YBOCS), and the Schwartz Outcome Scale (SOS). Measures were completed upon admission to the Obsessive Compulsive Disorder Institute at McLean Hospital and again at discharge. Results indicate an association between the extent to which an individual blames external factors for their present circumstances and change in OCD symptoms following treatment. Specifically, those whose level of externalization decreased over time demonstrated decreased OCD obsession symptoms, t(129) = 2.27, p = .03, and greater psychological health and well-being than t(129) = -1.75, p = .08, than did those whose tendency to externalize either increased over time. These preliminary results suggest that attending to the extent to which an individual attributes their psychological problems to external factors, and shifting patients to take a more balanced view of examining both internal and external contributions will be associated with better psychological outcomes during and post treatment.
Background: Negative health effects for siblings of a person with a chronic illness have been established for certain disease categories (e.g., autistic spectrum disorder, pediatric cancers, Alzheimer’s dementia); however, little is published about the negative health effects for siblings of those with SUD. The main support and education group serving siblings of those with SUD is Al-Anon; which serves 50,000 siblings (one-third of Al-Anon membership). Clinical supports specific to siblings are not commonly integrated into SUD treatment settings, despite a large number of siblings affected.

Methods: Started with generous support from a donor family, the Sibling Support Group is a novel program offered monthly to provide in-person support for siblings age 18 and older of those with SUD. It is designed to investigate and begin to address the needs of this often overlooked population by providing a forum where they can discuss their particular situations, and get support and ideas for improving the quality of their lives. The group was launched October 2014 with marketing efforts including in-person visits by group facilitators throughout the Division of Alcohol and Drug Abuse (DADA), educating staff and actively seeking referrals. Additional electronic advertising was distributed to all McLean Hospital staff, and flyers were also posted around campus. An all-McLean email reminding staff of the group and the date/time of the next group is sent out 7-10 days in advance of the next group. Participant feedback was collected using a participant satisfaction survey developed previously for use with general family services provided within DADA clinical care.

Preliminary Results: Two pilot groups had an attendance of 3 and 1 participants, respectively, and 3 of 4 surveys were voluntarily completed. Two out of three reported finding the group helpful; the one person who did not find it helpful came to support the group but did not have a sibling with SUD. Topics of interest to participants have thus far included resentment of the substance-using sibling and anger at parents regarding their treatment of the sibling with SUD. Enhancing self-care and maintaining boundaries with the sibling were also topics of interest to participants.

Conclusions: Interventions specifically designed for siblings of those with SUD are feasible. Research is needed regarding how best to engage, assess, and support adult siblings of those with SUD, including how to prevent potential negative health effects on these siblings.

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**Title:** Impulsivity During Emotional Distraction in Dually Diagnosed Adolescents With Substance Use Disorders and Co-morbid Depression or ADHD

*Keywords:* Impulsivity, Adolescents, Co-morbidity, Depression, ADHD

Adolescent risk-taking commonly includes initiation and escalation of alcohol and drug use during a time when the still-maturing brain may be particularly vulnerable, increasing the risk of long-term cognitive and health problems. In particular, late-maturing prefrontal brain regions important to emotion regulation and impulse control might be especially vulnerable to damage by substance use, thus elevating the risk for psychopathology among substance using adolescents. Most adolescents diagnosed with a substance use disorder also meet criteria for other forms of psychopathology, with depression and attention deficit/hyperactivity disorder (ADHD) being among the most common. The presence of such dual diagnoses is associated with poorer medical and psychosocial outcomes, including suicide. The current study examined performance on an inhibitory control task (Go-NoGo) in 117 patients between ages 14 and 19 years (mean age=17.1 years) enrolled in a two-week residential treatment program for dually diagnosed adolescents. Data were collected within 48 hours of intake and clinical diagnoses were established using the MINI-KID diagnostic interview. Participants were asked to respond or inhibit responding based on letters presented at the center of emotional distractor images that were negative, positive, neutral or scrambled. Using accuracy on NoGo trials as an index of inhibitory control, patient performance on the emotional Go-NoGo was first compared to a sample of age and gender-matched healthy control subjects drawn from a previous study sample (N=41). Healthy adolescents exhibited significantly higher accuracy on NoGo trials relative to patients (p<.001, Fig 1). The patient group was subsequently divided into four subgroups: 1) No Depression or ADHD (N=21), 2) Depression only (N=75), 3) ADHD only (N=8), and 4) Depression and ADHD (N=29). The ‘Depression only’ group showed increased impulsive errors on negative and positive trials relative to scrambled trials (p<.01) while the ‘Depression and ADHD group’ showed a distraction effect on negative trials only (p<.01) (Fig 2). The other two patient groups showed no significant effects of background on NoGo trial accuracy, although the absence of an effect in the ‘ADHD only’ group may be due to a limited sample size. While further studies are needed to parse the specific impact of substance use versus psychopathology on response inhibition, these findings suggest that adolescent depression and ADHD, when co-morbid with substance use disorders, are associated with distinct patterns of emotion-related impulsivity. Different patterns of impulsivity may reflect different areas of risk for rash actions, such as substance use, self-harm, and suicide. These differential patterns of risk may ultimately serve to inform substance use prevention strategies, as well as effective treatment interventions in dually diagnosed adolescents.
Concomitant with recent legalization of medical and recreational marijuana (MJ), MJ use has surpassed nicotine cigarette use among middle and high schoolers to become the second most frequently abused substance behind alcohol (Johnston et al., 2013). In 2013, nearly 9 percent of adolescents reported past month illicit substance use, and 5.2 percent met criteria for substance abuse or dependence within the past year (SAMSHA, 2014). Of these youths, 7.1 percent endorsed past month MJ use (SAMSHA, 2014). Chronic MJ use in adolescents and young adults has been associated with deficits in school performance, behavioral problems, and a withdrawal pattern characterized by mood and concentration difficulty (Medina et al., 2007; Budney & Stanger, 2012). While a number of psychosocial risk factors (e.g., peer deviancy, parental monitoring, school bonding) have been identified as predictors of MJ use patterns (Fallu et al., 2013), there are still gaps in understanding the resultant negative outcomes from MJ use in adolescents. The present analysis of historically collected data evaluated and characterized the effects of multiple risk factors and substance use patterns on negative outcomes in social and health domains in a group of adolescents while residing in an inpatient program at McLean Hospital.

Six hundred and eighteen adolescents (326 females) between the ages of 12 and 20 (Mean 16.51±1.34) completed an Adolescent Chemical Dependency Questionnaire upon admission to East House, a residential treatment facility. Using a multinomial logistic regression model, various health (emergency room visits; suicidality) and psychosocial (fights; loss of school/work) consequences were identified as negative outcomes. Frequency of marijuana, alcohol, amphetamine, opiate, and polysubstance use were entered into the model as primary substance use profile predictors. In addition, a number of psychosocial risk factors were entered into the model as covariates, such as family history of substance use, school problems (e.g., truancy), legal supervision (e.g., CHINS, probation), and history of previous psychiatric treatment predictors. Self-reported polysubstance and/or alcohol use were positively associated with most health and psychosocial negative outcomes (p’s=0.01-0.04), controlling for psychosocial risk factors. Conversely, MJ use was significantly less likely to predict all negative outcomes (p=0.04), after controlling for psychosocial risk factors.

Collectively, these results indicate that specific substance use patterns differentially influenced the occurrence of negative consequences, suggesting that a nuanced relationship exists among these factors. Not surprisingly, alcohol and/or polysubstance use were the strongest predictors of negative outcome in our sample (see Levy, Stewart, & Wilbur, 1999; Cooke et al., 2004). Interestingly, MJ use was significantly less likely to predict negative outcomes in health and psychosocial domains. One interpretation of this outcome is that MJ use may reflect an adaptive, albeit immature, coping mechanism that has evolved to overcome negative affect associated with behavior dysregulation in these adolescents. Overall, these findings capitalize on using clinically and ecologically valid information collected in a high-risk sample of adolescents. Moreover, they emphasize the
Title: Negative information-processing bias in social anxiety disorder masks the bias towards negative information in major depressive disorder

Keywords: depression, social, anxiety, bias, attention

Background: Mounting research suggests that depressed individuals have difficulty disengaging from negative information; furthermore, research shows a negative interpretation style for ambiguous social stimuli in individuals with social anxiety disorder. Although depression and social anxiety are highly comorbid, there has been limited research on how this comorbidity affects emotional attention bias at early stages of processing. In this study, individuals with Major Depressive Disorder (MDD), a portion of whom also had social anxiety disorder (MDD-SAD), performed a matching task while exposed to emotional interference. We hypothesized that MDD-SAD patients would show greater distraction than MDD patients in response to neutral and fearful face stimuli in automatic stages of processing.

Methods: 28 subjects with MDD-SAD and 25 subjects with MDD completed the Emotional Interference Task. On each trial, subjects were to determine whether two stimuli on the horizontal or vertical axis matched (targets), while ignoring stimuli on the other axis (distracters). Stimuli were fearful or neutral faces or houses presented for 250ms, and the face stimuli were either targets or distracters. A three-way repeated-measures ANOVA examined group (MDD and MDD-SAD), attention (attended or ignored faces), and emotion (fearful or neutral) as predictors of accuracy.

Results: There was a significant three-way interaction of group X attention X emotion on accuracy (F(1,51)=5.62, p=.02). For the MDD group, higher accuracy was observed for the fear condition when attending to faces (t(24) = 2.52, p = .02) and lower accuracy was observed for the fear condition when ignoring the faces (t(24) = -2.25, p = .03). For the MDD-SAD group, accuracy was consistently low across both affective conditions (t(27) = -.44, p = .67; t(27) = -1.05, p = .31).

Conclusions: While the MDD group showed an advantage when attending to fear faces and a disadvantage when ignoring them, the MDD-SAD group showed poor performance for both emotion conditions. The pattern of enhanced automatic attention (vigilance) to all emotional information seen in the comorbid group may be consistent with prior research showing that SAD is associated with a bias to interpret all social stimuli as threatening. Overall, our findings suggest that the pattern of automatic attention to mood-consistent information that characterizes depression extends to neutral social information in individuals with comorbid social anxiety.
New insights into the role of endothelial GABAA receptor mediated signaling in neuropsychiatric disorders

Abnormalities in GABA neurons and defects in GABAA receptor regulation are implicated as a major factor in schizophrenia, epilepsy and autism spectrum disorders. Given the significance of abnormal early brain development for these serious neuropsychiatric illnesses, GABA-mediated signaling by neurons has been extensively studied. But, there are two sides to every coin. Likewise brain development is supported by concomitant development of its vasculature. Based on anatomical location, independent growth patterns and developmental regulation, vascular networks in the embryonic forebrain (telencephalon) fall into two categories: pial and periventricular. A day after the periventricular vascular network is established, GABA neurons, born in defined germinative zones in the ventral telencephalon, migrate long distances to adopt their specific positions in the dorsal telencephalon.

Our recent studies reveal that pial and periventricular vascular networks provide support as well as critical cues to guide GABA neurons on their tangential journey in the embryonic brain. Interestingly, gene expression profiles of periventricular endothelial cells are distinct from pial endothelial cells. The genes expressed in periventricular endothelial cells were enriched in many neuropsychiatric disease categories like schizophrenia, epilepsy, autism spectrum disorders, mood, depressive and anxiety disorders. Furthermore, genes believed to independently regulate GABA neurogenesis and migration were expressed predominantly in periventricular endothelial cells signifying that the periventricular angiogenesis gradient and GABA neuron developmental gradients are related at mechanistic levels. For instance, GABAA receptors traditionally believed to be confined to GABA neurons were discovered on embryonic brain endothelial cells. The presence of endothelial GABAA receptors that could modulate GABA neuronal migration under in vitro conditions provided first insights into the importance of endothelial GABA and its receptors signaling for brain development.

To capitalize on these findings and to discover the functional significance of endothelial GABAA receptors in vivo, we selectively deleted GABAA receptor, β3 subunit (Gabrb3) highly expressed in periventricular endothelial cells using CRE-LOX conditional gene knockout strategy. Here we show that loss of endothelial Gabrb3 resulted in impaired angiogenesis in the embryonic telencephalon that persisted in the adult forebrain. Intrinsic vascular defects and alterations in vascular guidance during the critical developmental period affected tangential GABA neuronal migration and final distribution in the embryonic forebrain resulting in marked GABA cell deficits in the adult cingulate, motor and somatosensory cortex.

Most importantly, deletion of this single GABAA receptor, Gabrb3 from endothelial cells was sufficient to cause behavioral dysfunction. Our results illustrate a novel endothelial GABA signaling pathway that works independent of the classical neuronal GABA signaling pathway with far-reaching consequences for brain development and offer new understanding of serious neuropsychiatric disorders such as schizophrenia, epilepsy, autism and depression. Support: NARSAD Independent Investigator Award and R01NS073635 (PI: Vasudevan)

Topics areas: Psychotic disorders
Title: Age of Cigarette Smoking Onset is Associated with Impulsive Responding on a Smoking Go/No Go Task

Keywords: smoking, nicotine, impulsivity, early onset, inhibitory control

Introduction. The initiation of cigarette smoking during adolescence coincides with critical neurodevelopmental patterns of structural and cognitive maturation. Therefore, early onset smokers (EOS; <16 yrs age) may be at unique risk of interfering with normal executive function development relative to late onset smokers (LOS; >16 yrs age). The present study investigated the differential effects of age of smoking onset on response impulsivity and inhibitory control using a novel smoking Go-NoGo task (Luijten et al., 2011).

Methods. Adult EOS (n=6) and LOS (n=10) in acute nicotine withdrawal, and adult non-smokers (NS; n=10), were shown a series of Smoking or Non-Smoking related images with either a blue (Go) or yellow (NoGo) frame. Participants were instructed to respond to blue-framed Go trials with a specific button press as quickly and accurately as possible, and to withhold their response for yellow-framed NoGo trials. Each Smoking and Non-Smoking image was shown 4 times during the task, 3 times as a Go stimulus and once as a NoGo stimulus, for a total of 896 trials over a 20 minute session.

Results. EOS and LOS exhibited significantly more errors of omission (Go errors; p<0.01) and a greater false alarm rate (No Go errors; p<0.01) relative to NS. Furthermore, while EOS and LOS showed lower overall Go response accuracy (p<0.01) than NS, EOS also exhibited lower Smoking Go response accuracy (p<0.03) than NS. EOS and LOS also exhibited impaired Smoking NoGo response accuracy (p<0.02), however LOS also showed lower Non-Smoking NoGo response accuracy (p<0.02), than NS. Smoking Go response accuracy was significantly correlated with motor impulsivity (r=-0.41, p<0.04), age of smoking onset (r=-0.48, p<0.01), and daily cigarettes smoked (r=-0.49, p<0.01). Non-Smoking NoGo response accuracy was also associated with age of smoking onset (r=-0.54, p<0.01) and daily cigarettes smoked (r=-0.45, p<0.02).

Conclusions. EOS had difficulty in responding accurately to Smoking Go stimuli, suggesting that these stimuli were distracting and impaired their ability to pay attention to task demands. In contrast, LOS had difficulty withholding responses to both Smoking and Non-Smoking NoGo stimuli, indicating overall greater impulsive responding and deficits in inhibitory control, regardless of stimulus category. Collectively, these preliminary findings suggest that age of smoking onset can differentially impact cognitive task-related attention and response inhibition, suggesting that individualized cognitive approaches may be needed to improve the executive function in smokers as part of an overall treatment program.
Title: Patient factors associated with buprenorphine/naloxone maintenance in a psychiatric clinic

Keywords: buprenorphine, retention, drop-out, addiction, opioid

Background: Age less than 25 and opioid use within the first month of treatment predict patient drop-out from buprenorphine/naloxone (BN) maintenance of opioid use disorder (OUD) within office-based primary care and addiction treatment center settings. Patient factors associated with BN drop-out were reviewed for quality improvement of OUD treatment within the McLean Hospital outpatient BN stabilization/maintenance treatment program. This is a 50-minute weekly group therapy designed for patients with co-occurring OUD and psychiatric illness, co-facilitated by an addiction psychiatrist and addiction psychiatry fellow who also act as prescribers for the individual group members. The group content includes evidence-based relapse prevention skills, medication adherence monitoring, and psychiatric symptom monitoring integrated with symptom reduction skills.

Methods: Medical records and supervised urine toxicology reports were retrospectively reviewed for 90 patients initially hospitalized at McLean Hospital from 2006-2013 who discharged to care within the aforementioned McLean outpatient treatment program. Early drop-out was defined as leaving treatment altogether within the first 3 months of entry into the outpatient BN clinic. Data was extracted for demographics, opioid use, BN adherence, illness severity (as number of co-occurring substance use disorders and psychiatric diagnoses), history of suicide attempt, prior opioid agonist treatment, use of 12-step mutual help at time of outpatient admission, chronic pain, and substance use during the first 3 months of treatment. Incomplete medical records were excluded.

Results: 84 records were eligible. The majority of patients were male (57%), unmarried (80%), unemployed (54%), with a mean age 32 years (range 17-69 years). Most reported treatment entry for IV heroin (58%) and fewer reported prescription opioid use only (25%). 33% (28/84 patients) dropped out within the first 3 months of treatment. Early drop-out patients (EDPs) were twice as likely to be younger than 25 (19/28 or 68% of EDPs versus 17/56 or 30% of retained) and to have a legal history of arrest (19/28 or 68% of EDPs versus 19/56 or 34% of retained). Those retained were three times as likely to report chronic pain (18/56 or 32% of retained versus 3/28 or 11% of EDPs) and/or a history of making a suicide attempt (13/56 or 23% of retained versus 2/28 or 7% of EDPs). EDPs had nearly twice the toxicology-confirmed opioid use during the first month of treatment compared with those retained (9/28 or 32% of EDPs versus 10/56 or 18% of retained), despite equivalent rates of toxicology-confirmed BN adherence for both groups during the first month of treatment (27/28 or 96% BN adherent of EDPs and 53/56 or 95% BN adherent of retained).

