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Poster Session II - Tuesday

1. Diffusion Tensor Imaging in Cocaine Dependence: Evidence for Reduced Myelin in the Anterior Corpus Callosum

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Sponsor: Alan Swann

Background: Fractional anisotropy (FA) as measured by diffusion tensor imaging (DTI) is becoming increasingly used as a measure of subtle white matter pathology in psychiatric populations. However, diffusion anisotropy is affected both by the state of myelin and axonal structure and therefore lacks pathologic specificity. Evidence has been accumulating that the individual eigenvalues, which represent diffusion along the fiber track (λ 1) or perpendicular to the fiber track (λ2), provide enhanced pathologic specificity compared to anisotropic and mean diffusivity indices. The purpose of this study was to compare cocaine dependent subjects with non-drug using controls using individual DTI eigenvalues.
Methods: Eighteen cocaine dependent subjects and 18 healthy controls underwent full brain Diffusion tensor imaging (DTI) acquired with a diffusion sensitized dual spin echo prepared echoplanar imaging (SE-EPI) sequence, on a 1.5 T General Electric echospeed CNV MRI scanner using a standard quadrature RF Head Coil. The diffusion tensor encoding scheme was based on the uniformly distributed and balanced rotationally invariant Icosa21 tensor encoding set. Fast spin echo proton density and T2 weighted images were acquired from the same location as DTI. DTI post processing was performed using the Automated Image Registration (AIR) package. The distortion corrected images were decoded using a least squares singular value decomposition approach to estimate the diffusion tensor elements. The corpus callosum was the focus of this analysis, which was divided into 7 segments based on the previous work by Witelson (1989) in order to compare regions of the corpus callosum and thereby examine fiber tracts linked to different cortical regions. All 7 segments of the corpus callosum were compared between cocaine users and controls for using a Mixed Model ANOVA for λ1 and λ2.
Results: Results showed a significant increase in λ2 in the genu of the anterior corpus callosum in cocaine dependent subjects compared to controls. Within cocaine dependent subjects there was a significant positive correlation between years of cocaine use and λ2. There was no significant difference between groups for λ 1.
Discussion: Two prior studies found reductions in FA in cocaine dependent subjects on DTI (Lim et al., 2002, Moeller et al., 2005). However, based on reduced FA value, it is difficult to determine whether demyelination or axonal injury is responsible for the fiber tract damage. Based on prior animal and human studies suggesting that demyelination increases diffusion normal to the direction of fiber tracts λ2 with minimal effect on λ1 our findings are consistent with a reduction in myelin in the anterior corpus callosum in cocaine dependent subjects. These results will be discussed in light of other studies showing evidence of frontal-subcortical dysfunction in cocaine dependent subjects.

2. Effects of Self-Administered and Passive Cocaine Infusions on Dopamine, Norepinephrine and Corticosterone Concentrations in the Medial Prefrontal Cortex

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Background: Cocaine (COC) reinforcement is widely accepted to be mediated via the mesocorticolimbic dopamine (DA) system. However, the context of cocaine delivery can alter the neurochemical responses to the drug. In addition, increasing evidence suggests that stress can also influence COC reinforcement through extrahypothalamic brain regions. The present study was designed to determine differences in the neurochemical and neuroendocrine responses to COC during response-contingent and response-independent COC administration in rats.
Methods: Male Wistar rats were divided into triads of 3 rats each: one rat was selected as the self-administration (SA) rat, while the other two rats were designated as the yoked-cocaine (YC) and yoked-saline (YS) rats, respectively. Rats were implanted with jugular catheters and a microdialysis guide cannula aimed at the medial prefrontal cortex (MPC). SA rats were trained to self-administer cocaine (0.25 mg/kg/inf) under a fixed-ratio 2 schedule of reinforcement; 20-min samples were collected 2 hrs prior to, during and after the SA session.
Results: DA and norepinephrine (NE) concentrations in the microdialysates from the MPC were significantly elevated in SA and YC groups during the SA session. Similar results were observed for DA in the amygdala. The increases in DA and NE levels in the MPC during the session were greater in the YC group compared to the SA group. Moreover, the duration of the DA response in the MPC was greater in the YC group vs. the SA group. We did not find significant differences in DA levels between the SA and YC groups in the amygdala. To determine the effects of self-administered COC on corticosterone (CORT), the hormone was measured in the MPC using in vivo microdialysis. Dialysates were analyzed for CORT by radioimmunoassay (RIA). Baseline MPC CORT was low and stable in all groups prior to the start of the SA session and remained stable throughout the entire experiment in the YS rats, suggesting that the procedure itself was not stressful. MPC CORT was significantly elevated in the microdialysates from the SA rats during SA (269% increase), while MPC CORT was increased 553% above baseline in the YC rats. MPC CORT was significantly higher in the YC compared to the SA rats. Plasma CORT and ACTH were higher in YC group than in the SA and YS groups prior to the beginning of the SA sessions.
Discussion: It has been suggested that one of the numerous molecules involved in stress response pathways is P-gp (glycoprotein) or MDR1 efflux transporter. MDR1a is found in vascular endothelial cells and is active at the blood-brain barrier, whereas MDR1b is found mainly in astrocytes and microglia. We tested the hypothesis that MDR1 genes respond differentially to SA vs. YC administration. We found that levels of the MDR1a, but not MDR1b, transcripts were higher in each of the SA animals compared to its respective YC control. We are currently replicating and extending these preliminary findings and, if upheld, these data may suggest the possibility that the MDR1a gene contributes to the reduced toxicity in SA relative to YC rats. These results suggest that the context in which cocaine is administered can alter the neurochemical and neuroendocrine responses to cocaine. Furthermore, CORT in the MPC may mediate neurobiological responses involved in COC reinforcement.

3. Decreased Corticolimbic Responset To Monetary Reward in Cocaine Addiction: Association with Motivation and Self-Control

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Sponsor: James Swanson

Background: Our objective was to study the role of the corticolimbic reward circuit in sensitivity to reward/motivation and inhibitory control in cocaine addiction.
Methods: Sixteen cocaine users and 12 healthy controls performed a delayed forced-choice task under three blocked monetary value

conditions (high money=45 cents, low money=1 cent, no money=0) while brain activation was measured with BOLD fMRI. State measures of motivation on this incentive fMRI task were assessed objectively by speed (reaction time) and accuracy of responses (percent correct), and on a subjective level as self-reported engagement in this task. Inhibitory control was assessed by trait estimates from a personality questionnaire (Tellegen's Multidimensional Personality Questionnaire, MPQ, Self Control scale) and by state estimates from a conflict task (Fan's Attention Network Task, ANT, Conflict scale).

Results: The manipulated independent variable (monetary value) produced a differential pattern of neural response (fMRI signal change) in healthy controls: there was a trend in the orbitofrontal cortex (OFC) to respond in a graded fashion (45>1>0), the anterior cingulate gyrus (ACG) and cerebellum responded to the two conditions of monetary value equally (45=1>0), and the mesencephalon responded to the highest available reward only (45>1=0). This complex regional brain activation to monetary reward was lost in the drug-addicted subjects. Activation in the frontal regions to the highest monetary reward was instead correlated with the three state measures of motivation (speed, accuracy, engagement, all $r > |0.52|$, $p < 0.05$). Finally, activation in the left OFC to high monetary reward was significantly correlated with both trait (MPQ Control, $r=0.52$ $p < 0.05$) and state (ANT Conflict, $r=-0.63$, $p < 0.01$) measures of inhibitory control; both correlations reached significance only across all study subjects (note that these current correlation results extend our previous reports of a correlation between the left OFC and reduced self-reported sensitivity to gradations in monetary value in the cocaine addicted subjects). The ACG correlation with behavioral control (MPQ) was only observed in the non-drug users ($r=0.68$, $p < 0.05$) and with ANT Conflict in neither group. Also, an abnormally low level of self-control was self-reported by the drug addicted subjects: MPQ Z score = -3.1 compared to the mean of the healthy subjects.

Discussion: In conclusion, these findings of different neural responses of addicted subjects to a simple manipulation of value in a laboratory test suggest that the activation of corticolimbic reward regions to monetary value is altered in drug addiction, due either to preexisting conditions or to neural adaptations related to exposure to drugs. This abnormality may underlie the drug addicted person's difficulty with sustained motivation and self-control, as well as deficits in processing relative gradients in reward and controlling drug-taking behavior under emotionally salient conditions such as in drug-related or stressful environments. [Supported by grants from the National Institute on Drug Abuse (1K23 DA15517-01); NARSAD Young Investigator Award; Laboratory Directed Research and Development from U.S. Department of Energy (OBER), ONDCP, and General Clinical Research Center (5-MO1-RR-10710)].

4. Interactions Between Nalbuphine, Mood and Hypothalamic-Pituitary-Axis (HPA) Hormones

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Background: Nalbuphine (Nubain®) is a mixed mu-kappa agonist used clinically for the management of moderate to severe pain. Nalbuphine also attenuates cocaine self-administration by rhesus monkeys (Negus and Mello, 2002) and does not produce additive cardiovascular or subjective effects when combined with cocaine in clinical studies with cocaine abusers (Mello et al., 2005). Although the hypothalamic-pituitary-adrenal (HPA) axis is one modulator of cocaine abuse, relatively little is known about the effects of nalbuphine on the HPA axis hormones. Because nalbuphine has both mu and kappa activity, its endocrine effects are not predictable from data on the effects of mu or kappa opioids alone.

Methods: We examined the effects of two analgesic doses of nalbuphine on prolactin, ACTH and cortisol in 10 healthy male volunteers with a history of current cocaine abuse (DSM-IV, 305.6). Subjects provided informed consent for participation in these studies. Nalbuphine (5 mg/70 kg, IV) was administered to 7 men and 10 mg/70 kg, IV was administered to 3 men. Blood samples were collected 30 and 5 min before nalbuphine infusion, and 13 blood samples were collected at 10, 17, 19, 23, 27, 31, 35, 40, 45, 60, 75, 105, 135 min after nalbuphine administration. Heart rate and blood pressure were monitored and subjective effects of nalbuphine were measured on a Visual Analog Scale (VAS).

Results: Significant nalbuphine dose-related increases in prolactin occurred within 17 min (P=.04). Peak prolactin levels of 22.1 ± 7.1 ng/ml and 54.1 ± 11.3 ng/ml were measured at 60 min after low and high dose nalbuphine administration, respectively. ACTH and cortisol levels did not change significantly after either dose of nalbuphine. VAS reports of sick, bad and dizzy were significantly higher after 10 mg/70 kg than after 5 mg/70 kg nalbuphine (P=.05-.0001). Increases in prolactin were significantly correlated with ratings of sick and dizzy after both low and high doses of nalbuphine (P=.05-.0003), and sedation and emesis were observed only after 10mg/70 kg nalbuphine.

Discussion: These data are consistent with previous clinical reports that prolactin levels are influenced by stimulation of both kappa and mu opioid receptors (Rolandi et al, 1983). For example, increases in prolactin have been reported after administration of kappa opioid agonists (Bart et al, 2003, Ur et al, 1997) and mu opioid agonists, (Saarialho-Kere et al, 1989; Kay et al, 1985; Delitalia et al 1983; Uberti et al, 1983). Our findings are also consistent with previous clinical reports that ACTH and cortisol are not stimulated by kappa or mu opioid agonists. Several studies indicate that kappa and mu opioid agonists inhibit ACTH and cortisol secretion (Pfeiffer et al 1986; Hoehe et al, 1988; Delitalia et al, 1983; Auernhammer et al, 1994). Both ACTH and prolactin are considered stress-labile hormones and nausea and emesis followed high dose nalbuphine administration. It maybe that the sedative effects of nalbuphine attenuated the impact of these adverse effects even though subjects reported significant increases in VAS items, such as sick, bad and dizzy. Taken together, these data suggest that nalbuphine had both kappa-like and mu-like effects on prolactin, ACTH and cortisol. These studies were approved by the McLean Hospital Institutional Review Board and conducted in accordance with the Declaration of Helsinki. This research was supported in part by grants T32-DA07252, P01-DA14528, K05-DA00064 and K05-DA00101 from the National Institute on Drug Abuse, NIH.

5. Aripiprazole Decreases Alcohol Drinking in Syrian Golden Hamsters

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Background: Alcohol use disorder commonly occurs in patients with schizophrenia and substantially worsens their outcome. While typical antipsychotic agents, all of which are potent dopamine D2 receptor antagonists, do not limit alcohol use in these patients, recent data suggest that the atypical antipsychotic clozapine (CLOZ) may substantially limit their alcohol use. We have proposed that CLOZ may limit alcohol use because, through its broad actions on dopaminergic and noradrenergic systems, it is able to ameliorate a dysfunction in the dopamine-mediated mesocorticolimbic reward circuit that underlies substance use in these patients. In order to further elucidate the basis of CLOZ's ability to decrease alcohol drinking in patients with schizophrenia, we have studied its effect on alcohol drinking in the Syrian golden hamster, an outbred animal that naturally drinks alcohol. We have recently demonstrated that CLOZ, but not the typical antipsychotic haloperidol, dramatically limits alcohol drinking in these animals (with a decrease of 88% below baseline drinking). Since CLOZ's toxicity limits its use in patients with schizophrenia, we have

been searching for other antipsychotics that may share with CLOZ the ability to limit alcohol drinking in patients with schizophrenia, and we have used alcohol drinking in the hamster as a probe for antipsychotics that may have this effect. The current study assesses whether the atypical antipsychotic aripiprazole (ARIP), a partial dopamine agonist thought to function as a dopamine circuit "stabilizer", may share with CLOZ the ability to limit alcohol drinking in hamsters.
Methods: Fifty-four hamsters were given continuous access to food, water and an alcohol solution (15% v/v) for 26 days to establish stable alcohol drinking levels. Baseline alcohol drinking (average of the last 4 days of this 26-day period) for all hamsters exceeded 9 g/kg/day. In Exp. 1, 28 hamsters received daily administration (sc) of ARIP (10, 20, or 30 mg/kg/day) or vehicle (n=7 per group) for 14 days, while they continued to have free access to food and drinking solutions. To obtain further data on the effects of a wider array of doses and a longer treatment period with ARIP, in Exp. 2, the other 26 hamsters received daily administration (sc) of a wider dose range of ARIP (5, 30, or 50 mg/kg/day; n=8 per group) or vehicle (n=6) for 27 days. Water, alcohol and food intakes were assessed by a technician blind to the treatment.
Results: Exp. 1: Fourteen days of treatment with 10, 20 or 30 mg/kg/day ARIP decreased alcohol drinking more than vehicle ($p<.0001$), by approximately 60%, 75%, or 80% below baseline, respectively. Exp. 2: 27 days of treatment with 30 or 50 mg/kg/day ARIP, but not 5 mg/kg/day, decreased alcohol drinking more than vehicle ($p<.0001$); the 30 mg/kg/day decreased alcohol drinking approximately 50% below baseline (over the treatment period), while the 50 mg/kg/day dose was able to suppress alcohol drinking by approximately 30% over this period. In both experiments, ARIP increased water drinking as it decreased alcohol drinking.
Discussion: These data indicate that the partial dopamine agonist ARIP, like CLOZ, decreases alcohol drinking in hamsters. Whether the mid-range dose (30 mg/kg) has the greatest effect needs to be confirmed by further investigation. Studies of ARIP in other rodents, and using other alcohol drinking paradigms (e.g., limited access), will be needed to fully assess the effect of this antipsychotic on alcohol drinking in animals. Nonetheless, the data developed thus far suggest that ARIP should be tested to see whether, like CLOZ, it will decrease alcohol drinking in patients with schizophrenia and co-occurring alcohol use disorder.

6. Time-Dependent Dissociation Between Accumbal and Amygdalar Mediation of Cue-Induced Cocaine Seeking

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Sponsor: Ronald See

Background: Treatment of cocaine addicts is complicated by high rates of relapse after prolonged drug-abstinent periods. Cocaine craving has been modeled in rats as the rate rats in drug-free state will press for a cue that was previously associated with self-administered cocaine. Using this animal model, we have found that craving increases over the first months of forced abstinence (incubation of cocaine craving). In a separate study, we observed that after 1 wk of daily exposure to extinction conditions, cue reactivity was attenuated by inactivation of the basolateral amygdala (BLA), but not the nucleus accumbens (Nacc). As the incubation of craving may be a time-dependent change in motivation, we examined here whether inactivation of the Nacc at a later time point in forced abstinence would attenuate responding for the cocaine paired cue. Here we present preliminary findings (n=5-9 rats/group) from this study.
Methods: Intravenous catheters and bilateral steel intracranial guide cannulae were implanted into male, Long-Evans rats. Cannulae were directed at either the BLA or Nacc. Rats subsequently learned to press a lever for cocaine (0.5 mg/kg/injection) in 6h daily sessions for 10 days. Each injection was accompanied by a tone + light stimulus. Rats then remained in home cages for 7 or 30 days of forced abstinence. Cocaine craving was then measured in 2 ways. First, responding in the absence of cocaine or the tone + light cue was allowed for 6 h (extinction testing). In a subsequent 1h session, lever presses delivered the tone + light cue (responding for cue testing). Immediately prior to this session, rats were injected with 0.5 microliters tetrodotoxin (TTX) (3 nanograms/side) or saline. Locomotor activity was measured throughout testing.
Results: Rats pressed more in extinction testing on Day 30 than on Day 7 (mean of 228 vs. 114 responses/6h, respectively). Locomotor activity during extinction was slightly higher on Day 30. As TTX might induce non-specific effects as it diffuses from the injection site, only data from the first 30 min of the cue session were analyzed. Rats tested on Day 30 responded more for the cue than rats on Day 7, following saline (mean of 12.3 vs. 8.0 cue deliveries, respectively). Locomotor activity did not differ between these groups. Rats with TTX into the BLA decreased responding for the cue on both test days compared to saline injected rats with a 39% decrease on both Days 7 and 30. In contrast, rats with TTX into the Nacc showed no significant attenuation of responding on Day 30, but a 75% increase on Day 7. Locomotor activity following TTX was unchanged in the BLA groups, but was slightly increased in the Nacc groups.
Discussion: These results indicate that both the BLA and Nacc mediate responding for a cocaine-paired cue. The BLA appears to be necessary for maximum responding at both an early and later time point in forced abstinence, likely due to its role in stimulus-reward associations. The Nacc appears to be have control over responding only at an earlier time point, likely due to its role in motivational output. Although preliminary, and requiring neuroanatomical verification of injection placements, these time-dependent effects we have observed suggest that these structures may be central components of circuitry underlying the incubation of cocaine craving. All procedures performed on the rats followed the NIH guidelines for animal care, and were approved by the Western Washington University Animal Care and Use Committee.

