Title: Evaluating the Efficacy and Cognitive Sequelae of ECT for Patients with Dementia Exhibiting Agitation and Aggression

**Background:** Agitation and aggression are common in dementia and result in decreased quality of life for patients, increased caregiver burden and distress, and increased rates of institutionalization. There is no current standard treatment for agitation and aggression in patients with dementia. Atypical antipsychotics have been shown to be only modestly helpful in addressing these noncognitive behavioral symptoms and may possibly increase mortality and cerebrovascular adverse events. We will examine the efficacy of Electroconvulsive Therapy, a safe and effective intervention for mood disorders, to reduce agitation and aggression in patients with dementia. Previous studies have found that ECT was effective in reducing agitation and aggression in dementia patients (Sutor & Rasmussen, 2008; Bang et al, 2008; Grant & Mohan, 2001); however these studies involved a small sample size and did not include a control group. **Retrospective Data:** Based on a systematic chart review of patients admitted to the Geriatric Neuropsychiatry Unit of McLean Hospital, 16 patients with dementia (of various etiologies) and symptoms of agitation and aggression were identified. These patients received an average of 9.3 ECT treatments (mostly bilateral). Analysis of independent ratings of patient behavior on measures of agitation, aggression and global clinical functioning revealed sharp reductions in symptoms of agitation, aggression, shouting, motor agitation and resistance with care. Significant improvements were observed in global clinical functioning. This retrospective data gave impetus to the development of our proposed study. **Hypotheses:** For our prospective study, we hypothesize that dementia patients who undergo ECT will have a greater reduction in agitation and aggression. We also hypothesize that ECT will not have a significantly negative impact on cognitive and neuropsychiatric functioning as measured by pre- and post treatment neuropsychological and neuropsychiatric assessment. **Method:** We will include 30 participants with a diagnosis of dementia (of various etiologies), an MMSE <25, and symptoms of agitation and aggression, who are inpatients of the Geriatric Neuropsychiatry Unit of McLean Hospital and referred by their psychiatrist for ECT. Fifteen patients, whose healthcare proxy consent for ECT, will be in the ECT treatment group and 15 patients, whose healthcare proxy does not consent for ECT, will receive psychopharmacological intervention alone and will serve as controls. This will allow us to compare the efficacy of ECT and psychopharmacological intervention in the treatment of agitation and aggression. To our knowledge, this will be the first prospective study to compare the effect of ECT and psychopharmacological intervention on aggressive and agitated behaviors and cognitive and neuropsychiatric functioning pre and post treatment.
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Title: Cerebellar Lingula Size and Experiential Risk Factors Associated with High Levels of Alcohol and Drug Use in Young Adults

Previous studies have reported cerebellar abnormalities or static ataxia associated with risk for chronic use of alcohol and drugs. Adverse childhood experience (ACE) is another strong risk factor for later substance abuse. We therefore, sought to ascertain the relationship between morphological phenotypes of the lingula (Lobule I) of the anterior cerebellar vermis (ACV), and exposure to emotional (EM) versus physical (PM) maltreatment, on the degree of ongoing alcohol or drug use. The study design consisted of a cross-sectional in vivo neuroimaging study, utilizing retrospective assessment of maltreatment history and self-reports of alcohol and substance use. Study participants were 153 subjects (54M/99F, 21.9±2.2 years) selected for imaging from a database of 1,402 community participants 18-25 years of age, who completed a detailed online screening instrument, and met rigorous inclusion/exclusion criteria. Subjects were exposed to only physical abuse or harsh corporal punishment (PM group, n=37); parental verbal abuse and/or witnessing domestic violence (EM group, n=58); or had no history of maltreatment or Axis I disorders (n=58). The main outcomes measures consisted of the grey matter volume of Lobule I as measured by manual tracing, number and type of alcoholic beverages consumed during a drinking session, number of sessions per month, and monthly drug use, along with family history of drug and alcohol abuse. Lingula thickness was not attenuated by alcohol use or maltreatment history. However, increased lingula thickness was associated with greater consumption of drugs and hard liquor, particularly in physically maltreated subjects who consumed 2.5- and 2.7-fold more alcohol, and used drugs 6.1- and 7.8-fold more frequently than controls or EM subjects, respectively. In conclusion, physical maltreatment was observed to interact with cerebellar morphology resulting in a strong association with alcohol and substance use. Lingula thickness may represent a novel, experientially-sensitive, phenotypic risk factor for enhanced alcohol and drug use, that perhaps modulates sensitivity to these agents.
Title: Recent Studies of Clinical Characteristics of Bipolar Disorder

Based on the proposition that progress in biological psychiatry requires refinements of phenotype-definitions as well as technical advances, our international program of collaborative studies with clinical and research experts on bipolar disorder (BPD) aims to refine understanding of the diagnosis, nature, and course of BPD and its sub-types. Recent findings include large differences in diagnostic stability among major psychiatric disorders between onset and 2-years: ICD-10 was more stable than DSM-IV, and both were far-better for type-I BPD than other diagnoses. There also were marked differences in onset-ages among BPD types I vs. II and unipolar major depression (MDD) patients, by sex and by first-episode type. Two-year morbidity following a first-episode was remarkably similar to that reported in mid-course BPD patients ≥10 years later. First-episode polarity strongly predicted types and amounts of future morbidity: depressive and mixed-onsets led to more overall morbidity and much more depressive or mixed morbidity than mania or psychosis—opposite to illness following initial mania. Patients were ill 30%–50% of follow-up time. Much more time was spent in depressive-dysphoric states, despite use of modern mood-stabilizing treatments, underscoring limitations of current treatments for BP-depression. Residual depression was strongly associated with functional disability and very high suicide risks of BPD (possibly higher in type II than I). Lithium had abundant and compelling evidence of reducing suicidal risk in BPD patients, may also help in MDD, and may be more effective than anticonvulsants. The course of BPD as within-person recurrence-cycles, contrary to commonly claimed worsening over time based on other methods, was chaotic or random, with an excess of no-change vs. cycle-count; few patients showed clear cycle-acceleration or slowing. Recurrence-counts or years of untreated illness had little effect on clinical benefits of eventual trials of long-term mood-stabilizing treatments. These findings contribute to a more textured and complex view of BPD, indicate unsuspected prognostic predictability from onset, and point toward ways of improving biological and experimental therapeutic research.
Title: Examining Transactional Models of Depression through a Stress Generation Lens

Adolescence is a period marked by transition and growth. Such transition is stressful, and depressive symptoms may be experienced. Depressive symptoms are associated with an array of negative outcomes, and one of the most robust predictors of these symptoms is the occurrence of stress. At the same time, past research is divided with respect to the role that stress plays in the manifestation of symptomology. While many researchers have examined stress from a passive perspective in the context of a diathesis-stress framework, recently researchers have begun to adopt a transactional perspective in order to determine whether individuals play a central role in generating their own stressors and subsequent depressive symptoms.

The majority of research examining depression employs a diathesis-stress framework. Such an approach posits the occurrence of stress activates underlying diatheses which then trigger depressive symptoms. A diathesis-stress model is effective in examining individual difference variables; however, it implicitly assumes that (a) individuals are passive recipients of stress and (b) vulnerability factors are dormant in the absence of stress. In contrast, the transactional framework suggests that individuals actively contribute to the stressors they experience. Consistent with stress generation research (e.g., Hammen, 1991), these stressors then contribute to higher levels of depressive symptoms. Therefore, the transactional model may better address the causal process as it delineates the temporal relationship amongst diatheses, stress, and symptomology.

Prior research has indicated that social support is a key factor in the onset of depressive symptoms. While low perceived social support is associated with higher levels of depressive symptoms, there is a paucity of research examining such support in the context of prospective, integrative models. Further research is needed to examine specific domains of social support (e.g. peers, classmates, and parents) as these domains may have differential effects on both stress and depressive symptoms. The current study addressed these gaps by using a multi-wave, longitudinal design. At the initial assessment, adolescents (n=260) completed self-report measures assessing social support, stress, and depressive symptoms. Additionally, participants reported stress and symptomology in each of the four waves spanning six months. Results of time-lagged, idiographic, multilevel modeling were in line with our hypotheses. First, when examining the diathesis-stress framework (i.e., moderation), results indicated that dependent interpersonal stress was significantly associated with follow-up depressive symptoms for individuals who possessed low levels of classmate support. Second, with regard to the transactional perspective, both dependent interpersonal and non-interpersonal stress mediated the relationship between social support (i.e. total, classmate, and parent) and subsequent depressive symptoms. Last, in contrast to past research, results indicated that peer support did not buffer individuals from experiencing depressive symptoms following the occurrence of stress. Overall, findings suggest that a more active (transactional) versus passive (diathesis-stress) model may better predict depressive symptomology.
Background: Generalized anxiety disorder (GAD) is a chronic illness characterized by excessive anxiety and worry more days than not for at least 6 months. Even with effective treatment, many patients are vulnerable to relapse. This posthoc analysis sought to identify potential predictors of relapse among responders to treatment in a relapse prevention study.

Methods: Posthoc analyses were performed on data from a relapse prevention study of duloxetine for GAD using a randomized withdrawal design. Following open-label duloxetine 60-120 mg QD during a 26-week treatment phase, patients who met response criteria for the last 2 consecutive visits of the open-label phase (defined as a ≥50% reduction in Hamilton Anxiety Rating Scale (HAMA) total score from baseline to a score ≤11 and a Clinical Global Impressions-Improvement (CGI-I) rating of “very much improved” or “much improved”) were randomly assigned to either continued duloxetine 60-120 mg QD (N=216) or placebo (N=213) for a 26-week double-blind continuation treatment phase. Relapse was defined as an increase during this period in the CGI-Severity (CGI-S) rating of ≥2 points from randomization (end of open-label phase) to a score ≥4 (moderate) while meeting diagnostic criteria for GAD (other than duration) or by study discontinuation due to lack of efficacy as determined by the clinician. Six groups of variables were assessed as predictors of relapse including demographic characteristics, duration of meeting response status prior to randomization, physical symptoms (e.g., visual analog scales [VAS] for pain) and functional measures (Sheehan Disability Scale) at study entry and randomization, and anxiety (HAMA) and depression (Hospital Anxiety and Depression Scale [HADS]) measures at study entry and at randomization. Univariate analyses were performed to determine significant predictors in each of the 6 groups. A backwards elimination model was used in multivariate analyses to determine significant predictors among those significant in the univariate analyses.

Results: Overall, there was a significant benefit of duloxetine versus placebo for risk of relapse; the estimated 6-month probabilities of relapse were 13.7% for duloxetine and 41.8% for placebo. Race was a significant univariate predictor with Caucasians (87.7% of population at randomization) being more likely to relapse than other races. Only 1 measure at ‘study entry’ (HADS Depression >9) was a significant predictor. In contrast, all functional measures and most of the mood and pain measures ‘at randomization’ were significant univariate predictors of relapse. There were 20 significant treatment-by-predictor interactions. Following backwards elimination, the most significant predictors of relapse were HAMA item 1 (anxious mood) ≥1, VAS Pain While Awake >30, and race.

Discussion: Race, post treatment anxious mood (HAMA item 1 ≥1), and VAS Pain While Awake >30 were significant predictors of relapse found via multivariate analyses. Based on these results, clinicians should closely monitor residual anxiety as well as pain in patients with GAD who has responded to treatment. More depressive symptoms prior to treatment and Caucasian race may be associated with greater risk of relapse post-treatment.
Title: Blunted Stress Response in Young Adults Exposed to Harsh Corporal Punishment

BACKGROUND: Childhood exposure to harsh corporal punishment (HCP) is a stressor that increases risk of drug abuse. A critical factor in mediating risk for substance abuse, and risk for relapse, is stress responsivity. Pre-clinical studies indicate that early exposure to stress programs the stress-response systems to have altered response to subsequent stressors, and evidence suggests that this is also true in humans. We sought to test the hypothesis that HCP programs stress response systems leading to an enduring alteration in responsivity that might foster addictive behaviors. Especially we hypothesize that exposure to early stress would result in a diminished capacity to recover after exposure to stress.

METHOD: Nineteen healthy young adult controls (8M/11F - 18-25 yr) with no history of exposure to trauma, physical, sexual or emotional abuse, or HCP were compared in the Trier Social Stress Test (TSST) to 11 young adults (7M/4F - 18-25 yr) with a history of frequent corporal punishment to their buttocks, occasionally with an object (belt, hair brush, etc.) that was used specifically for discipline. They had no history of exposure to trauma or abuse, all subjects were unmedicated, had no history of substance abuse, and no evidence of drug or alcohol use prior to testing. The TSST was used to assess differential effects of cardiac and neuroendocrinal responses. Briefly, the TSST consists of an anticipation/preparation period and test period in which subjects have to deliver a free speech and perform mental arithmetic in front of an audience. The TSST was performed between 1:30 and 4:00 PM. Cardiac interbeat interval was measured continuously, and subject to spectral analysis to extract components that are predominantly indicative of sympathetic and parasympathetic activity. The high frequencies (HF) and low frequencies/high frequencies (LF/HF) components was considered to indicate the parasympathetic and sympathetic component of the heart rate variability. Blood samples were collected prior to challenge, at 15 min intervals for the first 90 minutes, and again at 120 minutes post challenge. Immunoassays have been performed for cortisol and are pending for ACTH, oxytocin, vasopressin and nitric oxide.

RESULTS: Controls had a robust heart rate acceleration increase in sympathetic arousal and decrease in parasympathetic tone during the TSST, with recovery to baseline in 10 – 20 minutes post stress challenge. Subjects with HCP showed almost no increase in heart rate during the stressor, and had a persistent drop in heart rate below baseline after the stressor accompanied by an increase in parasympathetic tone and loss of sympathetic arousal. Group differences in cortisol levels over time were also characterized by a significant quadratic interaction ($F_{1,19} = 5.11, p = 0.036$). Cortisol levels rose 51% in controls from baseline to stress challenge but only increased by 19% in HCP subjects.
Title: Physiological and subjective effects of nicotine versus smoking-associated conditioned reinforcers in dependent and non-dependent smokers.

In 2007, approximately 20% of US adults reported smoking cigarettes. Of these, 40% tried to quit within that year. However, only 4-7% of smokers are likely to succeed at any given quit attempt. While the most psychoactive chemical in cigarettes is nicotine, dependence on nicotine alone does not seem to account for the high failure rate associated with quit attempts. Rather, a great deal of evidence suggests that sensory aspects of smoking (including taste, smell, and tracheobronchial sensations, which are conditioned to be reinforcing through many thousands of pairings with nicotine) may be responsible for maintaining smoking behavior. To our knowledge, we are the first to investigate whether responses to nicotine and placebo cigarettes (which provide only conditioned reinforcement) differed between dependent and non-dependent smokers.

Fourteen smokers, who were blind to smoking condition, smoked two nicotine cigarettes through an fMRI compatible device during one visit and two placebo cigarettes thorough this device on a separate visit. Dependence was defined as a score of 6 or more; non-dependence as a score of 3 or less on the Fagerstrom Test for Nicotine Dependence. During smoking physiology was recorded and smokers reported subjective ratings using a computerized visual analog scale. Regardless of smokers’ dependence status, nicotine smoking increased positive ratings significantly more than placebo smoking (high p=0.008, feel p=0.02, like p=0.035). At the time of peak effect, dependent smokers felt the drug 47% more (p=0.02), liked the drug 48% more (p=0.037), and felt 48% higher (p=0.011) than non-dependent smokers during nicotine smoking. No significant differences were observed between time courses of subjective ratings of craving, anxiety, or irritability when the nicotine smoking condition was compared to the placebo condition, indicating nicotine and placebo cigarettes were equally efficacious in producing changes in subjective ratings! When dependence was considered, nicotine smoking produced greater reductions in craving (57%, p=0.009), anxiety (77%, p=0.001) and irritability (62%, p=0.004) in dependent smokers than non-dependent smokers. Significantly, placebo smoking produced greater reductions in craving (56%, p=0.042), anxiety (62%, p=0.015), and irritability (63%, p=0.023) in dependent smokers compared to non-dependent smokers. These data are consistent with the idea that the larger increases in smoking-induced positive feelings occurring for dependent smokers are largely due to the presence of nicotine. However, nicotine does not appear to be required for relief from withdrawal-associated negative feelings.

This research was supported by NIDA grants K01DA021730, R03DA021231 (KPL), K25DA14013 (BBF), K05DA00343 (SEL)
Title: Past As Prologue: Yesterday’s Vision Leads To A Lasting Legacy

Under the leadership of Edward Cowles, M.D., our seventh Superintendent, McLean Hospital became the world’s birthplace of psychobiological hospital based laboratory research in 1888. The combination of basic and clinical laboratories was a radical innovation in a clinical psychiatric institution at the time. From a $600 appropriation by the Board of Trustees, McLean Hospital receives over $40 million annually in Federal and private research grant awards. This significant and impressive accomplishment can be traced back to the strong scientific laboratory tradition established by Dr. Cowles. This legacy is a direct result of Dr. Cowles drive and unrelenting commitment to achieve progress in the advancement of psychiatry.

With the opening of the new, free-standing Biological Research Laboratory in 1946, there was no question that research had become, and would remain a valued, critical and permanent component of McLean Hospital. The arrival in 1955 of Dr. Alfred Stanton as Psychiatrist-in-Chief and Director signaled the advent of research investigations in the psychosocial sciences. In 1974 the Alcohol and Drug Abuse Research Center was established; followed by the Mailman Research Center in 1977 which created a unitary biological research center housing the Ralph Lowell Laboratories and the Laboratories for Psychiatric Research; and, most recently the establishment of the first magnetic resonance imaging facility in an independent mental hospital in the United States. The undying faith in the promise of research is impressive.

The history of research at McLean is one of constant determination and effort. At the dedication of McLean’s new Biological Research Laboratory in 1946, Professor Cecil Drinker, remarked:

“Time…is a feature of research in medicine peculiarly objectionable to hospital administrators. Research is interminably expensive, always technically in the red on hospital books; yet, in the end, it has vast potentialities for profit, on which we must risk our judgment if we hope for gain and are not satisfied to sit quietly by taking such care of our …patients as current practice dictates.”
Title: A Case of Off-Label Use of Delayed Auditory Feedback for Stuttering and Schizophrenia

Altered auditory feedback has been used in speech therapy for decades to improve the fluency of people who stutter. Altered feedback may be a delay between the onset of speech and the time the speaker hears her own voice, a shift in the pitch of the voice feedback and/or a change in the volume of the feedback. The kind of alteration with the longest history of use in stuttering therapy is delayed auditory feedback (DAF). Its common use in U.S. speech and language clinics dates to the 1970’s.

There is no published account of delayed auditory feedback being used to decrease auditory hallucinations or voices associated with schizophrenia. The observed side-effect of decreasing the interactions of a 17-year-old male patient – one with a long history of auditory hallucinations -- with his internal stimuli or voices was a welcome relief to the patient, his family and to the students and staff in his daily environment at Pathways Academy.

This poster presentation examines a case of a late-onset severe stuttering co-morbid with ADHD, psychotic disorder- NOS, Tourette’s Syndrome, and autism spectrum disorder. The patient received treatment for stuttering within his educational program at Pathways/CNS beginning in September, 2008. The fluency program using delayed auditory feedback (DAF) resulted in a sharp decrease in stuttering, supported his use of a lowered volume of speech in response to auditory hallucinations and decreased the intrusion of these voices into daily tasks and conversations.

This unpredicted clinical outcome raises questions about how DAF affected the auditory hallucinations:
1. Is it merely an effective distraction for this patient?
2. Does DAF truly suppress the hallucinations?
3. Can this result be duplicated in other cases with auditory hallucinations?
4. Is there some other underlying physiological change effected by the DAF?

The McLean community is invited to comment about whether DAF may warrant further study as a possible clinical tool to manage auditory hallucinations.
Title: Facilitating extinction of drug-seeking in adolescents

Drug addiction is a disorder characterized by compulsive drug craving, seeking, and use that persist even in the face of severe adverse consequences. Addiction is four times more likely if drug use begins in adolescence. Current treatments for addiction commonly aim to reduce drug use and the likelihood of relapse by diminishing drug-cue associations. Extinction of drug-seeking behavior is an integral part of these addiction treatments, and can reverse or ameliorate the harmful consequences of drug use. However, adolescents represent a difficult population to treat. We recently reported that adolescent rats take longer to extinguish drug-cue associations, e.g. are more resistant to extinction, than adults. Evidence suggests that adolescents may be resistant to extinction due to a unique dopamine receptor profile in the prefrontal cortex. Consequentially, drug-cue associations may be more strongly learned and retained by adolescents than adults. These studies aimed to facilitate extinction in adolescents using two separate approaches. First, we modified the extinction procedure by directly pairing a formerly drug-associated environment with the absence of the drug. This is known as explicit pairing. Second, we used pharmacological intervention with atomoxetine, which increases dopamine in the prefrontal cortex. We investigated whether atomoxetine administered prior to extinction sessions would facilitate extinction by focusing attention on the absence of reward.

Adolescent male rats (n=7-8) were conditioned to 20mg/kg cocaine in a place-conditioning apparatus. The first experiment compared two extinction procedures. In four daily extinction sessions, rats were either given full access to the entire apparatus (including both drug-paired and non-drug-paired sides) for 30 min in a drug-free state, or were confined for 30 min in the non-drug paired chamber, and then for 30 min in the drug-paired chamber, in a drug-free state. A test for extinction was performed 24-hr after the final extinction training session. The second experiment used pharmacological manipulation with atomoxetine. For the first four days of extinction training, rats were either administered saline or atomoxetine (2 mg/kg) 25-min prior to being given free access to the place-conditioning apparatus for 30-min. Passive extinction then continued daily for each rat until a criterion of extinction was reached. In both experiments, all animals were tested for reinstatement to 5mg/kg cocaine on the day following the extinction test.