Conclusions: Patients receiving BN treatment for OUD in an integrated outpatient psychiatric care setting show similar risk factors for early drop-out and retention factors as reported in the literature in other office-based BN treatment settings. Interestingly, in this clinical cohort, having a history of a suicide attempt was associated with BN treatment retention. This finding has not been reported in the literature to date examining BN treatment of OUD and merits further investigation. Interventions to augment BN treatment retention may improve outcomes in psychiatric populations.

Topics areas: Addiction
**Title:** PACAP promotes a PTSD-like phenotype in fear conditioned rats

**Keywords:** PACAP, PTSD, freezing, amygdala, anxiety

Pituitary adenylate cyclase-activating polypeptide (PACAP) shares identical amino acid sequence homology in species including mice, rats, and humans, indicating strong evolutionary conservation of this neuropeptide. The presence of high levels of PACAP in limbic brain areas such as the hippocampus, amygdala, and bed nucleus of the stria terminalis (BNST) suggests a role in modulating emotional states. In animal studies, PACAP systems have been shown to be involved in stress responsiveness and emotional learning. In humans, a relationship between elevated levels of PACAP and PTSD symptoms has been identified. Here, we examined the effects of PACAP on the acquisition of Pavlovian fear conditioning using the conditioned freezing paradigm.

Male, Sprague-Dawley rats were implanted with intracerebroventricular cannula for infusion of either vehicle (VEH) or PACAP-38 (1.5 µg) followed 30 min later by fear conditioning; rats received two pairings of a 30 s, 75 dB tone co-terminating with a 0.6 mA footshock. Freezing to the conditioning context and conditioned stimulus (tone) was measured 1, 4, 7 and 28 days later. Serum corticosterone (CORT) levels were measured after fear conditioning and the Day 1 freezing test. PACAP infusions prior to fear conditioning produced a bi-phasic response in freezing across test days. On Day 1, PACAP-treated rats showed a significant reduction in freezing compared to VEH-infused rats that rebounded by Day 7 and was now significantly elevated in this treatment group. The effect was long lasting as PACAP may partially interfere with consolidation of the fear memory trace by altering synaptic plasticity in some brain areas (e.g. the hippocampus) leading to the impairment of freezing seen on Day 1. This effect may resemble a type of peritraumatic amnesia or dissociation seen in people early after exposure to traumatic events. However, it appears that the fear memory is still retained (e.g. in the amygdala) such that with repeated test days and memory reactivation the freezing response re-emerges and is sustained at a higher level compared to controls. Hence, PACAP systems may represent an important axis for understanding how stress and exposure to trauma converge to promote maladaptive behavioral responses and influence the progression of PTSD symptoms over time.
Xenon gas impairs reconsolidation of fear memories in a rat model of PTSD

Xenon (Xe) is a noble gas that has been developed for use in people as an inhalation anesthetic and a diagnostic imaging agent. Xe inhibits glutamatergic N-methyl-D-aspartate (NMDA) receptors involved in learning and memory and can affect synaptic plasticity in the amygdala and hippocampus, two brain areas known to play a role in fear-conditioning models of post-traumatic stress disorder (PTSD). Because glutamate receptors also have been shown to play a role in fear memory reconsolidation – a state where recalled memories become susceptible to modification – we examined whether Xe administered after fear memory reactivation could affect the expression of subsequent fear-like behavior (freezing) in rats. Naïve male Sprague-Dawley rats were trained for contextual and cued fear conditioning; rats received two pairings of a 30 s, 75 dB tone co-terminating with a 0.6 mA footshock. Twenty-four hours later, freezing to the conditioning context and conditioned stimulus (tone) was measured. Immediately after this test, which served to reactivate the fear memory, rats were exposed to inhaled Xe (25%) or normal room air for 1 h and the effects on fear memory reconsolidation were measured 2, 4, or 18 d after reactivation/Xe administration. A second set of animals was trained as described above but did not receive a reactivation test 24 h later. Instead, at this time point, animals were exposed to Xe (25%, 1 h) to determine whether Xe must be paired with memory reactivation for it to affect memory reconsolidation. A third set of animals was trained as described above but did not receive a reactivation test 24 h later, and was exposed to Xe (25%, 1 h) beginning 2 h after the reactivation test, to determine whether delayed Xe exposure affected freezing. A fourth set of animals was trained as described above and exposed to Xe (25%, 1 h) twice to determine whether multiple Xe exposures enhance reconsolidation blockade. Xe administration immediately after fear memory reactivation – but not when given 2 h after reactivation – significantly reduced freezing to the context and cue when tested 2, 4, or 18 d after reactivation/Xe administration. Xe administration in the absence of fear memory reactivation had no effect on subsequent freezing behavior. Multiple Xe exposures did not further enhance the reconsolidation blockade. Together, these data suggest that xenon inhibits memory reconsolidation in a reactivation and time-dependent manner, that it could be used as a new research tool to characterize reconsolidation and other memory processes, and that it could be developed to treat people with emotional memory disorders such as PTSD.
**Original Research - Clinical**

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**Title:** Using Distress Tolerance to Differentiate Adolescents with Depression and Borderline Personality Disorder

**Keywords:** distress tolerance, depression, Borderline Personality Disorder, adolescents

Difficulties with distress tolerance represent a core feature of adolescent Borderline Personality Disorder (BPD) and Major Depressive Disorder (MDD; Ellis et al., 2013; Gratz et al., 2006; Iverson et al., 2012). To date, the majority of research has relied on self-report indices of distress tolerance (e.g., Gratz et al., 2006, Iverson et al., 2012); however, this approach is limited in that an adolescents may be unable to objectively report on their distress tolerance, and critically, it may be outside of their conscious awareness. To address this unmet gap, the current study examined an objective measurement of distress tolerance and further, explored whether dysfunctional levels of distress tolerance are associated with self-injurious thoughts and behaviors. The current study included depressed (MDD = 35), BPD (BPD = 31) and healthy (HC = 13; Target HC sample = 30) female adolescents aged 13-23 (M = 16.4, SD = 2.14). During a laboratory visit, all participants completed the Computerized Mirror Tracing Persistence Task (MTPT-C; Strong et al., 2003) wherein they traced four star figures using a mouse that moved opposite the cursor on the screen. Participants were instructed to discontinue when they became too frustrated with the task. Distress tolerance was defined as greater total distance traced (MT Distance) and longer time to discontinuation (MT Time) (Bornovalova et al., 2008). Group differences were examined on MT Time and MT Distance using two 1-way ANCOVAs, covarying the effects of participant age. For MT Time, the ANCOVA was statistically significant (F(2, 80) = 3.42, p = .038, partial η^2 = .079), and follow-up pairwise comparisons indicated that the MDD adolescents (M = 133.39s, SD =131.43s) performed worse than both the HC ((M=251.42s, SD=142.86s), t(50) = 2.75, p = .008) and the BPD ((M=221.67s, SD=162.79s), t(69) = 2.53, p = .014) group. The analysis for MT Distance approached statistical significance, (F(2, 80) = 2.34, p = .103, partial η^2 = .055), and the pattern of means was consistent with the MT Time analysis. In follow-up exploratory correlation analyses, we found that, among MDD adolescents, poorer performance on MT distance was associated with less frequent use of emotion regulation strategies (r = -0.391, p = 0.014) and greater problems with impulse control (r = -.371, p = .02). Although NSSI was not associated with MT performance in the MDD group alone, poorer performance on the MT Time and MT Distance was associated with higher frequencies of NSSI thoughts in the past month across the clinical groups at a statistical trend (r= -.24, p=.061 and r= -.23, p=.070, respectively). Overall, these findings underscore the importance of using objective assessments of distress tolerance in psychiatric patients as it may provide important insights into self-injurious thoughts and behaviors.

**Topics areas:** Borderline Personality Disorder, Depression
Title: Rejection Sensitivity and Borderline Personality Disorder

Keywords: rejection sensitivity, borderline personality disorder, depression

Background. Rejection sensitivity has been associated with borderline personality disorder (BPD) from its earliest descriptions. While a small body of research has established its relationship to BPD, this is the first study to investigate the relationship between rejection sensitivity, BPD, and its component parts in a rigorously diagnosed family sample using valid and reliable clinical assessments.

Method. To examine the relationship between rejection sensitivity and the affective, cognitive, impulsive, and interpersonal symptom sectors of BPD, we administered a newly validated scale ---the McLean Assessment of Rejection Sensitivity (MARS)--- and the Revised Diagnostic Interview for Borderline (DIB-R) to rigorously diagnosed subjects in four groups: 1) BPD plus MDD (MDD; n=158); 2) BPD alone (n=46); 3) MDD alone (n=295); 4) and comparison subjects with neither BPD nor MDD (n=669).

Results. Rejection sensitivity scores were highest for BPD alone and BPD plus MDD groups, and lowest for the MDD alone and comparison group without BPD or MDD. The differences in score were statistically significant for the comparison group when compared to all others as well as between the MDD alone and BPD plus MDD groups. Rejection sensitivity was significantly correlated with all four sectors of BPD, but not to the same degree as the sectors correlated to each other. Lastly, rejection sensitivity aggregates in families independent of aggregation of BPD.

Conclusion. Rejection sensitivity is a familial psychobiological disposition that relates to but does not represent BPD’s unidimensional liability and reflects a shared liability between MDD and BPD.
Title: Impact of family history of alcoholism on glutamine/glutamate ratios in anterior cingulate cortex in healthy substance-naïve adolescents

Keywords: MRS, adolescence, alcohol, family history, glutamate

Neuroimaging research on adolescents who are family history positive (FH+) or family history negative (FH-) for alcohol use disorders can help identify neurological factors that contribute to elevated risk for later alcohol abuse. Relative to FH- peers, FH+ adolescents perform worse on tasks that require inhibitory control, as well as exhibit altered functional activation in brain areas that subserve cognitive control, including the anterior cingulate cortex (ACC). Little is known, however, about neurochemical correlates of these behavioral and functional differences. In the current study, glutamate (Glu) and glutamine (Gln), amino acids vital to protein synthesis, cellular metabolism and excitatory neurotransmission, were measured using magnetic resonance spectroscopy (MRS) in the ACC and in a control region in the parieto-occipital cortex (POC). Proton metabolite data were acquired from 28 healthy adolescents (13 male), aged 12-14 years, and 31 healthy, emerging adults (16 male), aged 18-25 years, using 2D J-resolved MRS at 4 Tesla, from voxels placed in ACC and POC. Subjects were stratified within each age group into low (FH-) or high (FH+) risk for substance abuse based on family history interviews. Significantly higher Gln/Glu ratios were observed in FH+ compared to FH- adolescents in ACC but not POC. Furthermore, higher impulsivity (Barratt Impulsivity Scale, Stroop Interference) was significantly associated with higher Gln/Cr levels and lower Glu/Cr levels. As predicted, these effects were only observed in the ACC. In the adult group, no significant family history effects were observed for Gln/Glu, nor were any significant relationships observed between impulsivity measures and Gln and Glu concentrations. These findings suggest evidence for a distinct neurometabolic profile, elevated Gln/Glu that together with family history status may confer risk for substance use disorders. Further, this neurobiological vulnerability may manifest as a behavioral mechanism, reduced cognitive control, that enhances risk in adolescents, but dissipates by early adulthood, likely due in part to maturation of the prefrontal cortex.
**Title:** An Examination of Rostral Anterior Cingulate Cortex Function and Neurochemistry in Obsessive-Compulsive Disorder

**Keywords:** obsessive-compulsive disorder, fMRI, MRS, anterior cingulate cortex, glutamate

**Background:** The anterior cingulate cortex is implicated in the neurobiology of obsessive-compulsive disorder (OCD). However, few studies have examined functional and neurochemical abnormalities specifically in the rostral subdivision of the ACC (rACC) in OCD patients.

**Methods:** We used functional magnetic resonance imaging (fMRI) during an emotional counting Stroop task and single-voxel J-resolved proton magnetic resonance spectroscopy (1H-MRS) in the rACC to examine the function and neurochemistry of the rACC in individuals with OCD and comparison individuals without OCD. Between-group differences in rACC activation and glutamine/glutamate ratio (Gln/Glu), Glu, and Gln levels as well as associations between rACC activation, Gln/Glu, Glu, Gln, behavioral, and clinical measures were examined using linear regression.

**Results:** In a sample of 30 participants with OCD and 29 age- and sex-matched participants without OCD, participants with OCD displayed significantly reduced rACC deactivation compared to those without OCD in response to OCD-specific words versus neutral words on the emotional counting Stroop task. However, Gln/Glu, Glu, and Gln in the rACC did not differ between groups nor was there an association between increased rACC activation and Gln/Glu, Glu, or Gln in the OCD group.

**Conclusions:** Taken together, these findings strengthen the evidence for rACC dysfunction in OCD, but weigh against an underlying association with abnormal rACC glutamatergic neurotransmission.
Title: Behavioral analysis of nicotine self-administration

Keywords:
Despite the high prevalence of nicotine use in humans, robust nicotine self-administration has been difficult to demonstrate in laboratory animals. We conducted a parametric analysis of nicotine self-administration in non-human primates to better understand the conditions that support nicotine intake. Adult rhesus monkeys (N=6) were trained to self-administer intravenous nicotine (0.01 mg/kg) under a fixed ratio (FR) 1 schedule of reinforcement during daily 90 min sessions. After self-administration of vehicle and a range of nicotine doses (0.001-0.1 mg/kg) was evaluated, the dose was returned to 0.01 mg/kg nicotine and the FR was increased across multiple sessions in an ascending order (i.e. 1, 3, 6, 10, 18, 30, 60, 100, etc). To compare nicotine self-administration with that of another stimulant, monkeys were subsequently given access to 0.01 mg/kg cocaine using identical testing procedures. Finally, the effects of FR change on other doses of nicotine (0.0032 and 0.032 mg/kg) were assessed. Results indicate that nicotine self-administration followed an inverted-U pattern with the peak injections per session at 0.0032 mg/kg. Self-administration of nicotine (at each dose) and cocaine gradually decreased as the fixed ratio size was increased. Application of the exponential model of demand to the FR data found that essential value for cocaine was significantly higher than that for nicotine. Interestingly, elasticity of demand differed according to nicotine dose with the order: 0.0032 < 0.01 < 0.032 mg/kg/inj. These data show that high levels of nicotine self-administration can be achieved in non-human primates but that it’s reinforcing strength is limited.
The role of GABA-A receptor alpha subtypes in benzodiazepine-induced anxiolysis and reward

Benzodiazepines amplify the activity of GABA, the major inhibitory neurotransmitter in the brain, by acting as a positive allosteric modulator of GABA-A receptors. Although classic benzodiazepines such as diazepam (Valium®) reduce anxiety in patients, chronic use is associated with various side effects, including tolerance, abuse liability, and physical dependence. In order to engineer benzodiazepines with fewer side effects and less abuse potential, it is essential to understand how GABA-A receptors elicit specific effects.

GABA-A receptors are heteropentamers, and benzodiazepines modulate the receptors that contain the alpha1, alpha2, alpha3, or alpha5 (but not the alpha4 and alpha6) subunits together with beta and gamma subunits. Identification of individual GABA-A receptor subtype function would be important for the design of novel drugs with reduced side effects, but is significantly hampered by the lack of true subtype-specific ligands. Mice with histidine to arginine point mutations in the GABA-A receptor subunits alpha1 [alpha1(H101R)], alpha2 [alpha2(H101R)], alpha3 [alpha3(H126R)], or alpha5 [alpha5(H105R)] that render the respective subunits insensitive to benzodiazepine modulation have been used to test whether action on a particular receptor subtype is required for a specific action of diazepam (for review see U. Rudolph and F. Knoflach, Nature Reviews Drug Discovery 2011; 10:685-697). Our lab previously found that the alpha2 subunit is required for anxiolysis (K. Low et al., Science 2000; 290:131-134) and reward enhancement (L.M. Reynolds et al., Neuropsychopharmacology 2012; 37:2531-2540; E. Engin et al., Neuropsychopharmacology 2014; 39:1805-1815), while the alpha1 subunit is required for sedation (U. Rudolph et al., Nature 1999; 401:796-800). However, in these single point mutant mice, diazepam still acts on three other alpha subunits. To determine whether modulation of a particular receptor subtype is sufficient to elicit specific effects of benzodiazepines, we used triple-point mutated mice that maintain GABA function at all receptor subtypes but carry only one benzodiazepine-sensitive alpha subunit. Thus, these mice provide a unique model system to selectively modulate a single GABA-A receptor subtype and predict the effects of potential subtype-specific benzodiazepines.