7. Effects of Baclofen on Cocaine Self-Administration: Opioid-Dependent and Non-Opioid Dependent Volunteers

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Sponsor: Richard Foltin

Background: Preclinical and clinical studies suggest that GABAB receptor agonists selectively decrease cocaine use. The behavioral mechanism for the interaction between baclofen and cocaine in humans is not known, nor are its effects in individuals dependent on both cocaine and opioids. The objectives of this study are: (1) To determine how maintenance on baclofen modulates smoked cocaine's reinforcing and subjective effects, cocaine craving prior to and after the initiation of cocaine use, and overall mood under controlled, within-subject, laboratory conditions, and (2) To assess baclofen's effects in cocaine-dependent volunteers maintained on methadone or not.
Methods: 17 nontreatment-seeking volunteers (10 non-opioid dependent; 7 opioid dependent), residing on an inpatient research unit for 21 days, were maintained on each baclofen dose (0, 30, 60 mg po) for 7 days. A cocaine dose-response curve (0, 12, 25, 50 mg) was determined twice under each baclofen maintenance condition. Each cocaine session began with a sample trial, when participants smoked the cocaine dose available in that session, and 5 choice trials, when participants chose between smoking the available cocaine dose or receiving one $5 merchandise voucher.
Results: In both groups of volunteers, baclofen maintenance (60 mg) significantly decreased cocaine-induced increases in heart rate. In the non-opioid dependent group, baclofen decreased self-administration of the 12 mg cocaine dose, and decreased how much participants would be willing to pay for cocaine (50 mg). In the opioid-dependent group, baclofen decreased craving for cocaine and nicotine. Baclofen did not alter cocaine's robust subjective effects (e.g. high, stimulated), and did not produce any side effects for either group.

Discussion: These data suggest baclofen decreases the direct reinforcing effects of a low cocaine dose, and may decrease the desire for cocaine after use has been initiated. The methadone-maintained group had a distinct response to baclofen, demonstrating the importance of determining medication effects separately for this subset of cocaine users.

8. Modafinil Attenuates Disruptions in Performance and Mood During Simulated Night Shift Work

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Sponsor: Past Travel Awardee, NIMH, 2001

Background: Common complaints among shift workers are sleep disruptions and increased sleepiness while working, which may contribute to shift workers being more susceptible to diminished performance and work-related accidents. The purpose of this double-blind, within-participant study was to examine the effects of the alerting agent modafinil on cognitive/psychomotor performance, mood, and measures of sleep during simulated shift work.
Methods: Eleven participants completed this 23-day residential laboratory study. They received a single oral modafinil dose (0, 200, 400 mg) one hour after waking for three consecutive days under two shift conditions: day shift and night shift. Shifts alternated three times during the study, and shift conditions were separated by an "off" day. Beginning 2 hours after waking, participants completed a simulated work day doing computerized performance tasks for 8 hours with a planned 1.5-hour lunch break.
Results: When participants received placebo, cognitive performance and subjective ratings of mood were disrupted during the night shift, relative to the day shift. Objective and subjective measures of sleep were also disrupted, but to a lesser extent. Modafinil reversed disruptions in cognitive performance and mood during the night shift. While modafinil produced few effects on sleep measures during the night shift, the largest dose produced several sleep alterations during the day shift.
Discussion: These data demonstrate that abrupt shift changes produced cognitive performance impairments and mood disruptions during night shift work. Therapeutic doses of modafinil attenuated night shift-associated disruptions, but the larger dose produced some sleep impairments when administered during day shift work.

9. Psychiataric Symptoms Among Outpatients in an Open-Label Trial of Risperidone for Methamphetamine Dependence

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Sponsor: Murray Raskind

Background: Methamphetamine (MA) dependence has increased to epidemic proportions. Neuroimaging, neuropsychological testing, and clinical evaluation implicates MA as contributing to neuropsychiatric impairments including psychosis, mood disturbance, anxiety, cognitive deficits, and motor dysfunction.1-8 While validated behavioral treatments for MA dependence exist,9,10 effective pharmacotherapy data are sparse. Studies using imipramine,11 desipramine,10 and fluoxetine12 found no differences in MA use. These studies did not assess change in both objective and subjective psychiatric symptoms over time. Risperidone limits the ability of amphetamine-naive humans to identify d-amphetamine,13 suggesting that it may help treat MA dependence. We hypothesized that risperidone would be well tolerated, would be associated with less MA use, and would improve subjective and objective psychiatric symptoms.
Methods: Outpatients entering treatment at the Seattle VA who met DSM-IV criteria for MA dependence within the past year with last active use within the past 30 days were recruited. Following baseline assessment, subjects started taking risperidone 1mg qhs titrated over 4 days to 4mg qhs (or highest tolerated dose) and remained on risperidone for 4 weeks. Subjects attended weekly visits with a study psychiatrist to assess vital signs, urine toxicology, self-reports of substance use, adverse events, and concomitant medications. Subjects completed a neuropsychological battery as well as subjective (Brief Symptom Inventory (BSI)) and objective (Brief Psychiatric Rating Scale (BPRS)) measures of psychiatric symptoms at baseline and follow-up.
Results: Eleven (N=11, 1 female; mean age = 46.2 +/- 7.1) subjects enrolled. Completers (n=8, 72.7%) had a final mean risperidone dose of 3.6mg/d (SD=0.52) and decreased their days of MA use from a mean of 13.0 (SD=6.5) in the 30 days prior to starting risperidone to a mean of 0.125 (SD=0.4; t=5.7, p=.001). With the exception of improvement in fine motor function, neuropsychological performance did not change significantly over time. BSI somatization scores and positive symptom distress declined significantly during the trial. Aside from the depression subscale, all BSI scores were in the impaired range but declined to the normal range with the exception of the somatization subscale. However, there was no significant change in objective BPRS ratings of psychiatric symptoms.
Discussion: Risperidone was well tolerated and study completion was high. This may be the first evidence of a pharmacotherapy that may decrease relapse in MA dependence as well as prevent the cognitive decline that occurs in early MA recovery. In addition, this appears to be first study assessing both subjective and objective psychiatric symptoms over time in MA dependent adults. No objective decrease in psychiatric symptoms may be due to the low psychopathology of subjects. Subjects rated themselves as improved and while this may be an effect of risperidone altering monoamine activity, it is also possible that abstinence improved their health to a point where they were less somatic and less distressed by remaining symptoms. Subjective improvements would not have been captured by the BPRS. Without further study, it is unknown if the BPRS does not accurately assess objective psychiatric symptoms in MA dependence. The reduction in MA use indicates that risperidone may reduce MA use through a direct neuropharmacological action or indirectly through reduction of subjective psychiatric symptomatology but not via improvements in cognitive function or objective psychiatric symptomatology. This deserves further study in a longer, larger double-blind, randomized placebo-controlled trial using standardized DSM-IV diagnoses.

10. Gender Differences in Substance Use by Healthcare Professionals in a State Sample

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Sponsor: Gregory Oxenkrug

Background: Despite their advanced education and clinical experience, alcohol, tobacco and other illicit substance use (SU) by some healthcare professionals (HCP) is an ongoing issue as delineated by recent studies. Yet to our knowledge neither these or past studies have rarely if ever specifically examined SU and misuse by women in more than one healthcare profession. The aim of this study therefore was to more clearly delineate the prevalence of and etiological correlates of SU by women compared to men across a sample of HCPs.
Methods: Using highly validated self-report mail survey methods during the summer of 2002, a random sample of dentists, nurses, pharmacists and physicians were stratified by Zip-code in a northeastern state. More information regarding the survey method is available in detail elsewhere (e.g. Kenna & Wood, 2004). Assessed were lifetime and past year prevalence of alcohol, cigarette and illicit substance use, first drug use (before, during or after college), family history of alcoholism (FHP), ease of access to prescription drugs and offers to use alcohol and drugs made by others.

Results: Of the final pool of 697 responses, a total of 479 were usable for analyses with a response rate of 68.7% (n=179 women; n=231men; n=69 missing gender). The results show that there was no significant difference in weekly alcohol use between men and women HCPs, though men reported significantly greater lifetime (p=.0045) and past year (p=.017) heavy alcohol use (5 or more drinks at one sitting). Men reported significantly greater lifetime anxiolytic use (p=.006), with trends toward greater minor opiate (p=.06) and sedative (p=.07) use. Though there was no difference by gender in first use of illicit drugs before college, significantly more men than women first used illicit drugs during college (p=.048) and after graduation (p=.001). While no other lifetime or past year differences for other SU were significant, women reported significantly greater occasional drug use (less than monthly) during the past year (p=.01) than men. Examining etiological correlates, significantly more women replied they actively practiced a religion (p=.04). While women also reported significantly greater FHP than men, there was no relationship to their current alcohol use (transformed), though there was for men (p=.03). Men reported they were offered alcohol significantly more frequently by friends (p=.03) and pharmaceutical companies at meetings (p<.0001), and reported greater access to prescription drugs at work than women (p=.017).
Discussion: Most previous research on SU by HCPs focused on men, alcoholic women physicians or the predominantly female nursing profession. For lack of specific data, SU rates were assumed for women generally (Wasilow-Mueller & Erickson, 2001) and most likely for HCPs as well. Certainly, as with the general population, it was assumed HCP men use significantly more substances than women. This study found no difference in total weekly alcohol use between men and women. Additionally, with few exceptions (heavy alcohol use, lifetime anxiolytic use), there were no other significant differences in SU by men and women. Moreover, women reported significantly greater occasional past year drug use than men. Significantly more women also reported FHP, though arguably most of this effect was due to the predominance of women in the nursing profession known for greater FHP (Kenna & Wood, 2005). Given that most professional programs are encouraged to attract more women, the prospect grows that SU and misuse by women HCPs may potentially become a greater issue for intervention and treatment in the future, particularly in light of SU rates that approximate those of men and increasing rates of prescription drug abuse in the general population (CASA, 2005).

11. Intravenous Nicotine Self-Administration in C57BL6/J Mice

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Sponsor: Past Travel Awardee, Memorial, 2003

Background: Nicotine is one of the major components of tobacco smoke responsible for tobacco addiction in humans. The ability to assess intravenous nicotine self-administration in genetically modified mice will greatly facilitate our understanding of the neurobiological mechanisms that regulate the reinforcing properties of nicotine. Here, we report a novel intravenous nicotine self-administration procedure for otherwise drug-naive mice. Utilizing this procedure, we present data on the initiation and maintenance of intravenous nicotine self-administration behavior, and the dose-response function for nicotine self-administration in mice.
Methods: Male C57BL6/J mice (n=6) were trained to lever-press for food reinforcement under a fixed-ratio 5 time-out 20 sec (FR5TO20 sec) schedule of reinforcement. Mice were then prepared with intravenous catheters and trained to self-administer nicotine (0.03 mg/kg/infusion, free-base) under a FR5TO20 sec schedule during 1 hr daily sessions. After establishment of stable nicotine intake, the effects of varying the unit dose of nicotine (0.01-0.15 mg/infusion) available for self-administration on nicotine intake were assessed.
Results: Mice learned to lever-press for food (25 mg pellets) reinforcement under stringent (FR5TO20 sec) operant conditions. Mice rapidly acquired intravenous nicotine self-administration, and demonstrated stable nicotine intake (~20 infusions/day; ~0.6 mg/kg/day). Varying the unit dose of nicotine available for self-administration produced an inverted U-shaped dose-response function, with maximal intake at the 0.06 mg/kg/infusion dose.
Discussion: Thus, mice acquire nicotine self-administration without pre-training to self-administer cocaine or other drug reinforcers, demonstrating the potential utility of this procedure for assessing nicotine intake in genetically modified mice. Further, training mice to first respond for food reinforcement facilitates self-administration training, and will serve as a useful control procedure to ensure similar levels of operant performance in wildtype and mutant mice.

12. Behavioral Pharmacology and Pharmacokinetics of Cocaine Analogs in Rhesus Monkeys

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Sponsor: Leonard Howell

Background: Previous studies have shown that pharmacological manipulation of monoamine systems can attenuate the behavioral effects of cocaine and cocaine-induced increases in extracellular dopamine (DA). Accordingly, monoamine transporter inhibitors that block the reuptake of DA and serotonin (5-HT) may serve as effective medications in the treatment of cocaine abuse. Moreover, a pharmacokinetic profile of slow onset and long duration may effectively limit the abuse potential of the medications. In the present study, the behavioral effects of several phenyltropane analogs of cocaine with varying affinities for the dopamine transporter (DAT) and the serotonin transporter (SERT) were assessed using drug self-administration, reinstatement, and drug discrimination procedures in rhesus monkeys.
Methods: The cocaine analogs RTI-113, RTI-150, RTI-177, and RTI-336 were selective for DAT, whereas RTI-112 was non-selective for DAT and SERT. Each of the cocaine analogs was labeled with [^{11}C], and the rate of uptake in brain (n=3) was determined using positron emission tomography (PET). One group of rhesus monkeys (n=3) was trained to self-administer a range of doses of cocaine in a progressive-ratio procedure to determine relative reinforcing effectiveness. A range of doses of each test compound was substituted for cocaine and the reinforcing effectiveness relative to cocaine was determined. A second group (n=3) was trained to self-administer cocaine under a second-order schedule of operant conditioning. Self-administration behavior was extinguished by substituting saline for cocaine, then reinstatement of lever-pressing following pretreatment with a test compound was assessed. A third group (n=6) was trained to discriminate cocaine from saline in a drug discrimination procedure. The discriminative stimulus effects of cocaine were compared with a range of doses of each test compound.
Results: Relative to cocaine, each of the RTI compounds had a slower rate of uptake into the brain and slower clearance from the putamen. In the progressive ratio paradigm, RTI-113 produced responding very similar to cocaine in all 3 animals, while RTI-177 did not maintain break points comparable to cocaine in any animal. The remaining 3 compounds produced variable break points among the 3 animals. While pretreatment with cocaine or RTI-177 fully reinstated cocaine-seeking behavior in all animals, pretreatment with the remaining four compounds produced variable levels of cocaine-seeking behavior. Cocaine and the RTI compounds produced qualitatively similar discriminative stimulus effects, but the compounds differed in their potencies and time courses.
Discussion: The pharmacokinetics of drug uptake and clearance in brain determined with PET neuroimaging was reflected in drug time-course effects in the drug discrimination paradigm. Although the

drugs differed in their effectiveness to maintain high breakpoints under a progressive ratio self-administration paradigm, all drugs produced a dose-dependent and complete substitution for cocaine in the drug discrimination paradigm. Hence, reinforcing effectiveness was not predictive of discriminative stimulus effects. Similarly, drug-induced reinstatement of extinguished self-administration behavior did not correspond directly with the reinforcing or discriminative stimulus effects. Collectively, these results indicate that monoamine transporter inhibitors may exhibit a complex profile of behavioral effects that is influenced by relative affinity at multiple transporters and by pharmacokinetics.