Adolescents exposed to explicit pairing displayed lower preference scores for a previously cocaine-paired chamber after four days, compared to those exposed to passive extinction training (p<0.05). Importantly, adolescents also displayed significantly less reinstatement to a priming dose of cocaine after explicit pairing, compared to after passive extinction (p<0.05). Adolescent cocaine users may benefit from this subtle, but important, difference in extinction methods. Atomoxetine administration prior to extinction training reduced the number of days required for extinction by 33%, suggesting that this drug may have potential to aid as a ‘focusing agent’ to redirect associations away from those related to drugs of abuse. Taken together, exploiting the adolescent’s unique ability to learn about what is important may characterize a new approach toward the treatment of adolescent addiction.
Title: Rapid Enhancement of Glutamatergic Neurotransmission in Bipolar Depression Following Treatment with Riluzole

Background: Glutamatergic abnormalities may underlie bipolar disorder. The glutamate-modulating drug riluzole may be efficacious in bipolar depression, but few in vivo studies have examined its effect on glutamatergic neurotransmission. We performed an exploratory study of riluzole’s effect on brain glutamine/glutamate ratios and levels of N-acetylaspartate.

Methods: We administered open-label riluzole 100-200 mg daily for 6 weeks to 14 patients with bipolar depression and obtained imaging data from 8cc voxels in the anterior cingulate cortex (ACC) and parieto-occipital cortex (POC) at baseline, day 2, and week 6 of treatment, using 2-dimensional J-resolved proton magnetic resonance spectroscopy at 4 Tesla. Imaging data were analyzed using LCModel; the statistical analysis used random effects mixed models.

Results: Riluzole significantly reduced Hamilton Rating Scale Depression scores (d = 3.4; p < 0.001). Glutamine/glutamate ratios increased significantly by day 2 of riluzole treatment (Cohen’s d = 1.2; p = 0.023). N-acetylaspartate levels increased significantly from baseline to week 6 (d = 1.2; p = 0.035). Reduction in Hamilton Depression Rating Scale scores was positively associated with increases in N-acetylaspartate from baseline to week 6 in the ACC (d = 1.4; p = 0.053), but negatively associated in the POC (d = 9.6; p < 0.001).

Conclusions: Riluzole appears to rapidly increase glutamine/glutamate ratios – suggesting increased glutamate-glutamine cycling, which may subsequently enhance neuronal plasticity and reduce depressive symptoms. Further investigation of the glutamine/glutamate ratio as a possible early biomarker of response to glutamate-modulating therapies is warranted.
Schizophrenia patients display a poor capacity for understanding other people’s intentions, or ‘theory of mind’. Patients have additionally exhibited deficits in face perception. Yet, it is not fully understood whether or not this latter perceptual problem plays a role in patients’ ability to infer what other people may be thinking or feeling. To examine this relationship, we measured the performance of patients and controls on two types of tasks. First, the “Reading the Mind in the Eyes” task was administered to access the participant’s theory of mind. Second, a face detection task and a face discrimination task were administered to access the participant’s ability to identify an object as a face as well as to differentiate between varying facial identities of neutral expression, respectively. Patients performed significantly worse than controls on the face detection task ($t_{86}=2.2$, $p<0.05$), the face discrimination task ($t_{64}=2.1$, $p<0.05$), and the theory of mind task ($t_{53}=4.3$, $p<0.01$). The face detection performance was not significantly correlated with the scores on the theory of mind task in either group (patient $r_{16}=0.37$, control $r_{12}=0.31$). However, face discrimination performance was significantly correlated with scores on the theory of mind task in patients ($r_{15}=0.57$), though no significant correlation was found in controls ($r_{9}=0.34$). These results suggest that patients’ deficient capacity to understand the feelings of others is associated with their poor ability to process non-affective facial identities.
Title: Perceptual learning strongly improves visual motion perception in schizophrenia

Schizophrenia patients exhibit perceptual and cognitive abnormalities. Given that cognitive systems depend upon perceptual inputs, improving patients’ reduced perceptual abilities may be an effective means of cognitive intervention. Visual motion processing is deficient in schizophrenia. In healthy people, motion perception can be enhanced through perceptual learning, but it is unknown whether this perceptual plasticity remains in schizophrenia patients. The present study examined the degree to which patients’ performance on visual motion discrimination can be improved, using a perceptual learning procedure. While both schizophrenia patients and healthy controls showed significantly decreased direction discrimination thresholds (improved performance) with training, the magnitude of the improvement was greater in patients (47% improvement) than in controls (21% improvement). The training also transferred to performance improvement in an untrained task—speed discrimination—though to a lesser degree. These task-specific and transferable perceptual learning effects suggest that perceptual plasticity is rigorously present in schizophrenia and can be applied to develop bottom-up behavioral interventions in patients.
Title: ANALYSIS OF DOPAMINE AND SEROTONIN RECEPTOR AND TRANSPORTER, AND BEHAVIOR IN TETRAHYDROBIOPTERIN (BH4) DEFICIENT MICE

Tetrahydrobiopterin (BH4) as an essential cofactor involved in the synthesis of monoamine neurotransmitters including dopamine (DA) and serotonin (5-HT). Disturbances in DA and 5HT neurotransmission have been linked to the pathophysiology and treatment of schizophrenia. We quantified the levels of representative DA (D₁, D₂ and D₄), and 5-HT (5-HT₁₅ and 5-HT₂₃) as well as DA (DA₇) and 5-HT (5-HT₇) transporters in forebrain regions of BH4 deficient mice (spr⁻/-) and their wild-type littermates (spr⁺/⁺). DA and 5HT levels were barely detected in spr⁻/- vs. spr⁺/⁺. D₁ receptor binding decreased significantly in substantia nigra pars reticulata (SNpr) of spr⁻/- compared to spr⁺/⁺. D₂ receptor binding decreased in SNpr, substantia nigra pars compacta (SNpc), and ventral tegmental area (VTA) of spr⁻/- mice. D₂ and D₄ receptor binding increased in medial and lateral caudate-putamen (CPu). DA₇ binding decreased in VTA, SNpc, and SNpr of spr⁻/- vs. spr⁺/⁺ mice. The 5-HT system was also affected in spr⁻/- mice. 5-HT₁₅ receptor binding increased in VTA and SNpc of spr⁻/- mice. 5-HT₂₃ receptor binding increased in SNpc and SNpr of spr⁻/- mice. 5-HT₇ binding decreased in SNpc and SNpr. Behavioral locomotor studies showed that spr⁻/- mice were hyperactive compared to spr⁺/⁺ mice, and this hyperactivity was significantly attenuated after administration of the dopamine D₄ selective antagonist, L-745,870. Additional studies are evaluating the effects of dissimilar antipsychotic drugs on locomotor activity in spr⁻/- and spr⁺/⁺ mice. These results suggest that spr⁻/- mice present a novel genetic model that could be used to further clarify the pathophysiology of neuropsychiatric disorders and their improved treatment [Supported by KRF-2006-214-C00057, and HD-052752].
Abnormalities of attention and visual perception are well documented in schizophrenia. The global-local task is a measure of attention and perceptual organization that utilizes visual stimuli comprised of large letters (global level) made up of smaller letters (local level). Subjects identify target letters appearing at either the global or local level of the stimulus. In this study, we used a version of the global-local task specifically designed to examine lateralized hemispheric processing and attention shifting in 30 schizophrenia patients and 24 normal controls. Global-local stimuli were presented in couplets (consecutive pairs). Reaction time for the second target in a couplet was compared under conditions in which the target remained at the same level (global-global, local-local) and when the target changed levels (global-local, local-global). Level-specific priming (ie, global to global and local to local) and the local-to-global level shift were similar in both groups. Schizophrenia patients were significantly slower, however, shifting attention from the global to the local level. These results implicate an impairment in shifting attentional resources from predominantly right lateralized magnocellular/dorsal stream processing of global targets to predominantly left lateralized parvocellular/ventral stream processing of local targets. Local interference effects in global processing provide further support for impaired magnocellular processing in schizophrenia patients.
To date, there has not been a time-efficient and resource-conscious way to identify cognitive impairment in patients with substance use disorders (SUD). The present study assesses the validity, accuracy, and clinical utility of a brief (10 min) screening instrument, the Montreal Cognitive Assessment (MoCA), in identifying cognitive impairment among SUD patients. The Neuropsychological Assessment Battery-Screening Module (NAB-SM), a 45-minute battery with known sensitivity to the mild-to-moderate deficits observed in SUD patients, was used as the reference criterion for determining agreement, rates of correct and incorrect decision classifications, and criterion-related validity for the MoCA. Classification accuracy of the MoCA, based on receiver-operating characteristic (ROC) analysis, was strong, with an area under the ROC curve = 0.86 [95% CI: 0.75-0.97]. The MoCA also showed acceptable sensitivity (83.3%) and specificity (72.9%) for the identification of cognitive impairment. Using a cut-off of 25 on the MoCA, the overall agreement with the NAB-SM was 75.0%; chance-corrected agreement (kappa) was 41.9%. These findings indicate that the MoCA provides a time-efficient and resource-conscious way to identify SUD patients with neuropsychological impairment, thus addressing a critical need in the addiction treatment research community.
Title: Introducing Contemporary Cognitive and Mindfulness Based Treatment Approaches to Mood Disordered Patients (non psychotic) In An Inpatient Group Setting

Cognitive Behavioral and Mindfulness Based treatments have been well documented as treatments of choice for depression and anxiety. These treatment approaches are usually introduced to patients when they choose to enter outpatient and/or Partial Hospital specialty programs. The Short Term Unit at McLean Hospital is a locked unit for a general psychiatric population with symptoms of depression, anxiety (including PTSD and OCD) dual diagnosis, and bipolar illness. On this unit we have been introducing patients to a variety of contemporary treatment approaches within the psycho-educational group program. These groups are intended to help patients improve their understanding of psychiatric conditions in conjunction with obtaining information on skill development through examples. Each group has 1) a specific focus related to mental health management (i.e. symptom containment, life transitions, acceptance of illness, treatment goals) 2) psycho-education regarding the biological, psychological and lifestyle impact on mood regulation, and 3) a skill set from a specific treatment approach. The groups are structured by beginning with a patient “check in” which directs patients toward the stated topic and produces “self statements” which are then used by the facilitator to make the content of the group relative to the participants and encourages active engagement in the group process.

Cognitive Behavioral Therapy is paired with symptom containment. In this group, patients learn about identifying symptoms of the above stated illnesses and skills for coping with associated disruptive thought, emotions and behaviors. Patients practice identifying negative thought patterns and challenging those thoughts. Dialectical Behavioral Therapy is paired with coping with life transitions. Transitions (including changes in mental health and/or personal life disruptions) contribute to polarized thoughts and emotions. DBT skills are introduced as options for bringing realistic reactions “into dialogue” and using mindfulness skills for developing new coping strategies. Acceptance and Commitment Therapy is introduced through guided metaphor which encourages patients to learn observational skills which help defused negative thoughts. Patients are encouraged to then begin setting personal goals which are based in one’s values rather than negative self perceptions. Positive Psychology in paired with setting treatment goals. Patients are encouraged to use skills which help uncover one’s strengths and ideals. This approach is used to help patients develop treatment goals and aftercare plans which reduce isolation, avoidance and withdrawal.

Each group runs approximately 45-50 minutes and meets one time per week. Groups are concluded by reviewing the psycho-educational context of biological, psychological and lifestyle implications on mood and the particular skills of the introduced treatment approach. These groups tend to have patients interacting with each other in a positive, supportive way and produce lively discussion. They tend to have an activating impact on patient’s attitudes toward their illness.
Marijuana (MJ) is the most commonly used illegal drug in the U.S. with 14.4 million Americans aged 12 and older reporting at least one instance of abuse in the past month. Several studies which have examined the relationship of age of onset of MJ use have indicated that earlier onset of MJ use can lead to increased impairment on several cognitive domains, including verbal IQ, verbal memory, and time to complete visual scanning tasks. Further, a number of investigations have reported alterations in executive functioning, specifically on tasks requiring inhibitory function, in chronic marijuana smokers relative to control subjects. In a recent study, we administered a battery of standard neurocognitive tests, which included measures of executive function, to a group of twenty-three well-characterized, chronic, heavy marijuana smoking subjects. In order to help clarify the impact of early vs later MJ use on cognitive function, the group was separated into those who began smoking MJ prior to age 16 (N=10) and those who began MJ use at the age of 16 or older (N=13). All subjects completed a neuropsychological test battery, which included the Stroop Color Word Test. This task measures the ability to establish competing response tendencies, inhibit inappropriate responses, and resist interference and includes three timed sections (color naming, word reading and interference). Performance of the task is measured by the time taken to complete each subtest, with higher scores reflective of more difficulty. Correlation analyses revealed a significant inverse relationship between age of onset of MJ use and time required to complete both the color naming ($r = -.450; p = .016$) and interference ($r = -.474; p = .011$) conditions of the task. These findings suggest that early onset of MJ use may result in reduced efficiency in performing tasks requiring active inhibition of an overlearned tendency. Total number of smokes per week and years of MJ use were also inversely correlated with age of onset of MJ use ($r = -.525; p = .005$ and $r = -.535; p = .004$), despite no significant correlations with urinary cannabinoid level, suggesting that early onset of MJ use may result in more frequent episodes of MJ smoking as well as increased lifetime use of MJ, but not necessarily higher THC concentration. Results from this study underscore the importance of early intervention, as the use of MJ early in an individual’s development may result in altered cognitive function and higher frequency of MJ use.
Title: Cognitive Profile of Patients with Treatment-Resistant Depression (TRD): Presence of Abnormal Verbal IQ/Performance IQ (VIQ/PIQ) Split.

Background: Little is known about the cognitive profile of TRD in unipolar and bipolar patients. After observing repeated instances of atypical neuropsychological profiles within this population, we proposed that individuals with TRD might have a higher rate of nonverbal processing inefficiency compared to the normalization sample.

Methods: A retrospective chart review was carried out of the medical records of all admissions during 2000-02 to a private behavioral health service at McLean Hospital. We identified 81 TRD subjects (42 unipolar, 39 bipolar) who had undergone a full neuropsychological assessment and had complete clinical data sets. VIQ/PIQ split scores were converted into z-scores to be compared to the WASI standardization data. Calculated z-scores greater than 1.282 and 1.645 were considered statistically abnormal.

Results: The subjects’ corrected mean VIQ/PIQ split score (12.08) was significantly higher than standardization sample mean (0.35) at the group’s ability level. The incidence of statistically abnormal VIQ/PIQ split scores was greater in the TRD group than in the normalization sample; 35% of the TRD group had a Z-score>1.28 versus 10% of the normalization sample; 19% of TRD group had a Z-score>1.65 versus 5% of the normalization sample. There were no correlations between performances on Trails A and any other variables, suggesting that these differences are not attributable to slowed processing speed.

Conclusions: The current study provides a first step in elucidating the relationship between nonverbal processing difficulties and TRD in both unipolar and bipolar subjects. This should be taken into account when considering different treatment strategies.
Salvinorin A, a neoclerodane diterpene isolated from *Salvia divinorum*, is the first known compound acting on KOR selectively that is not an alkaloid—it does not contain a basic nitrogen atom in the structure. Salvinorin A is a highly potent and selective KOR agonist, it binds to KOR with affinity ($K_i=1.3$ nM) equivalent to U50,488H ($K_i=1.4$ nM). It does not show significant affinities to DOR, MOR and nociceptin/orphanin FQ receptors. It was also noted that the duration of action of Salvinorin A in vivo is short, may due to the hydrolysis of the acetate by esterase to produce Salvinorin B, a compound with much lower affinity to KOR. 2-methoxymethyl Salvinorin B (2), an analog of Salvinorin A prepared in our laboratory that has a longer duration of action in vivo than Salvinorin A. Almost all of the previous modified Salvinorin A analogues at C-2 position are mono-substituted derivatives. To explore the C-2 di-substituted derivatives of Salvinorin A, a series of 2-alkyl-2-methoxymethyl-salvinorins ether (3-8) were synthesized starting from 2-methoxymethyl Salvinorin B (2), the results including synthesis and biological evaluations will be presented.
Cannabinoid CB1 agonists produce tolerance that may be associated with dependence and increased sensitivity to the behavioral effects of the CB1 antagonist SR 141716A and AM 4113, perhaps indicative of antagonist-precipitated withdrawal. In the present studies, the effects of various CB1 agonists (AM 411, AM 4054, Δ⁹-THC, AM 356, WIN 55,212.2) and the CB1 antagonist (SR 141716A and AM 4113) on operant performance were examined in squirrel monkeys before and during chronic AM 411 treatment (1.0 mg/kg/day, i.m.). Prechronically, all drugs produced dose-related decreases in rates of lever-pressing; the highest doses of CB1 agonists and antagonists decreased behavior to approximately 20% of control values. Re-determination of drug effects during the chronic regimen revealed a >2 log unit rightward shift in the dose-response function for all CB1 agonists, indicative of tolerance. At the same time, the dose-response functions for SR 141716A and AM 4113 were displaced >2.0 log unit and 1.0–1.5 log unit leftward, respectively, indicative of sensitization. These data are consistent with the view that chronic CB1 receptor activation leads to tolerance to the effects of CB1 agonists and enhances sensitivity to the behaviorally disruptive effects of CB1 antagonists. The increased sensitivity to the effects of SR 141716A and AM 4113 may be indicative of antagonist-precipitated withdrawal. Differences in relative potency (prechronic v. chronic) of SR 141716A and AM 4113 may be related to dissimilar pharmacological actions, i.e., inverse agonist vs. neutral antagonism. (supported by DA19205).
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**Title:** \(^{31}P\) MR Spectroscopy Magnetization Transfer Study of CoEnzyme Q10 in Geriatric Bipolar Depression

**Background:** \(^{31}P\) magnetic resonance spectroscopy (MRS) studies have detected age-associated effects that may be related to changes in mitochondrial functioning, including reduced creatine kinase (CK) activity [Murashita, 1999]. Studies in Bipolar Disorder (BP) implicate the role of altered cerebral bioenergetic pathways (Stork 2005). CK plays a role in the maintenance of cellular energy requirements in tissues with high and fluctuating energy demands (eg. muscle and brain) (Schlattner 20065). Diminished CK activity may contribute to cognitive and emotional vulnerabilities in older adults. CoEnzyme Q10 (CoQ10) is a lipid-soluble benzoquinone present in the phospholipid bilayers of mitochondria (Battino 1990) which has been shown to restore CK activity to baseline levels following metabolic challenges (Kasparova 2005). We present data from a study of older adults with BP depression evaluated before and after 8 weeks of treatment with CoQ10 using a novel magnetization transfer (MT) \(^{31}P\) MRS method to directly measure the rate at which ATP is formed from PCr (k\textsubscript{for}).

**Methods:** Older adults, age > 55, with DSM-IV TR Bipolar Disorder, current episode depressed (BPD), and a Montgomery Asberg Depression Rating Score (MADRS) of > 20 and a Young Mania Rating Scale (YMRS) Score of < 6 were recruited along with age and sex-matched older healthy adults. All subjects underwent a 4T \(^{31}P\) MRS scan acquiring both static and MT data at baseline and after 8 weeks. The BPD group received adjunctive treatment with CoQ10 at dosages beginning at 400 mg/day and titrated upwards every two weeks as tolerated to a maximum dosage of 1200 mg/day. A 1 dimensional chemical shift imaging (CSI) technique (TR = 7 secs) was used to achieve localized detection of the frontal lobe. To evaluate k\textsubscript{for}, the PCr signal was measured with four different MT saturation durations at both the γ-ATP and the control frequency.

**Results:** Data is presented on 8 older adults with BPD (4 females, mean age = 65 years) and 5 controls (3 women, mean age = 72 years). There were no significant changes in mean MADRS scores before and after 8 weeks of CoQ 10 therapy in the BPD group (Mean MADRS scores at baseline = 21.9; Mean MADRS scores after 8 weeks of treatment = 20; p > 0.10). The mean dosage of CoQ 10 at 8 weeks was 1000 mg/day. However, k\textsubscript{for} values in the BPD were increased after 8 weeks of CoQ 10 therapy (k\textsubscript{for} pre treatment = 0.29; k\textsubscript{for} after treatment = 0.34; p < 0.02). Further pilot data including change in k\textsubscript{for} after 8 weeks in controls will also be presented.

**Discussion:** Preliminary data indicates an increase in the creatine kinase forward rate constant (k\textsubscript{for}) with CoQ 10 treatment in older adults with BP depression despite the absence of observable clinical changes. There is, however, a suggestion of improvement in depression at the 4 week time point at a mean dosage of CoQ10 of 700 mg/day. Study findings warrant further exploration of new treatment strategies based on pro-mitochondrial agents such as CoQ10 to stabilize mood in geriatric bipolar disorder.
Previous work from this laboratory has shown that activation of the basolateral amygdala (BLA) leads to increased firing of fast-spiking (FS) interneurons in stratum oriens (SO) of sector CA2/3 of the hippocampus. This effect involves changes in their membrane properties and is mediated, in part, by Ih channels. A recent postmortem study from this lab has also shown increased expression of GluR6 and 7 subunits of the kainate receptor (KR) at this same locus of schizophrenic subjects. Using our rodent model for abnormal neural circuitry in schizophrenia, we have explored the functional implication of increases or decreases in KR activity. After two weeks of picrotoxin (PICRO) infusion into the BLA, we have recorded action potential (AP) frequency and other membrane properties at postnatal day 45 (P45) in hippocampal slices. As in our previous study, increased action potential (AP) frequency was recorded in fast-spiking interneurons in SO of CA2/3 of PICRO infused rats compared to saline (SAL) controls. With the application of 200nM kainate, we observed a significant increase of AP frequency in the SAL controls (P=0.02). In contrast, the PICRO rats showed a decreased AP firing rate (P=0.0001) accompanied by an increase in after-hyperpolarization (AHP). Application of the GluR5 antagonist (UBP209) lead to a further decrease of AP frequency in PICRO-treated rats compared to SAL controls. In contrast, bath application of the GluR6/7 antagonist NS102 lead to a decrease of AP frequency in SAL compared to PICRO-treated rats. In the hippocampal network, GABAergic interneurons can phase the output of pyramidal cells, giving rise to oscillations in a number of frequencies. These results suggest that the BLA activation may influence the set point of both inhibitory and disinhibitory GABA cells via KR receptors expressed by both cell types. As previously suggested by others, a combination of these latter two effects could help to regulate rhythmic oscillations in the HIPP. Overall, these results may give new insight into the complex role KR receptors may play in regulating gamma oscillations in schizophrenia.
Title: Comparing group process in the single-gender Women’s Recovery Group versus mixed-gender Group Drug Counseling

Aims
While outcome studies have examined effectiveness of group therapy for substance use disorders, little is known about group process. Therefore, the aim of the current study is to examine the frequency of affiliative statements that represent supportive, cohesive, or empathetic connections between group members. We hypothesized that these types of statements may vary as a function of the gender composition of the group in a Stage I trial for women in a single-gender Women's Recovery Group (WRG) or in a mixed-gender control condition, Group Drug Counseling (GDC).