We performed both open field and elevated plus maze tests to examine which GABA-A receptor subtypes (as defined by their alpha subunits) are sufficient for benzodiazepine-induced anxiolysis. In addition, we utilized the conditioned place preference and two bottle choice drinking paradigms to investigate the subunits responsible for benzodiazepine-induced reward. Overall, our results shed light on the functions of individual GABA-A receptor alpha subtypes and are expected to provide valuable information for the development of novel anxiety medications.
Autism Spectrum Disorders (ASDs) affect millions of individuals worldwide, with a prevalence of 1 in 68 newborns. Emerging evidence suggests that mechanisms controlling the appropriate balance between excitatory and inhibitory synaptic transmission in the brain are critical for typical brain function. Consequently, genetic programs that regulate the development of excitatory and/or inhibitory synapses are proposed to underlie ASD, Epilepsy, and other neurodevelopmental cognitive disabilities. The myocyte enhancer factor (MEF2) family of transcription factors regulates activity-dependent excitatory synapse elimination in the mammalian brain. Recently, mutations in the MEF2C gene have been identified in patients who suffer from severe intellectual disability, Epilepsy, and autism symptoms. As a new candidate risk gene for autism, we sought to test whether MEF2C plays a critical role in the formation and/or elimination of excitatory and/or inhibitory synapses in the developing brain. To this end, we generated a conditional knockout (cKO) of the MEF2C gene throughout excitatory neurons of the forebrain. The MEF2C cKO mice display numerous autism-like phenotypes, including reduced social preference, deficits in social communication (ultrasonic vocalizations) as well as hyperactivity and intellectual disability, all of which are analogous to behavioral deficits observed in patients with MEF2C haploinsufficiency syndrome (see Harrington et al.). To identify MEF2C regulated gene targets in the brain, we performed RNA-seq analysis of somatosensory cortex tissue from MEF2C cKO mice. While we found numerous dysregulated genes in the mutant mice, we focused on a ~2.5-fold increase in the α5 subunit of the inhibitory synaptic GABAA receptor (Gabra5). Other than a smaller 1.5 fold increase in the β1 subunit, no other changes in GABA receptor gene expression were observed, suggesting that the specific increase in Gabra5 may be functionally relevant. As a mediator of inhibitory synaptic transmission in the cortex, we speculated that upregulation of Gabra5 levels might alter inhibitory synaptic transmission in the cortex of MEF2C cKO mice. Acute slice recordings from somatosensory cortex revealed that MEF2C cKO mice display a reduction in both the duration and amplitude of cortical UP-states as well as an increase in inhibitory synaptic transmission, as detected by an increase in both the frequency and amplitude of miniature inhibitory postsynaptic currents (mIPSC) in the MEF2C cKO mice. In contrast, we did not detect robust changes in excitatory synaptic transmission, suggesting that the balance of inhibitory to excitatory synaptic transmission is altered in these mutant mice. Consistent with these findings, we also observed that cultured cortical neurons from MEF2C cKO mice display a ~2-fold increase in GABAergic synapse density, suggesting that MEF2C negatively regulates GABAergic synapse density and strength, possibly via inhibitory synapse elimination. Ongoing studies are investigating the specific contribution of increased Gabra5-mediated inhibition in the MEF2C cKO mice by exploring the effect of α5 partial inverse agonists on both behavioral and electrophysiological phenotypes resulting from MEF2C loss of function. Taken together, our data reveals a unique role for MEF2C in the regulation of GABAergic synapse number and function, which might underlie the autistic-like behavioral phenotypes observed in both humans and mice lacking functional MEF2C.
Drug addiction is a serious medical, societal and economic problem around the world. A great deal of effort has been devoted to developing effective pharmacotherapy to combat drug addiction and dependence. To date, only a few medications have been approved by the U.S. Food and Drug Administration for the treatment of addiction. However, there is no effective medication for the treatment of addiction to psychostimulants such as cocaine, methamphetamine and amphetamine. Chinese herbal medicine used in the 19th century for stopping opium smoking may provide new sources for discovery and development of novel pharmacotherpies. Corydalis yanhusuo, a perennial herb in the papaveraceae family, is among the 10 most frequently used herbs to treat heroin addiction in China. L-tetrahydropalmatine (L-THP) isolated from C. yanhusuo has been used clinically in China for more than 40 years as an analgesic with sedative/hypnotic properties. Recently, L-THP has been shown in animal models to reduce the rewarding properties of cocaine, cocaine-induced reinstatement of drug seeking behavior and cocaine-enhanced brain-stimulation reward. However, its mechanism of action is still unclear.
Original Research - Clinical

Presenting Author: Lara Rifkin, Clinical Research Coordinator, Behavioral Health Partial Hospital Program, McLean Hospital

Co-Author(s): Lara Rifkin  Kean Hsu  Weilynn Chang  Dana Borkum  Throstur Bjorgvinsson

Title: Psychometric Properties of the ASI-3 in a Complex, Heterogeneous Treatment Sample

Keywords:

Background: Anxiety sensitivity is the fear of experiencing anxiety and associated bodily sensations due to perceived physical, social, or psychological consequences (Reiss & McNally, 1985). Utilizing the Anxiety Sensitivity Index-3 (ASI-3; Taylor et al., 2007), previous research has implicated anxiety sensitivity as a risk factor for anxiety disorders (Clark, 1986; Reiss, 1991; Olatunji, Bunmi, Wolitzky-Clark, 2009) as well as major depressive disorder (MDD; Tull & Gratz, 2008; Olatunji & Wolitzky-Taylor, 2009). However, little is known about the psychometric properties and sensitivity to change of the ASI-3 in acute, co-morbid populations.

To date, psychometric/validation studies of the ASI-3 have utilized homogenous and/or non-clinical samples (e.g. Taylor et al., 2007; Osman et al., 2010; Bernstein et al., 2010; Wheaton, Deacon, McGrath, Berman & Abramowitz, 2012; Ebesutani, McLeish, Luberto, Young & Maack, 2013) that are not representative of most treatment seeking populations and consequently may not capture as accurately the construct of anxiety sensitivity in these more complex clinical samples. We examined the factor structure, internal consistency, convergent validity, divergent validity, discriminant validity, and sensitivity to change of the ASI-3 in patients receiving CBT in a brief partial hospital setting. We chose to include self-injury as a measure of divergent validity as, to our knowledge, previous research has not indicated that anxiety sensitivity is associated with self-injury.

Methods: Participants (n=158) completed the ASI-3 upon admission and discharge from a partial hospital program. They also completed a structured diagnostic interview in addition to self-report measures of anxiety, depression, self-harm, and disgust sensitivity and propensity. We examined psychometric properties in the total sample and separately for patients with Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, Obsessive-Compulsive Disorder, Post-traumatic Stress Disorder and MDD.

Results: Confirmatory factor analysis revealed that the original 3-factor structure of the ASI-3 yielded strong fit indices for our patient population. In addition, the internal consistency of the proposed subscales (i.e., social, cognitive, and physical) were good to excellent (0.807 to 0.919). The ASI-3 showed convergent validity with constructs proposed to be associated with anxiety sensitivity, including anxiety and depression symptomatology and disgust. In addition, the physical and social concerns subscales showed good convergent validity for individuals with panic disorder and social phobia, respectively. Our measure testing divergent validity, self-harm severity, was not significantly associated with anxiety sensitivity as proposed a priori. The ASI-3 also showed good sensitivity to change, with changes from pre- to post-treatment in the moderate effect size range.

Discussion: This is the first study, to our knowledge, to validate the ASI-3 in a treatment setting with patients displaying varying levels of symptoms, in addition to co-morbid anxiety and mood disorders. Despite the heterogeneity and co-morbidity of our sample, the ASI-3 proved to be a valid measure of anxiety sensitivity and showed good convergent validity with clinical diagnoses. The current results support the use of the ASI-3 to assess anxiety sensitivity in heterogeneous, treatment-seeking samples. This utility in complex populations is of particular value given the increased emphasis on transdiagnostic mechanisms.

Topics areas: Anxiety
Original Research - Clinical
Presenting Author: Rena Fukunaga, Research Postdoctoral Fellow, McLean Hospital; Anxiety and Traumatic Stress Disorders Laboratory

Co-Author(s): Isabelle M Rosso  Christian Webb  Elizabeth A Olson  William DS Killgore

Title: Course of symptom improvement during treatment with internet-based cognitive behavioral therapy for major depressive disorder: a randomized controlled trial

Keywords: internet-based cognitive behavioral therapy, major depressive disorder, symptom improvement, randomized control trial

Background: Emerging evidence indicates that internet-based cognitive behavioral therapy (iCBT) is a viable treatment option for major depressive disorder (MDD), and may be as efficacious as traditional face-to-face treatment. Although there is growing evidence of overall therapeutic effects of iCBT, little is known about the time course of depressive symptom improvement during iCBT treatment. Our research group has been conducting a randomized controlled trial of an Australian iCBT program that we adapted for use in the United States, and preliminary findings show significant depression symptom reduction after 10 weeks of treatment. In this study, we examined the patterns of change in depressive symptoms observed in MDD subjects assigned to an iCBT treatment group or to a monitored attention control (MAC) group over the course of 6 lessons delivered during a 10 week period.

Methods: To date, we have recruited 47 participants (ages 19-45) who were diagnosed with MDD using the Structured Clinical Interview for DSM-IV-TR, and subsequently randomly assigned to either the iCBT treatment condition or MAC condition. Thirty-eight participants have completed all assessments at the time of this analysis (22 iCBT; 16 MAC). Participants had no history of alcohol/substance dependence, neurologic illness, or psychotic disorder. Current psychotropic medications were also exclusionary. Participants in the iCBT condition completed a ten-week intervention comprising six online lessons, printable content summaries and homework assignments. During the 10 week period, participants in both the iCBT and MAC conditions were required to log into the web-based system six times to complete a battery of self-report clinical scales. The primary depression measure that was repeated at each lesson was the 9-item Patient Health Questionnaire (PHQ-9). Significant group differences in PHQ-9 scores across the 6 lessons were evaluated using repeated measures ANOVA and followed-up with independent t-tests.

Results: Participants assigned to the iCBT group showed greater reduction in the PHQ-9 score (F(1,36) = 7.07 p = .012), at the 10 week follow-up, compared to participants in the MAC group. A 2 (group) x 6 (lesson) ANOVA revealed a significant main effect of lesson (F(5,180) = 12.10, p < 0.05), as well as a significant interaction between group and lesson (F(5,180) = 19.73, p = .049). Specifically, the iCBT group showed greater symptom improvement than the MAC group after completing lesson 3 (t(36)=-2.80, p =.008) and lesson 6 (t(36)=-3.76, p = .001).

Conclusions: Participants in this iCBT treatment protocol, compared with participants in an attention control condition, showed a significant decrease in depressive symptoms after the third and fifth lessons, but not the fourth lesson, of a six-lesson series. This pattern of results suggests that critical components of individual iCBT lessons may be enhancing therapeutic gains at particular time points. Future-dismantling studies can help to clarify the specific content and processes that might be driving session-to-session improvement in this and other web-based treatments.

Topics areas: Depression
Background: BPD exists in approximately 2-4% of the general population, up to 20% of all psychiatric inpatients and 15% of all outpatients. Childhood maltreatment and neglect have been strongly implicated as risk factors in the development of BPD and patients with BPD report increased rates of childhood maltreatment across a range of abuse types, such as sexual abuse, emotional abuse, physical abuse, and neglect. Although some investigations have found specific links between a particular type of maltreatment and individual personality disorders, however, considering the recent research findings regarding stress sensitive developmental periods, the timing of abuse and its overall impact on development of BPD is yet to be explored in detail.

Methods: Altogether 430 (173M/257F) unmedicated right-handed young adults (23.19±1.72 years) were interviewed (SCID) and severity and timing of exposure to maltreatment were assessed by the Maltreatment and Abuse Chronology of Exposure (MACE) scale and Traumatic Antecedents interview. Random forest regression was used to assess relative importance of exposure to specific forms of childhood abuse during specific ages and to ascertain whether timing and type of exposure were more important predictors of risk than overall degree of exposure.

Results: Risk for development of BPD was maximally increased by exposure at 9 years of age, and exposure at this age exceeded the importance of overall exposure by nearly two-fold. Of the 10 defined types of maltreatment on our MACE scale, Emotional Neglect at age 9 was the most significant contributor to development of psychopathology.

Conclusion: This study supports the hypothesis of developmental sensitive periods associated with risk for psychopathology and further evidence that certain types of maltreatment and the timing of exposure are crucial factors in development of Personality disorders.
Original Research - Clinical | Division: Child and Adolescent Psychiatry Division

Presenting Author: Kyoko Ohashi, Assistant Neuroscientist / Instructor of Psychiatry, DBRP McLean Hospital / Harvard Medical School

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Title: Effects of childhood maltreatment on brain connectivity of the fiber-stream networks

Keywords: childhood maltreatment, brain network, graph theory, diffusion tensor imaging

Background: Childhood maltreatment is a major risk factor for mood, anxiety and substance abuse disorders. Previous studies have shown alterations in specific brain regions for individuals with history of maltreatment. However, beyond specific brain regions and circuits, the effects of maltreatment on brain networks are not yet understood. The aim of this study was to test the hypothesis that exposure to childhood maltreatment alters the connectivity network of white matter pathways assessed by graph theory using diffusion tensor imaging and tractography.

Methods: Two hundred sixty three healthy unmedicated subjects (102M/161F; 18-25 years; 22.4±2.3, mean±SD) were neuroimaged and analyzed using DTI and fiber tractography. History of exposure to maltreatment was retrospectively assessed by Maltreatment and Abuse Chronology of Exposure (MACE) scale and Traumatic Antecedent semi-structured interviews. Cerebral cortex was parcellated into 90 regions. Numbers of fiber-streams interconnecting all pairs of regions were calculated to construct a white matter connectivity network. Each cortical region and number of fiber-streams interconnecting regions were defined as nodes and edges. Network measures were calculated for all individuals and compared between groups of subjects with exposure to maltreatment versus subjects without. Global/local efficiency, cost, strength, pathlength and clustering coefficient were calculated for the whole brain network. Relative importance of each node was assessed by determining their degree/strength, betweenness, local clustering coefficient, closeness and eigenvector centrality. Analyses were adjusted for effects of gender, age, parental education and household finances.

Results: Global efficiency (p<0.02), cost (p<0.02) and network strength (p<0.06) were significantly smaller and path length was significantly greater (p<0.04) in subjects with histories of maltreatment (corrected for multiple comparisons). The most marked reductions in nodal centrality measures were observed in right putamen (p<0.01: corrected) and in the left orbital part of inferior frontal gyrus (p<0.0007, uncorrected). Additional uncorrected differences were observed in temporal regions and other components of frontal cortex and basal ganglia.

Conclusions: Childhood maltreatment has global effects on the connectivity network of the white matter fiber-stream pathways. Frontal, basal ganglia and temporal regions were most severely affected. This may indicate altered information processing in these regions leading to enhanced risk for mental disorders.

Topics areas: Anxiety, Child, Depression, Imaging, PTSD
Title: Controlled Deactivation of CB1 Agonists: Time Course Studies of Discriminative-Stimulus Effects

Keywords: CB1 Discrimination, Carboxylation of CB1 Agonists, Preclinical pharmacology, Squirrel Monkeys, Controlled deactivation

Many CB1 ligands have long and unpredictable durations of action, which may lead to unwanted or adverse side effects that limit their clinical utility. Recently, a novel synthetic concept, involving the introduction of a metabolically vulnerable ester linkage (i.e., carboxylation) to achieve controlled deactivation, has been used with several CB1 ligands to design and synthesize shorter-acting analogs. Here we evaluated the ability of carboxylation to modify the time course of CB1-mediated effects by comparing the duration of the CB1 discriminative-stimulus (Sd) effects of the CB1 agonists Δ8-THC, nabilone, Δ9-THC, and their carboxylated analogs. In these studies, subjects were initially trained to discriminate administrations of the CB1 full agonist AM4054 (0.01mg/kg, i.m., 50' pretx) from vehicle injections using standard drug discrimination procedures. Next, dose-response functions were determined to identify the dose at which various CB1 ligands fully substituted for the Sd of AM4054. Subsequently, the durations of these effects, using behaviorally comparable doses, were determined by varying the time of administration prior to the discrimination test session.