13. Synergistic Interactions Between "Club Drugs": Gamma-Hydroxybutyrate and N-Methyl-D-Aspartate Antagonists

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Sponsor: Charles France

Background: Gamma-hydroxybutyrate (GHB) is an endogenous substance that binds to specific GHB receptors where it is thought to act as a neurotransmitter/neuromodulator. GHB is used therapeutically, to treat the sleep disorder narcolepsy and to treat alcoholism, and recreationally, as a "club drug". GHB is often abused together with alcohol. Combining GHB and alcohol is described in the popular press as producing synergistic effects. However, there has been little empirical support of this issue. Using rats trained to respond for food, we examined the response rate decreasing effects of GHB and alcohol when given alone and when given together, and found that alcohol did not potentiate the effects of GHB (Lamb et al., EJP 470:157, 2003). The steep dose-response curves of GHB and alcohol for many of their behavioral effects may account for the marked effects seen clinically when seemingly "moderate" doses of the two drugs are combined, rather than any synergistic actions of the drug combination. GHB is not only used together with alcohol, but also with other "club drugs", such as MDMA (Ecstasy), methamphetamine, and the N-methyl-d-aspartate (NMDA) antagonists ketamine and phencyclidine (PCP). Although GHB does not appear to interact synergistically with alcohol, we recently found that dizocilpine markedly enhanced directly observable behavioral effects of GHB (i.e., catalepsy) in rats (Sevak et al., EJP 483:289, 2004; EJP 517:64, 2005). Because dizocilpine is an NMDA antagonist, other NMDA antagonists are likely to interact synergistically with GHB. Some of these other antagonists are, like GHB, drugs of abuse. For example, like GHB, PCP and ketamine are "club drugs" that are used recreationally. Thus, our findings suggest a potentially important synergistic interaction with PCP and ketamine in the recreational use of GHB. Recently, we obtained evidence that potentiation of GHB by an NMDA antagonist is not limited to GHB-induced catalepsy.
Methods: Using standard two-choice food-reinforced drug discrimination procedures, pigeons (n=9) were trained to discriminate 178 mg/kg GHB from saline, and rats were trained to discriminate 2 mg/kg PCP from saline.
Results: In pigeons trained to discriminate GHB from saline, ketamine when given alone produced at most 38% responding on the GHB-appropriate key. When given as a pretreatment to GHB, however, 10 mg/kg ketamine shifted the dose-response curve for GHB's discriminative stimulus effects 4 to 5-fold to the left. This finding suggests the possibility that NMDA antagonists potentiate not only the cataleptic effects of high doses of GHB, but also the discriminative stimulus effects of low doses. Further evidence of synergistic interactions between NMDA antagonists and GHB is the finding that in rats trained to discriminate PCP from saline, 178 mg/kg GHB shifted the dose-response curve for PCP's discriminative stimulus effects 2 to 3-fold to the left.
Discussion: Because subjective effects in humans can often be predicted from drug discrimination experiments in animals, the present findings suggest that NMDA antagonists such as PCP and ketamine may potentiate the subjective effects of GHB, which are likely related to GHB abuse. Taken together, our results are further evidence of interactions of the glutamatergic system with the neuropharmacological systems (GHB, GABA) involved in the behavioral effects of GHB, and of the possible important role of glutamatergic systems in modulating/mediating effects of drugs of abuse. Supported by USPHS Grants DA14986, DA15692, and DA17918 (Senior Scientist Award to CPF).

14. Six-Month Trial of Bupropion with Contingency Management for Cocaine Dependence

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Background: No effective pharmacotherapies exist for cocaine dependence although contingency management (CM) has shown some effectiveness. Our objective was to compare the efficacy of bupropion plus CM for reducing cocaine use in methadone-maintained subjects.
Methods: This 25-week, placebo-controlled, double-blind, clinical trial randomly assigned subjects to one of four treatment conditions: CM+placebo, CM+Bupropion (300 mg/day), Voucher Control (VC)+Placebo, or VC+Bupropion. Treatment occurred on an outpatient basis at the West Haven, CT VA Healthcare System. One hundred six opiate-dependent, cocaine-abusing subjects were recruited. All subjects received methadone (range 60-120mg). Subjects receiving bupropion were given 300mg/daily beginning at week 3. In the CM conditions, each urine negative for both opioids and cocaine resulted in a monetary-based voucher that increased for consecutively drug-free urines during weeks 1-13. Completion of abstinence-related activities determined during weekly counseling sessions also resulted in a voucher. During weeks 14-25, only completion of abstinence-related activities was reinforced in the CM group, regardless of urine results. The VC group received vouchers for submitting urine samples, regardless of results, throughout the study. Vouchers were exchanged for mutually agreed upon goods and services. The main outcome measure was thrice-weekly urine toxicology for cocaine and heroin.
Results: Groups did not differ in baseline characteristics or retention rates. In the CM+bupropion group, the proportion of cocaine-positive samples significantly decreased over time during weeks 3-13 ($p < 0.04$) relative to week 3 and remained low during weeks 14-25. The CM+placebo group significantly increased over time during weeks 3-13 ($p < 0.02$) relative to week 3, but then significantly decreased relative to the initial slope during weeks 14-25 ($p < 0.01$). In contrast, cocaine-positive urine results significantly increased in the VC+bupropion and VC+placebo groups across weeks 3-25. Opiate use decreased significantly ($p<0.00001$) during treatment, with no differences among groups.
Discussion: These findings suggest that the combining CM with bupropion for treatment of cocaine addiction may significantly improve outcomes relative to bupropion alone. (NIDA grants R01 DA05626, P50 DA12762, K05-DA00454)

15. Naltrexone and Fluoxetine for Relapse to Heroin Dependence in St. Petersburg, Russia

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Sponsor: George Woody

Background: Heroin addiction and HIV have spread rapidly in Russia and former Soviet States during the last ten years. Agonist treatment is not permitted but Naltrexone is approved for use. This study tests the efficacy of Naltrexone with or without fluoxetine for relapse prevention to heroin addiction.

Methods: 280 heroin addicts who completed detoxification at addiction treatment units in St. Petersburg, Russia and gave informed consent were randomized to a 6 month course of biweekly drug counseling and one of four groups of 70 subjects/group: Naltrexone 50 mg/day (N) + Fluoxetine 20 mg/day (F); N + Fluoxetine placebo (FP); Naltrexone placebo (NP) + F; or NP + FP. Medications were administered under double-dummy/double-blind conditions. Urine drug testing and brief psychiatric evaluations were done at each biweekly visit with more extensive evaluations at 3 and 6 months. Medication compliance was evaluated using a urine riboflavin marker.
Results: 414 patients were asked if they would be interested in participating, 343 gave informed consent and 280 met study entrance criteria and were randomized. At the end of six months, 43% of subjects in the N+F group remained in the study and had not relapsed as compared to 36% in the N+FP group, 21% in the NP+F group, and 10% in the NP+FP group. Based on retention and non relapse at 6 months, N+F was more effective than NP+FP ($p<0.001$), or NP+F ($p<0.01$); N+FP was more effective than NP+FP ($p<0.001$) or NP+F ($p<0.05$); NP+F was not more effective than NP+FP ($p=0.1$), and N+F did not differ significantly from N+FP ($p=0.2$), however women receiving N+F showed a trend toward statistical significance as compared to women receiving N+FP ($p=0.09$), probably due to a higher level of depression, anxiety, and anhedonia in women at study initiation.
Discussion: Naltrexone is more effective than placebo and fluoxetine for treatment retention and relapse prevention to heroin dependence. The combination of N+F might be more effective than naltrexone alone in women.

16. Are Adolescent Rats Addiction-Prone and Hyperresponsive to Stimulants Because They Are Hypodopaminergic?

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Background: Drug use that begins during adolescence is more likely to progress to addiction than use which begins later in life. A growing literature suggests that age-related differences in the neural substrates of addiction may contribute to this vulnerability. The forebrain dopamine system which mediates the reinforcing effects of most addictive drugs is a likely candidate because it continues to develop through adolescence. However research findings conflict: some behavioral studies report that adolescents are hypoactive in response to drugs like psychomotor stimulants which increase synaptic dopamine, while others report exaggerated responses. Wide ranging differences in dose regimen and drug tested contribute to these conflicting findings. Even less is understood about neurochemical mechanisms which mediate such behaviors during adolescence. We have shown that binge pattern of stimulant administration elicits exaggerated behavioral responses to at least one psychomotor stimulant, cocaine. We hypothesize that underlying differences in dopaminergic function are responsible for these differences, which could contribute to the escalation of use that is critical for development of addiction. The purpose of the present study was to compare the behavioral response to cocaine and other psychostimulants and to quantitate basal dopamine clearance and its perturbation by one of these drugs (cocaine) across adolescence in rats.
Methods: We determined the behavioral and neurochemical response of rats to psychomotor stimulants across adolescence (day 28, 42 and 65). Male rats were treated with a binge pattern of cocaine (3 x 15 mg/kg), methylphenidate (3 x 10 mg/kg) or nomifensine (3 x 5 mg/kg). Horizontal and vertical locomotion were quantitated in a photocell apparatus, and individual behaviors were scored by an observer to obtain an integrated stereotypy score. In addition, voluntary cocaine consumption was evaluated in an oral self administration model. Rats received 3 initial trials with the cocaine solution and then were allowed to choose between saccharin and cocaine in 5 hour daily trials without water deprivation. Fast scan cyclic voltammetry was used to evaluate dopamine release and clearance in 28, 42 and 65 day old rats at baseline and after 15 mg/kg of cocaine and synaptosomal uptake of 3H dopamine was used to confirm the uptake findings
Results: Adolescent male rats exhibited greater behavioral responses to all three stimulants. Cocaine consumption rapidly increased in male rats that began drinking on PN28 to levels that were significantly greater than those of PN 65 rats. Both voltammetry and synaptosome data indicated that PN28 rats showed significantly greater dopamine clearance capacity, although maximal dopamine release capacity was significantly less than adults. In the presence of cocaine, extracellular dopamine levels increased proportionately much more in adolescent than in adult rats.
Discussion: These data suggest that young adolescent rats may have be relatively hypodopaminergic due to the greater uptake:release ratio. In the presence of a DAT inhibitor, extracellular dopamine then increases dramatically and can elicit an exaggerated postsynaptic response which can lead to increased consumption of drug. Such decreased baseline dopaminergic function during adolescence could lead to exaggerated responses to both addictive drugs and stimulant medications. These findings also suggest that developmental differences in dopaminergic function might contribute to enhanced responses to binge pattern stimulant administration that could contribute to escalation of drug use during adolescence. Supported by DA09079 and DA019114

17. Ethanol Does Not Affect Discriminative Stimulus Effects of Nicotine in Rats

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Sponsor: Richard Rothman

Background: Consumption of alcohol increases the number of cigarettes smoked, but the mechanism underlying this effect is unclear. One explanation is that ethanol, which possess central nervous system depressant effects, may reduce the subjective effects of nicotine and therefore produce a compensatory increase in smoking behavior.
Methods: Here, we used the two-lever drug discrimination choice procedure as an animal model for assessing the ability of ethanol to alter the psychomotor and subjective effects of nicotine. Male Sprague-Dawley rats (n = 24) were trained under a discrete-trial schedule of food-pellet delivery to respond on one lever after an injection of a training dose of 0.4 mg/kg nicotine and on the other lever after an injection of 1 ml/kg of saline vehicle. Injections of nicotine or saline were given subcutaneously 10 min before the start of the session. A range of doses of ethanol were substituted for the training dose of nicotine. Ethanol was also administered together with various doses of nicotine to assess possible alteration of the dose-response curve for nicotine discrimination.
Results: Ethanol failed to generalize to the nicotine training stimulus over a large range of doses (less than 5% of responses emitted on the nicotine-associated lever with doses of ethanol ranging from 0.1 to 1 g/kg). Also, when ethanol was administered in combination with nicotine it did not produce a significant shift of the dose-response curves for nicotine discrimination. Thus, the ability to discriminate the effects of nicotine does not appear to be altered by ethanol administration. However, the high dose of 1 g/kg ethanol given either alone or in combination with nicotine, markedly depressed food-maintained responding. This later effect was associated in some rats with an attenuation of the discriminative-stimulus effects of the training dose of nicotine.
Discussion: These results suggest that previous reports of increased tobacco smoking following ethanol consumption in humans are connected, in some way, with an increase in motivation to consume nicotine that is produced by ethanol, rather than with a decrease in the subjective response to nicotine. Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal

Care (AAALAC) and all experiments were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse (NIDA), National Institutes of Health and the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 2003).This research was supported by the Intramural Research Program of the NIH.

18. Blockade of D2/D3 Dopamine Receptors Selectively Impairs Reversal Learning, but not New Learning, in Monkeys Performing a Visual Discrimination Task

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Background: Converging evidence suggests a role for the dopaminergic system in the ability of an animal to shift behavior in response to changing stimulus-reward contingencies. One of the behavioral procedures used to assess this ability is reversal of a learned visual discrimination. Here, we characterized the effects of subtype-specific dopamine (DA) antagonists in a visual discrimination and reversal learning task to further delineate the influences of each DA receptor subtype on the capacity to shift response in nonhuman primates (*Chlorocebus aethiops sabaeus*).
Methods: We used a modified Wisconsin General Test Apparatus that was equipped with three samples boxes fitted with unique visual discriminanda (pictures). The locations of the samples boxes were pseudo-randomly changed across trials. Four Vervet monkeys were trained to learn a novel picture-reward discrimination (e.g., that one of three discriminanda concealed a reward) on Mondays and Thursdays before experiencing a reversal of the discrimination (in which the reward was then located under one of the previously unrewarded sample boxes) on the following day.
Results: The D2/D3 dopamine receptor antagonist raclopride (0.001 - 0.03 mg/kg, i.m.) did not significantly impair acquisition of a novel visual discrimination (in which the discriminanda were never seen before). Raclopride (0.03 mg/kg), however, impaired the performance of the reversal task. Specifically, raclopride significantly increased the number of reversal errors required before reaching the criterion (7 correct responses in 10 recent trials) in the reversal session. In contrast, the D1/D5 dopamine receptor antagonist SCH 23390 (0.001 - 0.03 mg/kg, i.m.) did not significantly modulate the performance of reversal learning. None of the drug treatments affected retention of a previously learned discrimination.
Discussion: In summary, the results strongly suggest that the D2/D3 dopamine receptors, but not D1/D5 dopamine receptors, selectively mediate reversal learning (i.e., the ability to adjust behaviors in response to changing stimulus-reward contingency), without affecting the capacity to learn a new stimulus-reward contingency. These data support the hypothesis that phasic dopamine release, acting through D2-like receptors, mediates behavioral flexibility.

19. Endocrine Challenge of the HPA Axis Differentially Modulates Plasma Deoxycortisosterone and Pregnenolone Levels in Cynomolgus Monkeys

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Sponsor: Fulton T. Crews

Background: Deoxycorticosterone (DOC) and pregnenolone (PREG) are precursors of the potent endogenous GABAergic neuroactive steroids allotetrahydrodeoxycorticosterone and allopregnanolone that are increased in rodent brain and plasma after HPA axis activation by acute stress or ethanol administration. However, no data are available for non-human primates.
Methods: Eleven adult 4-5 year old male Cynomolgus monkeys were housed individually for 3 months prior to testing. The monkeys had received prior extensive training to comply with awake venipuncture to collect blood for the steroid assays with minimal observable distress. Steroid concentrations were determined by radioimmunoassay in plasma samples following challenge of the HPA axis with naloxone (375 μg/kg), corticotropin-releasing factor (CRF; 1 μg/kg), dexamethasone (130 μg/kg), or adrenocorticotropic hormone (ACTH; 10 ng/kg) 4-6 hours after 0.5 mg/kg dexamethasone to increase plasma cortisol levels. Ethanol was tested at an intoxicating dose (1.5 g/kg).
Results: Naloxone increased DOC and PREG levels by 97 and 216%, respectively, ($p<0.001$). CRF infusion increased DOC (+50%), but not pregnenolone levels. DOC, but not PREG levels were positively correlated with cortisol or ACTH levels after naloxone challenge. Dexamethasone (130 μg/kg) decreased DOC levels by 42% ($P<0.001$), but had no effect on PREG levels. ACTH (10 ng/kg) challenge, 4-6 hours after 0.5 mg/kg dexamethasone, did not modify DOC and PREG levels. The effect of dexamethasone challenge on both DOC and PREG levels was highly correlated with subsequent voluntary alcohol drinking. The decrease in DOC levels following dexamethasone was negatively correlated with subsequent alcohol intake (Pearson r = -0.78, P = 0.006, n = 10). Greater suppression of DOC levels was predictive of lower voluntary alcohol consumption. In contrast, dexamethasone-induced changes in PREG levels were positively correlated with subsequent alcohol intake (Pearson r = 0.84, P = 0.001, n = 10). Greater suppression of PREG levels was predictive of higher subsequent alcohol consumption. Ethanol had no effect on DOC or PREG levels in monkey plasma, suggesting that these steroids are differentially regulated in monkeys vs. rats.
Discussion: These data show diverse and divergent regulation of GABAergic neurosteroid precursors by HPA axis activation at multiple levels that appears to be related to alcohol drinking behavior in monkeys. Furthermore, since the monkeys had no alcohol exposure prior to the HPA axis challenges, the correlations between subsequent alcohol drinking and DOC and PREG responses to dexamethasone may represent trait markers of propensity to drink alcohol. Supported by AA10564, UO1 AA13515 and AA13510.