Methods
Two expert coders identified five categories of affiliative statements and developed a coding manual with acceptable inter-rater reliability. 45 group sessions of WRG and GDC were then coded. Cohen’s effect sizes were used to determine if these statements varied significantly by treatment group, where significance is defined as a clinically meaningful difference between groups corresponding to a medium to large effect size (D>.5). All analyses controlled for within-therapist clustering.

Results
Given a high level of correlation between three of the categories, Agreements, Supportive statements, and Completing Thoughts, these were collapsed into a composite category termed Empathic Statements. Empathic Statements occurred more frequently in WRG than GDC (D:.882). However, the frequency of the remaining two statement types, Therapeutic Responses and Positive Statements About the Group, did not significantly differ between groups (D:-.095, -.166), although the rates of these statements were slightly higher in GDC.

Discussion
One type of affiliative statements, empathic statements, occurred more frequently in the single-gender WRG than mixed-gender GDC. This is the first study to examine differences in verbal interactions among participants in all-women and mixed-gender substance abuse treatment groups. Further study is necessary to examine whether these types of group process differences mediate substance abuse treatment outcomes.
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Title: The impact of drug use among social network members of patients with co-occurring substance dependence and bipolar disorder

Background: Research suggests that drug use among members of social networks has a powerful influence on drug use. In this exploratory analysis, we assessed the effect of drug use among social network members on recovery from drug use disorders in patients with co-occurring bipolar disorder.

Methods: Patients (n=57) enrolled in a group therapy study for patients with co-occurring substance dependence and bipolar disorder completed a social support interview at intake, during treatment, and at 1-year follow-up, as well as measures of substance use and mood.

Results: Patients who reported having 1 drug user in their social networks at intake had few days of drug use during treatment and follow-up, as did patients with no drug users. However, naming ≥2 drug users predicted more days of drug use over the next 15 months. Patients who consistently included multiple drug users in their social networks had more days of drug use per month than those who never or only occasionally reported ≥2 drug users. Multivariate analysis showed that patients who consistently named multiple drug users in their social networks had a marked increase in drug use over 15 months, while those who never named multiple drug users had a small decline in drug use over time.

Conclusions: These findings suggest that multiple drug users in social networks of treatment-seeking dually diagnosed drug abusers may be an indicator of poor drug use outcomes; efforts to reduce the association with these drug users may be useful.
Marijuana (MJ) remains the most widely abused illicit substance in the United States, with more than 14 million individuals reporting use within the past month. A number of investigations have reported alterations in chronic, heavy MJ smokers on tasks of cognitive performance, patterns of cortical activity as measured by fMRI techniques, and on measures of white matter microstructure relative to non-smoking control subjects, however, few thus far have examined the neurobiologic impact of age of onset of MJ use. Diffusion tensor imaging (DTI) methods provide a quantitative estimate of white matter integrity, offering new insight at the microstructural level. We studied fifteen chronic, heavy MJ smokers (mean age 25.8 years old) who completed a neuroimaging protocol including DTI, as well as neurocognitive measures of executive/inhibitory function to examine the relationship between white matter microstructure, inhibitory function and age of onset of MJ use. Fractional anisotropy (FA), a measure of directional coherence and integrity of white matter fiber tracts, and trace, a measure of overall diffusivity, were calculated for bilateral frontal regions placed anterior and lateral to the frontal horns, as well as regions within the genu of the corpus callosum using a region of interest approach. To assess the impact of onset of MJ use, we completed correlation analyses on the sample; subjects ranged from 11 to 20 years of age at time of first regular use. Within the left frontal region, age of onset was significantly positively correlated with FA values ($r = .43; p = .05$) and inversely correlated with trace ($r = -.52; p = .02$). Similarly, within the right genu, age of onset was significantly positively correlated with FA values ($r = .58; p = .01$) and inversely correlated with trace ($r = -.55; p = .02$). Further, early onset MJ use was also significantly inversely correlated with time to complete the interference condition of the Stroop test, a task that requires active inhibition of an overlearned tendency ($r = -.49; p = .03$). Total number of smokes per week was also inversely correlated with age of onset of MJ use ($r = -.50; p = .03$). Taken together, these findings suggest that early MJ use may result in decreased white matter integrity in frontal regions, which are critical for inhibitory function, and may also result in more frequent episodes of MJ smoking. These data represent the first report of alterations in frontal white matter fiber tract integrity which are associated with age of onset of MJ use as well as altered inhibitory function, lending support to the hypothesis that MJ use during a period of developmental vulnerability may result in alterations in brain structure.
Aim: To describe the ten year course of borderline personality disorder’s (BPD) psychopathology and functioning.

Results: This is an unpublished report from the Collaborative Longitudinal Personality Study (CLPS) comparing the ten year outcome of 175 BPD to that of 312 Cluster C other personality disorders (OPD) and to a sample of 95 with non-personality disordered major depressive disorder (MDD). The BPD sample remitted more often and more dramatically than expected, but still were slower than the comparison groups (p < .0001) and, once remitted, they relapsed infrequently and less often than did the comparison groups (p < .0001). Their improvement in functioning was comparatively small – and remained significantly worse than either comparison groups (p < .0001).

Conclusion: BPD has a course of remission and relapse that is encouraging and clearly distinct from that of mood, anxiety, and psychotic disorders, but it is associated with extremely severe functional morbidity.
Title: SENSORY GATING AND NEURONAL OSCILLATORY PATTERNS IN SCHIZOPHRENIA PATIENTS AND THEIR UNAFFECTED RELATIVES

Background: The P50 sensory gating deficit, a failure to inhibit or “gate” responses to repeated stimuli, is a leading endophenotype for schizophrenia (SZ). Both gamma and beta event-related oscillations (EROs) are major contributors to the auditory P50 event related potential (ERP) response. However, the topographic distribution of gamma and beta ERO responses to initial (S1) and repeat (S2) stimuli and the association of these oscillations with P50 sensory gating are not clear. Methods: 51 SZ patients, 25 unaffected first-degree relatives, and 34 healthy comparison subjects were tested using a paired click paradigm. Evoked power of gamma- and beta-band responses using wavelet analyses to S1 and S2 stimuli, and gating of EROs and P50 were the main outcome measures. Results: A P50 gating deficit was found in patients ($P<.001$) and at a trend level in relatives ($P=.087$). For gamma and beta EROs, patients showed widely distributed reductions in responses to S1 stimuli and S2 stimuli, respectively, and impaired gating in both frequencies. Relatives did not differ significantly from control subjects in either EROs power or gating. Gating of P50, gamma, and beta were not significantly correlated ($r =0.18-0.19, P>.05$). Conclusions: These results suggest that deficits in gamma and beta EROs to S1 and S2 stimuli and impaired gating are associated with schizophrenia, but are not related to genetic liability for the illness. The components of information processing assessed by gamma or beta gating appear to be independent from those mediated by P50 suppression, and under separate genetic control.
Implementing an Adapted Version of the Job Seekers’ Workshop in a Residential Program for Patients with Substance Use Disorders

**Objectives:** To evaluate the feasibility and effectiveness of implementing an adapted version of the Job Seekers’ Workshop (JSW) in a residential setting within a Massachusetts-based substance use disorder treatment agency.

**Methods:** Implementation of the adapted JSW consisted of a sequence of three weekly sessions that focused on job interview rehearsals, practice completing job applications, and identification of job leads. Data were compiled on the employment rates of the 188 patients discharged from the residential treatment program during July – December 2006 (baseline participants, n = 95) and January – June 2007 (JSW intervention participants, n = 93). The effectiveness of the adapted JSW was evaluated through a comparison of baseline and intervention participants’ employment rates at discharge from residential treatment.

**Results:** Analyses indicated a trend towards a significant increase in employment at discharge for the intervention period (40.9%) compared to baseline (29.5%), $\chi^2(1, N = 188) = 2.675, p = .051$.

**Conclusions:** Further evaluation of the JSW in residential settings is necessary, but this preliminary research suggests that the intervention could successfully address the need for vocational services in residential treatment for substance use disorders.
The rapid growth of online content is a mixed blessing. The ability to keep current, to comply with NIH mandates, and to find collaborators is complicated by constant change. Researching the literature thoroughly has become both easier and more difficult. The Mental Health Sciences Library and the Countway Library of Medicine at Harvard offer a wide range of services to simplify the process.

The Mental Health Sciences Library’s services include literature searching, current awareness services, training on database searching, Interlibrary Loan, electronic books and journals not available through Harvard, assistance with updating and editing the bibliographic section of your CV, and information about and assistance with the NIH Publishing Mandate. We also welcome suggestions for new journals, books, DVDs and electronic resources.

An initiative by the Countway Library has created an incredibly useful and dynamic web-based application called the Harvard Catalyst. Using the Catalyst you can

- **Find People:** Search by keywords for colleagues, collaborators, mentors. Build a trans-Harvard team. Customize your profile to reflect your present interests.
- **Continue Learning:** Degree programs, courses, nano-courses, colloquia, seminars. Customize your lifelong education.
- **Access Resources:** Apply for pilot funds. Use the human research labs. Access cores and emerging technologies.

All Harvard investigators have a page in the Catalyst. Examples and assistance with correcting and updating the record are offered.
Title: Evidence that years of school influence heavy drug use and mediate the correlations between heavy drug use, cognition and impulsivity

Our aim was to evaluate the quantitative relationships between years of school, years of illicit drug use, and several established cognitive and dispositional correlates of drug use in methadone clinic and community drug users. The project was motivated by recent research on the influence of schooling on mortality and other measures of health. The basic finding is that educational attainment predicts mortality after controlling for the obvious health correlates of school, such as income, access to medical care, and medical knowledge. This result suggests that school promotes healthy habits and/or decision-making patterns that yield healthy habits. We tested whether school played a similar role in drug use. Our basic result is that years-of-school was inversely correlated with years of illicit drug use, after statistically controlling for differences in IQ, working memory, impulsivity (as measured by the Barratt Scale), and psychiatric symptoms (as measured by the 90-R Symptom Check List). Moreover, years-of-school was the strongest predictor of whether illicit drug use led to heavy drug use (e.g., three occasions or more per week for at least a year). High impulsivity scores and low verbal IQ were strongly correlated with illicit drug use, but not for those with 14 years or more of school. Conversely, individuals with low impulsivity scores and high verbal IQ scores were much more likely to continue using illicit drugs if they had less than 14 year of school.

Methods. We tested 76 methadone clinic patients and 107 individuals who lived in nearby Boston neighborhoods. Each subject completed a series of verbal and spatial working memory tests, the Wechsler Abbreviated Intelligence Scale, the Barratt Impulsiveness Scale, the 90-R Symptom Check List, and demographic and drug history questionnaires. Clinic subjects also provide urine and breathe samples.

Results. Among the cognitive measures, verbal IQ (vocabulary) and verbal working memory were most strongly correlated with measures of drug use (r = 0.00 to 0.41). Among the drug measures, years of illicit drug use and the overall frequencies of opiate and stimulant use were most strongly correlated with cognition, impulsivity, and psychiatric symptoms. However, years-of-school was the strongest correlate of cognition, impulsivity, and drug use (r = 0.10 to 0.90). Step-wise multiple regression analyses revealed that years-of-school accounted for more of the variance in drug use than any of the cognitive measures, including IQ, and also explained more variance than any of the dispositional measures, including impulsivity. Indeed years-of-school typically accounted for at least as much of the variance in heavy drug use as all the other measures combined.

Conclusion. Educational attainment was a surprisingly powerful correlate of illicit drug use in a population of heavy clinic and community drug users. We believe these results may have significant practical implications. However, it is possible that years-of-school and heavy illicit drug use are not causally related but share a common third factor. Thus, we hope to follow up this research with studies that focus on the nature of the correlation between years of school and years of self-destructive drug use.
Title: Familial Aggregation and Heritability of Borderline Personality Disorder and its Component Traits

Background:
There has been continuing debate regarding the diagnostic criteria of borderline personality disorder (BPD). Furthermore, there has been limited methodologically rigorous assessment of the role of familial factors in BPD. The present study assessed the familial aggregation and heritability of BPD and its component traits of affective instability, impulsivity, and interpersonal instability.

Methods:
The sample was 1) 3 groups of female probands: with BPD by both Revised Diagnostic Interview for Borderlines (DIB-R) and DSM-IV criteria (N=132); without BPD (N=134); and with major depressive disorder MDD (N=102), either with (N=15) or without BPD (N=87); and 2) available parents and siblings in the 3 proband groups (N=314, N=337, and N=234, respectively). All participants were personally interviewed to assess BPD by DSM-IV criteria, BPD by DIB-R criteria, and the presence of affective instability, impulsivity, and interpersonal instability. Relatives were assessed while blinded to proband status. The measure of familial aggregation was for BPD, the risk ratio for BPD in a relative of a proband with BPD vs. BPD in a relative of a proband without BPD; and for the component traits, the increase in level of trait in a relative for each 1-unit increase in level of trait in the proband. The measure of heritability was the estimate for additive genetic effects from an ACE (Additive genetic effects, Common family environment, and unique Environment) model.

Results:
Among the relatives of probands with BPD, 13.5% met both DIB-R and DSM-IV criteria for BPD vs. only 6.0% of the relatives of non-BPD probands. The risk ratio for familial aggregation (95% confidence interval) was high and statistically significant: 2.8 (1.5, 5.2). The results were almost the same when only the DIB-R criteria for BPD in a relative were considered (risk ratio of 2.7 (1.5, 4.9)). By contrast, 16.7% of the relatives of probands with BPD and 12.1% of the relatives of probands without BPD met DSM-IV criteria for BPD, with a risk ratio of 1.5 (0.97, 2.2). The component traits all showed significant familial aggregation, with estimated increases in level of trait of 0.23 (0.14, 0.32) for affective instability, 0.16 (0.07, 0.24) for impulsivity, and 0.21 (0.14, 0.29) for interpersonal instability. Except for interpersonal instability, the estimate in ACE models for C was negligible and the estimate for A was statistically significant; hence, A was estimated from AE models for these variables. For interpersonal instability, estimates for both A and C were statistically significant, and hence A and C were estimated from an ACE model. The heritability estimates were: 55% for BPD meeting both DIB-R and DSM-IV criteria; 48% for affective instability, 34% for impulsivity, and 45% for interpersonal instability. The estimate for common family environment for interpersonal instability was 8%.

Discussion:
BPD and its component traits aggregated strongly in families and showed substantial heritability. Notably, BPD defined by DSM-IV criteria aggregated more weakly than BPD defined by DIB-R criteria, suggesting that the broader DSM-IV criteria may be less able than the narrower DIB-R criteria to identify a heritable BPD phenotype.
Title: Gender Invariance of Behavior and Symptom Identification Scale Factor Structure

The Behavior and Symptom Identification Scale 24 (BASIS-24) is a psychiatric outcome measure used for inpatient and outpatient populations. This 24-item measure comprises six subscales: depression/functioning; interpersonal relationships; self-harm; emotional lability; psychosis; and substance abuse. Earlier studies examined the reliability and validity of the BASIS-24, but none empirically examined its factor structure across gender. The purpose of this study was therefore to assess the construct validity of the BASIS-24 six-factor model and find evidence of configural, metric, strong and strict factorial invariance across gender. The sample consisted of 1398 psychiatric inpatients that completed BASIS-24 at admission and discharge at 11 facilities nation-wide. Confirmatory factor analyses were used to test measurement invariance of the BASIS-24 six-factor model across males and females.

The single confirmatory factor analysis showed the original six-factor model of BASIS-24 provided an acceptable fit to the male sample at admission (RMSEA=0.058, SRMR=0.070, CFI=0.975, NNFI=0.971 and GFI=0.977) and at discharge (RMSEA=0.059, SRMR=0.078, CFI=0.977, NNFI=0.972, and GFI=0.969). The goodness-of-fit indices for the female group at admission (RMSEA=0.055, SRMR=0.067, CFI=0.980, NNFI=0.976, and GFI=0.983), and at discharge (RMSEA=0.055, SRMR=0.079, CFI=0.98, NNFI=0.977, and GFI=0.971) also revealed that the six factor model fit reasonably well to the data. The goodness–of-fit indices between the unconstrained and constrained models showed that all four multi-group models were equivalent for both male and female samples at admission and discharge in terms of goodness-of-fit examined through the ΔCFI and that all of them show an acceptable fit to the data. The decrease in CFI was <0.008 for admission sample and <0.003 for discharge sample and both fell below the 0.01 cut-off. This indicates that the configural, metric, as well as the strong and strict factorial invariance of BASIS-24 exist across males and females.

Mental health assessment has become an important part of social work clinical practice and in research and policy. In this context, BASIS-24 can be used with inpatient psychiatric patients to measure their functioning and symptoms. Second, this test confirms that the mean score differences among males and females in BASIS-24 subscales are actual differences and are not due to the measurement error under normal circumstances. Thus BASIS-24 can be considered a reliable instrument for measuring mental health outcomes by comparing the pre (admission) and post (discharge) mean scores. This confirms the utility of the BASIS-24 for both clinical and research purposes. This has particular relevance to social work where there is a strong commitment to gender and culture-specific mental health services. These findings suggest that BASIS-24 can be used with confidence in practice settings in which practitioners require an assessment of symptoms across gender with inpatient-specific mental health services. The current study provides an example of useful statistical methodology for examining specific questions related to factorial invariance of the BASIS-24 instrument across gender.
Title: Insula Reactivity to Smoking-Related Cues and the Emotional Stroop Task Predict Slips in Tobacco Smoking Abstinence

While most tobacco smokers seek to quit, few achieve long-term success (Hughes et al., 2003). For those attempting to quit, smoking even one cigarette during abstinence (a slip) predicts relapse (Borland, 1990). Slips are induced by exposure to smoking-related cues, which are not effectively inhibited by existing treatments (Glover et al., 2007). Developing methods to identify vulnerable smokers may advance relapse prevention research, and when better treatments are available, may improve treatment planning. The insula, a brain structure mediating perception of interoceptive states (Craig, 2009) is activated by smoking-related cues (Rose et al., 2007) and is thought to play a role in maintaining smoking behavior (Naqvi et al., 2007). We used functional MRI (fMRI) in women about to begin a smoking cessation program to determine whether pre-quit insula reactivity to smoking-related cues predicts who will slip during treatment. We show that pre-quit insula hyper-reactivity to such cues predicts slips. Insula reactivity was positively correlated with pre-quit smoking-related interference effects in a separate emotional Stroop task. Subjects who slipped also had reduced functional connectivity between insula and cortical regions regulating emotional states, possibly reflecting reduced top-down control (Etkin et al., 2006, 2007). These findings suggest that insula hyperactivity and reduced functional connectivity may lead to heightened interoceptive awareness of smoking-related cues, increasing slip potential. Since a discriminant analysis using pre-quit fMRI cue reactivity and Stroop data yielded a 84.2% correct classification of slip outcome, these measures may have diagnostic utility for identifying vulnerable smokers.
Title: Medical Comorbidity and Cognition in Geriatric Patients with Bipolar Disorder and Major Depressive Disorder

Background: Elderly patients with major depression (MD) and bipolar disorder (BD) experience cognitive deficits in multiple domains including memory, attention, executive functioning, and processing speed. Additionally, patients with MD and BD tend to have more medical comorbidities than the general population. These medical comorbidities have been linked to poorer treatment outcomes in MD and BD as well as poorer cognitive functioning. Previous analyses reported from this data have shown that patients with MD and BD exhibit cognitive deficits relative to control participants. The present study examined to what extent cognitive functioning in elderly patients with BD, MD and healthy controls is associated with medical comorbidities. We hypothesized that a) both patient groups will exhibit greater medical burden than control participants, but will not differ from each other b) neuropsychological deficits in processing speed, memory, and executive functioning will be associated with overall medical burden and specific medical comorbidities (i.e. cardiovascular disease) for all groups.

Methods: Patients with MD (n=43) or BD (n=32) and healthy controls (n=30) were recruited for participation from the Geriatric Psychiatry Mood Disorders Research Program at McLean Hospital. Participants were administered a battery of neurocognitive, mood, and symptom measures, and the Cumulative Illness Rating Scale-Geriatric which assesses medical burden across multiple systems.

Results: Linear regression tested for associations between diagnosis and medical comorbidity and between medical burden and neuropsychological deficits in patients and control participants.