Results show that each CB1 ligand substituted for AM4054 in a dose-related manner, with full CB1 Sd effects at the highest dose. Further, time-course analyses demonstrated that, as predicted, carboxylation was able to decrease the duration of the Sd for each CB1 ligand. The present results indicate that carboxylation is a practical means for developing CB1 ligands that exhibit shorter duration of action and, consequently, may have enhanced clinical utility.
Intravenous (IV) self-administration procedures in nonhuman primates (NHP) have been widely-used to evaluate the reinforcing effects of drugs that people use. However, the reinforcing effects of nicotine, the primary psychoactive agent in tobacco, have been difficult to establish in laboratory animals. Here we evaluated conditions that may enable IV nicotine to maintain robust and consistent self-administration behavior in NHP. Six male squirrel monkeys were trained to self-administer IV nicotine under a 5-min, (fixed-ratio 5), SO-FI schedule of reinforcement. Initially, three subjects were trained to self-administer IV cocaine (0.01–0.1 mg/kg/injection), and the other three subjects were trained to respond for food (20-30% condensed milk) under the SO-FI schedule conditions. Subsequently, the ability of these subjects to self-administer IV nicotine (0.001–0.032 mg/kg/injection) under the same SO-FI schedule of reinforcement was determined. Results show that under SO-FI schedule conditions, subjects with a history of stable food-maintained responding can more readily acquire IV nicotine self-administration behavior and consistently maintain higher rates of responding (peak unit dose of 0.01 mg/kg/injection = 0.42 ± 0.058 responses/sec) compared to subjects with a prior history of stable cocaine-maintained responding (peak unit dose of 0.01 mg/kg/injection IV nicotine = 0.15 ± 0.069 responses/sec). The present results show that prior experimental history can profoundly impact the ability of NHP to acquire and consistently maintain long-term IV nicotine self-administration behavior. The data provides additional information regarding conditions under which IV nicotine self-administration behavior can be firmly established and evaluated in NHP.
Monitoring changes in opioid receptor function with positron emission tomography (PET) could lead to a better understanding of tolerance and addiction since altered opioid receptor dynamics following acute or chronic exposure to agonists has been linked to tolerance mechanisms. PET imaging of neurotransmitter systems allows the mapping of changes in both receptor occupancy and density following acute or chronic administration of exogenous ligands. We have studied changes in opioid receptor function in vivo with positron emission tomography (PET) following opioid agonist administration. Sprague-Dawley rats were anesthetized and treated with the kappa opioid receptor (KOR) agonist Salvinorin A (0.032 – 1.8 mg/kg, i.v.) prior to administration of the KOR selective radiotracer $^{11}$CGR103545. This is the first report of assessing tracer uptake and kinetics of $^{11}$CGR103545 via dynamic PET imaging in rodents. We observed specific binding in regions of highest kappa opioid receptor density in striatum, nucleus accumbens, amygdala, hypothalamus, midbrain, and periaqueductal gray. When Salvinorin A was administered 1 min prior to injection of the radiotracer, $^{11}$CGR103545 specific binding was decreased in a dose-dependent manner, indicating receptor binding competition. In addition, the unique pharmacokinetics of Salvinorin A (half-life ~8 min in nonhuman primates) allowed us to study the drug’s residual impact on KOR after the drug was eliminated from the brain. Salvinorin A was administered up to 3 h prior to $^{11}$CGR103545 and the changes in specific binding were compared to baseline and the 1 min pretreatment times. Our results indicate that Salvinorin A causes a persistent decrease in KOR function as indicated by decreased $^{11}$CGR103545 specific binding, well after Salvinorin A had been eliminated from the brain.

**Topics areas:** Addiction, Imaging, Pharmacology
Background: Individuals with psychotic disorders are at an increased risk of violence and aggression compared to the general population. However, the contribution of psychosis to violence as well as the clinical and demographic factors associated with these acts of aggression are heavily debated and remain unclear.

Methods: An IRB-approved, retrospective chart review of McLean Hospital medical records yielded 272 consecutive subjects admitted to the inpatient psychotic disorders units from January 2014-March 2014. DSM-V diagnoses included major affective (bipolar or depression) disorders, psychotic disorders (schizophrenia, schizoaffective disorder), and other psychiatric (anxiety, substance-abuse) disorders. We examined the prevalence of patients admitted for homicidal ideation (HI) and/or aggressive behavior, and identified clinical and demographic factors associated with HI, proximal aggressive behavior (aggressive behavior occurring within the episode leading to hospitalization), and aggressive behavior during hospitalization.

Results: Of the 272 patients admitted over the observed three month period, 6.6% were admitted with homicidal ideation (HI), 12.9% were admitted with proximal aggression and 9.2% displayed aggressive behavior during the course of their hospitalization. Notable factors associated with HI were command auditory hallucinations (CAH) (p<.05), panic symptoms (p<.01), proximal aggression (p<.01) and lifetime aggression (p<.01). Factors associated with proximal aggression were living status, with those in residential care showing an increased risk of aggression ($\chi^2(N=272)=15.670, p<.001$); employment status, with those unemployed being more likely to be aggressive (p<.05); absence of suicidal ideation (SI) (p<.05); general substance use ($\chi^2(N=272)=7.474, p<.05$); marijuana use ($\chi^2(N=272)=9.924, p<.01$); and HI (p<.01). Aggression during hospitalization was associated notably with the presence of disorganization (p<.05), mania (p<.05), general delusions (p<.05), persecutory delusions (p<.05), and lifetime aggression (p<.05); and with an absence of SI (p<.001) and depression (p<.001).

Conclusions: These results indicate that HI and aggression are not commonly seen in psychosis. However, when HI is present, it is often accompanied by aggression. Additionally, the data suggest that when SI and/or depression are present, patients are significantly less likely to engage in aggressive behavior toward others. The results further indicate that in addition to CAH, symptoms of anxiety are associated with HI.
Original Research - Pre-Clinical | Division: Division of Alcohol and Drug Abuse, Division of Basic Neuroscience

Presenting Author: Gordana Vitaliano, Instructor in Psychiatry, McLean Imaging Center (MIC)

Co-Author(s): David Rios, Lu Yang, Franco Vitaliano, David Lee, Perry F. Renshaw, Martin H. Teicher

Title: *New Dopamine Transporter Nanoprobes for CNS Molecular Magnetic Resonance Imaging and Targeted Drug Delivery*

Keywords: Clathrin nanoparticles, CNS nanoprobe delivery, Dopamine transporter imaging, Gd contrast agent, MRI

**Background:** Magnetic Resonance Imaging (MRI) is a noninvasive visualization technique with high spatial resolution, but low sensitivity for visualization of brain transporters and receptors. Gadolinium (Gd) contrast agents are used to improve MRI sensitivity, but they cannot cross an intact blood-brain-barrier (BBB). Our goal was to develop MRI Gd-nanoprobes with high T1 relaxivity that can cross an intact BBB and target dopamine transporters (DAT) in the rat brain.

**Method:** Gadolinium-2-(4-Isothiocyanatobenzyl) diethylene-triamine-pentaacetic acid (Gd-DTPA-ITC) was conjugated to clathrin protein through reactive lysine residues. The chelate to protein molar ratio was determined by using a standard Arsenazo III-based spectrophotometric method. Relaxivity of each sample was calculated by using T1 data and Gd concentrations as determined by NMR at 0.47 T. Clathrin nanoplatforms were radiolabeled with 153Gd-DTPA-ITC. DAT ligands (GBR-12935) were conjugated to clathrin cysteine residues via maleimide-PEGs. Biodistribution of DAT-nanoprobes was quantitatively assessed in rats at different time points after intravenous administration. Samples of blood, animal organs and brain regions (e.g., striatum and cerebellum) were removed and weighed, and their radioactivity measured with a gamma counter.

**Results:** The Gd-clathrin-nanoparticle was 18.5 nm in size. The mean chelate/protein molar ratio was 27±4.8/1. At 0.47 T, Gd-DTPA-ITC-Clathrin displayed relaxivity of 1,166 mM-1s-1 per particle, and 16 mM-1s-1 per Gd ion. Biodistribution studies showed a high accumulation of 153GdDTPA-DAT-nanoprobes in brain regions rich in DAT (e.g., striatum). The highest concentration (1.77 % ID/g) of GBR-153GdDTPA-nanoprobes was observed in the rat striatum 90 min after intravenous delivery. By contrast, brain regions with low concentrations of DAT (e.g., cerebellum) had a low accumulation of nanoprobes. Ninety minutes after intravenous delivery the concentration of GBR-153GdDTPA-nanoprobes in the rat cerebellum was 0.70% ID/g.

**Conclusions:** Clathrin triskelia can serve as robust MRI nanoplatforms onto which multiple functional motifs can be added through chemical modifications. Clathrin-nanoprobes displayed 300-fold greater molecular relaxivity than the MRI contrast agent gadopentetate dimeglumine and successfully crossed an intact BBB after intravenous administration. They were able to deliver adequate concentrations of Gd-contrast agent and DAT-ligand to the rat brain and to target dopamine transporters. These preliminary results should encourage further investigations into the use of clathrin as a new brain imaging and drug delivery nanoplatform. This technology may lead to development of non-radioactive, stable molecular nanoprobes to assist in early detection of neurobiological changes in dopamine related disorders (e.g., Parkinson’s, Huntington’s Disease, ADHD, drug addiction, psychotic disorders etc.); to monitor progression of the disease and recovery process; and to help evaluate the effectiveness of drugs aimed at treating these disorders.
Title: Barriers to Referral for Medication Assisted Treatment Upon Discharge from Inpatient Detoxification

Keywords: barriers, addiction, referral, detoxification, buprenorphine

Introduction: Enhancing treatment of substance abuse with medication assisted treatment (MAT) has the potential to improve clinical outcomes and decrease negative impact on patients, families and the healthcare system. However, implementation of MAT in the United States has been challenging. Surveys of healthcare providers have identified several barriers to MAT implementation, including a program’s lack of medical staff, funding barriers to implementing MAT, and lack of access to medical personnel with expertise in delivering MAT (Knudsen et al., 2011). We sought to identify barriers to initiation of MAT upon discharge from inpatient detoxification, as this is a critical juncture in substance abuse treatment.

Methods: Case managers used a survey to track discussions of MAT with each patient, patient receipt of a brief handout on MAT and the recommendation, referral and prescription of MAT upon discharge.

Results: According to our preliminary data on 73 patients, 85% (63) of patients engaged in a discussion of MAT and 95% (69) received the handout. However, only 31% (15) of patients who were recommended a MAT actually accepted referral or prescription of MAT upon discharge. The most common barriers were that the patient declined referral (32, 56%), or was transferred to another inpatient or residential facility (12, 21%). Provider availability, transportation, and insurance coverage were not identified as barriers to MAT referral for any of our patients.

Conclusion: These findings suggest that barriers to implementation of MAT may be evolving, highlighting the central role of the patient’s choices in a complex system, where adequate funding and staffing do not guarantee acceptance of MAT.

Knudsen, HK, Abraham AJ, Oser, CB. Barriers to the implementation of medication-assisted treatment for substance use disorders: The importance of funding policies and medical infrastructure. Eval Program Plann. 2011; 34(4): 375–381
Poster # 88
1:50-2:45

McLean Research Day 2015

Title: Reduced Striatal Dopamine Transporter Binding in Major Depressive Disorder

Keywords: Dopamine Transporter, Depression, Striatum

Introduction: Dopamine (DA) has important functions for reinforcement learning and motivation. Major Depressive Disorder (MDD) has been associated with a reduction in these functions, suggesting that MDD may involve reductions in DA signaling. The dopamine transporter (DAT) is a presynaptic receptor that terminates dopaminergic signaling by reuptake of synaptic DA. DAT density is sensitive to DA levels, with preclinical studies showing that DAT density decreases when DA signaling is reduced pharmacologically, which might represent a compensatory downregulation. Post-mortem studies have found decreased DAT BP in MDD, thought to be a result of decreased levels of mesolimbic DA. SPECT and PET studies of DAT density and BP in MDD have, however, been inconclusive, with some reporting increased, and others decreased DAT levels in MDD. These divergent findings may partly be due to differences in methodology (e.g. use of radioligands with similar DAT and serotonin transporter affinities), as well as the heterogeneity of MDD samples.

Aim: Therefore, the aim of this study was to compare striatal DAT BP in individuals with MDD and healthy controls using the PET tracer C-11 altopane which has high selectivity for DAT sites.

Methods: PET data were acquired in 25 unmedicated adults with MDD and 23 healthy controls using an ECAT EXACT HR + PET camera (in-plane resolution: 4.5 mm FWHM; 63 contiguous 2.5-mm slices) in 15 sec frames for the first 2 min, 60-sec frames for the next 4 min, and 120-sec frames until 60 min. Regional binding potential (BPND) estimates were generated using MRTM2 in the caudate, putamen, NAc and VTA.

Results: A Group (controls, MDD) x Region (caudate, putamen, nucleus accumbens) x Hemisphere (left, right) multivariate analysis of covariance (covariate: age) indicated a significant Group x Region interaction (p < .03). MDD subjects had decreased DAT BP in the left and right putamen compared to healthy controls (p < .03). Similarly, MDD subjects had lower DAT BP than healthy controls in the ventral tegmental area (VTA; p < .02). These effects were specific to the VTA and putamen, as similar analysis on the substantia nigra found no effects (all ps > .05). For both the putamen (r = -.36) and VTA (r = -0.36), mean DAT BP was negatively correlated with the number of prior major depressive episodes (MDE; p < .01). Additionally, length of current MDE was negatively correlated with mean DAT BP in both the putamen (r = -.41) and caudate (r = -.43; p < .05).

Conclusion: Results indicate decreased DAT BP in the striatum and VTA in MDD. The specificity of this finding highlights the significance of mesolimbic over nigrostriatal pathways in the pathophysiology of MDD. Decreased DAT in MDD may be explained as a compensatory down-regulation due to chronic low DA signaling. This is further supported by the finding that DAT BP was negatively correlated with number of previous MDEs, suggesting a progression of DAT down-regulation as MDEs accumulate. These findings have promising implications for understanding the physiological processes underlying MDD as well as potential for interventions.

Topics areas: Depression, Imaging
Title: Childhood Maltreatment and Neuroticism: Evidence for Developmental Sensitive Periods of Exposure

Keywords: Neuroticism, Personality, Sensitive Periods, Maltreatment

Background: Childhood abuse and neglect have multiple adverse outcomes including psychopathology such as depression, anxiety and substance abuse. We have previously reported that childhood maltreatment had a strong correlation with developing personality pathology, specifically neuroticism in early adulthood. In this study, we aimed to predict a sensitive period during which exposure to childhood maltreatment can be significantly predictive of developing neuroticism.

Methods: Our sample consisted of 83 young adults (27 M, 56 F), between the ages of 18-19 years (mean age 18.60 +/- 0.49). All participants were recruited through advertisements in the community. Subjects were interviewed (SCID) and severity and timing of exposure to maltreatment were assessed by the Maltreatment and Abuse Chronology of Exposure (MACE) scale and Traumatic Antecedents interview. The MACE collects information regarding the type and timing of exposure to 10 types of maltreatments. These types included: parental verbal abuse, parental nonverbal emotional abuse, parental physical maltreatment, witnessing physical abuse between parents, witnessing abuse towards siblings, peer verbal abuse, peer physical abuse, emotional neglect, and physical neglect. Personality was assessed using the NEO Personality Inventory Revised. The NEO is a 240-item personality assessment based on five personality traits: Neuroticism, Extraversion, Agreeableness, Conscientiousness and Openness to Experience.

Results: Generalized Linear Modeling (package: glm) and Random Forest with conditional trees (package: cforest) using R statistical software were used to assess the linear correlations and for predictive modeling respectively. Overall neuroticism was significantly correlated with multiplicity of exposure (p<.03) and overall severity of exposure (p<.02). Group comparisons between controls and maltreated group showed that the maltreated group was significantly higher in overall neuroticism (p<.01), significantly higher in neurotic depression (p<.008), and significantly higher in neurotic anger and hostility (p<.0002). Using Random Forest to calculate the maximal importance (± 95% confidence interval) of exposure across age and type of maltreatment in predicting overall neuroticism, in all subjects we found that the most important single predictor was degree of exposure to peer emotional abuse at 14 years of age. However, when broken down into sub-facets of neuroticism, for neurotic depression, emotional neglect at age 10, 11, and 18 followed by peer emotional abuse at age 14 were the strongest predictors. For neurotic symptoms of anger and hostility, emotional neglect at ages 1-4, and 13-15, parental non-verbal emotional abuse at ages 11 and 12 were significantly predictive.

Conclusion: This study further supports the hypothesis that childhood maltreatment is associated with the risk of developing personality pathology. It also provides additional support for the hypothesis of developmental sensitive periods associated with risk for psychopathology and furthers the evidence that certain types of maltreatment and the timing of exposure are crucial factors in development of psychopathology.
Every day we process an enormous amount of sensory input: we see people, listen to music, taste food, and so on. Most of these experiences are forgotten within minutes. However, some stay with us for a lifetime. Why do some memories last so long while most fade so quickly? The answer to this question may have implications for Major Depressive Disorder (MDD).

We hypothesize that the memory status of an experience—remembered vs. forgotten—depends on the activation of brain reward systems during encoding. Dopamine bursts signal unexpected, positive events, and dopamine bursts drive reinforcement learning. We propose that a similar mechanism applies to episodic memory: information encoded during dopamine bursting should be well remembered, because dopamine bursting triggers the shift from early- to late-phase long-term potentiation. Anhedonic MDD involves abnormalities in brain reward networks, thus we propose that depressed adults show poor memory for positive material because blunted dopamine bursting compromises episodic encoding.

To begin testing this proposal, we conducted pilot behavioral (n = 42) and functional magnetic resonance imaging (fMRI; n = 22) studies in community samples. Participants completed a widely-used reinforcement learning paradigm, the Probabilistic Selection Task (PST), and a novel episodic encoding task designed to elicit prediction errors (PEs). Positive PEs—triggered when outcomes are better than expected—elicit dopamine bursts that drive reinforcement learning. Our goal was to determine whether a similar phenomenon applies to long-term memory: we predicted that PEs would support episodic encoding and thus improve recognition memory. Thus, in our episodic encoding task participants learned to sort 240 images based on monetary feedback. By varying the sorting criteria, we induced PE signals that we measured using computational models. One day later, participants took a surprise recognition memory test. We expected a positive relationship between PEs and memory accuracy.