20. The Effect of Dopamine Precursor Depletion on Alcohol Self-Administration in Men: Individual Differences

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Sponsor: Paul Vezina

Background: It is thought that there are multiple neurobiological pathways to dysregulated alcohol seeking behavior, the best implicated being dopamine (DA) mediated interest in ethanol's rewarding effects. The present study sought to examine DA's role in alcohol self-administration in a heterogeneous sample of non-dependent drinkers using the acute phenylalanine/tyrosine depletion (APTD) method.
Methods: The subjects were 16 men (age: 21.8±3.3 years old) with variable individual (10.2±5.8 drinks / week, range = 2 - 20) and family drinking histories (1.2±1.5 1st and 2nd degree relatives with an alcohol use disorder, range = 0.0 - 3.5). Cardiac responses to the acute ingestion of 0.75 g/kg of alcohol (6.4±4.8 bpm, range = -3.0 - 14.0) were measured on a separate test session based on evidence that this is a peripheral index of activity in the DA-related behavioral activating system(1,2). In three randomized double-blind sessions participants ingested a nutritionally balanced (BAL) amino acid (AA) mixture, a mixture deficient in the DA precursors, phenylalanine and tyrosine, and APTD followed by the immediate DA precursor L-DOPA (Sinemet, 2 x 100mg/25mg). Beginning 5 hours following each AA ingestion participants

completed self-administration sessions where units of their preferred alcoholic beverage and glasses of water could be earned using a progressive ratio task.
Results: Alcohol self-administration progressive ratio breakpoints were reduced in both the APTD ($p \leq 0.03$) and APTD+L-DOPA ($p \leq 0.01$) conditions relative to the BAL condition. There were no significant effects of AA mixtures on water administration ($p \geq 0.4$). Stepwise linear regressions were used to determine how the observed changes in alcohol self-administration were related to various alcohol-related variables. For both APTD ($p \leq 0.002$) and APTD+L-DOPA ($p \leq 0.006$) induced changes in alcohol self-administration breakpoints, the sole statistically significant predictor was ethanol-induced cardiac change. Post hoc analyses revealed an effect of AA condition on alcohol consumption in individuals with a high cardiac response to ethanol ingestion ($p \leq 0.05$) but no differences in alcohol intake among those displaying a minimal cardiac response ($p \geq 0.4$).
Discussion: The findings suggest that DAergic manipulations affect alcohol self-administration in a subset of drinkers, and that this may be predicted on the basis of their cardiac response to acute alcohol ingestion. 1. Boileau I, Assad JM, Pihl RO, Benkelfat C, Leyton M, Diksic M, Tremblay RE, Dagher A. Alcohol promotes dopamine release in human nucleus accumbens. Synapse 2003;49:226-231; 2. Gray JA. Perspectives on anxiety and impulsivity: A commentary. Journal of Research in Personality 1987;21:493-501.

21. Examining White Matter Abnormalities in Cocaine Dependence with T2 Relaxography
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Background: Structural neuroimaging studies have found white matter abnormalities in subjects with cocaine dependence. Findings have included an increased amount of white matter hyperintensities. Studies using diffusion tensor imaging have reported reductions in fractional anisotropy in the orbitofrontal white matter and in the corpus callosum. These findings have been attributed to damage due to the vasoconstrictive effects of cocaine. Other magnetic resonance imaging methods for examining white matter have become available. T2 relaxography has been proposed as a method for the quantitative assessment of myelin water - sensitive to the water wrapped in the myelin sheath. Studies in multiple sclerosis and schizophrenia have reported reductions in the myelin water fraction in these disorders.
Methods: Subjects consisted of 6 actively using, cocaine dependent individuals and 5 age matched healthy, non drug using controls. MRI data were collected on a Siemens 3T Trio scanner. T2 relaxography data were collected using a multislice, spin echo acquisition of twelve 8 mm thick slices, skip 0mm, aligned and passing through the AC-PC plane. TR/TE: 698/8, 723/33, 800/110 msec, 24cm FOV, 128x128. Data from the three acquisitions were linearly combined to obtain estimates of the total water signal and myelin water. Myelin water fraction (MWF) was defined as the myelin water divided by the total water signal. A white matter mask derived from tissue segmentation was used to select the MWF from white matter. A frontal region was defined as anterior to a coronal plane located at the anterior extent of the genu and perpendicular to the AC-PC plane.
Results: There was no significant difference in age between the groups. For the frontal white matter, the cocaine using subjects had significantly higher MWF than the controls (p=.0001, 13.66 +/- .876, 10.75 +/- .492, d=4.1).
Discussion: These preliminary data suggest that the signal attributed to myelin water, an indicator of myelin status, is increased in cocaine using subjects. Current reports have found reductions in fractional anisotropy in cocaine using subjects, an indicator of reduced white matter integrity. The increase in MWF may reflect an alteration in myelin organization in the cocaine using subjects. Comparison with other white matter imaging methods such as magnetizaton transfer, another measure of myelin status may be informative.

22. Variation in the rhNPY Promoter Is Associated with Differences in CSF Levels of NPY and Alcohol Consumption
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Sponsor: Bryon Adinoff

Background: Neuropeptide Y (NPY) is an anxiolytic peptide that is involved in the modulation of stress response. As such, the NPY gene may be a good candidate for investigating genetic variation as it relates to individual differences in anxious responding and vulnerability to stress in nonhuman primates. Although results have been variable, dysregulation of the NPY system and NPY replacement have been associated with alterations in alcohol intake in both animal models and human subjects. We wanted to sequence the rhesus NPY gene to screen for functional genetic variants in the rhNPY gene and promoter.
Methods: Sequences of the Macaca mulatta NPY gene, exon/intron boundaries, and 5'flanking region were determined using PCR and direct sequencing from genomic DNA. DNA samples from 96 NIHAC animals were sequenced, and variants were detected by direct visualization of electropherograms generated by ABI Sequencing Analysis software. Primers were designed from published human sequence and, subsequently, from rhesus sequence generated in our lab.
Results: Sixteen polymorphisms were identified in the 5'flanking and coding regions of the rhNPY gene. One of these (−1002T>G) disrupts a putative androgen response element site, which would be expected to result in a diminution in androgen receptor-mediated regulation of NPY transcription. Consistent with the demonstrated role for androgens in induction of the NPY gene, haplotype analysis revealed that carriers of the −1002 G allele exhibited lower cisternal cerebral spinal fluid levels of NPY. This rhNPY promoter variant was also associated with decreased alcohol intake in animals without a history of dependence, with the effect being more marked among animals exposed to early adversity in the form of peer rearing.
Discussion: These data suggest that variation in the rhNPY promoter may alter rhNPY expression and NPY release. This variant is also associated with differences in alcohol intake in rhesus macaques exposed to early life/chronic stress.

23. The Effects of CRH-1 Antagonist Antalarmin on Cocaine Self-Administration and Discrimination
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Background: The hypothalamic-pituitary-adrenal (HPA) stress axis is involved in a number of clinical disorders including drug abuse. CRH-1 receptors mediate hypothalamic CRH-induced ACTH release, and CRH-1 receptor antagonists may be useful clinically for treatment of depression and anxiety. Clinical and preclinical studies indicate that cocaine stimulates ACTH release, and CRH-1 antagonists can reduce cocaine self-administration by rodents under some conditions (Goeders, 1997, 2002). Antalarmin is a systemically active CRH-1 receptor antagonist that attenuates CRH stimulation of ACTH (Broadbear et al., 2004), as well as fear reactions to social aggression in rhesus monkeys (Habib et al., 2000). We examined the effects of antalarmin on cocaine self-administration and cocaine discrimination in rhesus monkeys.
Methods: Monkeys were trained to self-administer cocaine (0.032 mg/kg/inj) under a fixed ratio schedule (FR 10 or FR 30) during daily 2hr sessions, then dose-effect curves for cocaine self-administration (0.001-0.10 mg/kg/inj) were determined. The effects of antalarmin were studied on unit doses of cocaine (0.0032, 0.01, and 0.032 mg/kg/inj) that maintained self-administration in all monkeys and reflected the ascending limb, peak and descending limb of the cocaine

dose-effect curve. Antalarmin (1, 3.2 and 10 mg/kg, IV) was administered 15 min before each test session. In drug discrimination studies, monkeys were trained to discriminate cocaine (0.4 mg/kg, IM) from saline. Saline or cocaine were administered 10 min before the 5 min response period, and during training, correct responses under a FR 30 schedule were reinforced with banana-flavored pellets. The effects of antalarmin (5 and 10 mg/kg IM, 30 min pretreatment) were examined on the cocaine dose-effect curve (0.013-1.3 mg/kg) and the time course of the training dose.
Results: Under these conditions, antalarmin did not significantly alter the reinforcing or discriminative stimulus effects of cocaine in rhesus monkeys. There was a non-significant dose-dependent decrease in responding maintained by 0.01 mg/kg/inj cocaine after acute administration of antalarmin (1-10 mg/kg, IV). Seven days of treatment with single daily doses of antalarmin (3.2 mg/kg IV) also did not significantly alter responding maintained by 0.01 mg/kg/inj cocaine. Antalarmin (3.2 mg/kg, IV) did not change the cocaine self-administration dose-effect curve. In drug discrimination studies, antalarmin (5 and 10 mg/kg, IM) did not significantly alter either the cocaine discrimination dose-effect curve or the time course of the training dose.
Discussion: The lack of significant effects of antalarmin on these behavioral endpoints may indicate that CRH activation is not essential for cocaine's abuse-related effects, or that antalarmin at these doses, does not affect CRH-1 receptors in brain. In previous studies, antalarmin over the dose range studied, attenuated CRH stimulation of ACTH, but not cortisol in monkeys (Broadbear et al., 2004). Given the feedback relation between ACTH and cortisol, antalarmin would be expected to affect both hormones. In rats, corticosterone is essential for acquisition and maintenance of cocaine self-administration (Goeders 2002). Clarification of the complex interactions between CRH receptors and cocaine will require centrally-acting CRH-1 antagonists. This research was approved by the IACUC and conducted in accordance with the Guide for Care and Use of Laboratory Animals. Supported by P01-DA14528, K05-DA00064 and K05-DA00101 from NIDA, NIH.

24. The Effects of 'Binge' Cigarette Smoking on Hypothalamic-Pituitary-Adrenal Axis Hormones and Mood in Men

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Background: Cigarette smoking is an addictive disorder and smoking a cigarette produces rapid nicotine dose-related effects on HPA axis hormones, mood and heart rate (Mendelson et al 2005). Activation of the HPA axis may contribute to the abuse-related effects of cigarette smoking, but relatively little is known about the effects of smoking several cigarettes in a binge pattern. This study was designed to determine if the hormonal, cardiovascular and mood changes observed after smoking a single cigarette increase, decrease or remain the same after repeated cigarette smoking at one hour intervals.
Methods: Cigarette smoking is an addictive disorder and smoking a cigarette produces rapid nicotine dose-related effects on HPA axis hormones, mood and heart rate (Mendelson et al 2005). Activation of the HPA axis may contribute to the abuse-related effects of cigarette smoking, but relatively little is known about the effects of smoking several cigarettes in a binge pattern. This study was designed to determine if the hormonal, cardiovascular and mood changes observed after smoking a single cigarette increase, decrease or remain the same after repeated cigarette smoking at one hour intervals.
Results: Plasma nicotine levels increased significantly from baseline within 8 min, and there was a cumulative effect of smoking successive cigarettes on plasma nicotine levels. Peak nicotine levels after the first, second and third cigarette averaged 14.7±2.9, 17.79±2.65 and 20.86±2.57 ng/ml. In contrast, there was a greater increase in cardiovascular, hormonal and subjective effects following the first cigarette than after the second and third cigarette. ACTH, DHEA, cortisol and heart rate increased significantly after each cigarette, but the magnitude of the increase diminished with repeated cigarette smoking. VAS ratings of positive subjective effects (high, rush, stimulated) also increased after each cigarette, but the magnitude of the increase was greater after the first cigarette than after the second and the third cigarette. There were no increases in VAS ratings of negative subjective effects (sick, dizzy, jittery, bad feeling) after successive cigarettes. Ratings of craving for cigarettes decreased significantly during smoking, then increased monotonically until the next cigarette was available. Peak craving levels did not differ significantly after successive cigarettes.
Discussion: Taken together, these findings indicate that despite cumulative increases in peak levels of nicotine after repeated cigarette smoking, increases in the ratings of positive subjective effects, heart rate, and HPA axis hormones diminished progressively after smoking the second and third cigarette. This dissociation between plasma nicotine levels and the subjective, cardiovascular and endocrine effects of smoking suggests that tolerance to nicotine develops quite rapidly during repeated cigarette smoking. These data are consistent with reports that the first cigarette of the day is most salient. Moreover, these clinical findings are also consistent with the hypothesis that stimulation of the HPA axis may be one important component of the abuse-related effects of cigarette smoking. These studies were approved by the McLean Hospital IRB and were carried out in accordance with the Declaration of Helsinki. This research was supported by grants R01-DA15067, P01-DA14528, T32-DA07252, K05-DA00064 and K05-DA00101 from the National Institute on Drug Abuse, NIH.

25. Dose-Dependent Effects of Topiramate on Alcohol Cue Reactivity and The Subjective Effects of Drinking: Preliminary Data

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Sponsor: Robert Swift

Background: Topiramate (TOP) was recently reported to be efficacious in reducing drinking rates and craving among men and women with alcohol dependence in a randomized controlled 12-week trial (Johnson et al., 2003). An important observation in this study was that significant differences on self-reported drinking measures started at the 200 mg/day dose in week 6, but doses continued to increase up to week 8. As a result, the effects of time and dose on drinking were confounded. To date, no dose response study of TOP with alcohol dependent individuals has been done. It is of considerable clinical importance to determine at what dose TOP has the most favorable benefit-to-side effect ratio. In addition, it has been recognized that improvements in pharmacotherapy may occur through identification of the biobehavioral mechanisms by which interventions exert their beneficial effects. Both trials of TOP conducted to date (Johnson et al., 2003; Rubio et al., 2004) suggest that an attenuation in craving may mediate its effects on drinking. However, no laboratory studies have assessed urge to drink while on TOP. Other mechanisms by which TOP could be beneficial for persons with alcohol dependence is through an attenuation of euphoric and stimulatory effects, and a potentiation of dysphoric effects of alcohol ingestion. These also have not yet been examined.
Methods: In the present study, heavy drinking alcohol dependent individuals who are not seeking treatment are randomized to one of 3 conditions in a 3-group (TOP 200 mg/day; TOP 300 mg/day; placebo) double-blind study. Participants reach the target dose after a 32-day titration period and are stabilized for 1 week. All then participate in a laboratory assessment to evaluate the possible dose-de-

pendent effects of TOP on craving and the subjective effects of alcohol ingestion. Participants undergo a cue reactivity protocol that involves auditory, tactile and olfactory exposure to their preferred alcoholic beverage. All then complete an alcohol-challenge procedure wherein they consume a dose of alcohol that is adjusted by gender, height and weight, such that the targeted blood alcohol level (BAL) is 0.06. All are given 20 minutes to consume the beverages followed by a 20-minute absorption period. Next, BAL is assessed and measures of the subjective effects of alcohol are completed. All remain in the laboratory until their BAL is < .04. Because identifying individuals most likely to benefit from TOP may improve treatment and cost-effectiveness, we are examining potential genetic moderators of TOP's effects.
Results: To date we have studied 12 participants. Of the 12, 7 were male, mean age was 39 (24-63), and 4 were in each group. All groups were highly compliant (MEMScaps; placebo 100%, 200 mg 96%, & 300 mg 98%). Thus far, no serious or non-serious adverse events have been reported. We continue to enroll participants and data will be presented on the full sample.
Discussion: Results of this project will provide an efficient and comprehensive analysis of putative biobehavioral mechanisms of TOP's effects on drinking and will afford a better understanding of whether large-scale randomized clinical trials with long-term follow ups are warranted.

26. 5-HT1B Receptors in Nucleus Accumbens Efferents Can Increase both Rewarding and Aversive Effects of Cocaine
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Background: We previously found that increased expression of 5-HT1B receptors in rat nucleus accumbens shell neurons that project to ventral tegmental area sensitized animals to the locomotor stimulating and rewarding properties of cocaine. Specifically, we detected a shift to the left of the biphasic dose-response curve for cocaine in a conditioned place preference task after increased 5-HT1B expression. This could have involved changes in both the rewarding and aversive properties of cocaine, which are theorized to oppose each other by the opponent process theory. To test this idea we examined the behavioral effects of increased 5-HT1B expression under conditions intended to selectively influence either conditioned place preference or aversion (CPP or CPA, respectively).
Methods: Male S/D rats received bilateral microinjections of HSV vector into the medial NAcc shell that expressed either 5-HT1B and GFP (HA1B/GFP) or GFP only as a control treatment. Animals then received place conditioning training with cocaine (5 or 20 mg/kg ip) or saline in a commercial place conditioning apparatus using either immediate pairing (for 15 mi—during the ascending limb of cocaine serum concentration) or after a 45 min delay (during the descending limb).
Results: In GFP-only control animals, there was neither CPP or CPA with the low (5 mg/kg) cocaine. However, increased 5-HT1B expression enhanced CPP to 5 mg/kg cocaine with immediate pairing but not with delayed pairing. Control rats trained with the higher cocaine dose (20 mg/kg) showed a significant CPP with immediate pairing and a strong trend for CPP after 45 min delay. On the other hand, rats with increased 5-HT1B expression showed no preference or aversion with immediate pairing and 20 mg/kg cocaine but a strong CPA with the delayed pairing.
Discussion: These results indicate that we were able to discriminate rewarding and aversive components of the behavioral response to cocaine by manipulating the timing of drug pairing with place. Furthermore, increased 5-HT1B expression in nucleus accumbens shell projection neurons enhanced both the rewarding and aversive properties of cocaine, depending on the temporal pairing of drug with place. We conclude that 5-HT1B receptors in these neurons increases the valence of both rewarding and aversive properties of cocaine.