Conclusions: Associations amongst neurocognitive functioning, medical burden and affective illness in elderly populations have important implications for functional outcomes in geriatric patients with mood disorders. As mood disorders and medical comorbidities are associated with cognitive deficits and poor functional outcomes, a more integrated treatment model may be indicated. Longitudinal investigations will help clarify the causal relationship between affective disorders and medical comorbidities. Determining the nature of this relationship and its impact on functional outcomes may address the burden faced by the elderly and the broader public health implications related to institutionalization, isolation, and healthcare resource utilization. Additionally, such work has implications for key treatment targets in elderly patients.
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**Title: The glycine transporter (GlyT1) inhibitor Org 25935 alters default network connectivity in healthy men.**

Glycine transporter 1 inhibitors (GlyT1-I) are being developed to treat schizophrenia (Scz), substance abuse disorders, and to act as cognitive enhancers. Few clinical neuroimaging data are available reporting GlyT1-I effects. Default network functional connectivity, temporally coherent neural activity in the resting brain (not cognitively engaged), has been reported to be abnormal in Scz subjects and their first-degree relatives. We conducted a double-blind placebo-controlled crossover study in healthy adult men (N=9) to determine effects of acute oral Org 25935 (16 mg) administration on default network functional connectivity, as measured with functional MRI (fMRI).

Study subjects were 9 healthy adult men (25.8±5.0 years old). None had current Axis I or II disorders as determined with the Structured Clinical Interview for DSM-IV. Subjects were compensated for participation. The study was approved by the McLean Hospital Institutional Review Board. Subjects were administered study drug (placebo or Org 25935) on 2 study days spaced out by at least 1 week.

Functional MRI scans were acquired on a Siemens Trio 3T scanner before and 4.5 hours after study drug administration. Multiplanar rapidly acquired gradient-echo structural images (TR=2100 msec, TE=2.7 msec, matrix=256x256, resolution=1.0x1.0x1.33mm) were acquired followed by gradient echo fMRI images (TR=2000 msec, TE=30 msec, matrix=64x64, resolution=3.5mm isotropic/0mm gap). During the 10-minute fMRI scan, subjects were told to relax with eyes closed and to not engage in any structured activity (e.g., counting, listening).

Data was preprocessed in SPM5 (Welcome Department of Cognitive Neurology, London, UK) followed by group level Independent Component Analysis (ICA) using the GIFT software package (v1.3e, http://icatb.sourceforge.net). The network having the best spatial overlap with the resting state default network was chosen for further analysis. Default network time courses were extracted from both baseline and both post-drug scans and converted into Brain Voyager (BV)-compatible predictors. To compare the default network between baseline and 4.5-hour post-drug states on both study days, data was preprocessed using BV 1.10.4 (Brain Innovation, The Netherlands). Beta maps were created for each subject on each day for the predrug>postdrug contrast. Beta maps then were used to run a random-effects ANOVA comparing placebo and Org 25935 day scans. Multiple comparisons were corrected to p<0.005 using a Monte Carlo procedure.

For the contrast placebo day (predrug>postdrug)>Org 25935 day (predrug>postdrug), the only functional connectivity difference (217 voxels, 5.9cc) was detected at the border of the left fusiform gyrus (FG)/Brodmann area (BA)19 (Talairach coordinates -34,-81,-13). This suggests that functional connectivity of the left FG/BA19 to the default network was reduced by Org 25935.

We found reduced functional connectivity between the left FG/BA19 and the default network after Org 25935 administration. As noted above, the default network is abnormal in Scz subjects and their first-degree relatives. Interestingly, in Scz, the FG is known to exhibit abnormal structure, function (including working memory function), and physiology. If Org 25935 induces similar effects in Scz subjects as observed presently, it may be therapeutically beneficial for treating FG dysfunction associated with the disorder.

**Acknowledgments:** Supported by a contract from Schering-Plough Corporation.
Title: Paralimbic Responses to Masked Emotional Faces in PTSD: Disorder and Valence Specificity

Background: Compared to controls, patients with PTSD show reduced activation of the ventromedial prefrontal cortex and exaggerated amygdala responses to masked threat-related emotional cues (e.g., fearful facial expressions presented below conscious awareness). No study has yet compared PTSD responses to a non-PTSD psychiatric control group. In addition, it is unclear whether the effect is driven by valence or arousal dimensions of the stimuli because prior masked affect studies in PTSD only contrasted fear and happy conditions directly (without comparison to neutral).

Methods: Thirty-one adults (7 PTSD; 8 animal phobia; 16 non-psychiatric controls) underwent functional magnetic resonance imaging (3T) while viewing blocks of backward-masked Fear, Happy, and Neutral faces (16 msec affective face target; 184 neutral face mask). In SPM5, masked Fear, Happy, and Neutral conditions were contrasted with one another. Amygdala, insula, and ventromedial prefrontal cortex (VMPFC) search territories were interrogated at p<.005, k>10 voxels.

Results: Compared to both control groups, PTSD subjects showed increased amygdala and anterior insula and reduced VMPFC activation during both the masked Fear>Neutral and Happy>Neutral conditions. The results of the Fear>Happy contrasts did not differ among the diagnostic groups.

Conclusions: PTSD subjects showed greater activation within amygdala and insular regions, and reduced activation within VMPFC compared to non-psychiatric and phobic controls during masked affect presentations. These effects do not appear to be specific to threat-related stimuli; rather PTSD subjects show exaggerated paralimbic responses to highly aroused emotional stimuli, regardless of valence. These findings appear to be specific to PTSD rather than anxiety disorders more broadly.
Title: Falls – Antipsychotic Medication – Clinical Implications

Introduction: Higher rates of falls generally occur in individuals over age 65. Some literature suggests that individuals hospitalized in psychiatric facilities are also at great risk. This quality initiative sought to determine factors associated with an increased rate of falls on an adult psychiatric unit treating primarily individuals with psychotic disorders.

Method: Each fall that occurred during a 3 month period was reviewed, followed by a careful review of the medical record. A data collection form was developed based on specific categories of data noted in the literature as important indicators. Observations, “hunches” and discussions with staff members on the treatment team also provided additional data categories.

Results: Fourteen individuals experienced a fall over a 3 month period with a mean age of 42 (range 21-65 years). The mean number of prescribed medication was 5.4 (range 3-12). Thirty-three percent complained of sedation, dizziness or lightheadedness at some point in the 24 hours preceding the fall, none had postural blood pressures. Sixty-four percent had elevated pulses greater than 100 in the 24 hours preceding the fall. The majority of individuals were on 3 or more psychotropic medications to manage acute symptoms. Conclusions: Young and middle aged adults with acute psychiatric problems are at risk for falls. The typical characteristics associated with risk of falls were absent (use of devices, older age, sensory alterations). Increased pulses, multiple psychotropic drugs and rapid titration of psychotropic drugs were more indicative of fall risk. Regulations regarding the reimbursement of psychiatric hospitalizations often lead to shortened lengths of stay and may impact treatment plans which seek to control psychiatric symptoms rapidly. An elevated pulse in 64% of the sample was an unexpected finding and must be investigated further.
Title: Feasibility of Incorporating Exercise in a Psychiatric Partial Hospital Program

Objective: We examined whether exercise, as an adjunct treatment strategy is feasible for individuals with severe mental illness.

Methods: This is a nonrandomized trial investigating the feasibility of an adjunct supervised exercise program in a psychiatric partial hospital program. The exercise group (N=38) met three times a week for fifty minutes while in the PHP. Individuals who chose not to exercise (N=28) attended a psychoeducational control group.

Results: Individuals attended the exercise group an average of 3.02 times while in the PHP, or approximately every other day. The exercise group had marginally higher average duration of daily exercise than the control group. Both groups improved significantly on all outcomes, but the only group difference was the exercise group had a greater reduction in hopelessness and a greater increase in autonomy.

Conclusions: These data highlight the feasibility for an adjunct exercise program in a psychiatric PHP and suggest that it may improve outcomes.
Deficits in the visual working memory (WM) system have been consistently reported in schizophrenia patients, but there has been some disagreement about the contribution of initial encoding/perception to these deficits. We assessed the role of visual perception on performance on an object WM task. Schizophrenia (SZ) patients (N=37) and nonpsychiatric control (NC) subjects (N=24) were tested on an object working memory task involving three delay periods: 200 msec, 3 sec, and 10 sec. Both SZ and NC subjects showed a significant decline in performance on the 3 and 10 sec delay intervals compared with the 200 msec delay interval. Performance on the 3 sec and 10 sec delay conditions did not differ significantly in either group. SZ performed significantly less accurately than NC on all three conditions. After removing the effect of perception/encoding (accuracy on the 200 msec delay condition) on performance in the two memory load conditions, SZ patients demonstrated intact WM (3 sec delay condition), but showed a weak trend for decreased accuracy on the 10 sec delay, compared with controls. Further, neither group showed a significant decrease in accuracy between the 3 sec and 10 sec delay conditions. Analysis of individual differences in pattern of performance revealed that a distinct subgroup of SZ who were poor encoders had significantly reduced accuracy at 3 sec than the other SZ subgroups and subgroups of NC. WM deficits in NC, in contrast, were independent of encoding ability. These results indicate that encoding ability titrates the magnitude of WM impairment in SZ but not in NC and that heterogeneity has to be taken into account to correctly estimate effects of perception on visual object WM deficits in SZ.
Title: Family Accommodation in OCD: A Survey of Perceptions and Practice

Background:
Family Accommodation refers to the tendency of family members to deleteriously participate in symptoms and modify routines in attempt to reduce anxiety in the OCD sufferer (Calvocoressi et al., 1995). Research on family accommodation suggests that it may reduce treatment effectiveness in a variety of ways (Amir et al., 2000; Stewart et al., 2008). This highlights the importance of related family psychoeducation and strategy development to best support their loved ones during treatment. In the current study, the families of incoming patients at an intensive residential OCD treatment program were surveyed to determine: 1) To what extent family accommodation has been addressed during outpatient therapy; and 2) Whether contact with treaters resulted in decreased accommodation.

Methods:
Consenting family members of consecutive subjects admitted to the MGH/McLean Hospital OCD Institute between May and July 2009 completed an Outpatient Treatment Experiences Survey. Separate surveys for patients and family members were developed. Final surveys included a 12-item measure for relatives and a 10-item measure for patients. For specific items, respondents were asked to circle a yes/no reply or to check all applicable answer options. The survey was designed to measure understanding and prevalence of accommodation, rates of family involvement in outpatient OCD treatment and efficacy of involvement with respect to decreasing accommodating behaviors. Consenting subjects included 20 patients and 29 relatives. Descriptive, frequency and comparative analyses between those with and without outpatient treater contact were conducted using SPSS. Significant threshold was set a p< 0.05.

Results:
Surveyed were completed by relatives including parents [65.5%; N= 19], siblings [20.7%; N=6] and spouses [3.4%; N=1]. Outpatient treaters included psychiatrists [65%; N=13], behavioral therapists [65%; N=13], psychotherapists [55%; N=11], social workers [30%; N=6] and others. Regarding treater-family communication: 95% met with at least one relative, 75% had phone communication, and 35% had email communication with family members. Patients and their relatives reported that the following accommodating behaviors were most common: providing reassurance [55% and 65% respectively], performing tasks due to OCD interference [30% and 55% respectively], and trying to stop rituals [37% and 41% respectively]. There were no notable differences in accommodation behaviors between relatives with and without outpatient treater contact. Among relatives communicating with a treater, 26.1% (n=6) had been asked to change their behaviors, or had heard the term “family accommodation”.

Discussion/Conclusions:
Most relatives in this sample reported participation in accommodating behaviors, yet few outpatient providers recommended their cessation. Despite the vast majority of relatives having had communication with outpatient treaters, there is no evidence that the information and/or recommendations provided impacted family accommodation behaviors in this sample. Further investigation of the efficacy of outpatient family interventions is warranted.
Title: Atypical Asymmetry of Superior Temporal Gyrus and Temporal Stem White Matter Microstructure in Autism

**Background.** Previous studies find that developmental deviations of functional hemispheric asymmetry in autism are associated with language functioning and cognitive ability impairments in the absence of volumetric differences. The pathogenesis of autism could thus involve atypical inter-hemispheric organization of white matter microstructure.

**Objectives.** We sought to determine if such atypicality is present in the superior temporal gyrus and temporal stem in autism and to quantify its effects on language functioning, if any.

**Methods.** Thirty high-functioning males with idiopathic autism aged 8-26 years and 30 matched controls participated in a case-control diffusion tensor magnetic resonance imaging study. All autism subjects met full criteria for autism. Convention tensor measures were recorded. A novel tensor asymmetry index, language functioning and psychotropic medication usage were also measured. We also studied an independent replication sample of 12 males with idiopathic autism and 7 matched controls.

**Results.** In our sample, we observed atypical losses and reversal of leftward asymmetry, atypical reductions in spatial organization and atypical age-related decreases of white matter microstructure in the superior temporal gyrus and temporal stem. Six of these measurements, including the novel tensor asymmetry index, discriminated between control and autism subjects with 91.6% accuracy, 93.6% sensitivity and 89.6% specificity. The classification ability of our method remained equally high with our second sample. Without the novel tensor asymmetry index, results dropped to unacceptably low levels between 66.7 and 71.4%.

**Conclusions.** Our results suggest that the hemispheric asymmetry, fiber organization and age-related changes in white matter microstructure in the superior temporal gyrus and temporal stem are atypical in autism. These brain circuitry abnormalities could be due to genetic and/or epigenetic dysregulation in brain development and are consistent with a hypothesis of increased proximal connectivity and underdeveloped distal connectivity in the disorder. We also find that six of these atypicalities, including our novel tensor asymmetry index, could serve as useful biological indicators of autism in populations of individuals similar to our own.

**Funding sources and Disclaimer.** The project described was supported in part by grant number R01 MH080826 and R01 MH084795 from the National Institute Of Mental Health, and the McLean Corneel Fellowship. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of Mental Health or the National Institutes of Health, or McLean Hospital.
Title: Predictors of Self-mutilation in Patients with Borderline Personality Disorder: A 10-Year Follow-up Study

Objective: The purpose of this study was to determine the most clinically relevant baseline and time-varying predictors of self-mutilation over 10 years of prospective follow-up among patients with borderline personality disorder (BPD).

Method: Four semi-structured interviews assessing axis I disorders, childhood adversity, adult experiences of abuse, and experiences of self-mutilation were administered at baseline to 290 patients meeting DIB-R and DSM-III-R criteria for BPD. Three of these interviews (all except for the childhood adversity interview) and two self-report measures pertaining to dysphoric affects and cognitions were also administered at each of five contiguous two-year follow-up periods.

Results: Eleven variables were found to be significant bivariate predictors of self-mutilation in five follow-up periods. Eight of these predictors remained significant in multivariate analyses: female gender, severity of dysphoric cognitions (mostly overvalued ideas), severity of dissociative symptoms, major depression, history of childhood sexual abuse, severity of other forms of childhood abuse, sexual assaults as an adult, and lifetime number of self-mutilation episodes assessed at baseline.

Conclusion: Taken together, the results of this study suggest that factors pertaining to traumatic experiences throughout the lifespan are associated with self-mutilation over time. These results also suggest that cognitive symptoms, particularly overvalued ideas and dissociation, are associated with self-injurious behaviors tracked for a decade.
**Title:** Chemical Analysis and Pharmacological Evaluation of Wutou and Fuzi: Two Different Root-Parts of *Aconitum carmichaeli*

*Aconitum carmichaeli* (Fuzi) has been used traditionally in China primarily for pain management. Wutou (mother root) and Fuzi (baby root) are two different parts of the root. It is conceivable that the secondary plant metabolites of the mother root and baby root are quite different; however, there is no chemical report on such difference. Previous pharmacological studies revealed that aconitine, a diterpennoid alkaloid, is a highly toxic substance and Fuzi has been traditionally processed (detoxified) either by heating in boiled water or treating with caustic soda solution to remove two ester groups of aconitine which are responsible for the toxicity. Since Fuzi is one of the 5 components of NPI-025, an effective herbal remedy for alcohol and drug abuse, we have conducted a comprehensive chemical analysis and pharmacological evaluation of various alkaloids of processed and unprocessed *Aconitum carmichaeli*. Interestingly, most of the Fuzi on the Chinese market as well as on the US market contains undetectable amount of aconitine, benzoaconine, and aconine indicating a serious problem of overprocessing. An analytical HPLC method has been developed for qualitative and quantitative analysis of all plant alkaloids derived from *Aconitum carmichaeli*. This study provides a scientific support of employing different root-part of *Aconitum carmichaeli* for different medicinal uses. This presentation will highlight the chemistry of *Aconitum carmichaeli*. 
Schizophrenia (SZ) patients show impairments in relational memory organization, which is dependent on an intact hippocampus. Transfer generalization (TG) is one component of relational memory organization. We examine whether 1) SZ patients demonstrate deficits on a TG task, 2) TG deficits are specific to SZ or also occur in bipolar disorder, and 3) TG deficits are over-represented in well relatives of SZ patients. In the TG task, subjects learn which member of a pair of stimuli hides a smiley face based on one attribute, shape or color. All groups performed equivalently when tested on the learned pairs. TG requires subjects to identify the relevant attribute (shape or color) in new pairs of stimuli based on the relevant attribute of the learned stimuli. The groups did not differ in accuracy on the shape pairs. On the color pairs, both SZ and bipolar patients performed significantly worse than controls. Relatives of SZ patients performed equivalently to controls and significantly better than SZ patients. Bipolar patients did not differ from SZ patients or relatives of SZ patients. These results indicate that TG deficits are associated with both schizophrenia and bipolar disorder, but are not co-familial. Transfer generalization paradigms provide a potentially useful behavioral probe of hippocampal function in relation to psychotic disorders.
Title: Longitudinal Course of Neurocognitive Functioning in Psychosis

Background and Significance: Cognitive dysfunction is a core feature of both SZ and BD and is a strong predictor of functional outcome. Patients exhibit global cognitive impairment as well as specific deficits in working memory, executive functioning, sustained attention, and processing speed. While cognitive dysfunction is relatively stable in patients with SZ after illness onset, some cross-sectional findings suggest that cognitive symptoms may be episodic in patients with BD. However, other reports indicate that patients with SZ and BD do not differ in terms of cognitive dysfunction, and that patients with BD continue to experience deficits into euthymia. Little longitudinal information on the course of cognitive functioning is available on patients with related disorders, such as SZA.

Goals and Hypotheses: The present study aimed to examine neurocognitive deficits in SZ, SZA, and BD participants and to track these over time and in conjunction with changes in clinical state. It was hypothesized that a) at baseline, patients with SZ, SZA, and BD would exhibit cognitive deficits in all domains compared to controls, b) cognitive dysfunction would remain stable over a 6-month follow up, independent of clinical state, and c) cognitive deficits would be associated with poorer community functioning across groups.

Method: 90 participants with BD, SZ, and SZA recruited through the McLean Hospital Schizophrenia and Bipolar Disorder Program and 20 healthy controls completed baseline clinical and neuropsychological assessments. To date, 27 patients and 7 controls have returned for the 6-month follow up assessment, during which participants repeat the same clinical and neuropsychological battery.

Results: Groups did not differ on most demographic variables; however, groups did differ in terms of number of prior hospitalizations. All patients were experiencing clinically significant symptoms at baseline assessment. ANOVAs comparing neurocognitive functioning revealed that patient groups did not differ on most neuropsychological variables at baseline. Preliminary analyses were conducted for the 27 participants for whom complete data were available for the 6-month visit. ANOVAs were conducted to examine group differences at follow-up in terms of clinical symptoms and neurocognitive and community functioning. Linear regressions predicting neurocognitive variables at time two were also performed. Change scores in terms of clinical and cognitive variables were examined by group, and regressions predicting change were also run.