Results supported our hypothesis. Participants performed well in the PST, learning to select more frequently rewarded over less frequently reward stimuli (Pair, p < 0.001; Block, p < 0.001). Moreover, PEs in the PST were associated with strong activation of brain regions implicated in reward responses, including the nucleus accumbens (NAcc) and ventromedial prefrontal cortex (VMPFC) (p < 0.05). Most importantly, we found a positive relationship between PE and memory in the episodic task: PE magnitude on trial t-1 predicted recognition accuracy for the stimulus presented on trial t (Z = 3.35, p < 0.001). An even stronger result emerged when we substituted reward delivery for PE on trial t-1 (Z = 5.44, p < 0.001). Finally, the fMRI data from this task also demonstrated that delivery of rewards (vs. non-rewarding feedback) elicited strong activation of NAcc and VMPFC, but also the bilateral hippocampus (p < 0.05, corrected). Thus, these data confirm that activation of reward networks supports episodic encoding. Importantly, our results indicate that PEs and reward delivery do not “stamp in” material already in the episodic system. Rather, they prepare the episodic system to process new information effectively. We are currently determining if this mechanism is disrupted in MDD.
Original Research - Pre-Clinical

Presenting Author: Elyssa Barrick, Research Assistant, Motivated Learning & Memory Laboratory (Center for Depression, Anxiety and Stress Research)

Co-Author(s): Dr. Daniel Dillon

Title: Investigating source memory and hypofrontality in unipolar depression

Keywords: Memory, EEG, Depression, Learning

Episodic memory deficits in unipolar depression are well-established but poorly understood. Many neuroscientific explanations focus on encoding, when information enters memory networks. For example, hippocampal volume reductions in depression may limit the amount of information that can be encoded. Alternatively, anhedonia-related dysfunction in brain reward systems may remove a crucial source of encoding support. However, encoding is but the first of several stages in the process of remembering; the final stage—retrieval—is equally important. We are testing the hypothesis that diminished frontal lobe function (hypofrontality) weakens memory retrieval in Major Depressive Disorder (MDD). Finding support for this prediction would indicate that depression not only impairs one’s capacity to place material into memory, but also weakens the ability to pull that information back out. This project is in its initial phase, and we welcome feedback on the conceptualization and design. Our methodology is based on two findings. First, work in the McLean Center for Depression, Anxiety and Stress Research has established a negative association between number of depressive episodes and thickness of the medial prefrontal cortex (mPFC), indicating that this brain region is sensitive to depressive illness. Second, cognitive neuroscientists have demonstrated that the PFC is robustly recruited by source memory retrieval, with the mPFC especially activated during retrieval of cognitive sources. Thus, we designed a task that involves retrieval from cognitive vs. perceptual sources, and we predict that, relative to healthy controls, adults with MDD will be especially impaired during cognitive source retrieval due to mPFC dysfunction. Electroencephalography (EEG) data will be recorded throughout, and we predict that diminished cognitive source retrieval in MDD will be accompanied by reduced power in the theta frequency band over fronto-central EEG electrodes. The memory task involves six study/test cycles. During each study phase, participants view 16 emotionally neutral words that appear on the left or right side of the screen: screen position constitutes the perceptual source. Furthermore, words appear above one of two questions: “Living/non-living?” or “Mobile/immobile?” The question on each trial constitutes the cognitive source. Following a 30 second distracter task, memory is tested. Participants view each word again and are asked to retrieve its perceptual source (screen location) and cognitive source (encoding question). An odd/even judgment task is also administered during retrieval as a sensorimotor control. We are currently recruiting healthy controls and depressed adults for the EEG study, and have tested a small sample in a behavioral pilot (n = 5). In this sample, accuracy (percent correct) was similar for cognitive (mean±SD: 79.53±0.40) and perceptual (77.66±0.42) sources (p = 0.59), with accuracy well above chance for both (ts > 16, ps < .001). However, participants responded more slowly when retrieving the cognitive (1.77±1.24) vs. perceptual (1.05±1.12) source, t = 9.72, p < 0.001, suggesting that cognitive source retrieval is especially demanding. We expect depression to exacerbate this RT slowing during cognitive source retrieval, and we predict that it will be accompanied by accuracy reductions relative to what is observed in healthy controls.
Keywords: Chondroitin Sulfate Proteoglycans, Schizophrenia, Olfactory System, Olfactory Bulb, Post-Mortem Study

Chondroitin sulfate proteoglycans (CSPGs), one of the main components of the brain extracellular matrix, have been found to be markedly altered in medial temporal lobe, prefrontal cortex and olfactory epithelium of people with schizophrenia. These molecules are robustly expressed in the olfactory system, where they are postulated to regulate neuronal differentiation and axon guidance throughout life. Interestingly, recent studies reported olfactory dysfunctions, particularly odor identification deficits, in patients with schizophrenia and unaffected, first-degree relatives. Together, these observations suggest that a disruption of CSPG expression in the olfactory system may contribute to olfactory deficits detected in patients with schizophrenia. As a first step toward testing this hypothesis, we are investigating the pattern of CSPG expression in the normal olfactory bulb. More precisely, we are testing the hypothesis that distinct CSPGs may guide odor-specific axonal bundles from the olfactory epithelium into odor-specific glomeruli within the olfactory bulb. Because this process occurs throughout life, as the axons of newly differentiated olfactory receptor neurons grow into the olfactory bulb, this model has the potential of providing important insight on the role played by CSPG in regulating axon guidance during brain development. Preliminary studies on the olfactory mucosa showed that CSPGs form complex structures surrounding the axons of olfactory receptor neurons. Importantly, distinct CSPGs segregate in these structures, suggesting CSPG-specific odor segregation. We postulate that a similar arrangement may be present in the olfactory bulb, where distinct glomeruli may express unique patterns of CSPG expression. Furthermore, this arrangement may also be present in the olfactory tract, where axons from the main olfactory bulb neurons travel to reach the primary olfactory cortex. If this hypothesis is correct, it could then be postulated that altered CSPG expression in the OB and olfactory tract of patients with schizophrenia might be responsible for the phenotypic manifestation of odor identification deficits.
**Title:** Self-Compassion as a Moderator of Worry and Repetitive Negative Thinking in a Severe Clinical Population

**Keywords:** Self Compassion, Partial Hospital Setting, Rumination, Depression, Anxiety

**Background:** Repetitive negative thinking and worry are symptoms that characterize and exacerbate anxiety and depressive disorders, and are often some of the first targets of therapeutic intervention (Ehring, & Watkins, 2008; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Startup & Erickson, 2006). Alternatively, self-compassion, a relatively new construct of interest in the field of psychology, is associated with well-being and may serve as a protective factor increasing emotional resilience (Neff & Lamb, 2009). Theoretical models propose that increased self-compassion leads to decreased rumination and negative thinking (Leary et al., 2007). The purpose of the current study was to examine post-treatment self-compassion as a potential moderator of the association between T1 (pre-treatment) and T2 (post-treatment) worry and repetitive negative thinking in a treatment sample participating in a brief partial hospital program.

**Methods:** The present study investigated 703 adults (46% female, 54% male; mean age=35.29, SD=14.35) presenting with severe psychopathology to a CBT, DBT, and ACT-based partial hospital program. Participants completed the Self Compassion Scale Short Form (SCS-SF), the Penn State Worry Questionnaire (PSWQ), Perseverative Thinking Questionnaire (PTQ) and the Mini International Neuropsychiatric Interview (MINI).

**Results:** Initial t-tests revealed that PSWQ and PTQ decreased significantly, while SCS increased significantly over the course of treatment. To test the first hypothesis, that SCS would moderate the relationship between T1 and T2 scores on the PSWQ, a hierarchical multiple regression was conducted. Step 1 produced the following results $R^2=.37$, $F(2, 298)=86.51$, $p<.001$, worry ($b=0.03$, $p=.70$), self-compassion ($b=-.93$, $p<.001$), indicating that T1 worry and T2 self-compassion accounted for 37% of the variance in T2 worry. Next, we added the interaction term into the model, which accounted for a significant amount of variance in T2 worry over and above the two indicators, $\Delta R^2=.02$, $\Delta F(1, 297)=7.35$, $p=.01$, $b=3.49$, T1 worry ($b=0.01$, $p=.90$), T2 self-compassion ($b=-.89$, $p<.001$), T1 worry * T2 self-compassion ($b=0.01$, $p=.01$). To test the second hypothesis, that SCS would moderate the relationship between T1 and T2 repetitive negative thinking scores, a hierarchical multiple regression was conducted. Step 1 produced the following results $R^2=.49$, $F(2, 378)=186.01$, $p<.001$, T1 repetitive negative thinking ($b=0.45$, $p<.001$), T2 self-compassion ($b=-.67$, $p<.001$), indicating that T1 repetitive negative thinking and T2 self-compassion accounted for 49% of the variance in T2 repetitive negative thinking. Next, we added the interaction term into the model, which accounted for a significant amount of variance in T2 repetitive negative thinking over and above the two indicators, $\Delta R^2=.01$, $\Delta F(1, 377)=9.73$, $p=.002$, $b=-.99$, T1 repetitive negative thinking ($b=0.45$, $p<.001$), T2 self-compassion ($b=-.69$, $p<.001$), T1 repetitive negative thinking * T2 self-compassion ($b=-0.01$, $p=.002$).

**Conclusions:** Analyses suggest that post-treatment self-compassion interacts with pre-treatment worry and repetitive negative thinking in predicting post-treatment worry and repetitive negative thinking. Though our program does not focus heavily on self-compassion, perhaps it is increased as a byproduct of intensive treatment in a supportive setting. Further analyses will explore the association of self-compassion change and other measures of treatment outcome to elucidate the relationship between symptoms...
**Program Description**

**Presenting Author:** Beth Murphy, MD, PhD  Medical Director,  Clinical Evaluation Center, McLean Hospital  
**Co-Author(s):** Wendy Currie, LICSW  Director of Psychiatric Triage  McLean Hospital  
**Title:** Experience of the LEADER program: View from Inpatient Admissions at McLean  
**Keywords:** clinical program, law enforcement, first responders, inpatient treatment, initial assessment  

**Introduction** In 2013, McLean began developing a program to meet the mental health needs of First Responders. Unlike other programs on campus, this program focuses on the needs of specific occupational groups across diagnostic categories and levels of care: Law Enforcement, Active Duty, Emergency Responders (LEADER). These occupations have distinct cultures, which include unique stressors, barriers, and routes to access mental health care.  

**Methods** To facilitate safe and rapid assessment of Peer Support Unit (PSU) and Self-referrals, a single experienced intake person (WC) and clinician (BLM) were designated to coordinate initial intakes and triage clinical assessments to inpatient or residential levels of care. This study looked at LEADER referrals to McLean’s inpatient/residential service between April 2013-November 2014. Other than this centralized supervision, all Intakes, Clinical Assessments, and Medical Reviews were completed by available staff using standard protocols and processes.  

**Results** As anticipated, the largest referral sources for the LEADER program were peer and self-referrals. 141 admissions were included in the assessment, accounting for 100 individual admissions. PSU referrals accounted for 44% of intakes. 15% of admissions were Self-referrals. Clinicians and emergency rooms, which are the majority of referrals for other programs, accounted for only 13% and 24% of admissions to LEADER. Using trained and experienced PSUs appears to provide reliable referrals—conversation between PSU and experienced intake individuals produce a high rate of concordance for diagnostic areas of concern on further assessment. Over 99% of intakes began treatment at an inpatient level of care. 49% of LEADER individuals were admitted for a primary diagnosis of depression or post traumatic stress disorder. 42% were admitted for a primary substance use disorder. Based on initial assessment in the CEC, most individuals were felt to merit additional assessment in more than one diagnostic domain (substance use, depression, anxiety/PTSD)—indicating that multiple diagnoses may be common when individuals in this program present for treatment.  

Most individuals within this program are relatively healthy, compared to the general population. However, a strikingly high percentage of individuals presenting to the LEADER program report a history of head injury with either loss of consciousness or a concussion diagnosis (27%). 5% of individuals within LEADER report a diagnosis of traumatic brain injury.  

**Conclusions** The LEADER program has had a successful start, with over 100 individual First Responders accessing inpatient treatment. While depression/anxiety and substance use disorders are equally common presenting problems, multiple diagnoses are prevalent. Peer referrals are a new, but effective and safe, method for initial clinical referral into the hospital. The high rate of concussions in this population is important to note, given the recent studies correlating multiple concussions with later cognitive disorders and psychiatric disorders. Clinical observation suggests that individuals with a traumatic brain injury diagnosis seem to have a higher risk for occupational jeopardy, legal difficulties, and social conflict. However, the current number of individuals is currently too small for meaningful assessment. Additional investigation and consideration for additional screening in this population is warranted.
Original Research - Clinical

Presenting Author: Ben Legesse, MD, Instructor, Geriatric Psychiatry Research Program

Co-Author(s): Ben Legesse MD, David Harper PhD, Atilla Gonenc PhD, Bruce Price MD, Joanna Georgakas BA, Brent P. Forester MD

Title: Psychomotor Retardation, Basal Ganglia Volumes and Depression Severity in Older Adults with Bipolar Disorder

Keywords: psychomotor retardation, basal ganglia, bipolar, depression

Background: Psychomotor retardation (PMR), characterized by slowing in thought processes and physical movement, is common in mood disorders. Patients with basal ganglia (BG) diseases frequently manifest high rates of mood disorders. Forty to fifty percent of patients with Parkinson’s disease develop depression. Twenty percent of elderly patients with depression also exhibit parkinsonian features which resolve with improvement in mood. Reduced putamen and caudate volume has been found in late life depression. These findings suggest that the well-defined neuropathology of specific BG diseases may provide a useful model for investigating the pathophysiology of mood disorders. To date, no studies have specifically assessed the association of PMR with BG volume.

Objectives: This proposed study will explore the association between basal ganglia (BG) volume and T2 white matter hyperintensity (WMH) Volume and symptoms of psychomotor retardation (PMR) in depressed older adults with bipolar disorder and healthy age-matched controls. The retardation subfactor of the Montgomery Asberg Depression Rating Scale (MADRS) will be used as the primary outcome measure of PMR and scores on Stroop test, Trails A test, and Verbal fluency will be used as secondary outcome measures. Hypotheses: We predict that older bipolar adults will have decreased basal ganglia volume and higher T2 WMH compared to controls. We also predict that basal ganglia volumes will correlate negatively with the retardation sub-factor of the MADRS as well as scores on Stroop test, Trail A test, and Verbal fluency in older depressed bipolar patients compared to controls. Finally, we hypothesize that increased WMH volume will predict higher scores on the retardation sub-factor of the MADRS and secondary outcome measures in older depressed bipolar patients compared to controls.

Methods: Retrospective study of bipolar patients (age 55-89), and age-matched healthy controls utilizing previously collected MADRS scores and 3T MRI scans. Risk factors for MRI T2/FLAIR hyperintensities, including hypertension, cardiovascular disease, diabetes, elevated cholesterol level, BMI and cigarette smoking will be collected. BG (caudate, putamen and globus pallidus), thalamus and total WMH volumes will be derived using previously described techniques.

Results: We analyzed 3T MRI structural data from 42 subjects (23 with Bipolar Disorder and 19 Healthy, age-matched control subjects) recruited to participate in studies of older adults with mood disorders from the McLean Hospital Geriatric Psychiatry Research Program. The mean age of the sample was 65.4 years (+/-8.4 years) and included 21 males and 21 females. Analysis of basal ganglia volumes identified reduced volume of the globus pallidus ($t(83)= 3.30, p < 0.002$) and caudate ($t(83)= 1.99, p=0.05$) in subjects with bipolar disorder compared with healthy controls, though no volumetric differences were identified for the thalamus ($t(83)= -0.37, p=0.71$) and putamen ($t(83)= -0.05, p=0.96$). Further analyses of the relationship between basal ganglia volume, T2 WMH volume, PMR and cognitive tests of executive functioning will be presented.

Conclusions: Reduced caudate and globus pallidus volumes in late life bipolar disorder compared with healthy older control subjects suggests neurobiological differences in neural pathways that impact motor function and help regulate mood. Our hypothesis that PMR better predicts BG volume than global depression severity, is consistent with the theory that the BG regulates psychomotor activity. This study has limitation of correlating volumes (static factors) with PMR measures (dynamic variable). Further studies using functional measures of BG activity may increase our understanding of anatomical correlates of PMR and identify neurobiological mechanisms that may lead to novel treatment approaches.

Topics areas: Bipolar, Geriatric, Imaging
Alexithymia is defined as a deficit in cognitive processing of emotional experiences, such that alexithmic individuals show reduced capacity to identify, express, and engage in their emotional experiences (Ogrodniczuk, Joyce, & Piper, 2012). Approximately 25 percent of individuals seeking psychotherapeutic treatment are considered to be alexithymic (Grabe et al., 2008). In addition, alexithymia is associated with the development and expression of several psychiatric conditions such as depression (Honkalampi et al., 2011), anxiety disorders (in particular, panic disorder; Zeitlin & McNally, 1993), eating disorders (Schmidt, Jiwany, & Treasure, 1993; Taylor et al., 1996) and personality disorders (Bach et al., 1994).

Given its role in the development of psychopathology and treatment outcome, examining possible mediational factors that underlie the association between alexithymia and psychopathology may hold clinical value in that findings may allow researchers to clarify how this relationship may influence and predict treatment outcome. Recent findings suggest that experiential avoidance serves as a mediator of alexithymia and emotion regulation (Lee et al., 2014). Building upon these lines of research, we sought to examine whether experiential avoidance and emotion regulation would additionally serve as mediators of the relationship between alexithymia and depression and anxiety symptom severity.

We tested the relationship in question by examining self report measures of alexithymia, experiential avoidance, emotion regulation, anxiety, and depression in a sample of 370 patients seeking treatment at an intensive CBT-based partial hospitalization program. Alexithymia, experiential avoidance, emotion regulation, and depression or anxiety symptoms were entered into a serial mediation model whereby the relationship between alexithymia and clinical symptoms was mediated by experiential avoidance followed by emotion regulation. This overall indirect effect was significant, as higher levels of alexithymia upon admission were associated with more experiential avoidance, resulting in poorer emotion regulation and more significant depression and anxiety symptoms. Of note, this indirect effect no longer held upon discharge for depression symptomatology, as emotion regulation did not mediate the relationship between alexithymia and depression symptoms.