27. Factor Analysis of the Y-BOCS in Autistic Disorder
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Sponsor: Eric Hollander

Background: Autism is a developmental disorder affecting social and language development. It is also characterized by repetitive behaviours and restricted interests. The domain of repetitive behaviours has not been adequately studied in this population. The purpose of this study was to carry out a factor analysis of the Y- BOCS checklist in an effort to reduce the number of variables in this domain and ultimately identify possible endophenotypes.
Methods: One hundred and eighty nine subjects with autistic disorder were enrolled. Diagnosis was confirmed by the ADI-R. All subjects were administered the Y-BOCS. We estimated tetrachoric correlations among the symptom categories and then submitted these correlations to a Principle Components analysis followed by a Varimax rotation.
Results: Our analysis supported a three-factor solution: obsessions, high order repetitive behaviors, and low order repetitive behaviors. The obsession factor accounted for 47.36% of the variance whereas the high and low order compulsion factors accounted for 35.19% and 17.45% of the variance respectively.
Discussion: We have identified a three-factor structure to describe the repetitive behaviors in autism. This data needs to be replicated, but is an important first step in our effort to identify genetically and biologically distinct groups within the autistic population. It may offer the ability to appropriately stratify autistic subjects for genetic and imaging studies and may facilitate the search for effective, factor-specific interventions.

28. Decreased Cortisol Response to the Trier Social Stress Test in Healthy Adults with Significant Childhood Adversity
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Background: In the past decade, both animal and human data have underscored the permanent and potentially deleterious neuroendocrine effects of exposure to stress during early infant or childhood development. In rodent and primate models, experimental conditions that provide stress to a subject through disruption of usual mother-infant interactions appear to produce exaggerated stress hormone responsivity in the animals which persists to maturity. As cortisol hyperactivity and deficient glucocorticoid feedback regulation have been consistently identified as biological correlates of adult major depression, and since early life adversity is associated with major depression in epidemiological studies, one could hypothesize that a pattern of excessive cortisol response in response to a stressful stimulus represents a biological marker, or endophenotype, which signals elevated risk for development of major depression.
Methods: The Trier Stress Test (TSST) is a standardized laboratory psychosocial stress paradigm that involves public speaking role-play and mental arithmetic tasks in front of a panel of confederate judges. Nondepressed, medically healthy adult subjects (ages 20 to 60) were selected for comparison groups based on self-report data regarding early life experiences (The Childhood Trauma Questionnaire). Plasma cortisol response to the TSST (i.e time points 0, 15, 30, 45, 60, 75, and 90 minutes) was examined in subjects with "moderate to severe" childhood abuse or neglect (ADV; n=22) and in subjects with "none or minimal" childhood adversity (CTL; n=29).
Results: Subjects in the ADV group were older (mean±SD years, 35.3±13.0 versus 24.7±6.6, t=3.5, p=.002) and had higher scores on

the Inventory for Depressive Symptoms, Self-Report (IDSSR; 12.3±6.1 versus 5.9±4.9, t=4.1, p<.001). After controlling for effects of age and depressive symptom score, both groups showed similar baseline cortisol concentrations (F=2.1, p=.16). However, ADV group subjects had significantly diminished cortisol responsivity overall, relative to the controls (repeated measures general linear model, F=5.6, p=.02), with the greatest between-groups effect on cortisol seen at 30 minutes after the stressor (estimated marginal means±SE: 22.4±1.6 versus 14.3±1.9, F=8.4, p=.006).
Discussion: Adults who had childhood abuse/neglect showed a relatively dampened cortisol response to the psychosocial stressor relative to adults reporting no history of abuse/neglect. This finding, which was significant in the opposite direction than that hypothesized, may represent differential alterations in stress system regulation which occur as a function of developmental timing, i.e., age of the subject at the time of exposure to stress. Alternatively, the data may reflect a biological correlate of resilience.

29. Variable Foraging Demand (VFD) Exposure of Primate Maternal-Infant Dyads and Impaired Insulin Action in Juvenile Offspring

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Sponsor: Bruce Lydiard

Background: The limbic-hypothalamo-pituitary-adrenal (LHPA) axis is implicated in the pathogenesis of obesity and insulin resistance, yet the effects of early-life LHPA axis alterations on these disorders have not been systematically studied. Using our naturalistic model of early-life stress, variable foraging demand (VFD), we have shown LHPA axis dysregulation manifested in persistently elevated or reduced concentrations of cerebrospinal fluid corticotropin-releasing factor and alterations in cortisol concentrations.
Methods: VFD imposes an unpredictable schedule of food procurement requirements on nursing mothers over a 4 month period critical for development of their offspring. The majority of food consumed is standard monkey chow, thereby eliminating the confounds of dietary manipulation or preference. 48 juvenile monkeys (30 VFD and 18 control; 25 males and 23 females; aged 3-4 years) were studied. Morphometric data was obtained, and blood samples run for lipid profiles and relevant peptides. Euglycemic hyperinsulinemic clamps were performed on a subset of male subjects. Studies were conducted according to the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health.
Results: Of the 30 juvenile VFD subjects, maternal-infant CSF CRF values in response to VFD were available on 18 mothers and 14 infants; both mothers and infants exhibited significant increases of CSF CRF concentrations in response to VFD ($p = .01$ and $p < .008$, respectively). VFD-reared offspring at the juvenile phase of development had significantly greater body mass ($p = 0.017$), body mass index (BMI) ($p = 0.004$), abdominal circumference ($p = 0.034$), and VLDL ($p = 0.009$) in comparison to controls. Glucagon-like peptide-1 was elevated nearly 2 fold in VFD-reared subjects vs controls. Among 14 male macaques from this group (7 VFD and 7 control), studied using a euglycemic hyperinsulinemic clamp, VFD-reared monkeys had significantly lower insulin mediated glucose disposal rates ($p = 0.036$). Within VFD subjects, relatively reduced mean maternal-infant proximity (greater distance between mother and infant) during VFD predicted relatively increased juvenile offspring sagittal abdominal diameter ($N=19$; $r = .53$; $p < .02$). The magnitude and direction of maternal cortisol response during VFD predicted juvenile offspring body mass; mothers who increased cortisol in response to VFD had heavier offspring whereas mothers who decreased cortisol to VFD had lighter offspring ($N = 17$; $r = .75$; $p = .0005$). Moreover, juvenile VFD offspring of mothers who increased cortisol showed greater plasma levels of the insulin by-product C-peptide in comparison to offspring of mothers who decreased cortisol ($N= 17$; $t = 3.07$; $p < .008$). Infant CSF CRF post-VFD was associated with reduced juvenile glucose utilization during the euglycemic clamp procedure ($N = 5$; $r = -.89$; $p = .045$).
Discussion: Early-life stress during a critical period of infant neurodevelopment, demonstrated to have induced activation of central CRF systems in both mothers and infants, was subsequently associated with appearance of insulin resistance in juvenile offspring. Moreover, the metabolic status of juvenile offspring could be predicted by maternal-infant attachment patterns and HPA axis response to VFD, with maternal cortisol increases, low maternal-infant proximity and high infant CSF CRF in response to VFD subsequently leading to the emergence of features of a nonhuman primate metabolic syndrome.

30. Early Postnatal Brain Structure and Development in Humans: Sexual Dimorphism and Cerebral Asymmetry are Present at Birth

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Background: The first year of life is the most dynamic and perhaps the most critical phase of postnatal brain development. Concurrent with the rapid pace of structural brain growth is an equally rapid development of a wide range of cognitive and motor functions. In spite of its importance for understanding brain structure-function in the developing brain, as well as the early origins of neurodevelopmental disorders such as schizophrenia and autism, our knowledge of human brain development in this crucial time period is minimal. While sexual dimorphisms and cerebral asymmetries are present in older children and adults, it is not known when in development they arise.
Methods: We have enrolled 134 control infants to date in a longitudinal study of prenatal and neonatal brain development in high risk children and controls. Neonates were scanned unsedated after birth on a Siemens head-only 3T scanner (Allegra, Siemens Medical System Inc., Erlangen, Germany). Three imaging sequences were used: a magnetization prepared rapid gradient echo (MP-RAGE) T1-weighted, a turbo spin echo (TSE), dual-echo (proton density and T2 weighted), and a single shot echo planar (EPI) diffusion tensor (DTI) sequence. Total scan time was approximately 15 minutes. To date we have obtained MRI scans on 84 neonates. Tissue segmentation, parcellation, and quantitative analysis of diffusion properties of white matter fiber tracts was accomplished using a novel automated approaches developed at UNC for neonatal MRIs.
Results: Analysis to date reveals that control males have significantly larger total gray matter volumes than females at birth ($p= 0.008$), even when controlling for intracranial volume ($p=0.02$). At birth, the left lateral ventricle is significantly larger than the right ($p=0.01$). There were no gender differences or laterality observed in the diffusion properties of the corpus callosum or corticospinal tract.
Discussion: These findings indicate that sexual dimorphism and asymmetry are present in the human brain at birth and therefore arises during prenatal brain development. Prior studies indicate that adult females have smaller overall gary matter volumes, though gray matter accounts for a larger percent of total brain volume in adult females compared to males. This pattern is not present at birth, suggesting that while sexual dimorphism is present at birth, there continues to be gender-specific trajectories of brain development in the postnatal period. While some gender differences in white matter diffusion properties have been described in adults, gender differences are not present at birth. The results of the ongoing study, including a more detailed analysis of brain parcellation will be presented.

31. Oxytocin Increases Social Cognition in Autism
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Background: Oxytocin dysfunction may contribute to the development of social deficits in autism, a core symptom domain and potential target for intervention. This study explored the relationship between increasing oxytocin levels and social information processing.
Methods: Oxytocin and placebo challenges were administered to fifteen adult subjects diagnosed with autism or Asperger disorder, and comprehension of affective speech (happy, indifferent, angry, and sad) in neutral content sentences was tested. The outcome measure (Comprehension of Affective Speech) was scored dichotomously and mixed regression analyses was used to model the change in comprehension scores over time.
Results: Subjects who received the oxytocin infusion first showed increased levels of retention in comprehension of affective speech when retested after a delay, whereas subjects who received placebo first showed lower levels of retention. The mean delay between infusions was 16.067 +/- 14.26 days. There was a significant three-way interaction of time X treatment X order for the dichotomus comprehension of affected speech (z=-2.134, p=0.033, estimate=-0.170). Subjects showed pretest to posttest improvement for 3 of the 4 treatment x order conditions (Oxytocin First, Placebo First, Oxytocin Second). For the Placebo Second condition, there was a slight drop in comprehension of affective speech from pretest to posttest (.958 to .898). This inconsistent pattern is most clearly driven by the finding that the second infusion placebo baseline scores were already high. Thus, subjects who received oxytocin first showed increased levels of retention in the task and did not show a tendency top revert to baseline when retested after a delay. In contrast, subjects who received placebo first did show a tendency to revert to baseline. The difference between the predicted pretest scores for subjects who received placebo second (0.958) and placebo first (0.712) is 0.246, which corresponds to a medium to large effect size (d) of 0.66.
Discussion: These results indicate that oxytocin may facilitate the retention of social information, and suggest a possible benefit of oxytocin in the treatment of social deficits in autism.

32. Individual Differences in Physiological Regulation and Early Development of African-American Infants Living in Poverty
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Sponsor: Travel Awardee, NIMH, 2005

Background: Individual differences in heart rate (HR) and heart period variability (HPV) may be related to a child's developing ability to control emotion, attention, and behavior. The goal of this research is to examine individual differences in resting cardiac measures within an understudied minority that is over-represented in subpopulations at high risk for mental illnesses (Surgeon General Report, 1999).
Methods: Participants were healthy African American infants whose mothers came from low-income environments and were recruited from the hospital nursery for a longitudinal study. Medical records, standardized questionnaires, behavioral observations and a diagnostic interview for depression were utilized to obtain information about the mother and child. Cardiac data was acquired from eighty neonates using standard electrode placement, equipment and software while the neonates were sleeping or resting quietly. During follow-up visits at 6 and 12 months, resting cardiac data was obtained in the laboratory. The physiology data reduction software identified R-waves in the ECG using an automated, multiple-pass, self-scaling algorithm. HPV was computed using the spectral method.
Results: Linear regression models revealed that significant correlates of HPV in neonates included sex of the infant (t=-2.07, p=.042), maternal psychological history of major depressive disorder (t=-2.24, p=.028), and feeding method (t=- 2.46, p=.016). At 6 and 12 months, stability of HR and HRV were examined. Girls continued to have a higher heart rate and lower heart period variability than boys. Infants of mothers with a history of major depressive disorder before birth, showed cardiac differences at 6 months, but not at 12 months.
Discussion: Further research is required to examine when these individual differences in HR and HPV are associated with behavioral and emotional problems in infancy. Identifying early patterns of physiological regulation that are associated with risk will be critical for developing interventions to prevent disabling psychiatric conditions.

33. Developmental Regulation of NCAM in Human Frontal Cortex
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Background: Neural cell adhesion molecule (NCAM) provides important regulation of cortical development. The 3 major isoforms of NCAM contribute to synaptic plasticity (180 kDa), axonal migration (140 kDa), and glial development (120 kDa). Furthermore, postmortem studies in schizophrenia have revealed altered expression of the NCAM extracellular domain (NCAM-EC, 105-115 kDa) in several brain regions including prefrontal cortex. To better understand the potential role of NCAM in the pathogenesis of schizophrenia and other neurodevelopmental disorders, expression of NCAM isoforms was studied in human prefrontal cortex from the fetal period through early adulthood.
Methods: Western blot was used to measure NCAM-180, -140, and -120 kDa isoforms, NCAM-EC, and NCAM intracellular domain (NCAM-IC) in postmortem prefrontal cortex (area 9/46) in 45 subjects (died from non-CNS causes, no known history of substance abuse or major psychiatric disorders) distributed evenly in age between gestational week 18 to 25 yrs. Subjects were batched into fetal, 0-1, 1-5, 6-10, 11-15, 16-20, and 21-25 yr age groups for statistical analysis.
Results: A significant effect of age emerged for the major isoforms of NCAM by ANOVA: NCAM-180 ($F=4.10$, $df=6, 38$, $p=0.003$), NCAM-140 ($F=9.87$, $df=6, 38$, $p<0.0001$), NCAM-120 ($F=11.21$, $df=6, 38$, $p<0.0001$). Using post hoc Tukey's, NCAM-180 was highest in fetal cortex, then decreased progressively into adulthood, but with a transient increase in the 11-15 yr period. NCAM-140 was highest during fetal and first postnatal year, then decreased into adulthood. NCAM-120 was lowest in fetal cortex, highest in first postnatal year, then stably expressed into adulthood. Data on NCAM-EC and NCAM-IC will also be presented.
Discussion: Each of the major NCAM isoforms is developmentally regulated in human prefrontal cortex. High NCAM-180 in fetal cortex is consistent with its established role in synaptic plasticity, given that the late fetal and early postnatal period is associated with synaptogenesis in human cortex. Intriguingly, the transient spike of NCAM-180 in the 11-15 yr group could indicate a role in regressive phenomena (incl. synaptic pruning) in the adolescent cortex. High fetal and early postnatal NCAM-140 suggests that axonal migration is active during this period. Low fetal NCAM-120 levels that spike during the 0-1 yr interval and remain high thereafter are consistent with the delayed onset of glial differentiation in cortex. Given the importance of synaptogenesis and axon growth during normal cortical development, a potential window of vulnerability may exist during which aberrant NCAM-mediated signaling could contribute to the pathogenesis of neurodevelopmental disorders such as schizophrenia. For example, recent evidence demonstrates that over-expression of NCAM-EC in transgenic mice produces abnormalities in GABAergic interneurons and behavior, consistent with multiple lines of evidence for disrupted cortical interneuron circuitry seen in schizophrenia. The pathogenesis of schizophrenia has been associated with

environmental insults including early life exposure to infection, trauma, and hypoxia/ischemia, factors that could potentially impact the developmental expression patterns of NCAM. Further study of the potential involvement of NCAM in neurodevelopmental disorders is warranted.