Conclusion: Neuropsychological functioning was compromised at baseline across diagnoses and did not recover over a 6 month follow up period for most variables. In all domains, patients performed below the mean for healthy adults. Additionally, clinical symptoms remitted substantially over the follow-up period in patients with BD, whereas cognitive and community functioning remained stable for most measures. These findings suggest that, in our sample, patients with psychosis exhibit significant cognitive impairment regardless of diagnosis, which does not improve significantly over time or with symptom remission. Additionally, neurocognitive deficits but not clinical symptoms were associated with poorer community functioning. These findings support the search for treatments targeting cognitive symptoms in all patients with psychotic illness.
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Title: Using functional magnetic resonance imaging to study sedative/hypnotics: The effect of zolpidem in healthy volunteers

Zolpidem (Ambien®) is a non-benzodiazepine hypnotic that binds preferentially to the benzodiazepine site of GABA<sub>A</sub> receptors containing an alpha-1 subunit. Despite the preponderance of studies describing the numerous behavioral effects engendered by zolpidem, there are few studies detailing zolpidem’s effects in the brain. To that end, the present study employed functional magnetic resonance imaging (fMRI) to begin probing the neuronal substrates of zolpidem’s action. Specifically, this study investigated the dose-response effects of zolpidem (0, 5, 10, and 20 mg) on the blood oxygen level-dependent (BOLD) signal in healthy adult volunteers (N=7) during stimulation of the visual cortex produced by the presentation of a flashing radial checkerboard (8 Hz). Each participant received all four doses in a counterbalanced order, and underwent scanning approximately 30 min post-drug (i.e., visual stimulation took place approximately 1 hr post-drug). While the highest dose appeared to result in sleep in several participants (eyes closed and therefore no activation in the visual cortex), there were no differences in activation following administration of the other two doses relative to placebo (p=0.134). These preliminary results indicate that zolpidem may have no effect on the robust visual activation produced by the flashing checkerboard, and they are supported by the absence of any drug effect on heart rate or blood pressure measured in these participants. Thus, it is unlikely that zolpidem will produce non-specific cardiovascular or systemic effects that could confound the interpretation of a drug-induced change in the BOLD signal in subsequent studies designed to probe the neurobiological basis of the sedative-like, dysphoric-like, anxiolytic, and/or reinforcing effects of zolpidem using fMRI. Support: NIDA grants K01 DA023659 (SCL) and K05 DA000343 (SEL).
Chronic cocaine exposure alters brain structure and function. Longitudinal MRS evaluation of chronic cocaine exposure may provide valuable information for understanding the cocaine addiction process and furthering the development of new treatments. Studying cocaine’s brain effects prospectively in humans is difficult, and it is impossible to conduct studies including baseline (pre-cocaine) assessments. Accordingly, we developed a squirrel monkey model to study the brain effects of chronic cocaine exposure prospectively. At baseline, 4 adult male monkeys underwent right putamen MRS on a 9.4-Tesla 29 cm horizontal bore MRI system (Varian Direct Drive, Varian Inc, Palo Alto, CA) in the Translational Imaging Laboratory at the Brain Imaging Center at McLean Hospital. For scanning, monkeys were sedated with IM ketamine (25 mg/ml), incubated, and maintained with isoflurane gas at 1.5-2%. Heart rate, body temperature, respiration rate and other vital signs are kept monitored during the whole MR scan. A STEAM sequence was used with parameters: TE/TM/TR of 9.7/7/4000 ms, 128 averages, voxel size=6x6x6 mm (0.216 mm³). Monkeys subsequently were administered cocaine intramuscularly 3 times/day, 5 days/week, at 1 mg/kg for 1 week, 2 mg/kg for 1 week, and 3 mg/kg, for 8.5 months. The same MRS scans were repeated at 1, 3, 6 and 9 months after starting cocaine administration. Spectral data were processed and fitted with a customized, automated Matlab script, and LCmodel. Metabolite ratios were calculated using total creatine (Cr) as the denominator. One-way within-subjects ANOVAs were run for each ratio to test for exposure time effects. Only the glutamate (Glu)/Cr ratio was significant (F_{4,12}=75, P<0.000001). Post-hoc tests revealed that Glu/Cr ratios decreased and increased from baseline, respectively, after 1 (t=6.85, p<0.01) and 9 (t=8.9, p<0.003) months cocaine. The early Glu/Cr decrease is consistent with reduced anterior cingulate Glu/Cr levels reported in human chronic cocaine users (Psychiatry Res. 174:171, 2009). The late Glu/Cr increase also is consistent with that study, which noted a positive correlation between cocaine use duration and Glu/Cr levels. These results suggest that this prospective squirrel monkey model may be suitable for studying some of cocaine’s chronic effects, as well as for testing novel treatment medications. Supported by NIH grants DA09448, DA017324, RR019356, and the Counterdrug Technology Assessment Center, an office within the Office of National Drug Control Policy, via Army Contract Number DBK39-03-C-0075.
Alternative medicine including traditional Chinese medicine (TCM) has been used for thousands of years, however, despite the extensive utilization of medicinal herbs and their products by a large population over a long period of time in China, the chemical basis of therapeutic actions remains unclear for most of them. Furthermore, standardization and proper quality control of Chinese medicinal materials are almost non-existing. Our alternative medicine program at McLean has been providing highly standardized TCM formula for clinical evaluations: HLXL for osteoarthritis at University of Maryland (P01-AT-002605), NPI-025 for alcohol and drug abuse study (P01-AT-002038) and NPI-031 and NPI-031G for reduction of alcohol drinking and conducting basic sciences study to find bioactive compounds responsible for the observed activities. In summary, the multi-targeted and multi-components approach of TCM would have better results in dealing with complicated human diseases, particularly in comparison of a single chemical entity approach employed by current pharmaceutical companies. This presentation will highlight some of the findings which serve not only as scientific bases for their traditional use but also provide justifications for future clinical trials.
Background. The unique antipsychotic drug clozapine treats both the positive and negative psychotic symptoms associated with schizophrenia with greater efficacy than other antipsychotic drugs, including other atypicals. In addition, clozapine improves the cognitive dysfunction associated with poor social and occupational outcomes and may stabilize mood. However, side effects limit clozapine's use to treatment-refractory psychosis in spite of its superior therapeutic value. A challenge in advancing the treatment of schizophrenia is therefore to identify the signaling pathways involved in both the therapeutic and harmful effects of clozapine.

Rationale. Schizophrenia is associated with abnormal levels of trace amines, suggesting a role for trace amine signaling in this disease. Behavioral genetic studies, by our group, in the nematode *Caenorhabditis elegans* have recently implicated trace amine signaling in the biological effects of clozapine.

Methods. We conducted behavioral studies in a trace amine associated receptor 1 (TAAR1) knockout mouse strain to determine whether this receptor mediates some of the biological effects of clozapine in mammals. We assayed prepulse inhibition (PPI) of the acoustic startle response, a behavior known to be abnormal in schizophrenia. Knockout and wild-type mice received once-daily IP injection of 4 mg/kg clozapine or vehicle for three days. PPI was evaluated on day 1 prior to injection and on day 3 one hour post-injection.

Results. At n=25 per strain (12 clozapine-treated wild-type, 13 clozapine-treated knockout) an ANOVA (2 strain x 2 treatments x 2 repeated measures of prepulse intensity) of the pre- vs. post-injection difference in percent PPI showed a trend to strain by treatment interaction (p=0.067). Follow-up analysis within each strain showed that knockout mice receiving clozapine failed to exhibit elevated PPI after three days of treatment compared to vehicle-treated controls (p>0.6) whereas clozapine-treated wild-type mice exhibited significantly enhanced PPI compared to vehicle-treated controls (p=0.004).

Conclusion. Weak inhibition of the startle response by a prepulse implies that the functions recruited to process the prepulse are easily interrupted. Patients with schizophrenia exhibit weak PPI and show significant association of psychotic symptoms with PPI impairment. PPI improves in step with other symptoms in patients on antipsychotic treatment. Our results thus implicate TAAR1 in the therapeutic effects of clozapine.
Salvia divinorum, a Mexican psychoactive plant, has been used in traditional spiritual ritual for hundreds of years. It is widely available on the internet. Salvinorin A (1), a non-nitrogenous neoclerodane diterpenoid, was isolated from S. divinorum, and was identified as a potent and selective kappa (κ) opioid receptor (KOR) agonist and the key ingredient responsible for psychoactive effects. Smoking the leaves represents one of the common practices for experiencing the psychotropic effects, including hallucination and mood changes. In addition, it was reported that smoking the leave extract is the preferred route of administration among recreational user, and the effects are potent and intense. However, the chemical components in the smoke of S. divinorum leaves and extracts are still unknown. Therefore, in order to understand the biological and pharmacological principles, we have isolated several thermo-degradation products including one new compound (2) from the smoke. The structures of these compounds were characterized by spectroscopic methods. Furthermore, the isolated compounds were evaluated for their binding affinity at the human KOR, and salvinorin A (1) is still the most potent compound in the smoke.
Title: Memory and response conflict in schizophrenic patients and normal controls

The resolution of interference from immediate previous memory and response representations that conflict with current task is a requirement of cognitive control. This ability is deficient in schizophrenic patients. The current study involved a short term memory task where subjects determined whether a “probe” letter was part of an immediately preceding 4 letter “memory set”. This task was adapted from an fMRI study (Nelson et al 2003) in which the authors found that familiarity conflict (the current probe was from the previous memory set) was associated with left dorsolateral cortex activation. Trials where the current probe was not only in the previous memory set (memory conflict) but also was the previously responded to probe set up an additional response conflict, that was associated with cingulate gyrus activity.

Thirty-six schizophrenic patients (27M, 9F) and 35 normal controls (24M, 11F) were tested on an EEG version of this task. Subjects were recruited from inpatient units at McLean Hospital (patients) and via internet and posted advertisements (control subjects). All reported normal vision or wore corrective lenses. Groups were matched on age, gender, parental socioeconomic status, education level, handedness and pre-morbid IQ. Subjects were presented with the four letter memory set for 1 sec. After a 250 msec inter-stimulus interval the probe letter appeared. Subjects were required to decide if the probe was in the current memory set. Half of the trials (120) had a probe in the current memory set, and half did not (120). Of the trials where the probe was not in the memory set, 40 caused a memory conflict because the probe appeared in the preceding memory set. In another 40 dual conflict arose because the probe appeared in the previous memory set and the previous probe (response conflict).

Overall, patients made more errors than control subjects, but did not show selectively increased on conflict trials. However, patient, but not control, error rates on conflict trials correlated with semantic and working memory measures. Patients and controls did not differ in a negative-going N2-like event-related potential (ERP), but patients showed a significantly smaller positive-going P3-like ERP. Furthermore, error rates in patients correlated with the N2-like ERP, whereas error rates in controls correlated with the later P3-like ERP.

The N2-like ERP may reflect a quick “pigeonholing” or superficial stimulus classification. The later P3-like activity may reflect more in depth processing of the probe stimuli. The results here suggest that schizophrenia patients may rely more on cursory evaluative processes whereas controls use a more elaborate evaluative process in the face of working memory conflict. It remains to be determined whether specific ERP-activity on this task can be localized to dorsolateral cortex and to cingulate gyrus.
Title: Healthy volunteers feel “high” and “like” the subjective effects of zolpidem but do not choose it over money

Empirical evidence to date suggests that abuse potential of benzodiazepines is greater among individuals with a drug use and/or abuse history compared to the general population. Recent case reports suggest that non-drug-abusing individuals may be vulnerable to abuse of and/or dependence on the benzodiazepine-like hypnotic zolpidem, particularly at doses higher than those recommended for treating insomnia. The present study measured zolpidem-induced subjective effects in drug-naïve volunteers in order to study the constellation of effects that may contribute to the abuse-related properties of this commonly prescribed sleep-aid. Eleven healthy male (6) and female (5) non-smoking volunteers were recruited as part of a larger fMRI study. Participants received oral zolpidem (0, 5, 10, or 20 mg) in a double-blind, placebo-controlled design, and answered computerized questionnaires assessing drug-induced subjective effects periodically over the course of a 7-hr experimental session. When rating “How high do you feel right now?”, participants reported significant increases relative to placebo at a number of time points following administration of the 20 mg dose (p=0.01). Across time, the 5 and 20 mg doses increased ratings of “How much do you like the drug you took?” (p=0.04), while the therapeutic dose (10 mg) did not. A questionnaire administered at the end of the session indicated that all three doses increased ratings of “Drug Strength” (p<0.001), but only the 20 mg dose increased ratings of “Drug Liking” (p=0.008), “Good Effects” (p=0.006), and “Willingness to Take Again” (p=0.055). While 20 mg and 10 mg (p=0.021) also increased ratings of “Bad Effects”, no dose of zolpidem was chosen over money ($0.35 - $10) at any time point when participants made hypothetical choices between the two. These results suggest that zolpidem-related ratings of high, drug liking, and a willingness to take the drug again may be not be powerful enough to facilitate the abuse of and/or dependence on this drug.
Aim: This study has two main objectives. The first is to assess the rates of adult experiences of verbal, emotional, physical, and sexual abuse reported by borderline patients and axis II comparison subjects over ten years of prospective follow-up. The second is to determine time-to-cessation, resumption, and new onset of these four types of abuse.

Method: The Abuse History Interview (AHI) was administered to 290 borderline patients and 72 axis II comparison subjects at baseline. Similarly, the AHI Follow-up Version (AHI-FUV) was administered at five contiguous follow-up waves.

Results: Over ten years of follow-up, the rates of all four types of abuse declined significantly for both borderline and axis II comparison subjects. However, each type of abuse was reported by a significantly higher percentage of borderline patients. By the time of the ten-year follow-up, 95% of borderline patients had a cessation of verbal abuse, 96% of emotional abuse, and 100% of borderline patients who experienced physical or sexual abuse. While rates of cessation were high for all four types of abuse, resumptions also occurred frequently. More specifically, 68% of borderline patients experienced a resumption of verbal abuse, 68% a resumption of emotional abuse, and 36% and 25% experienced resumptions of physical and sexual abuse, respectively. In terms of new onsets, 64% of borderline patients without a baseline history experienced a new onset of verbal abuse, 72% had a new onset of emotional abuse, 32 percent experienced a new onset of physical abuse, and 17 percent had a new onset of sexual abuse.

Conclusion: The results of this study suggest that cessations of all four types of abuse are very common. They also suggest that resumptions and new onsets are relatively common, particularly resumptions of verbal and emotional abuse.
This exploratory study examining potential buffers to depression in couples is grounded in Interpersonal Theory, which postulates that individuals who occupy social roles that allow for a sense of satisfaction and self-efficacy are at decreased risk for depression. Since partners of depressed individuals are at greater risk for depression (Benazon & Coyne, 2000; Coyne, 1987; Tower & Kasl, 1995; 1996a; 1996b) this theory was expanded to incorporate couples in committed intimate relationships. This study aimed to test the hypothesis that role quality (i.e. personal satisfaction derived from occupying a particular social role such as parent or employee), the number of multiple roles an individual occupies (i.e. employee, friend, parent, partner), and self-efficacy in multiple roles serve as buffers to depression for partners of depressed individuals. Participants were 42 couples in which one partner was a patient at the Behavioral Health Partial Program (BHP) at McLean Hospital. Patients were only assessed for depression, while partners were assessed for depression, number of social roles occupied, the quality of these social roles, marital satisfaction, and self-efficacy. Findings revealed a significant positive association between patient and partner depression. Results demonstrated support for the hypotheses that Job Role Quality and Friend Role Quality significantly moderate the association between patient and partner depression, while Parent Role Quality and Marital Role Quality did not significantly moderate this association. Neither self-efficacy nor total number of social roles occupied significantly moderated the association between patient and partner depression. However, using ordinary least squares (OLS) regression, self-efficacy predicted 30.5% of the variance in partner depression, and number of roles occupied predicted 9.0% of the variance in partner depression.
Title: The orexin-1 receptor antagonist SB334867 elevates thresholds for brain stimulation reward and attenuates cocaine-induced impulsivity in the 5-choice serial reaction time task

Background. Hypocretin (orexin; hcrt/orx) peptides have a well established role in maintaining uninterrupted wakefulness. Recent work demonstrates that hcrt/orx may also be important for mood, reward learning, and animal models of addiction. Impaired hcrt/orx signaling reduces the rewarding properties of biological reinforcers like food and sex, and blocks sensitization to psychomotor stimulants as well as stress- and cue-induced reinstatement of cocaine self-administration. Indeed, antagonists at the orexin-1 (OX₁) receptor may be indicated for preventing the development of and relapse to compulsive drug use. Little is known, however, about the acute effects of OX₁ antagonists on brain stimulation reward. We sought to characterize the acute effects of the OX₁ antagonist SB334867 on reward threshold using the intracranial self-stimulation (ICSS) paradigm in C57BL/6 mice. Because central hcrt/orx insufficiency is responsible for the symptoms of narcolepsy (e.g. sleep attacks, cataplexy), we also used the 5-choice serial reaction time task (5-CSRTT) in rats to validate that the effects of SB334867 on ICSS thresholds were not due to nonspecific response decrements caused by impaired sensory processing or somnolence.

Methods. Adult male mice were surgically implanted with stimulating electrodes directed to the medial forebrain bundle within the lateral hypothalamic area and trained to spin a wheel manipulandum for electrical stimulation. The effect of SB334867 (3 – 30 mg/kg, IP) on reward thresholds was determined using the rate-frequency procedure for ICSS testing. In 5-CSRTT experiments, rats were trained using a 0.5 sec stimulus duration and 5 sec inter-trial interval to a criterion of >65% accuracy with <10% omissions. Animals were then treated with either SB334867 (0.1 – 30 mg/kg, IP) or cocaine (0.3 – 10 mg/kg, IP). During the latter group’s final test session, cocaine (1 mg/kg) was given 5 min after a SB334867 (30 mg/kg) pretreatment.

Results. Compared to vehicle-treated animals, mice receiving SB334867 showed elevated reward thresholds (i.e. required higher stimulation frequencies to support responding). In the 5-CSRTT, SB334867 had no effect on accuracy, latency, or number of omitted responses. However it dose-dependently decreased the number of premature responses. Cocaine had no effect on accuracy, latency, or omissions, although it caused a two-fold increase in premature responses. This effect was abolished by pretreatment with SB334867.

Discussion. Hcrt/orx-bearing projections from the hypothalamus exert potent excitatory effects on ventral tegmental area dopamine neurons. Given the putative role of these neurons in ICSS and other rewarding behaviors, it follows that blockade of OX₁ by SB334867 would attenuate ICSS, thus indicating an anhedonic effect. Elevations in reward threshold do not appear to be the result of nonspecific response decrements, as rats performed with high accuracy and few omissions in the 5-CSRTT. Interestingly, SB334867 did attenuate both spontaneous and cocaine-induced premature responding, a measure generally interpreted as an impulsive-like behavior. Because impulsivity and impaired executive function are thought to be important features of addiction, these data may shed new light on the earlier finding that OX₁ antagonists reduce drug-seeking behavior in animal models of relapse.
Cues paired with drug administration trigger relapse to drug-seeking behavior in both humans and animals by inducing conditioned drug craving and conditioned withdrawal states. Because drug cues represent a barrier to long-term abstinence in recovering addicts, there has been considerable interest in incorporating therapies to reduce responsiveness to drug cues into addiction treatment programs. Extinction is a means of reducing Pavlovian conditioned responses and involves exposure to the conditioned stimulus (CS) in the absence of the unconditioned stimulus (US) with which it was paired previously. In animal models including cue-induced reinstatement of drug seeking and conditioned place preference, drug craving elicited by drug-paired cues can be extinguished by presenting the cues repeatedly without drug administration. Recent studies have begun to identify the neurobiological mechanisms of extinction in these paradigms, which are similar in a number of respects to those underlying extinction of conditioned fear. By contrast, extinction of conditioned withdrawal has received almost no attention. We have begun studying conditioned withdrawal extinction using naloxone-induced conditioned place aversion in morphine-dependent rats as a model system. In this paradigm, conditioned withdrawal motivates avoidance of an environment previously paired with acute withdrawal induced by administration of the opiate receptor antagonist naloxone. We have found that conditioned withdrawal can be reduced by confining the animals in the formerly naloxone-paired environment in the absence of acute withdrawal. Thus, after several sessions of confinements, animals no longer avoid that environment when given free access to the place conditioning apparatus. This loss of the avoidance response is due to extinction rather than forgetting of the previous significance of the environment because animals not receiving exposures to the environment in the absence of naloxone continue to exhibit persistent, robust place aversions. Finally, like extinction of conditioned fear (Walker et al. 2002) and cocaine conditioned place preference (Boteau et al. 2006), extinction of naloxone-induced conditioned place aversion in morphine-dependent rats is facilitated by systemic administration of the NMDA receptor partial agonist D-cycloserine. Continuing examination of the mechanisms of conditioned withdrawal extinction will extend our understanding of drug cue responsivity, a significant element of addiction, and has the potential to inform extinction-based addiction treatments.
Title: Integrating Alcoholics Anonymous teaching within psychiatry training programs

Background: Trainees in psychiatry programs frequently treat patients with co-occurring substance use disorders, yet rarely is a full didactic seminar dedicated to teaching them about the history and use of Alcoholics Anonymous (AA) and other 12-step programs. Given the lack of education and exposure to AA, it was unclear if residents were engaging substance abusing patients in discussion regarding participation in AA as part of a comprehensive recovery and relapse prevention plan. This didactic served to both educate the trainees and measure their use of and comfort with AA in clinical practice.

Methods: A literature and internet search was performed to review the history and development of AA in the context of significant figures in medicine (William Silkworth), psychiatry/psychology (Carl Jung, Williams James) and society (John D. Rockefeller). This information was integrated into the introductory half of a didactic teaching seminar for psychiatry trainees; the second half reviews programmatic aspects of AA and how to effectively engage patients in using AA as well as a literature review of its effectiveness and efficacy. AA resources and literature are paired with the didactic to provide tools for clinicians referring patients. The didactic was presented to trainees and staff in multiple clinical contexts with brief pre-seminar and post-seminar feedback surveys that measured the overall learning experience including knowledge of AA, comfort in referring and confidence in discussing AA with patients.

Results: The didactic was presented to psychiatry residents in training, psychology and social work interns as well as teaching and research faculty and administrative staff. Audience feedback was overwhelmingly positive and trainees reported greater confidence in making referrals to AA as well as appreciating the evolution of AA within a broader context of the history of psychiatry.