Our findings suggest that the relationship between alexithymia and depression/anxiety symptomatology is due (at least in part) to high experiential avoidance and emotion regulation deficits. Alexithmic traits can complicate psychotherapy in relation to therapeutic alliance and response to treatment (Ogrodniczuk, Joyce, & Piper, 2012) and is negatively associated with therapeutic outcome (Grabe et al., 2008); our results support this detrimental effect for anxiety but not depression symptoms. As alexithymia may be a pre-existing deficit (Ogrodniczuk, Joyce, & Piper, 2012) it is unclear the extent to which alexithymia itself may be modified by existing psychotherapeutic interventions. Continuing to clarify the malleability of alexithymia and its impact on treatment outcome can improve our understanding of how best to tailor interventions for individuals who may be treatment resistant on account of alexithymic traits, as well as how to target specific symptoms often associated with alexithymia (e.g., more
DBT is a psychotherapeutic intervention that has been adopted across multiple treatment settings and incorporates specific cognitive and behavioral strategies for emotion regulation (Lew et al., 2006). While DBT was originally developed as a treatment for individuals with Borderline Personality Disorder (Linehan et al., 1996), it has proven to be an effective treatment for individuals with drug dependence (Linehan et al., 2002), major depression (Harley et al., 2008), and eating disorders (Safer & Jo, 2010). While preliminary studies have suggested DBT may decrease anxiety symptoms (e.g., Neacsiu et al., 2014), it is unclear what the psychotherapeutic mechanism of action is. Impaired emotion regulation and/or distress tolerance appear to play a role in the occurrence of anxiety disorders (Leyro et al., 2010; Neacsiu et al., 2014); as DBT explicitly focuses on these areas of emotional functioning, it may be a meaningful approach for the reduction of anxiety symptoms in a clinical sample.

This study addresses the above question by examining DBT skill acquisition in a partial hospital setting and more specifically how skill acquisition is associated with potential reductions in anxiety symptoms. In addition, we tested whether this relationship is moderated by specific diagnostic categories. We predicted that individuals meeting diagnosis for an anxiety disorder would show an increase in DBT skills that would be associated with positive treatment outcome, even after controlling for CBT skill acquisition. However, as trauma processing and exposure are considered critical treatment components for PTSD and OCD, respectively (Rothbaum, 2000; Stanley & Turner, 1996), and not present in our specifically offered interventions, we predicted that individuals with those diagnoses would not demonstrate a similar relationship between DBT skill acquisition and anxiety symptom reduction.

A total of 478 subjects were assessed during the course of treatment in a partial hospital program. Patients received a structured diagnostic interview in order to assess for clinical diagnoses, along with DBT and CBT skill acquisition questionnaires, and an anxiety symptom questionnaire. Linear regression was utilized in the analyses, with anxiety symptoms being regressed onto DBT skill acquisition, with CBT skill acquisition as a covariate. A diagnostic group X DBT skill acquisition interaction term was also entered to test our moderation hypothesis. DBT skill acquisition was significantly associated with positive treatment outcome (i.e., reductions in anxiety symptoms) even after accounting for CBT skill acquisition. As hypothesized, this effect was moderated by diagnostic group, as individuals with OCD and PTSD diagnoses did not show reductions in anxiety symptoms that were associated with skill acquisition (through either CBT or DBT).

These results suggest that individuals in a partial hospital setting with anxiety diagnoses (except PTSD and OCD) may benefit specifically from teaching of DBT skills. DBT may be helpful due to its explicit emphasis on improving emotion regulation and distress tolerance as compared to CBT skills that work on the thought and behavior level of change over time. How these results generalize to different treatment settings with different lengths of treatment will be worth further study.
Title: Brain default mode network functional connectivity in poly-substance using emerging adults being treated for opioid dependence

Keywords: opioid, dependence, resting, state, fMRI

Opioid dependence is characterized by impaired cognitive functioning that may in part be due to disrupted brain organization following chronic drug exposure. One brain network implicated in opioid use is the default mode network (DMN), which is a commonly studied set of brain regions typically active at rest and during low cognitive demand conditions. For example, in one study, heroin-dependent adults showed brain DMN functional connectivity abnormalities that correlated with lifetime use of heroin. However, abnormalities in brain functional organization are especially pertinent to younger persons engaged in substance use for whom neurodevelopment is still ongoing. Compared to older adults, emerging adults are at higher risk of relapsing to drug use and more often leave treatment prematurely. The present study examined brain connectivity indices and their association with acute (past 30 day) drug use in a sample of ten emerging adult patients (age 18-27) receiving treatment for opioid dependence at the Alcohol and Drug Abuse Treatment Program (ADATP) at McLean Hospital. Characteristic of the poly-substance use commonly observed among emerging adults entering drug treatment, potential participants were not excluded on the basis of other drug use or dependence, which included marihuana and/or nicotine in most cases. Patients who completed a three-day detoxification program and who were stepping down into the partial hospital program for relapse prevention treatment were approached for study participation. Patients who met DSM-IV criteria for current opioid dependence and who used heroin and/or other opioids in the 30 days prior to partial hospital admission were enrolled into the study. All participants received resting-state functional magnetic resonance imaging (fMRI) scans within 24 hours of partial hospital admission. Resting-state fMRI data were analyzed using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components), followed by dual regression to identify subject-specific spatial maps of the DMN. A non-parametric permutation testing method was used to correlate DMN with total days of opioid plus other drug use in the past 30 days. This analysis revealed that increases in opioid use over the past 30 days was correlated with less connectivity between the DMN and insula, dorsal striatum, and post central gyrus (cluster corrected Z = 2.3, p < 0.05, 5,000 permutations). These findings provide evidence that poly-substance use is associated with functional adaptations in the DMN of emerging adults; these changes in connectivity may also be related to the recent detoxification—further research will be needed to delineate these relationships.
**Title:** Implications of perfectionism in an intensive residential treatment facility for obsessive-compulsive disorder.

**Keywords:** Perfectionism, Obsessive-Compulsive Disorder, Treatment, cognitive flexibility

Perfectionism, a phenomenon characterized by exceedingly high expectations coupled with distress when these standards are not met, is a rampant phenomenon affecting much of the population. One study suggests that nearly a quarter of all college students experience distress due to perfectionism (Research Consortium of Counseling and Psychological Services to Higher Education, 1995, as cited by Ashby & Bruner, 2005). Perfectionism may also play an insidious role in suicide with approximately 56% of victims being described as “perfectionists” (AIPC Suicide Follow-back Study, 2006). Within the scope of obsessive-compulsive disorder (OCD), much of the extant literature suggests that perfectionism is more prevalent among people with OCD compared to healthy controls, and that it may play a primary role in the presentation of OCD. The Obsessive-Compulsive Cognitions Working Group (1997, 2001) has identified perfectionism as a key component in the development and maintenance of OCD. Further research supports the notion that perfectionism does not exist as a single, negative concept, but as a multidimensional phenomenon.

Although the literature disagrees on the number of subgroups of perfectionism, Hamachek’s (1978) early argument for normal and neurotic perfectionism (i.e. health and unhealthy (Stumpf & Parker, 2000), adaptive and maladaptive (Rice & Slaney, 2002)) is now widely accepted. The Revised Almost Perfect Scale (APS-R) is a valid and reliable measure of perfectionism across three domains of perfectionism: high standards (HS), ordering (O), and discrepancy (D) (Slaney, et al., 2001). Correlations between the High Standards subscale and measures of wellbeing, including depression, worry and student’s grade point averages (GPA), suggest that HS may be a measure of adaptive perfectionism. Additionally, scores on the Discrepancy subscale were found to be correlated with these measures of wellbeing suggesting that the Discrepancy subscale may be an appropriate measure of maladaptive perfectionism (Rice & Ashby, 2007; Rice & Slaney, 2002; Sironic & Reeve, 2012). Identification and analyses of perfectionism subgroups is necessary to effectively treat perfectionism within the context of OCD. In the present study, 83 patients at an intensive residential treatment facility for OCD took a battery of measures, including the APS-R, at admission and discharge to measure change over the course of treatment. Preliminary analyses show a decrease in scores on the APS-R over the course of treatment (M = 6.7, SD = 16.7, t(82) = 3.7, p < .001) suggesting that patients experience a relief in overall perfectionist tendencies. However, further investigation show that scores on the High Standards and Ordering subscales did not change significantly whereas scores on the Discrepancy subscale decreased significantly (M = 5.5, SD = 12.1, t(82) = 4.2, p < .001). This suggests that patients experienced a greater decrease in maladaptive over adaptive perfectionism. This study, albeit preliminary, suggests that interventions targeting cognitive inflexibility (i.e. maladaptive perfectionism) may yield more beneficial results than interventions that target the individuals’ high standards. Further analyses are warranted to determine the role perfectionism plays across the course of treatment in different OCD symptom domains.
**Original Research - Clinical | Division: Division of Basic Neuroscience**

**Presenting Author:** Elizabeth Quattrocki Knight, MD., Ph.D., Staff Psychiatrist; Clinical instructor, part time, Psychiatry, Scott Rauch

**Co-Author(s):** Lisa Nickerson, Steven Lowen, Blaise de Frederick, Xiaoying Fan, Bruce Cohen

**Title:** Independent component analysis of passive listening reveals alterations in inter-network connectivity that correlate with emotional valence

**Keywords:** Independent Component Analysis, connectivity, networks, auditory processing, emotional processing

**Purpose:** This study explores whether the specific context created by emotionally salient sounds can alter the coupling between networks during auditory processing.

**Background:** Impairments in accurately perceiving the emotional content embedded in sounds are associated with several psychiatric diseases. Diminished awareness of social and emotional communication in vocal prosody hinders social interactions in autism and schizophrenia; whereas, hypersensitivity to various sounds contributes to the enhanced startle and alarm activation evident in anxiety and depression. Because both pleasant and unpleasant sounds can enhance arousal, traditional GLM analysis of stimulus-evoked responses have difficulty distinguishing regionally specific responses to emotional valence type. Emotional sounds can readily engage traditional limbic structures when compared to neutral sounds, but both pleasant and unpleasant sounds tend to activate overlapping regions common to emotional processing. In contrast, approaches that can examine network activity of the resting state reveal that distributed brain regions organize into discrete, relatively reproducible networks. The myriad of different tasks accomplished by the brain suggest that these systems must dynamically respond to the ever-changing processing demands of the moment.

**Methods:** Here, we have used a passive listening stimulation paradigm of emotionally salient sounds, devoid of cognitive or motor requirements, to examine whether interactions between these distributed networks differentially respond to the emotional salience of auditory stimuli. This study aimed to explore how the coupling between networks during auditory processing might adjust to contrasting emotionally salient sounds and whether emotional context alters inter-network correlations with known resting state networks. Whole head BOLD fluctuations acquired during passive listening of auditory stimuli (International Affective Digital Sound (IADS) library, Bradley, 2007) were decomposed into a series of independent components using group independent component analysis (GIFT http://icatb.sourceforge.net). Dual regression was used to back reconstruct the subject specific timeseries and spatial maps for each component. Negative inverse covariance matrices were constructed to examine differences in the coupling between networks during two separate conditions (all pleasant sounds versus all unpleasant sounds).

**Results:** The initial ICA distinguished 70 separate components, including the previously identified resting state networks. Of these, 9 networks were selected, based on their hypothesized role in auditory and emotional processing for assessment of inter-component connectivity. Paired t-tests of the precision matrices indicate that the coupling between the auditory network, amygdala network, and the default mode network differs between the pleasant and unpleasant sessions.

**Conclusions:** Our findings suggest that inter-network changes in coupling might provide one possible mechanism for a differential response to contrasting emotionally valenced auditory stimuli. Additionally, subcortical networks, such as the amygdala network,

**Topics areas:** Anxiety, Depression, Imaging, Psychotic disorders
**Original Research - Clinical**

**Presenting Author:** Miranda Beltzer, Clinical Research Assistant II, Center for Depression, Anxiety and Stress Research, McLean Hospital

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**Title:** A preliminary analysis of reward processing and affect under stress in depression and childhood sexual abuse

**Keywords:** Reward, Stress, Depression, Abuse

**Background:** Major depressive disorder (MDD) is a prevalent illness that can be caused by numerous factors, including stress. Acute stress has been shown to induce behaviors involved in depression, such as decreased reward responsiveness. Less is known about how early life stress contributes to depression and what factors make a person resilient to early life stress. This study aims to explore how depression and abuse history may modulate stress reactivity with regard to reward processing and affect.

**Methods:** Twenty-six women with and without MDD and with and without a history of childhood sexual abuse (CSA) (2 HC/CSA+, 4 MDD/CSA+, 8 MDD/CSA-, 12 HC/CSA-) completed the Probabilistic Reward Task (PRT), a computerized test of reward processing, before undergoing a stress manipulation involving difficult math, social evaluation, and a cold pressor. In order to prolong the effects of the stress manipulation, participants were informed that they would later need to redo the task due to poor performance. Under this sustained stress, they completed the PRT again, followed by “relief” (the experimenter told participants that they did not need to redo the test). Participants completed self-report assessments of state anxiety and affect at baseline, immediately after the stressor, and after relief.

**Results:** Interim results indicated that reward processing was not impacted by MDD or stress, and neither was state anxiety. For state negative affect, there were significant main effects of both MDD and time. Participants with MDD reported more negative affect than controls, and negative affect peaked immediately after the stressor. Participants with MDD also reported less positive affect than controls, but there was no main effect of time on positive affect. After controlling for baseline affect, there was a significant Time (post-stress, post-relief) x Abuse history (CSA-, CSA+) x Group (MDD, control) interaction for positive affect $F(1, 21) = 4.93, p = .04$. Specifically, individuals with a history of CSA and without MDD showed a trend for faster recovery of positive affect following relief from stress, relative to those with CSA and MDD ($p = .07$). There were no differences in positive affect recovery in MDD and controls without a history of abuse (all $p$s > .05). The Time x Abuse history x Group interaction also approached significance for negative affect $F(1, 21) = 4.08, p = .056$. All groups except the CSA+ MDD showed significant reductions in negative affect following relief from stress ($p = .15$ for CSA+MDD; all $p$s < .05 for other groups).

**Conclusions:** These results suggest that effects of stress on depression are modulated by abuse history, as shown by the different responses of women with and without MDD who had a history of CSA. Resilience to this earlier stress is characterized by enhanced positive affect following relief from stress, whereas non-resilience is characterized by prolonged negative affect even after relief.
**Original Research - Clinical**

**Presenting Author:** J. Alexander Bodkin, Director, Clinical Psychopharmacology Research Program; Assistant Professor, Harvard Medical School, Associate Psychiatrist McLean Hospital; Clinical Psychopharmacology Research Program

**Co-Author(s):** Bodkin JA, Mann T, Saxena PP, Gibbs KJ, Murphy BL, Lasser RA, and Miller BO

**Title:** The effect of adjunctive lisdexamfetamine versus placebo on residual symptoms in depressed subjects on serotonin reuptake inhibitor treatment who display persistent dysphoric apathy and retardation

**Keywords:** major depression, residual symptoms, serotonin reuptake inhibitors, adjunctive treatment, lisdexamfetamine

**Background:** The limited efficacy of standard antidepressant therapy has been amply demonstrated, and augmentation strategies have proliferated. Fatigue, apathy, cognitive impairment, and reduced hedonic tone constitute a frequently encountered cluster of residual symptoms in treated depression, which may be specifically unresponsive to serotonin reuptake inhibitors. This symptom cluster is largely captured in the Dysphoric Apathy/Retardation (MDAR) factor of the MADRS. We report here a placebo-controlled crossover trial of the stimulant lisdexamfetamine dimesylate in SRI treated partial and non-responding depressed subjects suffering from significantly elevated MDAR.

**Method:** We recruited residually symptomatic unipolar depressed patients between ages 18 and 65 undergoing adequate treatment with SSRI or SNRI antidepressants with ≥10 on the MDAR. At screening SRI dosage must have been constant ≥4 weeks. Subjects were informed that to participate they would need to continue at that dosage for the duration of the protocol. After giving informed consent to participate, subjects underwent diagnostic evaluation with the MINI and were rated on the MADRS and CGI to screen for inclusion criteria. Physical examination, clinical labs and EKG were performed. Appropriate subjects returned for comprehensive clinical evaluation to determine baseline values on a wide range of behavioral measures. Here we report changes in MDAR, MADRS, 28-item HAM-D, CGI-S and CGI-I under adjunctive drug versus placebo treatment. After baseline evaluation, subjects received adjunctive flexibly dosed lisdexamfetamine (20-50 mg/d) or matched placebo for four weeks, followed by 2-4 weeks washout and then the alternate treatment, in random order under double-blind conditions. For each measure we compared each patient's change on drug versus placebo using t tests for dependent samples.