34. Gender-Specific Longitudinal Changes in Cortical Thickness in Children and Adolescents

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Sponsor: Jay Giedd

Background: The cortex undergoes complex remodeling during childhood and adolescence. Little is known about gender effects on this process, although post-mortem studies have found gender-based differences in cortical cellular structure, and longitudinal MRI studies have shown robust gender dimorphism in developmental trajectories of regional brain gray and white matter. Existing studies of gender effects on cortical measures have been cross-sectional and performed primarily in adult populations. In this study we provide the first large-scale longitudinal study of gender effects on cortical development in childhood and adolescence, a time of emerging differences in cognition and behavior.
Methods: MRI scans were obtained longitudinally from 511 healthy children (287 male, 224 females, age range 4-25); up to 6 scans were acquired from each child at 2 year intervals for a total of 909 scans. Scans were registered into standardized stereotaxic space using a linear transformation, corrected for non-uniformity artifacts, and segmented into white matter, gray matter, cerebrospinal fluid and background using an advanced neural net classifier. The white and gray matter surfaces were then fitted using deformable models resulting in two surfaces with 81920 polygons each. The differences between these surface models was used to determine cortical thickness. Statistical analysis: Mixed model regression was used to examine group differences in cortical thickness developmental trajectories. The resulting statistical maps were thresholded to control for multiple comparisons using the false discovery rate (FDR) procedure with q= 0.05.
Results: Average cortical thickness was not different between males and females at the youngest (age 8, female 4.17mm, male 4.22, p=.13) and oldest ages (age 18, female 3.96, male 4.0, p= .28), but was significantly greater in males between ages 10-14 (age 12, female 4.14, male 4.21, p=.04).Specific regions showed more pronounced age-related differences, including the superior temporal gyrus, dorsolateral prefrontal cortex, middle occipital gyrus, and parietal cortex, with a strong lateralization effect for thicker cortex in males in the left hemisphere. Longitudinal trajectories show that whereas cortical thickness in girls is decreasing in most regions during the ages studied, boys continue to have an increase in cortical thickness until between ages 9-12 depending on region and then begin to decrease. Gender differences are most pronounced at age 12-14, when males show broad regions of thicker cortex across both hemispheres, and then gradually diminish. At the oldest timepoint studied (age 18), areas with thicker cortex in males are primarily lateralized to the left hemisphere, including regions in occiput, central sulcus, and temporal pole. Females show one thicker region on the inferior surface of the right temporal lobe. In addition to later peak thickness than females, males had significantly more rapid rates of increase in regions within the bilateral frontal and occipital gyri, left central sulcus and medial parietal cortex, and right orbitofrontal cortex. Females showed steeper rates of increase in the right superior frontal gyrus.
Discussion: Cortical thickness develops along different trajectories in males and females during childhood and adolescence. Significant gender differences appear during the ages associated with puberty which are diminished or no longer detectable by adulthood. Specific regions such as the superior temporal gyrus show more pronounced effects, consistent with gender-related cognitive differences in areas such as verbal ability. Contrasting trajectories may have implications for gender differences in normal and abnormal development.

35. Behavioral and Electrophysiological Characterization of the Role of MeCP2 in the Brain

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Sponsor: Eric Nestler

Background: Mutations in the methyl-CpG binding protein 2 (MECP2) gene cause Rett Syndrome (RTT), a neurodevelopmental disorder that is accompanied by a broad array of behavioral phenotypes mainly affecting females. MeCP2 is a transcriptional repressor that is widely expressed in all tissues although the behavioral phenotypes observed have a strong neurological basis.
Methods: To investigate whether the postnatal loss of MeCP2 in the forebrain is sufficient to produce the behavioral phenotypes observed in RTT, we have generated conditional MeCP2 knockout mice. We have also examined the potential role of MeCP2 in the brain by studying the elementary properties of synaptic transmission between neurons cultured from hippocampi of MeCP2 knockout and littermate control mice.
Results: The conditional knockout mice display behavioral abnormalities similar to RTT phenotypes including forelimb clasping, impaired motor coordination, increased anxiety and abnormal social behavior with other mice. These knockout mice, however, have normal locomotor activity and unimpaired context-dependent fear conditioning suggesting that the behavioral deficits observed are due to loss of MeCP2 function in postnatal forebrain and not the result of generalized global deficits. Using electrophysiological recordings, we found a specific decrease in the frequency of spontaneous excitatory synaptic transmission (mEPSC) in neurons lacking MeCP2. In the absence of a reduction in the number of recycling synaptic vesicles and the number of synapses in MeCP2 knockout cultures, we surmised that this decrease in mEPSC is due to impairments in the rate of synaptic vesicle trafficking. Accordingly, we found that in the MeCP2 knockout cultures synaptic responses to 10 Hz train stimulation showed a faster depression and slower recovery after depression. To explore whether these functional effects can be attributed to MeCP2 role as a transcriptional silencer, we compared the defects in MeCP2 knockout cultures to alterations in spontaneous transmission seen after 24-hour treatment with drugs that impair DNA methylation and histone deacetylation. Treatment with these compounds induced a two-fold decrease in mEPSC frequency in control cultures but this decrease was occluded in MeCP2-deficient neurons.
Discussion: We show that the loss of function of MeCP2 in the forebrain is sufficient to recapitulate features of Rett Syndrome, an important first step in elucidating the neural circuitry that may be involved in mediating the behavioral phenotypes of the disease, including autistic-like behavior. We also show that MeCP2 plays an important role in the regulation of synaptic transmission through its action as a transcriptional repressor. Taken together, these data start to elucidate the role of MeCP2 in the brain.

36. A Prospective, Open-Label Study of Atomoxetine for ADHD Symptoms Associated with Higher-Functioning Pervasive Developmental Disorders

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Background: There are currently no drugs approved by the Food and Drug Administration specifically for the treatment of autism and per-

vasive developmental disorders (PDDs). One problem area that has been especially challenging has been the effective treatment of hyperactivity occurring in autism. Stimulant drugs are less efficacious and more poorly tolerated in autism when compared to their use in ADHD. Atomoxetine is a selective norepinephrine reuptake inhibitor approved for the treatment of ADHD in children. Because of the above limitations of available drugs in the treatment of hyperactive children with PDD, our group conducted a prospective, open-label pilot study of atomoxetine targeted towards hyperactivity in the context of PDD.
Methods: Children with PDDs and nonverbal IQ of > 70 received atomoxetine (target dose 1.2-1.4 mg/kg/day) during the course of an 8-week, open-label prospective study. Standardized assessments of efficacy and tolerability were collected at regular intervals during the trial.
Results: Sixteen children and adolescents (mean age 7.7 + 2.2 years, age range 6-14 years) with autistic disorder (n = 7), Aspergers disorder (n = 7), or PDD not otherwise specified (n = 2) received atomoxetine (mean dose 1.2 + 0.3 mg/kg/day). Twelve participants (75%) were rated as much or very much improved on the Clinical Global Impressions-Improvement scale. The most significant improvement was seen in the area of ADHD symptoms as measured by the SNAP-IV and Aberrant Behavior Checklist (effect size = 1.0-1.9). Improvements of lesser magnitude (effect size = 0.4-1.1) were seen in irritability, social withdrawal, stereotypy, and repetitive speech. Atomoxetine was well tolerated with the exception of 2 participants (13 %) who stopped medication due to irritability.
Discussion: Placebo-controlled studies are needed in order to make a definitive statement about the efficacy of atomoxetine for ADHD symptoms in PDDs.

37. Relationship Between Behavior and Neurochemical Changes in Rhesus Macaques During a Separation Paradigm
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Sponsor: J. Dee Higley

Background: Human research has demonstrated a strong link between adverse experiences during childhood and later development of various neuropsychiatric disorders, including substance abuse disorders. Rhesus macaques raised without adults in a group of peers (peer-only rearing, PR) rather than with their mother (mother-reared, MR) have been proposed as a model to study the consequences of early life stress exposure. PR animals show altered monoamine metabolites and stress hormones that persist later in life. These environmental and biochemical differences are associated with individual differences in temperament and behavior.
Methods: This study used a factor analysis to relate a range of behaviors, produced by rhesus monkeys during a social separation, to biochemical measures of cerebrospinal fluid metabolites and of hormonal blood levels, and to compare differences between MR and PR animals.
Results: Our results show that during the acute phase of separation, cortisol and distress-calling were positively correlated in MR animals but not in PR animals. Unlike PR animals, most behavioral factors of MR animals were associated with endocrine measures. For the PR, but not the MR subjects, high monoamine concentrations were correlated with depression/despair.
Discussion: These findings suggest differential rearing affects both the risk for depression and its underlying biochemical systems. All research was carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health.

38. Dysfunction of Critical Regulators of Serotonergic Signaling Confers Autism Susceptibility
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Sponsor: Randy Blakely

Background: Autism is a neuropsychiatric and developmental disorder affiliated with deficiencies in language and social reciprocity, and patterns of obsessive-compulsive behaviors. Autism has an estimated prevalence of ~1 in 500 individuals, with disease-expression biased toward males. Twin and family studies show that autism etiology is substantially genetic in nature and arguably the highest for psychiatric conditions. Hyperserotonemia, or the heritable elevation of circulating serotonin (5-HT) that is observed ~25-30% of autistic subjects, has fueled the "serotonin hypothesis": that dysfunction or dysregulation of serotonergic systems during prenatal and/or early childhood development is a key element in autism etiology.
Methods: Linkage analyses were performed on an overall sample of 341 multiplex (267 Autism Genetics Resource Exchange, 74 Vanderbilt) or 202 male-only and 139 female-containing multiplex families. Screening for variants at SLC6A4 was performed in a "linked" sample of 120 families with allele-sharing at 17q11.2. Functional studies of SERT were conducted in natively-expressing lymphoblastoid cell lines from mutation carriers. Family-based association studies at ITGB3 and HTR1A were performed using a two-stage statistical design in a total sample of 659 combined multiplex and trio families.
Results: We report genetic and functional data regarding three molecules exhibiting key roles in 5-HT biology: the 5-HT transporter (SERT), integrin β3, and the 5-HT1A receptor. We have identified an allelic heterogeneity framework for autism risk involving the SERT locus (SLC6A4). Following detection of highly-significant linkage to 17q11.2, restricted to families with male subjects (HLOD=8), we identified multiple novel coding variants at highly-conserved residues and numerous non-coding variants clustered predominantly around the promoter and 5′ end of the gene. One previously known coding variant (Gly56Ala) exhibits (1) deviation from Hardy-Weinberg equilibrium, (2) a significant association with disease-expression in males compared with females, and (3) elevated basal transporter activity and insensitivity to regulation via PKG and p38 MAP kinase signaling pathways. Another mutation (Ile425Leu) acts on the identical nucleotide and amino acid residue affected (Ile425Val) in two pedigrees with Asperger syndrome and obsessive-compulsive disorder (OCD). The coding mutations in SERT are significantly associated with increased severity in rigid-compulsive behaviors in the autism families. We have also found that a functional coding variant of the 17q21.3-encoded integrin β3 locus (ITGB3), previously identified as a male quantitative trait locus (QTL) for circulating 5-HT levels, is significantly associated with autism in a sample of 659 autism families ($P<0.002$). Thus, both SLC6A4 and ITGB3 contribute to the extraordinary male-biased genetic effects observed on proximal 17q. Finally, we find that the HTR1A locus shows significant linkage (HLOD=2.8) and association ($P<0.008$) to autism, preferentially in males, at a functional promoter polymorphism, also associated with depression and other phenotypes. Here, the associated allele was previously demonstrated to exhibit a partial loss of transcriptional repression.
Discussion: Together, these data reveal a striking pattern of functional variation at loci encoding critical regulators of serotonergic function as important male-biased genetic risk factors in autism and related disorders. Functional studies of the 56Ala and 425Val-encoded SERT suggests that elevated basal transporter activity may be a fundamentally-important disease mechanism in autism and obsessive-compulsive disorder.

39. Cortical and Amygdala Overgrowth in Autism Associated With 5-HTTLPR

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Sponsor: Raymond Crowe

Background: Individuals with autism have heavier post mortem brain weight, greater head circumference, and increased MRI volumes of various brain structures, compared to normal controls. We recently confirmed these data, finding enlargement of the cerebral cortex and amygdala in very young autistic children. Autism is also characterized by neurochemical abnormalities, particularly in the serotonin system. 5-HTTLPR potentially unites these findings, having been independently associated with autism, brain structure and activity, and SLC6A4 expression. In this study we tested, therefore, whether 5-HTTLPR was associated with volumes of the cerebral cortex and the amygdala in our sample of children with autism.
Methods: Subjects included 29 Caucasian males with autism who had received brain MRIs and provided DNA; their age was 2.71 ± 0.30 years. Subjects were scanned on a 1.5 Tesla MRI scanner. Automated tissue segmentation generated gray and white matter volumes for the cerebral cortex and the frontal, temporal, and combined parietal-occipital lobes; the amygdala was manually traced. 5-HTTLPR was genotyped using a standard protocol. ANCOVAs were used to test genotype-volume relationships. ROI volumes were dependent, genotype was independent, and covariates included age and head circumference. For significant genotype F tests, we calculated omega-squared (ω^2) to estimate the variance in ROI volume accounted for by genotype. Both additive and dominant genotype models were tested.
Results: The additive genotype effect was significant for total cortical volume ($F = 3.29$, $p = 0.05$). A separate test for cortical gray matter was significant ($F = 4.41$, $p = 0.02$), but for cortical white was not. Tests of the lobe-based subregions were significant for frontal ($F = 5.17$, $p = 0.01$) and temporal gray matter volumes ($F = 3.58$, $p = 0.04$). For these ROIs, genotype ω^2 ranged from 5-9%. While these tests were significant, the least squares means pattern suggested a recessive effect of the short (S) allele to produce larger volumes or, conversely, a dominant effect of the long (L) allele to produce smaller volumes. In line with this, ANCOVAs comparing ROI volumes between S/S homozygotes and L carriers were substantially stronger for cortex ($F = 6.82$, $p = 0.02$), cortical gray ($F = 8.64$, $p = 0.007$), and all subregion gray matter volumes (frontal, $F = 7.88$, $p = 0.01$; temporal, $F = 4.94$, $p = 0.04$; parietal-occipital, $F = 4.77$, $p = 0.04$); ω^2 values for these ROIs ranged from 3-8%. The ANCOVAs for amygdala also indicated an S/S effect. Testing S/S homozygotes against L carriers for total amygdala volume was significant ($F = 4.83$, $p = 0.04$), while an additive model was not. Subsequent tests showed that the effect was stronger on the left ($F = 5.90$, $p = 0.02$) than on the right (n.s), and genotype ω^2 was substantial: 0.10 for total and 0.13 for left amygdala.
Discussion: We therefore find that variation in the 5-HTTLPR polymorphism is associated with the overgrowth in the cortex and amygdala that is characteristic of autism. These findings appear to have specificity for gray matter, given that genotype effects were not significant for cortical white matter and the amygdala comprises primarily gray matter nuclei. The findings also highlight the necessity of examining very young affected children, as the relative amygdala enlargement has been shown to be more pronounced early in the course of autism and to diminish with age. These data thus describe an independent biological predictor of developmental brain volume and they demonstrate the potential utility of brain endophenotypes in the search for autism susceptibility genes.

40. The Sp4 Transcription Factor Gene is Critical for Postnatal Development of Dentate Gyrus in Mice and Associated with Bipolar Disorder in Humans

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Sponsor: Mark Geyer

Background: The hippocampus plays central roles in the formation of contextual memory and sensorimotor gating, a putative endophenotype for schizophrenia and related psychiatric disorders. Reduced hippocampal volume has recently been identified as an important susceptibility factor for schizophrenia, bipolar disorder, and major depression. Nevertheless, the underlying molecular pathways that link hippocampal abnormalities with sensorimotor gating deficits remain unclear. The Sp4 gene, a member of the Sp1 family, codes for a transcription factor recognizing the same GC-rich binding sequence as Sp1, but is predominantly expressed in the nervous system. Previously, we reported that hypomorphic Sp4 mice, in which the Sp4 gene expression is partially reduced, display deficits in memory (fear conditioning) and sensorimotor gating (prepulse inhibition) associated with hippocampal vacuolization. The Sp4 mediated genetic pathway is therefore critical for the functional integrity of the adult hippocampus. Nevertheless, it is unclear whether the Sp4 gene is important for the development of the hippocampus, although the expression of Sp4 gene is abundant during the development.In humans, genome-wide linkage analysis identified a susceptibility locus, near the marker D7S1802 (700 kb away from SP4 gene), for bipolar disorder on human chromosome 7p15 in the families obtained from the NIMH Genetics Initiative for Bipolar Disorder first-wave pedigree collection.
Methods: Here, we analyzed the postnatal development of hippocampus in the complete absence of the Sp4 gene.To further examine whether human SP4 is a risk gene for bipolar disorder, we conducted association studies with bipolar disorder, most of the samples coming from the NIMH Genetics Initiative for Bipolar Disorder first-, second-, third-, and fourth-wave pedigree collections. Nine SNPs encompassing human SP4 genomic locus were selected for initial association studies.
Results: As expected, the hippocampal vacuolization observed in the hypomorphic Sp4 mice was verified in the Sp4 null mutant mice. In contrast to the Sp4 hypomorphic mice, the Sp4 null mutant adult mice displayed fewer dentate granule cells, and the reduced number of dentate granule cells appeared to result from a disorganization of the proliferative zone of the dentate granule layer during postnatal development. Despite the impaired postnatal development, the dentate granule cells displayed normal expression of Prox1 gene, a marker for the granule cell differentiation. In human studies, analysis of individual SNPs by ETDT revealed that the single SNP Marker 7 was significantly associated with bipolar disorder with a p value of 0.0008. This single SNP haplotype displays a transmission:non-transmission ratio of 251:181 in the triad families. In addition, we identified a three-SNP haplotype (rs40245-rs2282888-hCV2625432) in the middle of the human SP4 gene that displayed a significant association with bipolar disorder.
Discussion: Taken together, the data from Sp4 hypomorphic and null mutant mice suggested that the level of Sp4 expression is critical for hippocampal neurogenesis and function. Human genetic studies suggested that the Sp4 gene could be a susceptibility gene for bipolar disorder. Thus, further studies of Sp4 transgenic mice may provide novel insights for our understanding of the relationships among hippocampal development, sensorimotor gating, and bipolar disorder. All animal studies were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals. This work was supported by NARSAD, the Veteran's Administration VISN 22 MIRECC, and NIH grant MH59567.