Conclusions: Teaching residents, fellows and mental health staff about the historical evolution of AA within the context of the history of psychiatry provides a novel approach to engaging clinician interest in 12-step programs. This is effectively followed with training on 12-step program use and referral resources. This seminar is now being refined by presentations to trainees and staff in multiple clinical contexts, including medical and surgical residents with brief pre-seminar and post-seminar feedback surveys. The final seminar will be made available for public use.
Growing evidence supports a pivotal role for the amygdala in the pathogenesis of schizophrenia (SZ) and bipolar disorder (BD). The amygdala receives substantial dopaminergic innervation, raising the possibility that this region may be vulnerable to abnormalities relative to dopaminergic transmission, as suggested by postmortem investigations and association of these diseases with dopamine-related gene polymorphisms (Reynolds, 1983; Greenwood et al., 2006; Tunbridge et al., 2006). To test this hypothesis, we measured numerical densities of dopamine transporter- (DAT) and tyrosine hydroxylase-(TH) immunoreactive (IR) fiber varicosities in the lateral (LN), basal (BN), accessory basal (ABN), cortical (CO) nuclei and in the intercalated cell masses (ITCM) of the amygdala of 12 normal control subjects, 14 BD and 10 SZ subjects. Two sets of serial sections (1.04 mm interval) through the whole amygdala were obtained using systematic random sampling criteria and processed for immunocytochemistry using antibodies raised against DAT and TH. Numerical densities (NV) of DAT- and TH-IR varicosities were measured with computer-aided light microscopy using stereology-based sampling methods. Differences between groups were analyzed using a stepwise linear regression process. NV of DAT-IR varicosities were significantly decreased in SZ, but not BD, subjects. In SZ, decreases were detected in the LN (t= -4.6; p= 0.0002), BN (t= -2.63; p= 0.017), ABN (t= -3.51; p=0.0025), and CO (t= -5.05; p= 0.0001). Exposure to antipsychotics significantly, and positively, correlated with NV of DAT-IR varicosities in these regions. No significant changes were detected in the ITCM. Differences between SZ and BD were found to be statistically significant in LN (p= 0.0057), BN (p= 0.05), ABN (p= 0.015) and CO (p= 0.002). No changes of NV of TH-IR varicosities were found in SZ and BD subjects in any of the nuclei examined. These results point to abnormalities of the dopaminergic system in the amygdala of SZ. Such abnormalities may represent a poignant difference between the pathophysiology of SZ and BD, one that may account for pharmacological and clinical dissimilarities. In the presence of normal density of TH-IR fiber varicosities, a decrease of DAT expression implies that dopamine is released from presynaptic terminals while its re-uptake may be insufficient. These results also suggest that antipsychotic drugs may increase densities of DAT-IR terminals, thus correcting for reductions associated with this disease. Funded by NIH MH066955 and MH066280.
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Title: Dimensions of Success: an Assessment Tool for Informal Science Education

Aim: In the USA there are approximately 15 million children unsupervised in after-school hours every day. This lack of supervision puts teens at a very high risk for sex, drugs and alcohol. Violent juvenile crime rates are higher during 3 to 6 p.m. On the other hand, children participating in after-school programs reported improved skills in maintaining self-control and avoiding fights. The academic performance of these children is also known to be better; they show increased interest in school and lower rates of drop-out.

To ensure children’s consistent attendance in afterschool programs, they have to be high quality and at the same time be interesting and engaging. So what is a quality afterschool program? How do we define and measure quality?

To answer these questions, researchers at the Program in Education, Afterschool and Resiliency (PEAR) at Mclean Hospital and Harvard Medical School developed an observation tool – Dimensions of Success (DOS). DOS assesses quality indicators of Out-of-School Time (OST) Science Technology, Engineering and Math (STEM) learning.

The proposed poster will illustrate the DOS tool and the theoretical frameworks it is based upon.

Methods: DOS was developed based on National Science Foundation’s (NSF) “impact categories”, “the quality triangle” developed by PEAR and initial data from PEAR’s Informal Learning in Science Afterschool (ILSA) study. DOS has four domains and twelve dimensions.

The tool was developed over a fourteen-month period, during which time PEAR researchers conducted in-depth observations in afterschool and summer programs that offer STEM activities.

Initial field tests of DOS were conducted in programs serving approximately 1,700 children from grades K-12 in urban, suburban and rural settings in 2007 and 2008. A subset of these programs was observed weekly for approximately five months. Programs varied in location (i.e., school, museum, community center) and focus (e.g., career awareness, college preparation, and hands-on science exploration). The tool was presented at the First National Conference on Science and Technology in Out-of-School Time, and received feedback indicating the need to continue to develop the instrument for wide dissemination and use.

Conclusion: Data from ILSA survey shows that over half of OST programs do not evaluate their STEM programs. Most programs that had internal evaluation used “home-made” assessment tools. By their nature, site-developed, site-specific assessment tools have questionable validity because they are based on the site’s existing objectives and goals, and are often only suitable for those programs. The findings that emerge from individualized assessment tools cannot be compared with other STEM OST programs because these site-specific tools are not standardized to be compatible with programming across sites.

Of the few existing assessment tools that purport to focus on STEM, many are constrained by focusing too narrowly on one quality indicator – often content knowledge. Other tools measure science with the same criteria as art or recreation.

Ultimately, there is a clear need for a formal assessment tool to assess numerous indicators of quality STEM learning in out-of-school time. In this respect DOS is a unique instrument for assessing STEM program quality in informal environments.
Research Administration at McLean operates closely with several centralized Partners HealthCare research departments, including Research Finance, Grants Management, Corporate Sponsored Research & Licensing, and Research Information Systems. Our goal is to assist investigators with the preparation and submission of their grant applications, help them with budgets, and assist in setting up new grant awards. In addition, we are responsible for ensuring that funds are expended according to the terms, conditions, and proposed research in the awarded grant, and for ensuring that the grants are expensed in a timely and fiscally appropriate manner. We also oversee all subcontracts (in and out), review all sponsored research agreements including industry-sponsored trials, and assist with all technology transfer and intellectual property disclosure and prosecution. Our office of Research Information Systems has responsibility for all the research servers, email, the research intranet, and the maintenance and operation of more than 1,300 computers, computer assisted instrumentation, and peripherals.

Much of Research Administration’s responsibilities are also regulatory in nature. Since almost 80% of our external funding is federal, there are numerous policy and regulatory requirements that need to be reported on a regular basis. Research Administration has oversight of our Animal Welfare program, and is directly responsible for annual reports to the NIH’s Office of Laboratory Animal Welfare (OLAW) and the United States Department of Agriculture (USDA). In addition to internal audits, Research Administration is also audited annually by PriceWaterhouseCoopers, and has had no findings of noncompliance for 4 years straight. We also liaison frequently with the hospital’s Institutional Research Board (IRB) as the financial administrator for many human research studies.

Our federal sponsors include the National Institutes of Health (NIH), the National Science Foundation (NSF), the Department of Defense (DOD), the Department of Education (DOE), and the Executive Office of the President’s Office of National Drug Control Policy (ONDCP). We also have foundation and industrial sponsors, and are fortunate to receive substantial philanthropic support for our research programs.

McLean has over three acres of floor space dedicated to the research enterprise, including 5 buildings solely used for research (the Mailman Research Center, Oaks, The Neuroimaging Center, the 9.4T Building, and Mill Street Lodge). We have 136 Principal Investigators and a total of 371 research personnel, 266 active sponsored research grants, and a total of 435 open funds. We have $68,000,000 of committed future funding. Further, as part of the President’s Economic Recovery and reinvestment Act (ARRA) our researchers have received $7,544,712 in Stimulus funding as of 10/01/2009.
Cigarette smoking elicits increases in heart rate, alters subjective reports of mood, and produces reliable alterations in subjective reports of smoking sensations. The relative contribution of nicotine alone versus cigarette smoke containing nicotine is under investigation. Six female and two male volunteers (average age 24.9 ± 4.2 yrs) compared the characteristics of their usual brand of cigarette to a commercially available cigarette with varying levels of nicotine. Subjects smoked their own brand of cigarette after at least a two hour abstinence period. Then at 30 minute intervals, they smoked one of 3 varying strength cigarettes in a counterbalanced order (nicotine content: 0.6 mg, 0.3 mg, or 0.05 mg). Smoking satisfaction and sensations were measured on a 13-item cigarette evaluation questionnaire. Additionally, visual analog scales measured self-reported changes in happy, stimulated, anxious, desire to smoke, and desire not to smoke. Heart rate and skin temperature were recorded continuously.

**Results:** As nicotine content decreased, there were clear decreases in all ratings on the evaluation questionnaire with the placebo nicotine cigarette always rated lower or less potent than the subject’s usual brand. “Desire to Smoke” scores were low following each cigarette and gradually increased during the 30 minute interval, but were not dose-related. Heart rate was significantly increased by the subject’s usual brand and to a lesser extent by the low nicotine cigarettes, but was not affected by the 0.05 mg nicotine cigarette. These results suggest that nicotine content is a major factor in determining both the physiological and subjective effects of smoking and that nicotine-free cigarettes as a treatment may need further assessment.
Title: Effects of Parent Verbal Abuse and Affection on Well-being and Psychiatric Symptoms

Objective: We have previously reported that exposure to parental verbal aggression exerts enduring adverse psychiatric effects, and is comparable in magnitude to witnessing domestic violence and extra-familial sexual abuse. This goal of this study was to ascertain if parental verbal affection mitigates some of the adverse impact.

Methods: Childhood exposure was assessed in a sample of 1454 young adults (18-25 years of age; 63% female) who underwent screening as part of a series of studies on the effects of early experience on brain development. They completed on-line assessments that provided standardized self-report measures of current psychiatric symptoms, lifetime stressors, and history of exposure to verbal abuse (frequency of scolding, threats, ridicule, criticism) and verbal affection (frequency of expressions of love, praise, verbal comfort, meaningful conversations).

Results: Multiple linear Regression analyses were computed for each of the psychiatric symptom measures as dependent variables, and the Parental Verbal Aggression and Affection Scores as independent variables. Parental verbal aggression was strongly associated (p<0.0001) with symptoms of limbic irritability, anxiety, somatization, and hostility, and was not attenuated by verbal affection. In contrast, verbal affection was strongly associated (p<0.0001) with measures of wellbeing (contentment, relaxation, somatic health and friendliness). Analysis by gender of parent and child showed both males and females are significantly negatively affected by mother’s verbal aggression, but males are less impacted by father’s verbal aggression than females. Also, father’s verbal affection has a more significant positive impact than mother’s verbal affection.

Conclusions: Childhood maltreatment is an important risk factor for psychiatric illness. Parental verbal aggression is a potent and insidious form of childhood maltreatment. We sought to ascertain whether positive expression of praise and affection could attenuate the negative effects of verbal aggression. Parental verbal expressions of love, praise and comfort, did not attenuate the negative effects of verbal abuse on symptoms of limbic irritability, hostility and anxiety. However, childhood levels of parental verbal affection clearly shaped adult feelings of friendliness, well-being, and contentment.
Title: Client Nurse Interaction with Individuals with Schizophrenia: A Descriptive Study

Significance: Currently, an estimated 1.2% of the population in the United States is diagnosed with schizophrenia. These patients are hospitalized for an estimated 300,000 acute psychotic episodes on an annual basis. The long term sequeli of the disorder contribute to this recidivism rate. Social dysfunction, one of the most salient characteristics, interferes with their ability to form relationships and subsequently to utilize interpersonal supports. Recent advances in the study of social dysfunction have focused on social cognition, especially the role of vocal and facial affect recognition and social cue perception. Each of these functions influences an individual’s ability to respond in a social situation. Despite this growing body of literature, it has not been applied to the study of the nurse – client relationship.

Purpose: Describe the verbal and nonverbal communication between a psychiatric clinical nurse specialist (CNS) and clients with schizophrenia. Methods: A descriptive study utilizing videotaped recording of clients with schizophrenia and a CNS during medication monitoring sessions. There were three client participants. Analysis proceeded in five steps. Communication analysis of nonverbal and verbal behavior was conducted. Results: Several patterns emerged. As might be expected, the clients showed marked difficulty with eye contact which interfered with their interactions with the nurse. However, they did respond to the nurse when she used exaggerated facial and vocal cues. Conclusions: Clients with schizophrenia have difficulty with facial and vocal affect recognition. An inability to read social cues can interfere with an individual’s ability to relate to others. This descriptive study opens the way for further research on the interaction between a nurse and patients diagnosed with major mental illnesses. The findings can ultimately lead to improved nursing interventions for this vulnerable population which could significantly improve their quality of life.
Title: Poor Sleep Associated with Long-Term Mood Outcomes in Patients with Co-Occurring Bipolar Disorder and Substance Use Disorder

**Background:** Poor sleep has been shown to predict subsequent depressive episodes when present before treatment for mood disorders. However, the relationship between sleep and clinical outcomes may be different in a population with co-occurring bipolar disorder and substance use disorder.

**Method:** 61 patients meeting criteria for both bipolar disorder and substance use disorder participated in a randomized trial comparing integrated group therapy for bipolar disorder and substance use disorder to group drug counseling for substance use disorder alone. Poor sleep was assessed with the Pittsburgh Sleep Quality Index, which provides 7 component subscores and an overall sleep score.

**Results:** When controlling for baseline mood, substance use, and group, each additional 3 points on the PSQI (an increase equivalent to the range of each component) increased the odds of a mood episode by 72% during treatment and by 160% in the 6 months after treatment. An ANOVA using these same predictors showed only baseline sleep score to be significant, with an adjusted $R^2=14.3\%$ for number of mood episodes during treatment and 20.5% for number of mood episodes in the 6 months after treatment.

**Conclusion:** When presence of mood episode and days of substance use at baseline were controlled, poor sleep at baseline increased the odds of a mood episode and predicted the number of months with mood episodes during treatment and the 6 months follow-up. Further investigation is warranted into the long-term clinical outcomes of poor sleep in the population with co-occurring bipolar disorder and substance use disorder so that appropriate interventions can be developed.
Title: Structural Brain Changes and Attention-deficit Hyperactivity Symptom Severity in Young Persons with Autism Spectrum Disorder

Background: The high degree of inter-individual heterogeneity found in autism spectrum disorder (ASD) is a well-recognized major impediment to effective study and treatment. Variation in the severity of features of other psychiatric disorders often but not always associated with autism, including attention-deficit hyperactivity (ADHD), is a relevant but understudied contributor to this heterogeneity. Research associating structural brain changes, including changes in caudate volume and asymmetry, with ADHD and, separately, with ASD suggest in combination that variation in ADHD severity may contribute to the heterogeneity in structural brain changes present in ASD.

Objectives: The goal of this study was to investigate changes in regional brain volume and asymmetry in young persons with ASD and ADHD. Our primary hypotheses were that caudate volume is increased in ASD and that this volumetric increase is negatively correlated with ADHD severity. We studied other regional and global volumes to determine whether any findings supporting our hypotheses were specific to the caudate nucleus and to support hypothesis generation for future research.

Methods: Structural MRI scans and the Conners’ ADHD/DSM-IV Scales (CADS) were completed for N = 36 high-functioning males with ASD 6-15 years of age and N = 20 typically developing aged-matched males. Regional brain volumes by hemisphere were extracted using FreeSurfer software, including total cortex, gray matter, white matter, the head of the caudate nucleus, putamen, globus pallidus, thalamus, hippocampus, and amygdala; total brain volume, intracranial brain volume, and volumes of the posterior, mid-posterior, central, mid-anterior and anterior corpus callosum were also extracted. These volumes and their asymmetries were compared between the groups and associated with CADS total score among those individuals with ASD.

Results: We observed a highly significant increase in CADS total score in our ASD sample (p<0.001). We also found a significant association between ASD and reduced rightward caudate asymmetry (p =0.006). No association was found, however, between hemispheric asymmetries and CADS total score in our ASD sample. Neither the volumes nor asymmetries of any of the other brain structures we examined were associated with ASD or ADHD severity.

Conclusions: Our preliminary findings suggest that the development of typical rightward asymmetry of caudate volume is disrupted in autism independently of ADHD severity. Our findings also suggest that the volumetric correlates of ADHD in autism are different from correlates reported in non-autistic individuals with ADHD. Similar clinical ADHD phenotypes may have different underlying neurobiological mechanisms in individuals with and without autism. Longitudinal volumetric, diffusion tensor imaging, and fMRI studies are needed to identify unique signatures of brain development in autism with and without ADHD, and in ADHD with and without autism.

Funding Sources and Disclaimer: The project described was supported by grant numbers RO1 MH080826 and RO1 MH084795 from the National Institute of Mental Health and the Corneel Fellowship at McLean Hospital. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.
Title: Positive Affective and Cognitive States in Borderline Personality Disorder

Objective: The aim of the current study was to compliment previous studies identifying negative states present in borderline personality disorder by investigating the presence of positive affective and cognitive states.

Method: Ninety-six patients with criteria-defined borderline personality disorder and 24 axis II comparison participants completed the Positive Affect Scale, a 50-item self-report measure designed to assess positive states thought to be characteristic of borderline patients (and axis II comparison participants).

Results: Seventeen positive states (4 affective, 10 cognitive, and 3 mixed) were found to be significantly more common among axis II comparison participants than borderline patients. Twelve of these states were common to both borderline patients and axis II comparison participants. Furthermore, 4 positive states, when co-occurring together, were particularly strongly associated with borderline personality disorder (three negatively and one positively): (a) Fond of myself, (b) That things around me are real, (c) That I’ve forgiven others, and (d) Assertive. Finally, the overall mean score on the PAS significantly distinguished patients with borderline personality disorder from axis II comparison participants.

Conclusions: Taken together, these results suggest that borderline patients are far less likely to report experiencing positive states of an affective, cognitive, and mixed nature than axis II comparison participants. They also suggest that being assertive is a positive state particularly discriminating for borderline personality disorder.
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Title: Bidirectional modulation of the effects of intravenous general anesthetics by a Gabra3 knockout.  

GABA_A receptors, the major inhibitory neurotransmitter receptors in the CNS, have been shown to mediate the hypnotic, immobilizing and amnestic actions of many intravenous general anesthetics. When performing stereotaxic surgery on mice lacking the GABA_A receptor □3 subunit (□3KO mice), a remarkable, unexpected and apparently paradoxical increase in sensitivity to ketamine/xylazine was observed. We then set out to study whether this increased sensitivity would be due to increased NMDA receptor antagonism and/or □2-adrenergic agonism, or whether the □3KO mice display a general hypersensitivity to intravenous general anesthetics, including etomidate, midazolam, and pentobarbital. Furthermore, we wanted to test the hypothesis that the increased sensitivity to ketamine/xylazine might be caused by a lack of □3-containing GABA_A receptors on noradrenergic neurons. To this end, we generated mice expressing the □3-containing GABA_A receptor selectively in noradrenergic neurons. These mice carry a dopamine □ hydroxylase cre transgene, which is specifically expressed in noradrenergic neurons, and an □3KO allele with a loxP-flanked duplicated exon. Cre-loxP-mediated recombination leads to excision of this exon and rescue of □3 subunit expression selectively in these cells.  

□3KO mice showed an enhanced response to the hypnotic (loss of righting reflex), immobilizing (loss of hindlimb withdrawal reflex), and hypothermic actions of ketamine/xylazine, compared to wild-type mice. In mice expressing the □3 subunit exclusively in noradrenergic neurons, only the hypothermic effect of ketamine/xylazine was increased compared to wild type mice. Medetomidine, an □2-adrenergic agonist, induced a comparable decrease in locomotor activity in □3KO and wild-type mice, whereas the duration of the loss of righting reflex was increased and the hypothermic effects were slightly less pronounced in □3KO mice. All anesthetic endpoints were comparable for both genotypes with ketamine, only the decrease in body temperature was more pronounced in □3KO mice. The hypnotic, immobilizing and hypothermic responses to pentobarbital were enhanced in □3KO mice. In contrast, the hypnotic and hypothermic response to the GABAergic drugs midazolam and etomidate was reduced in □3KO mice.  

Our results show that □3 subunit-containing GABA_A receptors differentially modulate the effects of intravenous general anesthetics, depending on the mechanism of action of the anesthetic agent. The increased sensitivity to ketamine/xylazine in □3KO mice is at least in part due to the lack of □3 subunit-containing GABA_A receptors in central noradrenergic neurons.
Title: First-Rank Symptoms and Cycloid Features in First-Episode Psychotic Disorder Patients

Background: Schneiderian first-rank symptoms including influence experiences, thought alienation, auditory hallucinations of thought echo, commenting/dialoguing, and imperative voices, as well as delusional perception were considered pathognomonic for schizophrenia. More recently, they were deemed as ubiquitous in functional psychoses, yet they seem to predict worse prognosis. Cycloid characteristics, according to Perris, including acute onset, paranoid features, hallucinations, ecstasy, pananxiety, overconcern with death, motility disturbances, and mood swings seem to represent good prognosis factors among functional psychoses. Since the risk of these psychopathological elements among psychoses remains uncertain and their impact on diagnostic stability over time is to be further investigated, we estimated prevalence and prediction of diagnostic stability/instability among 489 patients at first hospitalization for various psychotic disorders in the McLean-Harvard First Episode Project, and during follow-up for ≥2 years thereafter.

Method: Procedures of patient assessment, diagnosis, and follow-up are detailed in previous reports from this project. All subjects were evaluated with SCID at intake and 2-year follow-up; final DSM-IV consensus diagnoses were based on all available clinical information. Psychopathology was assessed applying AMDP and BSABS systems.

Results: First-rank symptoms were identified in 387/489 (79.1%) subjects overall, and more with schizoaffective (93.3%) than affective (71.7%) or nonaffective psychoses (89.9%) (p<0.001). Cycloid features were present in 80/489 (16.4%) subjects overall, and more with brief psychosis (55.6%), mania (24.8%) and psychosis NOS (15.1%) than schizophrenia (4.2%) and schizophreniform disorder (5.9%) (p<0.001). Risk was lower for first-rank symptoms and greater for cycloid features among women versus men (76.8%/80.9%; 19.4%/14.0% respectively). As regards diagnostic stability at 24 months, cycloid features were significantly highly predictive of congruence of diagnostic categorization whereas any first-rank symptom type was significantly correlated with change of diagnosis at two years.

Conclusions: Schneiderian and cycloid features were highly prevalent among first-episode psychoses of various types, and particularly in schizoaffective and acute nonaffective disorders, as well as among men and women respectively. Specific psychopathological elements at first presentation may predict diagnostic trajectories.
Title: Hurtful Words: Exposure to Peer Verbal Aggression is Associated with Elevated Psychiatric Symptom Scores and Corpus Callosum Abnormalities

Objective Previous studies have shown that exposure to parental verbal aggression (VA) in childhood was associated with higher rates of adult psychopathology and alterations in brain structure. Here we examined the potential long-term consequences of exposure to peer verbal aggression in childhood.

Method A total of 848 young adults (ages 18 to 25 years) with no history of exposure to domestic violence, sexual abuse, or parental physical abuse rated their childhood exposure to parental and peer VA and completed a self-report packet that included the Kellner Symptom Questionnaire, the Limbic Symptom Checklist-33, and the Dissociative Experiences Scale. Diffusion tensor images were collected on a subset of 63 young adults (23M/40F; 21.9±1.9 years) with no history of abuse or exposure to parental verbal aggression selected for varying degrees of exposure to peer VA. Images were analyzed using tract based spatial statistics (TBSS).