**Results:** 28 Subjects completed both treatments. Mean baseline MDAR=13.0 (SD=4.0) with no significant difference between subjects initiated on drug vs placebo. Mean baseline MADRS total = 20.3 (SD=6.1) with no difference between drug vs placebo groups. Initial lisdexamfetamine dosage = 30.0 mg/d, mean endpoint dosage = 38.8 mg (SD=11.2). Mean MDAR baseline score prior to active drug=13.5 (SD=3.94), baseline MDAR prior to placebo=12.6 (SD=3.98). Mean MDAR showed greater improvement at week 4 on drug than placebo (-7.1 vs -3.5, p=0.013). Mean MADRS showed greater improvement at week 4 on drug than placebo (-8.7 vs -4.6, p=0.045). Mean 28-item HAM-D showed greater improvement at week 4 on drug than placebo (-8.9 vs -3.8, p=0.011). Mean CGI-Severity showed greater improvement at week 4 on drug than placebo (-1.4 vs -0.9, p=0.020). Mean CGI-Improvement bordered on greater improvement on drug than placebo (2.2 vs 2.8, p=0.053). Adverse events were more common in subjects on active drug (83.2%) versus placebo (64.3%). Most frequently reported adverse effects were insomnia (35.7% on active drug, 10.7% on placebo), decreased appetite (28.6% on active drug, 7.1% on placebo), and dry mouth (25.0% on active drug, 3.6% on placebo). No subject discontinued due to adverse effects.

**Conclusion:** Subjects with residual depressive symptoms featuring high MDAR showed a superior response to adjunctive lisdexamfetamine than adjunctive placebo at 4 weeks of treatment on multiple measures. Though adverse effects were frequently reported, the drug was well tolerated.
**Title:** Role of the Medial Prefrontal Cortex in Reward-Guided Learning

**Keywords:** medial prefrontal cortex, reward-learning, fMRI

**Background:** The medial prefrontal cortex (mPFC) is a region of the brain strongly modulated by positive and negative outcomes, and is believed to be central to reward-guided learning. This area has also been implicated as a key structure mediating risk for the development of psychopathology, including symptoms of anhedonia and low reinforcement sensitivity. Consequently, further insight into the function of the mPFC in the context of reinforcement learning may improve our understanding of the etiology and expression of anhedonic symptoms. The current study sought to elucidate the role of the mPFC in mediating reward learning and adaptive behavior. Using an instrumental reinforcement task, we examined whether mPFC responses to rewarded vs. non-rewarded cues would predict better accuracy.

**Methods:** Twenty-nine healthy females, ages 18-45, underwent functional magnetic resonance imaging. Individuals completed a reward reinforcement learning task before, during and after a psychosocial stress challenge which consisted of completing a series of mental arithmetic problems varying in difficulty and under time constraints. To further increase the socio-evaluative threat of the situation, participants were given negative feedback about their performance.

**Results:** Wholebrain voxel-wise analyses identified bilateral mPFC activity in a contrast of Win Cues > Neutral Cues (cluster-corrected $p < .005$) during stress. Pairwise correlations revealed a significant relationship between mPFC activity during this contrast and performance accuracy ($r = .73$, $p < .05$). These effects remained even after controlling for birth control and menstrual cycle.

**Conclusion:** These findings suggest that greater cue-evoked activity in mPFC during win vs. neutral trials was associated with better detection of the more rewarded stimulus. Our results support the role of the mPFC as a region responsible for guiding adaptive behavior as it selects the most favorable outcome in a given situation. Considering its critical function in reward learning, abnormalities in the mPFC may represent a particular vulnerability to reduced reward responsiveness. With the collection of additional participants we will examine how exposure to stress may disrupt reward-learning behavior and affect mPFC functioning.
Original Research - Clinical

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

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Title: Predicting Nonsuicidal Behavior in Adolescents with Borderline Personality Disorder

Keywords: Borderline Personality Disorder, Tower of London, Adolescents, Executive functioning

Borderline Personality Disorder is characterized by deficits in executive functioning, emotion dysregulation, and self-harm behavior; however, the putative mechanisms underlying this dysfunction are unclear. The current study included female healthy adolescents (HC = 16) and youth diagnosed with BPD (BPD = 32) aged 14 to 23 years (target sample: HC = 35, BPD = 35). During the initial assessment, all participants completed a diagnostic interview to assess current and past psychopathology, including a structured clinical interview assessing suicide attempts, suicide gestures, and nonsuicidal self-injury (NSSI). Additionally, participants completed a modified version of the Tower of London (ToL), which is a performance-based computer task designed to provide an objective assessment of executive functioning. For each trial, participants arranged a series of colored discs to match an exemplar on the top of the screen. Participants were provided 18s to complete each trial, and successful completion of a given trial is indicative of more intact executive functioning. In the modified version of this task, neutral, negative, or suicide-related words were superimposed on the discs to determine whether emotional stimuli interfered with task performance. Participants also completed a 4-week follow-up structured clinical interview assessing suicide attempts, suicide gestures, and NSSI. When controlling for baseline NSSI behaviors in the past month, preliminary findings suggest that BPD adolescents completing more suicide-related trials at baseline were less likely to have engaged in NSSI behaviors during the 1-month follow-up period (β = -.737, p = .001). As a whole, these findings suggest that executive functioning deficits play a key role in understanding the presence of NSSI behaviors in adolescents with BPD.
**Title:** Differential Impact of Early Versus Late Onset MJ Smoking on Brain Structure in Adults.

**Keywords:** Marijuana, Early-Onset, Brain, Neuroimaging, Cortical Volume

**Background:** Recent public health data highlights a growing perception that recreational exposure to marijuana (MJ) is largely benign or even beneficial, and that this view may be related to increasing rates of MJ use among emerging adults. However, research findings suggest exposure to MJ may impact brain structure and function, especially during adolescence and emerging adulthood.

**Method:** We collected high resolution Magnetic Resonance Imaging (MRI) data from 60 individuals including those who began routine MJ use prior to or at age 16 (Early onset, N=15), after age 16 (Late onset, N=15) and those who did not use MJ (Control, N = 30). While all three groups were matched with respect to gender, handedness, age and IQ, the combined smoking group had significantly fewer years of education relative to the control group (p< 0.002). All subjects’ MRI data were processed in the FreeSurfer Recon-all processing pipeline to generate whole brain surface-based and morphometric data. These data were then subsequently statistically analyzed via the FreeSurfer v 5.3, Qdec (Query, Design, Estimate, Contrast) Tool.

**Results:** Comparing cortical volumes between the control and MJ smoking group as a whole after covarying for gender, education and Total Intracranial Volume (TIV; as generated by FreeSurfer) revealed that the control group had significantly (p< 0.01) greater cortical volume in the bilateral precuneus, lateral orbitofrontal, rostral middle frontal, cingulate and superior frontal regions. Additional lateralized findings included greater volume in the left hemisphere parietal regions, and right hemisphere insula cortex in the control group relative to the entire MJ smoking group. In order to understand the potential contribution of age of onset of MJ use on brain structure, and to determine if either of the MJ-smoking groups might be driving the larger between group findings, subsequent analyses considered the MJ groups independently. Differences in cortical morphology between the early onset and late onset MJ smoking groups will be explored further.

**Discussion:** Data from the present study provide evidence that regular marijuana exposure impacts brain structure in young adults. The findings are particularly relevant given the growing number of states with legislation regarding medical and recreational MJ, and the increasing rates of MJ use among our nation’s youth.
**INTRODUCTION**: Diffusion Tensor Imaging (DTI) is a MRI-based neuroimaging technique that assesses the location, orientation, and anisotropy of white matter (WM) fiber tracts in the brain. Although a number of different anisotropy indices exist, it remains unclear which index is most sensitive for the detection of WM changes in patients with mood disorders. The purpose of this study was to investigate different indices of anisotropy and macrostructural measures and to assess their usefulness in bipolar disorder (BPD).

**METHOD**: Thirty subjects, including fifteen who met DSM-IV criteria for BPD (type I) and fifteen matched psychiatrically healthy comparison, completed a neuroimaging protocol, which included a 48 direction DTI acquisition on the McLean Imaging Center Siemens 3T system. In addition, all subjects completed a series of clinical rating scales designed to assess symptom severity, which included the Young Mania Rating Scale (YMRS), Beck Depression Inventory (BDI) and Montgomery-Åsberg Depression Rating Scale (MADRS). The anisotropy and macrostructural measures included fractional anisotropy (FA), generalized fractional anisotropy (GFA), quantitative anisotropy (QA), linear anisotropy (LA), planar anisotropy (PA), lattice index (LI), volume ratio (VR) and relative anisotropy (RA). Since the anterior corpus callosum has been implicated in previous studies of patients with BPD, the genu of the corpus callosum was selected for all measurements.

**RESULTS**: Although most of the indices, including FA, were reduced in patients with BPD as compared to the control subjects, none of them reached statistical significance, except for the PA (independent samples Mann-Whitney U test; p=0.021). Further, in patients with BPD, PA was inversely correlated with scores on both the MADRS (p=0.006) and BDI (p=0.088). No correlations were observed with YMRS with any of the indices.

**DISCUSSION**: Data from this investigation, although preliminary, suggest that PA may be a more sensitive index of WM changes in patients with BPD relative to the other, often widely used DTI generated indices. The correlation demonstrated between PA and both the BDI and MADRS scales designed to assess depressive symptoms, indicates that PA may be useful for the prediction of the severity of depression in patients with affective disorders. Further, given the heterogeneity in DTI findings among clinical populations, utilizing different anisotropy indices may prove more advantageous than simply examining FA. While these findings should be replicated in additional brain regions, they provide evidence for the utility of alternative anisotropy indices and hold promise for both identification and prediction of clinical severity, which may ultimately result in improved treatment regimens in patients with affective disorders.
Title: Influence of Perceived Physical Health, Mental Health, and Social Support on Psychiatric Readmission among Patients with Suicidal Ideation

Keywords: readmission, suicide, self-harm, physical health

Self-harm is one of the leading factors for hospital admission and readmission. However, little research has been conducted on influential factors that contribute to readmission of psychiatric patients with self-harm. This research is a part of a larger study on predictors of readmission to inpatient psychiatric care over numerous clinical and social variables. Self-harm was identified as one of the predictors that significantly increased patient odds of readmission. This study explores the factors affecting self-harm in relation to readmission. Previous research has found that self-harm and suicide account for a significant portion of readmission.

This study used a convenient sample. The purpose of this study was to examine the relationships among perceived physical health, mental health, social support and hospital readmission for psychiatric patients with suicide following hospital discharge. Using the McLean IDX, HBIPS, BASIS-24, and PoC databases, 16,095 inpatients discharged from McLean Hospital between 2005 and 2011 were analyzed in the current analysis. Patients who were readmitted were identified. Descriptive statistics for social and clinical variables as well as BASIS-24 domains were performed. Preliminary analysis shows that poor physical health, being female, being unemployed due to disability, and interpersonal relationship issues are significantly associated with suicide and readmission. The overall results of the study provide direction to guide future studies of readmission among patients with self-harm. The study will also help clinicians and mental healthcare providers/payers reinforce the need for identification of self-harm risk for readmission and discharge planning interventions to improve the quality of life of patients with self-harm.
Ample evidence suggests that response inhibition is impaired in obsessive-compulsive disorder (OCD; Bannon et al., 2002, Penades et al., 2007). This cognitive deficit may be a manifestation of lateral orbitofrontal loop dysfunction, which may itself serve as an endophenotypic marker for OCD and related disorders. Despite such findings, little research to date has evaluated the putative relationship between response inhibition and psychosocial treatment response. Further, few studies have assessed the variability in response inhibition by symptom subtype and the extent that interactions between these two variables may predict treatment course and outcome. The current study sought to address this gap in the literature. 29 patients with severe, treatment-refractory OCD performed the stop-signal task (Logan et al., 1984) prior to engaging in multi-week intensive residential treatment. A multilevel modeling approach was used to estimate the growth trajectory of weekly OCD symptom severity (Y-BOCS scores) as a function of baseline stop-signal reaction time (SSRT; an index of response inhibition) and continuous indices of symptom subtype. Preliminary findings indicate an interaction between SSRT and the Unacceptable Thoughts (UT) subtype, such that greater impairment in response inhibition was associated with less linearity in symptom improvement trajectory, but only in the relative absence of UT symptoms. At lower levels of UT, worse response inhibition evidenced a “flattening out” of symptom improvement after the second week of treatment. SSRT had little effect on treatment course at higher levels of UT symptoms. Both impaired SSRT and greater UT symptom severity predicted higher overall Y-BOCS scores. These preliminary findings suggest that the nature of response inhibition impairment may vary by OCD symptom subtype, and may have implications for the course of treatment.
Theoretical/Commentary

Presenting Author: Nathaniel Van Kirk, Post-Doctoral Fellow; Ph.D., Obsessive Compulsive Disorder Institute (OCDI)

Co-Author(s):

Title: The Motivation – Compliance Connection: Conceptual Implications for Predicting Treatment Outcome in OCD

Keywords: OCD, Motivation, Compliance, Treatment

Epidemiological studies indicate OCD's lifetime prevalence rate is as high as 3.1% (Kessler et al., 2005). This is in addition to the approximately 25% of individuals who have sub-clinical OCD symptoms (Zucker, Craske, Blackmore, & Nitz, 2006). These numbers are even more alarming given the high degree of impairment endured by sufferers. While exposure and response prevention and cognitive behavioral treatments for OCD have been shown to be efficacious, with meta-analytic effect sizes as high as 1.41 (Abramowitz 1996) and 1.39 (Eddy, Dutra, Bradley, & Westen, 2004) respectively; all sufferers do not recover following empirically supported treatments. Drop-out rates as high as 25% have been reported, with an additional 20% of individuals being considered treatment refractory (Abramowitz, 2006). This is supported by Kozak (1999) who indicated as many as 56% of patients may not respond optimally to ERP. To explain this lack of treatment response multiple prognostic factors have been evaluated. While the empirical literature surrounding prognostic factors associated with OCD has been highly inconsistent, clinically, many identify low motivation and lack of compliance as primary causes of treatment failure. This presentation will identify prognostic factors with the greatest empirical support, including symptom sub-type (specifically hoarding and scrupulosity/sexual obsessions), therapeutic alliance, treatment compliance, employment status, age of onset, symptom duration, comorbidity, initial symptom severity, and insight. Further, a conceptual framework for understanding the impact of prognostic factors using motivational theory and its relationship to treatment compliance will be presented. More specifically, the applicability of a self-determination theory (Deci & Ryan, 2002) for providing a motivational framework to further understanding of how prognostic factors may attenuate empirically supported treatment was evaluated. Empirical support for the theoretical integration of SDT and the prognostic literature was found across multiple domains of psychology, indicating SDT provides a parsimonious framework to answer the question of how prognostic factors attenuate treatment outcome. Recent research supporting the link between motivation (conceptualized through SDT) and treatment compliance in OCD will be presented, focusing on the implications of these findings for understanding how prognostic factors may impact the treatment process. This presentation will build upon the empirical framework established between SDT and the other domains of pathology by presenting a conceptual framework stemming from the motivational literature to guide future research and further understanding of the mechanisms through which prognostic factors may influence treatment outcome, acting through the motivation-compliance relationship.
**Original Research - Clinical | Division: Psychotic Disorders Division**

**Presenting Author:** Ann Shinn, Instructor, Schizophrenia and Bipolar Disorder Program (Ongur Lab)

**Co-Author(s):** J.T. Baker, K.E. Lewandowski, D. Öngür, B.M. Cohen

**Title:** Abnormal Cerebro-Cerebellar Functional Connectivity in Schizophrenia

**Keywords:** cerebellum, schizophrenia, networks, motor, association cortex

**Background:** Schizophrenia is a devastating illness characterized by disturbances in multiple domains. The cerebellum is involved in both motor and non-motor functions, and the “cognitive dysmetria” and “dysmetria of thought” models propose that abnormalities of the cerebellum may contribute to schizophrenia signs and symptoms. The cerebellum and cerebral cortex are reciprocally connected via a modular, closed-loop network architecture, but few schizophrenia neuroimaging studies have taken into account the topographical and functional heterogeneity of the cerebellum.

**Methods:** Using a previously defined 17-network cerebral cortical parcellation system (Yeo et al. J Neurophysiol. 2011 Sep;106 (3):1125-65) as the basis for our functional connectivity seeds, we systematically investigated connectivity abnormalities within the cerebellum of 44 schizophrenia patients and 28 healthy control participants.

**Results:** We found selective alterations in cerebro-cerebellar functional connectivity. Specifically, schizophrenia patients showed decreased cerebro-cerebellar functional connectivity in higher level association networks (ventral attention, salience, control, and default mode networks) relative to healthy control participants. Schizophrenia patients also showed increased cerebro-cerebellar connectivity in somatomotor and default mode networks, with the latter showing no overlap with the regions found to hypoconnected within the same default mode network. Finally, we found evidence to suggest that somatomotor and default mode networks may be inappropriately linked in schizophrenia.

**Conclusion:** We conclude that the cerebellum ought to be considered for analysis in all future studies of network abnormalities in SZ, and further suggest the cerebellum as a potential target for further elucidation, and possibly treatment, of the underlying mechanisms and network abnormalities producing symptoms of schizophrenia.
Background: Childhood abuse and neglect have been found to have numerous outcomes of psychopathology. Assessing for the presence or absence of a traumatic event may not be the only factor involved in predicting an outcome. A person's perception of the experience in terms of severity may perhaps determine impact as well.