41. Genetic Correlates of Cortico-Limbic Activity and Connectivity in Major Depression

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Background: Genotypic variations of a common polymorphism in the promoter region of the serotonin transporter (5-HTT) gene SLC6A4 (5-HTTLPR) have been reported to be associated with differential vulnerability to depression. Individuals homozygous for the short (S) allele (population frequency 20%) and S/L genotypes (population frequency = 40 %) have reduced 5-HTT sites compared to individuals homozygous for the long allele (L/L) (population frequency = 40%) who have higher expression of 5-HTT (Lotrich et al 2001). Recently, a new low expressing variant of the long polymorphism of 5-HTTLPR (LG) has been reported (Hu et al 2005) which has a frequency of 10% in the general population. Therefore, a more appropriate classification of 5-HTTLPR polymorphisms is to divide them into groups of high expressing (HE, LA/LA; frequency 25%), medium expressing (ME, LA/S and LA/LG; frequency: 50%) and low expressing (LE, S/S, LG/LG and LG/S; frequency 25%) genotypes. Recent studies, in healthy subjects, have reported that 5-HTTLPR variation is associated with differences in amygdala activation in response to negative stimuli as measured with fMRI (Hariri et al 2005; Hariri et al 2002a). Furthermore, it has been reported that healthy subjects with one or two S alleles have decreased connectivity (as measured by co-activation of these brain regions in response to a facial emotion recognition task) between the ventral anterior cingulate cortex (vACC) and the amygdala (Heinz et al 2005; Pezawas et al 2005). Therefore, limbic activity and connectivity with the vACC may serve as plausible endophenotypes for depression (Hasler et al 2004). In this study, we investigated the relationship between 5-HTTLPR genotypes and corticolimbic activity and connectivity in unmedicated depressed patients.
Methods: Corticolimbic activation was measured as percent signal change in response to passive exposure to negative versus neutral pictures. Cortico-limbic connectivity was measured using a novel technique - correlation of resting state low frequency BOLD fluctuations (Anand et al 2005) between the vACC and amygdala. Data has been collected from 10 unmedicated depressed patients from two different studies on 1.5 T (5 patients) and 3.0 T (5 patients). Blood was genotyped for 5-HTTLPR using previously described methods (Hu et al 2005) and patients were divided into 3 genotypic groups - HE, ME and LE.
Results: Genotype distribution for the 10 patients was: 2 HE, 6 ME and 2 LE. Patients with the HE genotype had less (-0.02 +/- 0.17) of an increase in left amygdala activation in response to negative versus neutral stimuli while ME (0.19 +/- 0.26) and LE (0.13 +/- 0.0) genotypes had similar activation. Conversely the HE genotype was associated with the highest vACC-left AMYG (define AMYG) connectivity (11.25 +/- 3.0) while the ME (1.0 +/- 6.0) and LE (4.0 +/- 2.5) genotypes had lower cortico-limbic connectivities.
Discussion: Preliminary data with a small number of patients is consistent with the hypothesis that depressed patients with the 5-HTTLPR HE genotype may have higher cortico-limbic connectivity and less amygdala activation in response to negative stimuli. Data from more patients is presently being collected. Supported by an Independent Investigator Grant (AA) from National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD) and Indiana University Genomics Initiative (INGEN) fund.

42. Comparison of the Effects of Tolcapone and Entacapone on Cognition and fMRI in Normal Volunteers

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Background: Neuroimaging studies have shown that variations in DA flux in PFC affects the efficiency or signal to noise of the physiologic response during the N-back working memory (WM) task, i.e. the degree of cortical activation. Moreover, recent evidence suggests that catechol-O-methyl transferase (COMT) may play a unique role in regulating DA flux in the PFC. Early studies showed that Tolcapone, a COMT inhibitor which penetrates the blood brain barrier, improves working memory and PFC efficiency as measured by BOLD fMRI in normal volunteers. Since Tolcapone also exerts a peripheral effect on dopamine metabolism, it is not yet clear whether the effect of Tolcapone on cognition and PFC efficiency is centrally mediated.
Methods: We have performed in normal volunteers a double blind, parallel study against placebo to assess the effect of Tolcapone (n=47 for neuropsychological testing [NPT] and n=34 for fMRI) and Entacapone (n=16 for NPT and fMRI), a COMT inhibitor that does not readily crosses the BBB, on neuropsychological tasks and on BOLD fMRIs while performing a PFC-dependent task, the N-back WM task with increasing levels of task difficulty.
Results: Analysis of variance showed that Tolcapone enhances prefrontal efficiency on fMRI during 2-Back and 3-Back working memory tasks. Behavioral testing also indicated the presence of a main effect of Tolcapone (on Trail Making, n-Back RT, verbal episodic memory and attentional set shifting). On the contrary, Entacapone seems to display a paucity of effect with no significant changes observed in a preliminary analysis of variance for both the neuropsychological and Bold fMRI data.
Discussion: These results possibly confirm the hypothesis that Tolcapone exerts its effect of neurocognition as well as on PFC efficiency through a centrally mediated mechanism.

43. Altered Serotonin Transporter Binding After Recovery from Anorexia Nervosa Using PET and [11C]McN5652

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Background: Alteration of serotonin (5-HT) circuits are thought to contribute to disturbances of feeding, mood, and impulse control in eating disorders. While several lines of evidence implicate disturbances of the 5-HT transporter (5-HTT), this is the first study to use positron emission tomography (PET) and [11C]McN5652 to determine whether 5-HTT alterations persist after recovery from anorexia nervosa (AN).
Methods: To avoid confounding effects of altered nutrition, positron emission tomography (PET) with [11C]McN5652 was used to assess regional 5-HTT binding potential (BP) in 14 women recovered from AN [7 women recovered from bulimia-type AN (REC BAN) and 7 women recovered from restricting type AN (REC RAN)] and 10 healthy control women (CW). A 2-compartment, 3-parameter tracer kinetic model was used to determine [11C]McN5652 distribution volume (DV) in each region of interest (ROI) and specific 5-HTT binding was assessed using the binding potential (BP) measure [BP = (DVROI/DVCER) - 1].
Results: Compared to CW, the REC BAN had decreased [11C]McN5652 BP in the dorsal raphe (1.10 + 0.26 vs 0.70 + 0.35; p = .02) and a trend (.07) towards decreased [11C]McN5652 BP in the

mesial temporal cortex (0.37 + 0.12 vs 0.26 + 0.13). Compared to CW, REC RAN had a trend (.08) towards elevated (1.29 + 0.14, p = .08) [11C]McN5652 BP in the dorsal raphe. Compared to REC BAN, REC RAN had elevated [11C]McN5652 BP in the dorsal raphe (.04), mesial temporal cortex (.02) and thalamus (.002).
Discussion: These preliminary data raise the intriguing possibility that reduced 5-HTT binding may be associated with BAN and elevated 5-HTT binding associated with RAN. Extremes of 5-HTT binding between subgroups of anorexia nervosa might explain differences in response to SSRIs since there is limited evidence that BANs respond poorly to fluoxetine. These data contribute to a growing literature showing a disturbance of 5-HT neuronal function persisting after normalization of weight and nutritional status in people who have had AN.

44. CBT vs Sertraline in OCD: Effects on Brain Regional Serotonin Synthesis Index

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Background: CBT and SSRI's are both effective treatments in Obsessive-Compulsive Disorder. Although a favorable treatment response to either of these two modalities has been reportedly associated with common regional brain metabolic changes, as indexed by the PET/FDG method, little is known about their corresponding neurochemical correlates. Here we have investigated one aspect of serotonin metabolism, regional 5HT synthesis index, using the 11C-AMT /PET method, prior and following a 12-week treatment with either of Sertraline or CBT, in OCD.
Methods: 16 un-medicated OCD patients were randomly assigned to a 12-week treatment with either CBT or Sertraline alone. CBT consisted of cognitive therapy with prolonged exposure and response prevention administered twice weekly in a specialized clinic. All subjects were medication-free for a minimum of three weeks and tested negative on a urine tox screen for drugs of abuse. OC symptoms (YBOCS), mood (BDI) and Go-No-Go performances were assessed prior to, during and at completion of the 12-weeks treatment, together with measurements of the regional brain uptake and trapping of α-[11C]-alpha-methyl-tryptophan (α-[11C]-MTrp) (K*). All subjects completed two 60-min dynamic PET studies, using an ECAT-HR+ scanner and an MRI examination for PET-MRI co-registration. K* was calculated by means of the Patlak plot method, using venous/sinus input function and time activity curves, extracted from dynamic PET. Comparisons of treatment-related changes in regional normalized K* values, were carried out using a brain-wide voxel-by-voxel approach using Statistical Parametric Mapping (SPM99). Statistically significant regional differences were identified on the basis of an extent threshold of 40 voxels, with a peak threshold of p=0.002 uncorrected. SPM was also applied to identify regions where baseline regional α-MTrp K* predicted outcome and treatment-related changes across and within each treatment modality, correlated with clinical change.
Results: 8 patients were treated with CBT (3 F / 5 M; age = 34.8 ± 9.1 y) and 8 with Sertraline (2 F / 6 M; age = 33.4 ± 8.5 y). After 12 weeks of treatment, both treatments proved equally effective, with a mean decline in OC symptoms severity, as indexed by the change of YBOCS total score of 30.9 ± 33 %. 5/8 and 4/8 were deemed responders, respectively to Sertraline and CBT. Both α-[11C]-MTrp -PET were obtained in all patients, except in one (CBT). In the CBT group, α-[11C]-MTrp trapping increased in the pons, the right cerebellum and the left inferior parietal lobule (BA 40) and decreased in the left hippocampus (BA 30), the left middle temporal gyrus (BA 22) and the left precuneus (BA 7/19), respectively. Chronic administration of Sertraline had little or no effect on regional α-[11C]-MTrp trapping, except for a decrease in the right medial frontal gyrus (BA 10). In both treatment groups, a higher baseline α-[11C]-MTrp trapping in the Pons (Raphe Nucleus), correlated with clinical improvement. Clinical improvement also correlated with a decrease in α-[11C]-MTrp trapping in the left middle temporal gyrus (BA 22/39) after CBT and an increase in the right precuneus (BA 7) after Sertraline, respectively.
Discussion: Time-related changes in regional α-[11C]-MTrp trapping in response to either Sertraline or CBT, as a function of treatment in OCD, were more marked during CBT.

45. The Neural Correlates of Social Decision-Making: An Event-Related fMRI Study

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Sponsor: John Holaday

Background: The ability to flexibly alter prepotent emotional responses across a dynamic range of contexts is fundamental to the successful navigation of highly complex social landscapes. This faculty, a form of social decision-making, lies at the crossroads of cognitive control and emotion regulation. Recent evidence suggests that a neural network comprised, in part, of anterior cingulate and prefrontal cortex subserves both affect regulation and attentional control. However, the mechanisms underlying the regulation of affectively mediated social behavior have yet to be elucidated. We employed a novel social decision making task to examine neural activations associated with modifying prepotent responses to socially relevant emotional stimuli.
Methods: We studied ten healthy subjects (six female, four male) using 3T-fMRI. Subjects were presented with a series of facial expressions (fearful, happy, or neutral) from the NimStim/Macarthur faces set, on either a green, red, or blue background field. We instructed subjects to indicate whether or not they would approach or avoid the person presented on the screen by pressing the left or right button on a fiber-optic button box. We asked subjects to approach or avoid the face as they would normally if it was presented on a green background (congruent condition), to go against their natural response inclination if the face was presented on a red background (incongruent condition), and to indicate the gender of the face when on a blue background. The appropriate buttons for approach and avoid were kept constant across conditions.
Results: Regulating approach and avoidance invokes a distributed network of structures previously implicated in behavioral inhibition and cognitive control. Approaching fearful faces engaged anterior cingulate, posterior cingulate, lateral prefrontal cortex, thalamus, dorsal and ventral striatum, and insula. Avoiding happy faces activated a similar network, with some notable differences. The fusiform and parahippocampal gyri were deactivated in both conditions. Additionally, we observed an inverse correlation between dorsal cingulate and amygdala activation in the incongruent fearful (approach fearful faces) condition.
Discussion: These results demonstrate that successful social decision-making requires the coordinated activation of structures that are known to play a key role in inhibition, attention allocation, conflict monitoring and interference resolution. The present data also suggest that regulating prepotent affective responses to social stimuli involves the top-down suppression of regions that are responsive to affective facial expressions. We believe that this paradigm will be useful for investigating individual differences in social emotion regulation, and could also benefit neuroimaging investigations of social deficits in major depressive disorder, social phobia, autism and Williams syndrome.

46. Role of Medial Prefrontal Cortex in Intention Deficit in Schizophrenia

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Sponsor: Ronald Kuczenski

Background: In schizophrenia, an intention disorder is revealed in many patients in the form of reduced spontaneous language and reduced task initiation. Likewise, the finding of reduced output during verbal fluency tasks is one of the most consistently reported neurocognitive deficits in schizophrenia. The intention deficit that underlies poor language and task initiation interferes with successful social and occupational functioning, as well as optimal utilization of healthcare services. The purpose of this study was to determine if this intention deficit is associated with disordered medial prefrontal function in the pre-supplementary motor area (pre-SMA), a region known to be consistently active during healthy word production performance, and during other cognitive tasks that place a heavy demand on internally mediated initiation.
Methods: An event-related overt word fluency paradigm and functional magnetic resonance imaging (fMRI) were used to investigate medial prefrontal function. Data was collected on 5 patients and 4 controls. Single word generation to semantic categories alternated with single word repetition and rest. Motion correction was applied after which time series analysis was performed using a deconvolution algorithm available through AFNI software. To generate a region of interest in medial prefrontal cortex, a one-sample t-test was used to identify brain regions in which the area under the curve (AUC) of the hemodynamic response (HDR) to generation trials was significantly different than zero across the groups. A functional region of interest was present in the pre-SMA. Averaged hemodynamic responses within this functional ROI were compared between groups.
Results: Relative to word repetition and rest, the semantic word generation task led to robust medial prefrontal activity in the pre-supplementary motor area for healthy comparison patients. In contrast, patients demonstrated significantly reduced or absent activity in this region despite behavioral performance equivalent to the healthy comparison group. Thus, a significant difference was observed between the averaged hemodynamic response in the pre-SMA between patients and controls.
Discussion: Preliminary findings are consistent to suggest that the pre-SMA region functions abnormally in chronic schizophrenia patients during a word production task. This likely relates to a more general deficit in intentional aspects of cognition. The intentional deficit has been linked to social skills deficits in this population. In conclusion, the pre-SMA region appears to be an excellent candidate as an outcome measure in pharmacological and psychosocial treatments that target the debilitating intentional disorder observed in many chronic schizophrenia patients.

47. Amygdala Hyperactivity to Angry Faces in Patients with Intermittent Explosive Disorder

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Background: Patients with intermittent explosive disorder (IED), characterized by impulsive aggression, exhibit affective dysregulation, lack of anger control, and impaired recognition of negative emotions in facial expressions. This social-emotional phenotype resembles the affective and behavioral patterns observed in humans with amygdala and orbitofrontal (OFC) lesions. However, little is known about the functional neuroanatomy these deficits in patients with IED, or about the neural mechanisms of human aggression.
Methods: The present study employed BOLD-sensitive whole-brain functional magnetic resonance imaging at 3Tesla (reverse spiral: TR=2s; TE=25ms) to examine the neural correlates of social-emotional processing. Ten patients with IED (5 females; age 34.3 ±7.3 years) were studied along with 10 healthy controls (HC) matched on gender, age, and socio-economic status. Subjects performed a gender identification task while viewing alternating 20-sec blocks of Ekman Faces expressing discrete emotions (anger, fear, disgust, happy, sad, surprise, neutral), interleaved with 20-sec blocks of blank screens. Imaging data were analyzed with a standard, random effects model ($p<0.05$, SVC) using statistical parametric mapping software (SPM2). Estimates of activation (e.g., BOLD response) were extracted from a priori atlas-based regions of interest (e.g., amygdala, OFC).
Results: Patients with IED had exaggerated activation of the left amygdala ([-14, -8, -18], Z=2.78) and OFC ([-12, 64, -6]; Z=2.60) in response to faces expressing harsh emotions (anger, fear, and disgust), relative to healthy controls. Follow-up voxel-wise analyses revealed that the amygdala hyperactivity was driven predominantly by faces of anger ([-22, 0, -26], Z=3.06), which was confirmed by extraction of BOLD parameter estimates of activation extracted from a 10mm atlas-derived amygdala ROI centered at [-20, -4, -20] showing a significant group-difference to anger (IED: 0.32 ± 0.19 vs. HC: 0.05 ± 0.22; t=2.93, df=18, $p < 0.01$, 2-tailed), but not to other emotional expressions.
Discussion: The results suggest that amygdala dysfunction in patients with IED is specifically linked to faces of anger. More generally, these preliminary findings suggest that altered responses in the amygdala and OFC, regions important for social cognition, threat perception, and emotion/anger regulation, may contribute to the deficits in social-emotional processing observed in impulsive aggression.