Results Analysis of covariance, controlling for the effects of gender, parental education and family finances revealed ‘dose-dependent’ effects of exposure to peer VA on ratings of anxiety, depression, anger-hostility, dissociation, ‘limbic irritability’, and drug use. Multiple regression showed that exposure to peer verbal aggression and parental verbal aggression were essentially equivalent in their degree of effect on these ratings. Path analysis indicated the exposure during elementary school was associated with symptoms of somatization whereas exposure during middle school and high school were associated respectively with symptoms of dissociation and anger-hostility. Degree of exposure to peer VA correlated with increased mean diffusivity and decreased fractional anisotropy in the splenium of the corpus callosum.

Conclusions These findings parallel previous reports of psychopathology associated with childhood exposure to parental VA, and support the hypothesis that exposure to peer VA is an aversive stimulus associated with increased symptom ratings and meaningful alterations in brain structure.
Title: Scrupulosity Characteristics and Treatment Outcome from use of PIOS-R in OCD Residential Treatment Program

Background:
Scrupulosity, a complicated OCD subtype, involves religious/morality-related obsessions that are typically accompanied by excessive perfectionistic religious and/or moralistic rituals. Sufferers typically have poor insight into the fact that these are OCD symptoms, believing instead that they indicate sinfulness or immorality, which interferes with exposure and response prevention (ERP) compliance.

Methods:
To identify the prevalence of scrupulosity symptoms in patients with severe, refractory OCD, the Pennsylvania Inventory of Scrupulosity-Revised (PIOS-R) (Abramowitz, et al, 2002) was administered to OCD Institute patients at McLean Hospital at admission, monthly, and at discharge. Patients clinically-identified with scrupulosity symptoms were referred by their therapists (blinded to PIOS-R scores) to the program’s weekly Scrupulosity Symptom Specific Group (SSSG). Other measures used to characterize subjects included the YBOC-S, BDI, SOS, and WSA. Subgroups of individuals participating in the SSSG (N=29) were statistically compared with those not participating in SSSG (N=30) regarding clinical characteristics and treatment outcome. SPSS (v. 17.0) was used for analyses, with a significance threshold of p<0.05.

Results:
Scrupulosity severity at admission and discharge was greater in SSSG subjects versus non-SSSG subjects (p<0.001). Differences between SSSG and non-SSSG subjects included YBOC-S obsession subtotals at admission (p<0.02) and discharge (p<0.006) and OCD severity (p<0.03) and psychosocial functioning (p<0.02) at discharge. There were no compulsion subtotal differences (p>0.2). For those in SSSG, there was a significant improvement between admission and discharge PIOS scores (p<0.001) and between “fear of sin” (p<0.02) and “fear of God” (p<0.01) PIOS symptom types. PIOS improvement was significantly greater in SSSG versus non-SSSG (p<0.04) subjects. BDI, SOS, and WSA scores were all significantly improved between admission and discharge (p<0.001).

Conclusion:
As indicated by PIOS scores at admission, appropriate referrals were made to the SSSG by OCDI staff. Notably, OCD severity differences between SSSG and non-SSSG groups were limited to obsession but not compulsion severity. Further, attendance at the SSSG was associated with significant improvement of the scrupulosity total severity and “fear of God” and “fear of sin” subtypes, and improvement was significantly greater compared to non-SSSG subjects. Participation in a scrupulosity psychoeducational/support group appears to significantly improve treatment outcome for residential patients who suffer with this complicated and typically treatment-resistant OCD subtype. Further study is warranted.
Title: Resting State Functional Connectivity of Primary Auditory Cortex to Other Brain Regions in Current- vs. Never-Hallucinators with Schizophrenia or Schizoaffective Disorder

Background: Auditory hallucinations (AH) are a common feature of psychosis. The “dysconnectivity” hypothesis of schizophrenia proposes that psychosis arises from abnormal functional integration of brain processes. The aim of the current study is to use resting state functional MRI (rs-fMRI) to investigate functional connectivity of the primary auditory cortex (PAC) to other brain regions in schizophrenia (SZ) and schizoaffective (SZA) patients.

Methods: We compared low frequency (<0.1Hz) resting state spontaneous oscillations in brain activity between 3 groups: SZ and SZA patients with AH (n=12); SZ and SZA patients with no history of AH (n =7); and healthy controls (n=14). Patients were men and women recruited from an inpatient unit, 18-65 years old (mean age ± SD: AH 43.7 ± 9.3; never-AH 37.8 ± 10.9; control 36.7 ± 8.9), right or left handed, stably medicated, with no substance abuse in the past 3 months, no significant medical or neurologic disease, and no electroconvulsive therapy in the previous year. Spontaneous oscillations were measured via the blood oxygen dependent level (BOLD) signal from a 10 minute rs-fMRI scan acquired using a Siemens 3T Trio MR scanner. We collected detailed information about both symptom history and experience of AH in the scanner. We focused preliminary analyses on the left PAC, a region implicated in speech processing where abnormalities are reported consistently in SZ patients with AH. Left PAC was identified using the Juelich Histological Atlas. The time course from this region was entered into a general linear model using FMRIB Software Library (FSL). Resulting whole-brain statistical maps, showing regions temporally coherent with left PAC, were entered into higher level analyses with the 3 groups, using a statistical threshold of p<0.001, uncorrected for multiple comparisons.

Results: Compared to healthy controls, the AH group had increased connectivity of the left PAC to bilateral inferior parietal lobules (IPL) and to the hippocampus (HIP) bilaterally. The never-AH group showed increased connectivity of the left PAC to the anterior cingulate cortex (ACC) bilaterally compared to healthy controls. Patients with SZ or SZA, regardless of AH status, showed increased connectivity of the left PAC to the IPL bilaterally, ACC bilaterally, and right parahippocampal gyrus compared to healthy controls. No statistically significant differences were detected between the AH and never-AH groups.

Discussion: Results from preliminary analyses of this ongoing study suggest that patients with AH have abnormally increased coupling of the left PAC with HIP and IPL compared to healthy individuals. Inappropriate coupling between left PAC and HIP suggests abnormalities in encoding or retrieval of episodic memories in relation to auditory processing. Inappropriate coupling to the parietal lobes suggests abnormalities of source attribution. The AH vs. never-AH group analysis is currently underpowered; increased sample size should provide greater power to detect differences between these two groups.
Magnetic resonance spectroscopy (MRS) studies have demonstrated abnormalities on the cellular level, in brain chemicals that serve as markers of cellular health and energy in heavy alcohol users, and in individuals with alcohol abuse and dependence. Such alterations in proton metabolites have been observed in frontal lobe regions, however there are limited MRS studies that have examined frontal lobe GABA metabolite levels in alcohol-using populations, particularly in young adults who exhibit binge alcohol consumption patterns, but who are not alcohol dependent. In the current study, proton (1H) metabolite data were acquired using a MEGAPRESS protocol at 4 Tesla from 18-24 year old binge and light alcohol drinkers. Reduced GABA metabolite levels were observed in the anterior cingulate cortex region of the frontal lobe in binge drinkers relative to light drinkers. A significant correlation was observed between reduced frontal lobe GABA levels and greater amounts of alcohol use. In addition, reduced frontal lobe GABA levels were correlated with greater impulsivity, measured using the Barratt Impulsivity Scale, and with reduced cognitive response inhibition, measured used the Stroop Color-Word Task. These findings may reflect a consequence of binge alcohol use, in young individuals who are heavy, frequent drinkers, but who do not yet meet the criteria for alcohol dependence. Thus, the characterization of neurochemical correlates associated with binge alcohol consumption may help identify risk factors for the later manifestation of alcohol abuse and dependence. Supported by K01 grant AA014651 (MMS).
The Internet has changed the way we practice medicine and psychiatry. With the increasing integration of online interactions into our daily lives, Internet searches by patients and physicians now include looking online for personal information about one another. The practice of physicians’ searching online for information about patients—which we call patient-targeted googling (PTG)—poses a new challenge for physicians to define and maintain appropriate professional boundaries with patients.

Although PTG occurs among all types of physicians, psychiatrists face particularly complex questions when considering Internet boundaries, due to the unique nature of their relationships with patients, e.g., focused on intimate personal details and often dealing with analysis of the relationship as a key part of treatment. Psychiatrists need to consider the intention of Internet searches, the anticipated effect of gaining information online, and its potential value or risk to the treatment before searching online for a patient. Based on our clinical experiences, we have published a pragmatic model for physicians to consider before engaging in PTG, focused on the practical results of searches and aimed at minimizing the risk of exploiting patients.

We now report on a curriculum for psychiatric residents to address the impact that emerging information technologies have on patient care. The goal of this curriculum is to familiarize residents with the complex ethical issues generated by the use of the Internet in clinical practice and to provide guidance to trainees when they consider searching online for a patient. We are piloting the curriculum in the Massachusetts General Hospital/McLean Hospital Adult Psychiatry Residency Training Program. The curriculum centers on an interactive discussion of two composite clinical cases that have been formulated to address a number of complex questions: Are psychiatrists ethically justified to learn about their patients on the Internet? Should physicians obtain consent prior to conducting searches? How might Internet searches alter the standard psychotherapeutic stance of working only with information the patient brings into the room? Should a clinician disclose discovered information to the patient? How should the clinician document such information in the medical record? Should physicians interact with patients in online social networking sites, such as MySpace™ and Facebook™? The curriculum presents our pragmatic model for PTG as a framework for considering these issues and additionally includes didactic material on information technology, professional boundaries, and clinical ethics.

We hope this curriculum will encourage residents to think in a structured way about the establishment of appropriate boundaries on the Internet. This poster includes a summary of the pragmatic model taught to residents, along with outlines of sessions of the curriculum and data from participant feedback.
Anxiety disorders are the most prevalent types of psychiatric illness affecting approximately 15% of the adult population worldwide. The recent surge in the diagnosis of post-traumatic stress disorder (PTSD) from combat-exposed veterans has prompted an urgent need to understand the neuropathology underlying this debilitating condition. Anxiety and fear responses are predominantly modulated by GABAA receptor-mediated synaptic inhibition. Benzodiazepines potentiate GABAergic inhibition and are a first line of prescribed medications to treat most anxiety disorders even though this class of drugs has a high abuse liability and can evoke negative side-effects (e.g., sedation). Many genetically-modified mouse strains designed to examine the neurobiology of anxiety disorders are generated on the C57BL/6J background (C57), a strain where manipulation of anxiety-like behavior using benzodiazepines in classic tests is difficult. Fear-potentiated startle (FPS), a test of conditioned fear, is a useful preclinical tool to study PTSD-like responses in mice but has also been difficult to establish in the C57 strain. Building on previously published FPS studies, we optimized the FPS paradigm to more effectively assess conditioned fear responses in this strain. The protocol involved a 6-day regimen consisting of 3 startle Habituation days, a Pre-Test day followed by Training and Testing for FPS. Results showed that male C57’s had low levels of unconditioned fear assessed during the Pre-Test (15-18%). In contrast, mice showed robust FPS (80-100%) during the Test session which occurred 24 hours after tone+shock conditioning. Extinction of conditioned fear responses was assessed over four consecutive days following Test. Results showed that FPS values reached baseline Pre-Test levels by the fourth extinction day. We examined whether administration of the benzodiazepines chlordiazepoxide (CDP; 5 or 10 mg/kg i.p.) or diazepam (DZ; 2 mg/kg i.p.) at non-sedating doses would attenuate the expression of FPS. While CDP at both doses significantly reduced FPS to Pre-Test levels, a moderate dose of DZ did not yield an expected decrease in FPS as seen in other mouse strains. These results demonstrate that not all benzodiazepines are effective in reducing conditioned fear responses and further illustrate the challenge assessing anxiety- and fear-related behaviors in the C57 strain of mice. Together, these data support a novel, pharmacologically-validated paradigm to assess FPS in mice thereby providing a powerful tool to assess the neurobiology of PTSD in preclinical models of anxiety generated on the C57BL/6J background.

Support: NINDS Neuroscience Scholars Program, Andrew P. Merrill Memorial Fellowship to KSS; Howard Hughes Medical Institute Collaborative Initiative Award to WAC; NIMH R01MH080006 to UR.
Title: Brain activation differences between marijuana users and controls during performance of a spatial navigation task

A number of animal studies have demonstrated cannabinoid-associated impairments in spatial memory and hippocampal function. The hippocampus, an area implicated in spatial navigation, is of particular interest given the high density of cannabinoids receptors found in this region. The present study examined differences in fMRI BOLD signal during the performance of a hippocampus-mediated spatial navigation task in current marijuana smokers (MJ; n=10) and non-using control subjects (n=11). Imaging data were acquired using an fMRI BOLD sequence on a 3.0 Tesla Siemens MRI scanner, while subjects performed a computerized virtual analogue of the Morris water maze task consisting of 2 conditions: retrieval (locating a hidden platform) and control (navigate to a visible platform). Subjects were pre-trained (learning phase) on the task offline prior to imaging, followed by a probe trial (platform is removed from the pool) to measure behavioral performance. Data were motion corrected, and analyzed in SPM5. fMRI data showed that non-using controls exhibited greater BOLD activation of key areas involved in spatial processing, the hippocampus and parahippocampal gyrus, during retrieval relative to the control condition. Overall, MJ smokers exhibited hypoactivity in the hippocampal/parahippocampal area during retrieval. For behavioral performance, MJ smokers had shorter latencies to first movement during pre-training, but did not differ from controls in the percent of time spent in the correct quadrant during the probe trial. During the retrieval condition, MJ smokers displayed shorter latencies to first movement compared to controls whereas during the control condition, MJ smokers had a longer path length to find the visible platform, but did not differ for speed or swim latency. These data show that while both MJ smokers and controls show modest performance differences, significant differences in brain activation are observed during retrieval. These findings suggest that MJ smokers utilize neuronal resources in a manner that differs from non-smokers during spatial navigation. Given the paucity of data on visuospatial memory function in marijuana users, these findings contribute to our understanding of the neural changes underlying the effects of marijuana use on learning and memory.
Title: mRNA/miRNA expression networks in substantia nigra dopamine neurons and Parkinson disease

The main cause of the progressive loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) in Parkinson disease (PD) is not known. It is commonly thought that their degeneration is the consequence of a combination of genetic and environmental factors that affect key signaling pathways necessary for their proper cellular function. Our recent microarray data on laser microdissected (LMD) DA neurons from the SNc of normal subjects and PD patients demonstrated dysregulation, and in particular profound downregulation of several functional groups of genes relevant to PD pathogenesis (Simunovic et al., 2009, BRAIN 132:1795-809). Because of their role in regulating gene expression, we hypothesized that miRNAs might be involved in these processes. miRNAs are a recently discovered class of small 18-23 nucleotide non-coding RNA molecules that regulate target gene expression in various organisms and, thus, introduce a new concept of regulatory control over gene expression by modifying post-transcriptional mRNAs. miRNAs have been implicated in the development of the nervous system as well as function and identity of neuronal cell populations including DA neurons. There is also emerging evidence that suggests a role of miRNAs in neurodegenerative disorders. Using high-throughput TaqMan® miRNA qRT-PCR assays we analyzed the expression profiles of 381 miRNAs in LMD DA neurons from the same subject population as for the microarrays. Regardless of disease and gender we found that in all samples the SNc DA neurons exhibited a distinct pattern (“fingerprint”) of miRNA expression. In addition, miRNAs were differentially expressed between individuals and across genders and predominantly upregulated in PD-affected DA neurons. Furthermore, computational analysis demonstrated that several deregulated miRNAs were linked to mRNA targets that are part of dysregulated signaling pathways in PD pathogenesis. These data indicate that miRNAs may be part of the regulatory gene expression network in SNc DA neurons and may play a role in their normal function as well as in their dysfunction. Altogether, our miRNA/mRNA data set provides a unique platform to further delineate a functional role of miRNAs in the disease process of PD. In addition, results from this research could be translated to other (neuro)degenerative or psychiatric disorders and could lead to the identification of new therapeutic targets for future therapy developments.
The McLean OCD Institute (OCDI) is an intensive residential treatment program that was opened in 1997. This program admits approximately 125 patients annually. This poster will outline the timeline of events that led to the current OCDI research program, which has been used for quality assurance purposes as well as for use in phenomenology, treatment outcome and translational research applications. In brief, pre-admission data and outcome measures for patients entering the program have been systematically collected since the inception of the OCDI. Following initial grant support, a database was designed to store this information and to conduct a preliminary effectiveness study. This study was followed by several studies of severe, refractory OCD, including short and long-term outcome prediction, comorbidity correlates, family accommodation and other phenomenology and outcome related aspects. Furthermore, emergent knowledge of outcome predictors and time-course has permitted program development, resulting in shorter length of stay and OCDI discharge planning. This database has also provided the basis for research training among PhD candidates and interns, graduate students and multidisciplinary staff members. A translational component of the program has most recently been developed as consenting patients provide DNA samples and eligible patients participate in ongoing neuroimaging studies. Challenges and successes in the development of this program within the context of a busy, clinical unit will also be discussed.
Schizophrenia, a debilitating mental illness, is associated with a loss of GABAergic activity in the hippocampus, particularly sector CA2/3. A gene expression analysis of human post-mortem hippocampal tissue using microarrays and qPCR showed a number of differentially regulated genes in schizophrenic patients vs normal controls. Aim of our study has been to establish a hippocampal GABA neuron culture model to further characterize genes influencing the cellular activity and phenotype of post-mitotic GABA neurons in adult hippocampus. We have stimulated the hippocampal precursor cell line, HiB5, with different growth factors (BDNF, aFGF, neuregulin, bFGF, VEGF and PDGF) to assess their influence on the expression of the GABA-synthesizing enzyme, GAD$_{67}$, and several other genes of interest. Q-RT-PCR demonstrated that VEGF and PDGF had the most consistent effects on neuronal differentiation. Since the established growth factor for HiB5 differentiation is PDGF, we used it for further experiments. To characterize a cell as GABAergic, it was necessary that they express GAD$_{67}$ and the GABA transporter GAT1. Moreover, the cells should also show neurite outgrowth. We differentiated the cells using (1) N2 with PDGF (2) N2 with PDGF + 50 ng/ml BDNF or (3) N2 with PDGF + 100 ng/ml BDNF. mRNA expression for GAD$_{67}$ and GAT1 was compared in “differentiated” versus “undifferentiated” HiB5 cells using Q-RT-PCR; the respective proteins were assessed using Western blots and immunohistochemistry (IHC) of markers associated with neuronal differentiation, including neurofilament 200, acetylated tubulin and post synaptic density protein 95. All treatments resulted in increases of both GAD$_{67}$ and GAT1 in differentiated vs undifferentiated cells. In summary, a GABAergic neuron phenotype can be induced in these stem cells, making them useful to evaluate effects of various transcription factors on the maturation of post-mitotic hippocampal GABA cells in the. Supported by MH042261.
Background: Synchronous activity of local and distributed neural circuits has been postulated as the physiological underpinning for distributed cognitive processing. Retrieval of an object from memory requires activation of a spatially distributed semantic network. Language studies have shown the importance of synchronization in the theta frequency range (4 – 8 Hz) in this semantic retrieval. The fragmentation of thought and language in schizophrenia suggests a possible role of impaired synchronization in semantic memory retrieval. EEG has the temporal resolution to non-invasively explore neural synchronization. The current study utilized a lexical decision task (words vs non-words) in psychiatrically-well participants and individuals with schizophrenia and examined language-related neural synchronization in the theta range.

Methods: 39 controls and 17 individuals with schizophrenia performed a lexical decision task, comprising 100 word-word pairs and 100 word-nonword pairs. Subjects indicated if the second word of the pair was a “real” or “fake” word (e.g. shelf, plorg). Wavelet analysis between 2-20 Hz of the average of all trials formed the basis for time-locked evoked power, and wavelet analysis of individual trials yielded total power and an intertrial phase locking factor (PLF). Theta was measured as the mean activity over the 200-400 ms post stimulus interval in the 3.7-4.8 Hz range.

Results: Controls showed a greater PLF (p < .001) and evoked power (p< .001) than patients. PLF was greater to word than non-words in both controls and individuals with schizophrenia (p = .03).

Conclusions: Both patients and controls showed increased trial to trial phase synchronization to words than to non-words, suggesting the task was sensitive to access of “real” semantic stores, and patients and controls modulated activity similarly to real versus fake words. However, individuals with schizophrenia showed deficits in overall PLF and evoked power measures of neural synchronization in theta, which likely index efficiency of semantic network activation. Thus, although patients displayed greater power and synchrony to real versus fake words, the activity was not as great as normal. Schizophrenia may be characterized by deficits in the activation of underlying neural networks serving distributed semantic memory stores, in turn likely associated with basic circuit abnormalities.
Childhood adversity is a major risk factor for development of psychopathology. Findings from the Adverse Childhood Experience Study, conducted by Kaiser-Permanente and the CDC, found that early adversity accounted for 50-75% of the population-attributable risk for major depression, suicide attempts, alcoholism and drug abuse. We proposed that the consequences of exposure to abuse stem, at least in part, from effects on trajectories of brain development. The purpose of this study was to compare the effects of exposure to different forms of childhood abuse on brain morphometry.

Specifically, we assessed the effects of exposure to childhood sexual abuse (CSA), parental verbal aggression (PVA) and witnessing domestic violence (WDV) in subjects who had been exposed to only one form of adversity. Subjects were 18-25 years of age, unmedicated, right-handed and recruited from the community. We used voxel-based morphometry (VBM) to delineate in an unbiased manner brain regions that were most significantly affected. High-resolution T1-weighted MRI data sets (1.5 T GE Signa scanner) were obtained on 23 females with CSA and 14 healthy female controls. 3.0 T volumetric scans (Siemens Trio Scanner) were obtained on 21 subjects (18-25 years) with histories of PVA and 15 subjects who witnessed DV. They were compared to 33 psychiatrically healthy control subjects of equivalent age, gender distribution and socioeconomic status with no history of trauma or CSA.