Methods: The sample consisted of 560 young adults (223M, 337F), between the ages of 18-25 years (mean age 22.75 +/- 2.09). All Participants were recruited through advertisements in the community. Subjects were interviewed by clinicians using the (SCID) and also current symptomatology was assessed using self report Kellner's Symptom Questionnaire. Symptoms of past and current PTSD were assessed using the SCID and MISSISSIPPI Civilian PTSD Scale. Information regarding the type and timing of exposure for ten types of maltreatment was collected using The Maltreatment and Abuse Chronology of Exposure (MACE) Scale. The MACE collects information on the following types of maltreatment; parental verbal abuse, parental nonverbal emotional abuse, parental physical maltreatment, witnessing physical abuse between parents, witnessing abuse towards siblings, peer verbal abuse, peer physical abuse, emotional neglect, and physical neglect. Along with type and timing of exposure, the MACE scale also asks the subject to indicate if they felt "helpless" and/or "terrified" at the time of the maltreatment.

Results: The key question is whether the subject’s recollection that they felt helpless or terrified added to the impact of exposure to specific types of maltreatment. Interestingly, it did not appear so. Current symptoms of depression were strongly influenced by number of different types of maltreatment reported (F4,387 = 5.61, p = 0.0002) and accounted for 6.8% of the variance in depression scores. In contrast, neither feeling helpless (F1,387 = 1.69, p > 0.19) nor terrified (F1,387 = 0.75, p > 0.38) were significantly associated with current depression scores, and only accounted for 1.7% and 1.2% of the variance, respectively. Similarly, PTSD symptoms were very strongly influenced by number of different types of maltreatment reported (F4,241 = 13.69 p < 10-9) and this accounted for 20.2% of the variance in this measure. In contrast, neither feeling helpless (F1,241 = 0.58, p > 0.44) nor terrified (F1,241 = 0.17, p > 0.67) were significant factors. The same statistical relationships emerged in the analysis of categorical diagnoses.

Conclusions: The current findings show that on the MACE the number of types of maltreatment experienced is a strong determinant of current symptom ratings and history of MDD or PTSD. Whether or not they recalled feeling helpless or terrified by the event did not appear to add anything over the recollection of the exposure, per se. This fits with recommendations made by Brewin et al [1] to focus on events themselves and not subjective feelings about the events when assessing degree of exposure to childhood maltreatment.


Keywords: Childhood maltreatment, PTSD, Depression
Title: Messenger and microRNA expression profiling in neurons and oligodendrocytes in schizophrenia and Parkinson’s disease

Keywords: Gene expression, Pyramidal neurons, GABA neurons, Oligodendrocytes

The human brain is an extraordinarily complex structure consisting of heterogeneous subsets of neurons that mediate distinct aspects of information processing. Disturbances of these neurons compromise the functional integrity of the connectional architecture of the brain, resulting in various psychiatric and neurological disorders. To explore how the molecular integrity of various neural subtypes might be compromised in psychiatric and neurodegenerative diseases, we determined the mRNA and miRNA expression profiles of pyramidal, parvalbumin (PV)-immunoreactive, and dopamine neurons, and oligodendrocytes in schizophrenia (SZ) or Parkinson’s disease (PD), and ascertained the convergence and specificity of the transcriptional networks and signaling cascades that are altered in these disorders. In pyramidal neurons from the superior temporal cortex in SZ, we found differentially expressed mRNAs that belong to the transforming growth factor beta and the bone morphogenetic proteins signaling pathways. In the PV neurons from the same region, differentially expressed transcripts were associated with WNT, NOTCH, and PGE2 signaling and transcription factors such as LHX6, in addition to genes that regulate cell cycle and apoptosis. In PD dopamine neurons of the substantia nigra, there was a predominant down-regulation of mRNAs, including PARK gene family members and genes associated with programmed cell death, mitochondrial dysfunction, neurotransmitter and ion channel receptors, as well as an upregulation of transcripts that are involved in neuronal survival mechanisms. We also assessed oligodendrocytes from SZ subjects, which exhibited a distinct expression pattern that is consistent with dysregulation of cell cycle events. In addition to the mRNA expression profiles, we identified a set of differentially expressed miRNAs in both SZ and PD. Enrichment analysis of their predicted targets or from negative correlation analyses, revealed an association of miRNAs with dysregulated signaling pathways, raising an interesting possibility that dysfunction of neurons or oligodendrocytes in SZ and PD may in part be mediated by a concerted dysregulation of gene network functions as a result of the altered expression of miRNAs. Our data show mostly distinct, but also overlapping dysfunctional gene and miRNA networks between different neural cell populations in SZ and late stage PD, and provide a platform for future downstream analyses aiming to understand the disease-specific and shared molecular processes of individual neuronal dysfunction in these disorders.
Clusterin is a multifunctional disulfide-linked heterodimeric chaperone protein that is involved in many biological processes. Several studies have found clusterin dysregulation to contribute to a number of disorders, from tumorigenesis to neurodegenerative states, such as Alzheimer’s disease, by acting to either promote or inhibit oxidative stress, apoptosis, synaptic plasticity, amongst other functions. Because of our recent observations that the mRNA that encodes clusterin was upregulated by more than 2-fold in both pyramidal and parvalbumin-containing inhibitory neurons in the cerebral cortex in schizophrenia, in this study, we address the hypothesis that clusterin protein expression will also be increased in subjects with schizophrenia. In a cohort of postmortem brains from 20 schizophrenic and 20 demographically matched normal control subjects obtained from the Harvard Brain Tissue Resource Center, we immunohistochemically visualize the cellular localization of clusterin in the dorsolateral prefrontal cortex (Brodmann’s area 9) and primary visual cortex (Brodmann’s area 17). Qualitative examination reveals that clusterin is expressed in various cell types, including both pyramidal and non-pyramidal neurons in addition to glial cells across all cortical layers. Quantification of the densities of clusterin-immunoreactive cell subtypes is underway. Findings of this study will determine if clusterin expression is disturbed in schizophrenia and will thereby shed light on the possible mechanistic link between this protein and known pathophysiological processes of the illness, such as oxidative stress, cellular injury and synaptic deficit.
Effects of self-administered nicotine on fear conditioning in rats

Nicotine can reduce stress and improve coping. It can also enhance cognitive performance and alertness, and facilitate certain forms of learning. These two actions can be conceptualized as having opposite effects on vulnerability to develop post-traumatic stress disorder (PTSD). We designed experiments to examine how nicotine self-administration (SA) followed by a period of abstinence affected the development, expression, and persistence of PTSD-like symptoms as assessed in the fear-potentiated startle (FPS) paradigm.

Exaggerated startle and resistance to extinction are observed in humans with PTSD, and these signs can be studied in animal models using FPS. Experimentally naïve Long-Evans rats were allowed to self-administer nicotine (0.03 mg/inj) or saline in 12-hr (overnight) extended access sessions in standard operant conditioning chambers for a minimum of 14 sessions. This amount of access was expected to produce nicotine dependence, determined by SA of >0.7 mg/session for 4 out of 5 sessions and observable signs of spontaneous withdrawal 11.5 hrs post SA session. After meeting these criteria, separate groups of rats (N=9-10/group) were fear-conditioned at either of 2 time points: immediately after or 12 hrs after their last SA session. Fear conditioning consisted of 10 pairings of a 3-sec light co-terminating with a 1-sec 0.6 mA footshock. After fear conditioning, SA sessions were discontinued. Percent FPS (%FPS) was quantified across 3 test sessions, 48 hrs apart, 10-12 days after fear conditioning and expressed as the percent change in startle on light + startle trials over startle alone trials. In rats fear conditioned immediately after the final SA session, there were no significant differences in %FPS over the 3 test sessions between rats that had self-administered nicotine or saline. However, during test session 1, nicotine-treated rats had lower responsiveness to startle alone than those treated with saline. In rats fear-conditioned 12 hrs after the last SA session, there were no differences in %FPS, but nicotine-treated rats had higher responsiveness to startle alone during test session 1. These findings may indicate that rats self-administering nicotine immediately prior to fear conditioning show signs of protection from exaggerated responses to the startle stimulus, whereas rats conditioned during nicotine withdrawal show signs of vulnerability. This work provides the basis for exploring the effects of nicotine SA on the development and persistence of fear in rats with continued access to nicotine after fear conditioning, and may ultimately provide deeper insight on how nicotine use affects vulnerability to stress related illnesses.
Title: Pituitary adenylate cyclase-activating polypeptide (PACAP) disrupts motivation, attention, and social interaction

Keywords: PACAP, Stress, ICSS, Social Interaction, Attention

Exposure to severe or prolonged stress can cause psychiatric illnesses including anxiety and depressive disorders. The mechanisms by which stress induces these illnesses are not fully understood. Recent work has shown that PACAP (pituitary adenylate cyclase-activating polypeptide) is released in the brain in response to stress and produces anxiety-related behaviors. For example, PACAP treatment in rats causes persistent anxiogenic responses as reflected by increases in acoustic startle. It is well established that stress can also disrupt cognition, motivation, and social interaction. The present studies were designed to investigate how PACAP (0.25-1.0 µg, administered intracerebroventricularly [ICV]) affects behaviors that reflect these core features of mood disorders in adult Male Sprague-Dawley rats. First, we confirmed that PACAP induces anhedonia (reduced ability to experience reward) in the intracranial self-stimulation (ICSS) test. Rats implanted with an ICV cannula and an ICSS electrode were trained in the rate-frequency variant of the ICSS procedure. When reward thresholds were stable (<10% variability) for 3 consecutive days, rats were infused with PACAP and tested immediately for 90 min. Second, we examined if PACAP disrupts performance in the 5-choice serial reaction time task (5CSRTT), which quantifies attention, impulsivity, and motivation. A separate cohort of rats were food-restricted to 85% of free-feeding weight and trained in the 5CSRTT until reaching criteria (>60% correct responses and <20% omissions on 3 consecutive days). Following ICV cannula implantation and re-stabilization of performance, rats were infused with PACAP and tested in 5CSRTT 1 hr later. Finally, we examined if PACAP alters social interaction and social withdrawal. One week after ICV cannula implantation, rats were infused with PACAP and placed in a 60 x 60 x 40 cm Plexiglas chamber with a weight-matched partner rat 1 hr later. Social behavior was videotaped for 10 min and scored by an observer blinded to treatment condition. PACAP produced dose-dependent disruptions in motivation, attention, and social interaction as reflected by increases in reward thresholds in ICSS, disruptions in 5CSRTT metrics (e.g. decreases in correct responses, increases in omission errors, and decreases in post-error performance), and decreases in social interaction behaviors. Interestingly, unlike previously reported effects on acoustic startle, the effects of PACAP on these behaviors were not long-lasting. A better understanding of the impact and persistence of PACAP effects on behavior may facilitate the development of improved treatments for stress-related illnesses.
**Title:** Sex differences in the depressive-like effects of kappa opioid receptor activation do not depend on circulating gonadal hormones in rats.

**Keywords:** dynorphin, sex differences, stress, CRF, depression

The neuropeptide dynorphin activates kappa opioid receptors (KORs) in neural stress circuits to produce depressive-like states. There are pronounced sex differences in behavioral responses to stress. For example, females are more sensitive to the aversive effects of drugs of abuse and stress-induced relapse. Using intracranial self-stimulation (ICSS), we previously found that gonadally intact female rats are less sensitive than males to the depressive-like effects of the KOR agonist U-50,488, regardless of estrous cycle stage. U50,488 induced sex-dependent elevations in c-Fos expression in the paraventricular nucleus of the hypothalamus (PVN) and the bed nucleus of the stria terminalis (BNST), two stress-responsive regions that express corticotropin releasing factor (CRF). We hypothesized that the effects of KOR activation on reward depend on interactions between circulating gonadal hormones and CRF.

To examine the activational effects of gonadal hormones on aversive responses to U50,488, we gonadectomized male and female rats that had previously been trained in ICSS. After five weeks, during which plasma sex hormones decreased (measured with ELISA), baseline ICSS responding was similar across groups (male and female, gonadectomized and sham). Rats were treated with U50,488 (0.0, 2.5, 5.0, and 10.0 mg/kg, IP) and stimulation thresholds compared. No significant differences to U50,488-induced increases in ICSS thresholds were detected between sham and gonadectomized rats. These data suggest that sex differences in KOR-mediated depressive-like states are not due to circulating gonadal hormones. Using quantitative real-time RT-PCR, we found higher basal levels of prodynorphin mRNA in the female PVN, BNST, and amygdala, and lower KOR mRNA in the BNST. Finally, levels of CRF receptor 1 (CRFR1) mRNA were lower in the amygdala and BNST of intact female compared to male rats. These findings raise the possibility that elevated dynorphin tone in females occludes the effects of KOR agonists, and that KOR-mediated activation of CRF systems is blunted in females due to decreased CRFR1. This underscores the importance of understanding KOR function in both sexes such that pharmacotherapeutics targeting mood disorders can be rationally designed.
Clinical studies have demonstrated associations between maternal infection and inflammation during pregnancy and increased risk of autism. Furthermore, preclinical investigations of maternal immune activation and the development of autism-like phenotypes support the hypothesis of immunological involvement in the etiology of at least some forms of autism. Alterations in neural connectivity and abnormal functioning of numerous brain regions, such as the medial prefrontal cortex (mPFC), have been reported in autism spectrum disorders (ASDs). Further examination of the biological consequences of in utero infection may elucidate the specific role of the immune system in the onset of ASDs.

To investigate whether in utero infection alters function of the prelimbic (PL) division of the mPFC in C57BL/6J mice, we administered the viral mimic polyinosinic:polyctydyllic acid (Poly I:C) (20 mg/kg) or vehicle (phosphate buffered saline) to female C57BL/6J mice on day 12.5 of pregnancy. The offspring were tested for core behavioral features of autism, including deficits in communication (measured by analysis of ultrasonic vocalizations in early childhood and in adulthood), diminished social behavior (measured in the social interaction test), and increases in repetitive or stereotyped behaviors (measured in open field and marble burying tests). Following these behavioral tests, we conducted electrophysiology studies in brain slices of representative mice from both treatment conditions to examine the consequences of maternal immune activation on membrane excitability and glutamatergic synaptic transmission in the PL mPFC. Although membrane excitability of PL neurons remained unchanged, Poly I: C treated offspring had reductions in the amplitude of NMDA receptor-mediated synaptic responses at inputs to PL neurons without affecting AMPA receptor-mediated synaptic responses. Examining the behavioral consequences of in utero inflammatory responses together with cellular and molecular consequences may provide evidence for an etiologic subtype of neurodevelopmental disorders triggered by insults (e.g. exposure to viruses or bacteria, stress, toxins) that cause immune activation. Our results provide evidence that early immune challenge can trigger behavioral changes that share features with the core signs of autism and corresponding changes in brain glutamate function. Establishing cause-effect relationships among these findings may facilitate the development of interventions that target the immune system to more effectively treat, or even prevent, certain types of ASDs.
Involvement of Kappa Opioid Receptors in Chronic Social Defeat Stress-Induced Alterations in Sleep, Body Temperature, and Motor Activity in Mice

Keywords: sleep, stress, depression, circadian, kappa opioid receptors

Stress is a critical component in the etiology of many chronic psychiatric illnesses, including Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD). Research into the mechanisms by which stress produces symptoms of mood disorders will facilitate the development of new pharmacotherapies for these illnesses. In MDD and PTSD, dysregulation of sleep and circadian rhythms (i.e., processes following an entrainable, 24 h oscillation) are two such symptoms. In rodents, a single conflict with an aggressive conspecific (i.e., social defeat) increases subsequent non-rapid eye movement (NREM) sleep duration and intensity. Moreover, five consecutive exposures to social conflict impair the circadian amplitude of body temperature in rats. However, it is unknown how repeated, daily (i.e., chronic) social stress alters sleep architecture and circadian rhythm of body temperature and motor activity.

We first examined the effects of chronic social defeat stress (CSDS), a behavioral paradigm that engenders a long-lasting depressive-like phenotype in mice, on sleep and the circadian rhythms of activity and body temperature. Adult male C57BL6/J mice were surgically implanted with telemetry transmitters that enable continuous wireless recording of cortical EEG, neck EMG, body temperature, and activity. Following recovery from surgery, continuous recordings were obtained for 5 baseline days, 10 days of the CSDS (or control) regimen, and for 15 days post-defeat. On each day of social defeat, 1 h into the light cycle (zeitgeber time 1), defeated mice were exposed to a novel, aggressive CD-1 mouse for 10 min, followed by continuous, protected sensory exposure. Control mice were similarly housed opposite a conspecific with continuous, protected sensory exposure, but were never exposed to defeat stress. In a follow-up experiment, we tested the effects of JDTic (30 mg/kg, i.p.), a long-acting kappa opioid receptor antagonist, or saline vehicle (VEH) pretreatment on CSDS-induced changes in these measures.

Our findings revealed a transient increase in rapid eye movement (REM) sleep duration and number of episodes in the defeated mice on days 6-10 of CSDS, relative to baseline and to controls. There was an increase in NREM episodes in defeated mice, but not in controls, on days 1-5 of CSDS, relative to baseline. These measures returned to baseline levels during the post-defeat period. Analysis of circadian amplitude (the difference between the maximum and the mean of the wave) and period (duration of a complete oscillation) for activity revealed a decrease in amplitude, but not period, in defeated mice, relative to controls, throughout and following CSDS. Body temperature amplitude, but not period, was similarly attenuated in both groups on defeat days 6-10, but this impairment manifested earlier (defeat days 1-5) in the defeat group. Pretreatment with JDTic attenuated increases in REM duration and episodes, but had no effect on NREM episodes, relative to VEH. JDTic pretreatment also ameliorated the impairment in circadian amplitude of both activity and temperature, relative to VEH. Overall, these findings provide a foundation for studies to further explore the neural mechanisms by which CSDS alters sleep and circadian amplitude and support the development of KOR antagonists for the treatment of stress-related disorders.
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