CSA subjects had a 14.1% reduction (P< 0.0001, corrected) in left primary visual (LV-1) cortex gray matter volume (GMV). Degree of GMV reduction correlated with duration of CSA before age 12, and with deficient visual memory (r=0.45, P=0.005). Parcellation analysis with FreeSurfer confirmed the association between CSA and GMV reduction in primary and secondary visual cortex. CSA subjects had an 18.0% GMV reduction in left fusiform gyrus (P = 0.004), 9.5% reduction in the left middle occipital gyrus (P < 0.05), and an 8.9% reduction in the right lingual gyrus (P = 0.002).

The most prominent finding in PVA-exposed subjects was a 14.1% increase in GMV in the left superior temporal gyrus (STG) (BA 22; P = 0.004, corrected cluster level). GMV in this region correlated with levels of maternal verbal abuse, paternal verbal abuse and extent of parental education. This region plays a critical role in processing of language and speech. De Bellis et al had previously reported increased STG GMV in children and adolescents with PTSD stemming from early abuse.

Results in subjects who witnessed DV were similar to results in subjects with CSA, as the primary region affected was visual cortex. WDV subjects had a 20.5% GMV reduction in right lingual gyrus, (BA17: P = 0.001, FWE corrected cluster level), 6.8% reduction in right BA18, and 16.4% reduction in left BA17. It is interesting that exposure to CSA and WDV were associated with decreased GMV in visual cortex (right more affected than left), whereas PVA was associated with left-sided increase in GMV in auditory association cortex. Brain regions that process and convey the adverse sensory input appear to be specifically modified by this experience.
Title: Use of antidepressants and emerging mania: A metanalysis

Association of antidepressant (AD) treatment with mood-elevation, or switching from depression, has been recognized since the 1950s. However, it remains unclear if newly emerging excited-states (mania, hypomania, mixed-states, or psychosis) are natural manifestations of affective disorders or causally associated with AD-treatment. Mood elevation/excitation associated with AD-treatment might indicate: [a] treatment efficacy, [b] an adverse pharmacologic effect, [c] unrecognized bipolar disorder (BPD), or [d] actual conversion from major depressive disorder (MDD) to BPD. Computerized searching identified 73 reports (109 trials, 114,521 adult patients) of largely incidental mood-switching during AD treatment. Some reports (35/73) and trials (48/109) provided information in mood-switching both with and without AD treatment. This information supported random-effects meta-analyses and multivariate-regression modeling to test for effects of AD-treatment, AD-type, trial-design (open vs. randomized), and simultaneous mood-stabilizer treatment. Overall switch-risks averaged 12.5% with ADs vs. 7.5% without (computed relative risk [RR]=1.76, \( p<0.0001 \)). AD-associated mania/hypomania was more frequent in BPD than MDD patients, but RR was higher with a diagnosis of MDD (6.0/1.2=5.0) than with BPD (15.3/13.8=1.1). Tricyclic antidepressants (TCAs) had a higher risk (12.7%) than serotonin-reuptake inhibitors (SRIs; 8.7%) or monoamineoxidase inhibitors (MAOIs; 4/6%). Mood-stabilizers had minor effects, probably confounded by preferential use in mania-prone patients. Factors independently associated with mood-switching in AD treated/untreated patients were: [a] prior diagnosis of BPD (but RR was greater with MDD), [b] longer follow-up, [c] younger age, and [d] open > controlled trials. These findings should be considered cautiously in view of heterogeneity of studies included and prevalent absence of precise exposure-times. Nevertheless, the findings indicate that risk of mood-switching among identified BPD patients given ADs was only slightly greater than their spontaneous rates, and greater with longer follow-up. MDD-diagnosed patients had little spontaneous tendency to become mania/hypomanic, but some experienced mood-elevation during AD-treatment that may represent either diagnostic or pharmacologic effects. Despite lack of compelling evidence that mood-stabilizers limit AD-associated mood elevation in this study, their use is recommended, pending development of appropriate evidence.
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**Title:** Prescription opioids alter brain morphology and function.

Prescribed opioids are a common therapeutic option for treatment of chronic pain. Abuse of these prescription drugs has increased in association; recent figures suggest that over 10% of chronic pain patients (~50 million Americans) have a drug abuse problem. Thus, the therapeutic benefit of opioid use for pain control may be counterbalanced by the potential for abuse or other effects on brain systems. In order to begin to address the question of what extent long-term use of opioids alter the brain, we have evaluated morphology and functional connectivity in a group of social opioid addicts who have no history of pain or major psychiatric condition. Ten adult subjects who had a history of long-term use of opioids and ten age-gender matched controls were recruited for this study. Brain scans (Siemens 3-T) were taken for morphometry measures (gray matter: volumetric and cortical thickness (Freesurfer); white matter: fractional anisotropy (FSL)) and resting-state functional connectivity (interstructural coherence of functional MRI timecourses (In-house crosscorrelation analysis and FSL). Measures for gray matter showed a significant (p < 0.05) decrease in cortical thickness in the prefrontal regions, and increased cortical thickness in the anterior and posterior cingulate regions, in addition volumetric loss in the amygdala. White matter tract integrity was altered with significant (p < 0.05) anisotropic changes in opioid subjects relative to controls. Decreased anisotropy was observed in axonal pathways such as the genu region of the corpus callosum, claustrum (bilateral) and thalamocortical pathways. Based on the above observations we evaluated functional connectivity. Data show that the coherence of the fMRI timecourse amongst the amygdala and cingulate cortex, anterior and middle sections, was significantly (p < 0.05) decreased. An anatomical segregation of the amygdala into laterobasal, centromedial and superficial sections in functional connectivity analysis yielded a more specific characterization of the change in coherence amongst the amygdala and the rest of the brain. Significant changes in coherence involving the striatum were also observed. Taken together, the data is indicative of major changes in brain systems in subjects on chronic opioids and has implications for understanding both opioid addiction and opioid use in chronic pain patients.
Title: Use of mood-stabilizers for hospitalized psychotic and bipolar disorder patients

**Background:** Treatments for patients with psychotic or severe mood disorders overlap, including use of mood-stabilizers with antipsychotics and other psychotropics. Such treatments are particularly poorly studied in psychotic disorders and generally lack explicit regulatory approval.

**Methods:** We analyzed records of 636 McLean Hospital inpatients in 2002 (n=155), 2004 (n=278), or 2009 (n=203), diagnosed with bipolar (n=318) or schizoaffective disorders (n=210), or schizophrenia (n=108), to evaluate mood-stabilizer usage, drug-selections, combinations and doses, adverse-effect risks, and factors associated with mood-stabilizer-use.

**Results:** From 2002-2004 to 2009, mood-stabilizer-use increased by 76% (from 53% to 94%) overall, and by 90% in schizophrenia patients, as mood-stabilizer count/patient increased by 74%, and total final daily doses (mg Li-eq) increased by 35%. Most commonly prescribed were valproate, lithium, and lamotrigine. Mood-stabilizer-use was initially associated (bivariate) with affective features, agitation, and co-morbid personality, anxiety, and substance-use disorders. With mood-stabilizer treatment, overall, hospitalizations averaged 18% longer, CGI ratings improved 55% more, but adverse-effect risk was 22% lower. Mood-stabilizer-use was associated (multivariate) with: [a] year (2009 > 2002-2004), [b] more psychotropics/patient (discharge), [c] diagnosis (least in schizophrenia), [d] longer hospitalization, [e] younger age, and [f] more substance-abuse.

**Comment:** Mood-stabilizers, in combination with antipsychotics, are used increasingly to treat hospitalized patients, including those with schizophrenia, and involved use of anticonvulsants for non-approved psychiatric indications in 50% of patients given mood-stabilizers.
Title: Clathrin Nanoparticles As Potential High-Relaxivity Magnetic Resonance Nanoprobes For Molecular Brain Imaging

Background: Magnetic Resonance Imaging is a noninvasive visualization technique with high spatial resolution, but low sensitivity for visualization of molecular targets. In order to improve MRI sensitivity for molecular brain imaging, our goal was to develop clathrin-based nanoprobes with high molecular relaxivity that incorporate high payloads of Gadolinium (Gd) contrast agents, which can be delivered non-invasively and target specific receptors in the rat brain.

Methods: Gadolinium-DTPA-ITC was conjugated to clathrin cages through reactive lysine residues. We determined the chelate to protein molar ratio by using a standard spectrophotometric method based on the reaction between a DTPA-ITC ligand protein conjugate and an yttrium (III) complex of Arsenazo III. Relaxivity for each sample was calculated using T1 data and gadolinium concentration as determined by NMR analysis. Maleimide–PEG–Dopamine-3 Antibody (D3Ab) and Maleimide-PEG–rhodamine conjugates were prepared, clathrin-nanoparticles were PEGylated and delivered intranasally. Animals were sacrificed 3 hours after intranasal administration of D3Ab-labeled fluorescent Clathrin nanoparticles.

Results: Electron Microscopy has shown a large proportion of Gd-DTPA-clathrin cages that form hexagonal barrels 52 nm in size. The mean Ligand/Protein molar ratio was 27±2.4. At 0.47T, Gd-DTPA-ITC-Clathrin-Cages displayed relaxivity of 283,176mM-1s-1 per particle, and 97mM-1s-1 per Gd ion. Three hours after intranasal administration D3Ab-labeled Clathrin nanoparticles were found only in D3 related brain regions in rats. Fluorescent and light microscopic examination of the D3 brain regions confirmed specific targeting of the D3 receptors with D3Ab-nanoprobes. Confocal laser microscopy confirmed integrity of the nanoparticles in the rat brain. Clathrin and D3Ab fluorescence co-localized in the D3 brain regions.

Conclusions: New Clathrin nanoparticles displayed an unusually high molecular relaxivity, were successfully delivered non-invasively nasally into the rat brain, were able to target specific receptors, and remained stable in the rat brain. They showed over 50,000-fold greater molecular relaxivity than any currently approved Gd-MRI contrast agent. These preliminary results should encourage further investigations into the use of clathrin cages as a new nanoplatform for MR contrast enhanced molecular brain imaging.
Objective: The purpose of this study was to identify risk factors for obesity in female patients with borderline personality disorder (BPD).

Method: Two hundred and thirteen female borderline patients who met DIB-R and DSM-III-R criteria for BPD were interviewed concerning their symptomatic and psychosocial functioning as well as medical history at six, eight, and ten years after their index admission. Their BMI at baseline was calculated using their measured height and weight. It was assessed at each follow-up period using subject self-report. Family history of obesity, psychiatric medication, and meeting criteria for binge eating disorder (BED) were considered as predictors of obesity. We conducted a longitudinal analysis of obesity based on a generalized estimating equations (GEE) approach that accounted for the correlation among the repeated measures of obesity. These analyses modeled the log prevalence of obesity, yielding an odds ratio (OR), and 95% confidence interval (95%CI), for each of the predictors.

Results: Over ten years of follow-up, a family history of obesity, taking atypical antipsychotics, and a diagnosis of BED were significant predictors of obesity. More specifically, those women with a family history of obesity have a 53% (OR: 1.527, 95%CI: 1.070, 2.178) greater odds of becoming obese, those reporting taking atypical antipsychotics have a 79% (OR: 1.787, 95%CI: 1.247, 2.561) greater odds, and those with a diagnosis of BED have an 85% (OR: 1.848, 95%CI: 1.216, 2.809) greater odds of obesity.

Conclusion: These results suggest that the risk factors for obesity in women with BPD are complex, including aspects of family history, concurrent treatment, and disordered eating.
Introduction: Despite increasing regional overdose (OD) rates in the US, circumstances surrounding an overdose, especially events that may trigger these life-threatening events, are poorly characterized. Recent evidence from community and treatment samples suggests a potential role for depressive symptoms in the etiology of OD. Methods: We studied 301 subjects with alcohol and drug dependence recruited from a detoxification unit. Subjects were asked, “Have you ever overdosed?” Drug use, depression, and intentionality in the four hours prior to an OD were assessed for subjects reporting a recent OD (i.e., in the past three months). Results: At least one past OD was reported by 43% (128/301) of subjects. Of these 128 subjects, 79% had at least one OD requiring emergency medical care and 31% were recent. With a recent OD, 85% injected just prior to the OD; 88% used heroin, 8% OxyContin, 8% fentanyl and 13% other opioids. No subject reported buprenorphine use and only 5% used methadone. Other drugs used prior to the OD included: cocaine 43%, benzodiazepines 35%, alcohol 35%, marijuana 18%, methamphetamine 3%, antidepressants 10%, and OTC meds 13%. Although only 13% reported that a recent OD was a suicide attempt, 33% reported “wanting to die” and 73% reported feeling ‘depressed, sad or blue’ just prior to the OD. Conclusions: Injection drug use, opioids, polydrug use, and depression are present at the time of OD and represent potential triggers for OD. Supported in part by grants DA20030 and DA10019 from NIDA and AA10870 from NIAAA/NIH
Phenylethanolamine N-methyltransferase (PNMT), which produces epinephrine, is a marker of adrenergic function. While pituitary adenylate cyclase activating polypeptide (PACAP), independently and cooperatively with NGF, activates PNMT promoter-driven and endogenous PNMT gene expression in PC12 cells, molecular mechanisms remain unknown. Transfection assays in PC12 cells and PKA-deficient and PLCγ1-deficient PC12 cells using PNMT promoter-luciferase gene constructs and signaling inhibitors showed that PLCγ1 and cAMP-dependent PKA signaling are critical for PACAP activation and PI3K, PKC, ERK1/2 MAPK, p38 MAPK downstream. The inhibitors also abrogated PACAPergic induction of endogenous PNMT. Western analysis of nuclear protein from PACAP-treated PC12 cells showed that Egr-1 and AP-2 underlie PACAP responses. Results with nested deletion or site-directed mutant constructs support this possibility. Exposure of PACAP-treated transfected and untransfected PC12 cells to histone deacetylase (HDAC) inhibitors, Na butyrate or Trichostatine A, incrementally activated the PNMT promoter and endogenous PNMT. Findings indicate that PACAP transcriptionally activates the PNMT gene with HDAC being limiting. Presence of long and short forms of PNMT mRNA further suggest post-transcriptional regulation by PACAP. Support: Spunk Fund, Inc., Sobel-Keller Fund and McLean Hospital
Title: The Geriatric Mood Disorders Research Program: Studying the Clinical Characterization and Bioenergetic Abnormalities in Older Adults with Bipolar Disorder and Major Depression

The Mood Disorders Division of the McLean Hospital Geriatric Psychiatry Research Program is conducting research studies focusing on Bipolar Disorder (BD) and Major Depressive Disorder (MDD) in older adults. These projects involve clinical characterization of older adults with mood disorders (including neuropsychological testing, mood symptom severity measures, medical co-morbidity and functional status) and neuroimaging modalities (including MR spectroscopy (MRS) and diffusion tensor imaging).

The aims of this program are to examine the following relationships: (1) bioenergetic metabolism, measured by both proton and phosphorus spectroscopy, and disease state and symptom severity; (2) bioenergetic measurements as predictors of treatment response; (3) geriatric mood disorders and longitudinal changes in cognition and functioning; (4) predictors of pharmacological treatment response and (5) predictors of cognitive function in the geriatric mood disordered population.

The Geriatric Mood Disorders Research Database is a longitudinal study in which controls and subjects with BD or MDD are followed for three years. We annually collect clinical, medical and neuropsychological information and subjects complete interviews on mood symptoms and functional status at three month intervals. Additionally, subjects may participate in a number of sub-studies including neuroimaging with proton and phosphorus MRS, validation of a computerized cognitive test, genetic testing, and referral for postmortem tissue donation to the Harvard Brain Tissue Resource Center. This research will contribute to the understanding of mental illness and age-related changes in cognitive and functional status.

In addition, we are conducting two short term treatment studies. “Lamotrigine therapy in the treatment of Geriatric Bipolar Depression: An evaluation of markers of Cerebral Energy Metabolism” is an open-label study of lamotrigine treatment. We are interested in identifying cerebral energy metabolism abnormalities in older BD patients compared to age-matched controls using 4 Tesla $^1$H MRS. Through pre- and post-treatment scanning, we are examining whether lamotrigine therapy will rectify these abnormalities. Furthermore, we hypothesize that successful treatment and correlate with measures of improved bioenergetic metabolism.

We are also conducting a treatment study entitled “Oral Administration of CoQ10 and Phosphorous-31 Magnetization Transfer Magnetic Resonance Spectroscopy in Geriatric Bipolar Disorder and Healthy Older Adults.” This open-label treatment study utilizes a novel $^{31}$P magnetization transfer protocol on the 4 Tesla MRI, allowing for the forward rate constant ($k_{for}$) of creatine kinase to be measured in the frontal lobe. Creatine kinase, a marker for mitochondrial function, is an enzyme responsible for the conversion of ADP to ATP in tissues with high and fluctuating energy demands. We hypothesize that baseline measures of $k_{for}$ will be reduced in individuals with BD compared with age matched controls and that $k_{for}$ will increase with CoQ10 treatment.

Our initial studies have suggested that there is evidence of deficits in energy production and utilization in older adults with MDD and BD compared to that of healthy controls, which further supports the mitochondrial dysfunction hypothesis of mood disorders. We seek to initiate studies testing novel compounds that have mitochondrial enhancing properties in the treatment of older adults with MDD and BD using $^1$H and $^{31}$P MRS. Finally, we hope to expand our efforts by collaborating on multi-center trials using spectroscopic imaging.
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Title: Synthesis and Biological Evaluation of C-2 Halogenated Salvinorin A Analogues

Salvinorin A (1), a highly potent and selective naturally occurring κ opioid receptor (KOPR) agonist, has attracted much attention for its potential in the treatment of psychiatric disorders including drug abuse. It represents the only non-nitrogenous small molecule activator of G-protein coupled receptor (GPCR). The unique structural and biological features of salvinorin A made it an attractive template for exploring the chemical space of opioid receptors and more importantly for the development of novel KOPR antagonists. The current efforts in the chemistry and structure activity relationship studies of 1 is mainly focused on its C-2 position and more than 80 analogues as esters, carbamates, carbonates, ethers, amines, amides and sulfonate esters have been synthesized and biologically evaluated. A number of C-2 halogenated salvinorin A has been synthesized, however, there is no biological data reported. Halogen bonding or halogen to oxygen interactions plays critical roles in natural system and the peculiar chemical features of halogens make them attractive motifs in designing protein inhibitors and drugs. With the aim to find KOPR antagonists and to explore the biological potential of the halogen bonding between the KOPR binding pocket and the C-2 halo salvinorin A analogues, a library containing all possible C-2 halogenated analogues has been synthesized. KOPR binding studies have shown that halogenation of the C-2 position of 1 attenuates its binding affinity which is consistent with the fact that the interaction strength of halogen bonding is lower than classical hydrogen bonding. Interestingly, the C-2 iodo analogue (2) is evidenced to be a partial agonist with E\text{max} of 60\% of U50 and K_i values at 250 nM. This compound could potentially become a good antagonist when affinity increased. In summary, use of halogen bonding in modification of 1 may be a viable way to find novel KOPR antagonist.
Title: Examining Long-Term Outcomes of Individuals in a NIDA CTN Study of Prescription Opioid Dependence Treatment

Introduction: Rising rates of prescription opioid dependence and gaps in understanding the optimal course of treatment for this population prompted the National Institute on Drug Abuse Clinical Trials Network to launch the Prescription Opioid Addiction Treatment Study (POATS). POATS employed a multi-site, two-phase adaptive, sequential treatment design to approximate clinical practice. Researchers from the McLean Hospital Alcohol and Drug Abuse Treatment Program led POATS, the largest study yet conducted examining the treatment of prescription opioid dependence. The study took place at 10 community treatment programs across the United States. Participants were randomized at the beginning of Phase 1 to receive buprenorphine/naloxone (bup/nx), paired either with standard medical management or standard medical management plus individual drug counseling. POATS was developed to determine what benefit, if any, the addition of individual drug counseling would offer in short-term and longer-term treatment paradigm. The current study is an extension of POATS and examines long-term outcomes for individuals with opioid analgesic (OA) dependence who participated in POATS. Research has examined long-term outcomes of individuals following methadone treatment. However, only one study has examined longer term outcomes for patients treated with buprenorphine/naloxone, and that study focused on treatment for opioid dependence in general, but did not specifically investigate prescription opioid dependence. Little is known about the substance use trajectories of individuals with prescription opioid dependence.

Aims: The aim of this study is to investigate the natural history of prescription opioid dependence and to identify factors associated with long-term recovery from prescription opioid dependence for future research.

Methods: Participants who agree to participate in this study (370) are assessed by research staff at McLean Hospital via semi-structured telephone interviews at 1.5 (18 months), 2.5 (30 months) and 3.5 (42 months) years post-Phase 1 randomization to POATS. Interviews are typically 45-60 minutes in length and include a subset of instruments from POATS. Participants are assessed for pain using the Pain and Opioid Analgesics Use History instrument, severity of substance use and its associated problems using the Addiction Severity Index (ASI), and diagnosis of substance-related disorders using the Composite International Diagnostic Interview (CIDI). Standard follow-up tracking techniques, including frequent contact by telephone and mail, are used to enhance retention rates.

Conclusion: As of November 30, 2009, we completed 154 18-month follow-up assessments, 52 30-month follow-up assessments, and 1 42-month follow-up assessment. This exploratory, naturalistic study provides preliminary evidence that it is feasible to collect data long-term for individuals with prescription opioid dependence. This study will help to generate hypotheses and guidance for further treatment research on prescription opioid dependence.