48. Prefrontal Neurochemical Abnormalities in Adolescent Bipolar Disorder

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Background: Recent findings suggest that adolescents with bipolar disorder exhibit abnormalities in ventral prefrontal cortical development. Indeed, the results of magnetic resonance spectroscopy studies suggest that compared with healthy controls, bipolar youth have increased anterior cingulate myo-inositol (mI) levels and elevated ventral prefrontal glx (glutamate/glutamine), indicating abnormalities in putative biomarkers of second messenger and cell membrane metabolism and neuronal excitation, respectively. However, most of the patients in these studies were treated with a variety of medications and were in variable mood states making it difficult to interpret whether the neurochemical alterations were due to medication effects or an acute mood episode, or were core features of the underlying illness. The aim of our study was to examine neurochemical differences in glx and mI in prefrontal cortical regions among unmedicated bipolar adolescents with a mixed episode, unmedicated bipolar adolescents with a depressive episode, and healthy adolescents.
Methods: Unmedicated adolescents (ages 12-18 years) hospitalized for a mixed (N=18) or depressive (N=31) episode of bipolar I disorder were recruited. Demographically matched control adolescents without a psychiatric disorder (n=10) were also recruited. Three single voxels (8cc) were positioned from the sagittal T1 weighted series each based upon anatomical landmarks for the left and right ventral prefrontal cortex (VPFC) and anterior cingulate (ACC). Spectra were acquired using the point resolved spectroscopy (PRESS) sequence with the following parameters: TE=35 msec and TR=5 sec with 64 averages. Each of the spectral areas associated with mI and glx were quantified using the LC Model program. Gray and white matter and cerebral spinal fluid contribution to voxel volumes were determined and concentrations of metabolites were adjusted accordingly.
Results: There were no statistically significant group differences in gender, race, or socioeconomic status among the three groups, and

rates of co-occurring ADHD or psychosis between patient groups. There was a statistically significant, although not clinically meaningful group difference in age. Specifically, bipolar mixed adolescents had a mean (SD) age of 15 (2) years, bipolar depressed adolescents has a mean (SD) age of 15 (2) and healthy controls has a mean (SD) age of 14 (2). Analyses of covariance adjusting for age revealed statistically significant group differences in mI levels in the ACC [$F(2, 49) = 2.3$, $p=0.05$] as well as the left [$F(2, 48) = 5.2$, $p=0.009$] and right [$F(2, 48) = 3.4$, $p=0.04$] VPFC. Specifically, in the ACC and left and right VPFC bipolar depressed adolescents exhibited elevated mI as compared to bipolar mixed adolescents ($p=0.05$, 0.006, 0.04, respectively) and healthy controls ($p=0.05$, 0.03, 0.04, respectively). Additionally, group differences in glx levels were observed in left [$F(2, 49)=5.4$, $p=0.008$] and right [$F(2, 46)=5.9$, $p=0.006$] VPFC. Specifically, in the left and right VPFC bipolar depressed adolescents exhibited elevated glx as compared to mixed bipolar ($p=0.005$ and $p=0.007$, respectively) and control ($p=0.02$ and $p=0.007$, respectively) adolescents.
Discussion: Our results indicate that depressed bipolar adolescents exhibit abnormalities in prefrontal biomarkers of second messenger pathways and neuronal excitation that are distinct from those of bipolar adolescents in a mixed state, suggesting that there are mood state specific neurochemical abnormalities in adolescents with bipolar disorder. Future studies clarifying mood state dependent neurobiological abnormalities as well as abnormaliies that are independent of mood state and therefore, may underlie the neurophysiology of bipolar disorder are needed.

49. Low Frequency Oscillations of Oxy-Hemoglobin in Brain: A Near-Infrared-Spectroscopic Feasibility Study
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Sponsor: F. Xavier Castellanos

Background: Low frequency oscillations (LFO) (< 0.1 Hz) of regional cerebral blood flow have been used to map functional neuronal connectivity (Lowe et al., 1998; Hampson et al., 2002). Similar LFO in human DC-EEG correspond to K-complexes during sleep indicating a link to fluctuations in cortical excitability (Vanhatalo et al., 2004). Such LFO are present in most basal ganglia output neurons during wakeful baseline, and are exquisitely modulated by dopaminergic agonists (Ruskin et al., 2001). LFO spectral power in heart rate variability is inversely related to vigilance (Egelund, 1982) and is greater in children with attention-deficit hyperactivity disorder (ADHD) than in controls (Beauchaine et al., 2000; Borger & Van der Meere, 2000). Eriksen Flanker Task reaction time variability at frequencies between 0.02 - 0.07 Hz were significantly higher in children with ADHD compared to controls and were normalized by methylphenidate in a randomized placebo controlled study (Castellanos, 2005). In preparation for studying cerebral hemodynamic LFO in children and adolescents with ADHD, we are examining the feasibility of detecting LFO in cerebral hemoglobin fluctuations of healthy adults with a new near-infrared spectroscopic imager (NIRx, LLC; Glen Head, NY).
Methods: To date, 22 healthy young adult volunteers have been scanned while performing cognitive tasks such as the Eriksen Flanker task and modifications under varying conditions. Data are collected using a multichannel continuous-wave near-infrared optical tomographic imager operating at 760 nm and 830 nm. Six to 15 coaxial optical fibers are positioned on the forehead between Fp and Fp7. After normalization of raw detector readings, mean oxygenated hemoglobin (Oxy-Hb) concentrations in the illuminated tissue are estimated using a modified Beer-Lambert law. Areas under the curve of the power spectrum in the frequency band between .03 and .06 Hz are analyzed with Fast Fourier Transform.
Results: Analyses are in progress, as we proceed to develop relevant criteria in an iterative fashion. Preliminarily, we have some evidence that manipulating the level of cognitive challenge is associated with changes in the amplitude of the frequency of interest, with most subjects exhibiting an inverse relationship between LFO power and cognitive demands.
Discussion: Near-infrared spectroscopy allows the measurement of cerebral hemodynamic LFO that appear to be modulated by gross changes in cognitive activity. Application of this approach to the study of attention-deficit hyperactivity disorder is ongoing. The long term goal is to characterize LFO in cerebral oxygenated hemoglobin, heart rate variability, and reaction time as potential quantitative physiological endophenotypes in ADHD and related disorders.

50. Neural Activation During Encoding of Emotional Faces in Pediatric Bipolar Disorder
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Sponsor: Travel Awardee, Young Investigator Memorial, 2005

Background: A major problem affecting research on pediatric bipolar disorder (BD) is that the pathophysiology of mania is difficult to study. Studies of the neural circuitry mediating the processing of happy or angry faces may help to address this problem. Happy face processing is relevant to euphoric mania because (a) euphoria involves aberrant pleasure-seeking and reward behavior, and (b) both happy faces and reward tasks activate striatum, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Similarly, angry faces are relevant to irritable mania because (a) irritability is characterized by a decreased threshold for experiencing anger, and (b) both angry face recognition and anger modulation involve the OFC. Therefore, we conducted an event-related fMRI study in pediatric BD to determine brain regions engaged when angry and happy faces are encoded, meaning the process through which perceived events are transformed into enduring cognitive representations.
Methods: In the GE 3 Tesla fMRI scanner, BD (N=23; mean age 14 years; 14 female 9 male) and control (N=22; mean age 14 years; 12 female 10 male) children completed an attentional task with emotional faces. Then, 30 minutes later, a surprise memory task was given asking them whether they had seen each of 48 faces in the scanner (24 novel and 24 previously viewed). Finally, fMRI events were binned based upon whether or not a face was remembered during the post-scan test. This provided tight experimental control for stimulus features, since we contrasted regions engaged by similarly appearing stimuli that either did, or did not, receive sufficient psychological processing to be remembered.
Results: During successful encoding of angry faces, BD subjects had greater activation than controls in the right OFC. During successful encoding of happy faces, BD subjects had greater activation than controls in the striatum bilaterally and right ACC. Post-hoc analyses to examine state effects showed that euthymic BD subjects (N=11) demonstrated increased striatal activation during successful encoding of happy faces compared to controls.
Discussion: Our study provides evidence that encoding of emotional faces particularly relevant to mania-e.g. happy (euphoria) and angry (irritability)-is associated with increased fronto-striatal activation in children with BD, compared to controls. Moreover, it also shows the utility of using positively- and negatively-valenced emotional faces to study emotion regulation in pediatric BD.

51. Altered Dorsal or Ventral Prefrontal Morphology May Differentiate Risk for Schizophrenia or Bipolar Disorder: Preliminary Evidence from *in vivo* MRI studies
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Sponsor: Past Travel Awardee, Bristol-Myers Squibb, 2003

Background: Both schizophrenia (SCZ) and bipolar disorder (BP) are thought to result in part from disruptions in neurodevelopment

(Blumberg et al., 2004; Murray & Fearon, 1999). However, how these illnesses gradually develop during their pre-morbid phase remains poorly understood. Characterizing the differences between the developmental bases of these illnesses may be crucial to understanding the differences in their expressed phenotypes (Murray et al., 2004). Adolescent offspring of SCZ and BP parents are at high risk for these illnesses and provide important samples in which to assess possible developmentally based deficits in brain morphology in individuals vulnerable to SCZ and BP. Understanding abnormalities in the prefrontal cortex may be particularly important. Whereas schizophrenia may particularly impact dorso-lateral prefrontal morphology (Lewis, 1997), bipolar disorder may particularly impact ventro-lateral and ventro-medial prefrontal morphology (Drevets, Ongur, & Price, 1998). We conducted preliminary voxel-based morphometric analyses on MRI images to assess whether adolescents at risk for illness for schizophrenia (HR-S) or bipolar disorder (HR-B) showed distinctions between dorsal and ventral impairment in prefrontal morphology compared to controls with no family history of psychosis (HC).
Methods: Voxel based morphometric analysis was conducted on T_1-weighted MRI images (acquired at 1.5 Tesla) of HC (n=48; mean age=16.3 yrs), HR-S (n=62; mean age=15.1 yrs), and HR-B (n=5; mean age=14.8 yrs) using SPM2's optimized protocol (Good et al., 2001). Smoothed gray matter maps (FWHM=12 mm) were analyzed in an analysis of covariance (age, gender, handedness as covariates). Relative reductions in gray matter concentration in HR-S and HR-B were identified by comparing with HC (t>3.38, p<.0005, extent threshold=50 voxels).
Results: Differentiated patterns of morphometric reductions in gray matter concentration were observed in HR-S and HR-B subjects compared to HC subjects. Particularly, in the frontal lobe, HR-S showed significant reductions primarily in dorso-lateral prefrontal cortex, including Brodmann areas 9 & 46. HR-B showed significant reductions primarily in ventro-lateral and ventro-medial prefrontal cortex, including Brodmann area 10. Differences in ventral prefrontal cortex in HR-B were observed even when analysis was restricted to age and gender matched subjects across each of the three groups (n=5 in each group; t=2.72, p<.01, extent threshold=50 voxels).
Discussion: These data while preliminary, suggest plausibly divergent pathways of vulnerability of prefrontal cortex to schizophrenia or bipolar disorder in offspring who are known to be at genetic and familial risk for the illness. Vulnerability to schizophrenia may be characterized by dorsal prefrontal deficits that may be correlated with the pattern of cognitive processing deficits associated with the illness (Murray et al., 2005). Vulnerability to bipolar disorder may be characterized by ventral prefrontal deficits that may be correlated with the pattern of emotional processing deficits associated with the illness (Phillips et al., 2004). Our ongoing work in these samples is further evaluating these distinctions using magnetic resonance spectroscopy, fMRI and neuropsychological measures.

52. Emotional Numbing in PTSD: fMRI Neuroimaging of Reward Circuitry

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Background: PTSD is a complex mental disorder with features beyond anxiety. Among these are symptoms of "emotional numbing", which include diminished interest in significant activities, feelings of detachment or estrangement from others, restricted range of affect, and a sense of a foreshortened future. The pathophysiological significance of emotional numbing remains unclear. One interpretation posits that processing of emotional stimuli in PTSD is essentially normal, but expression of positive feelings is constrained by painful affects triggered by trauma-related memories. Our clinical data obtained by using validated probes of reward function (Elman et al, Psychiatry Research 2005) suggest, however, an alternative explanation that similar to diminished hedonic capacity in substance use disorders (SUDs), emotional numbing in PTSD may result from deficits in reward mechanisms subserving enjoyment from naturally encountered pleasures and reinforcers.
Methods: To further explore this issue, we examined the effects of two distinct categories of reward (that were previously demonstrated to reliably activate reward centers in humans), one social and the other monetary, on local hemodynamic responses, using BOLD functional magnetic resonance imaging in 9 patients with PTSD and 22 healthy volunteers (matched by demographic and educational characteristics). The social reward was viewing female and male facial images that were categorized into "liked and non liked" and "wanted and unwanted" groups by employing computerized key-press and attractiveness rating tasks. The monetary reward involved financial incentives incorporated in a gambling-like game, which allowed assessment of signal changes that either anticipate or accompany monetary gains and losses under varying conditions of controlled expectation. All images were acquired on a 3 Tesla Siemens Trio MR imaging system; subjects responses were analyzed using the General Linear Model in BrainVoyager. An algorithm for acquisition of match-warped images developed at McLean Brain Imaging Center was employed to allow exact registration of the functional and anatomic data in the presence of severe magnetic field inhomogeneities.
Results: Compared with healthy controls, patients with PTSD displayed significantly smaller signal changes in the nucleus accumbens, cingulate gyrus, insula and prefrontal cortex (p<0.05, corrected for multiple comparisons).
Discussion: These data implicate decreased reward functioning in the pathophysiology of PTSD and suggest that high comorbidity of SUDs in PTSD could be an attempt to artificially stimulate the reward system in order to compensate for the underlying deficit.

53. Influence of Low and High Dose Hydrocortisone Infusion on Hemodynamic Response in Amygdala While Viewing Emotional Faces

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Sponsor: Wayne Drevets

Background: Increased glucocorticoid (GC) hormone secretion in response to stress differentially regulates glucose uptake in distinct tissues, and modifies gene expression in specific areas of the brain. The amygdala contains particularly high GC receptor concentrations, and plays a major role in modulating GC hormone secretion and resultant processes. The amygdala is a major mediator of the stressed component of GC secretion. Evidence exists that low versus high circulating levels of GCs may have differential behavioral effects; 5 mg of hydrocortisone (HC) increased while 20 mg decreased eyeblink startle reflex compared to placebo (Buchanan et al 2001). The current study investigated effects of low-dose compared to high-dose HC on the amygdala. We hypothesized that hemodynamic response of the amygdala would differ across low and high HC infusion.
Methods: 221 healthy volunteers (15 M; age 30.7±8.4, IQ 113.5±9.9) participated. Each received placebo and HC infusion (0.15 or 0.45mg/kg) on 2 separate visits in this double-blind randomized, cross-over study while in a 3-Tesla MRI scanner 10 min prior to an fMRI task. All infusions took place between 11:30 a.m. and 12:00 noon. 10 subjects were in the low-dose (0.15mk/kg) group and 11 were in the high-dose (0.45mg/kg) group. Anatomical T1-weighted axial MRI scans (.93 x .93 x 1.2 mm resolution) were acquired for registration with functional data. During the fMRI task, subjects made gender judgments of photographs of faces expressing sadness, happiness, fear, and a neutral expression. 40 faces of each emotion were shown once during 4 runs. Faces appeared for 750 ms with a 2.75-second ITI. Unique faces were shown at each visit. Axial EPI images were

acquired (TR = 2.5; 3.75 X 3.75 X 3.3 mm resolution). Using SPM2, ROI analyses of amygdala were performed with a height threshold of p=.05 for neutral, happy, sad and fear faces. 3-group ANOVAs were then performed to establish significant differences in regional BOLD activation during HC and placebo conditions within ROIs.
Results: Plasma cortisol increased to low- (to 32.1±22.1ug/dl) and high-dose (to 52.4±6.9ug/dl) infusion (p<.0001), but not placebo (8.8ug/dl). A significant dose by emotion (p=.01) interaction effect for gender judgment accuracy scores was observed; high-dose decreased accuracy to fear faces. ROI analyses of fMRI data revealed bilateral increases in amygdala hemodynamic response in placebo and high-dose conditions to neutral, happy, sad and fear faces compared to fixation point baseline; no significant amygdala responses were found following low-dose infusion to faces compared to baseline, although a trend for more activation was noted (p=.07) in right amygdala to fear faces. Amygdala activation was greater bilaterally during placebo compared to low-dose to all faces; in high-dose, right amygdala was more activated to all face categories compared to low-dose.
Discussion: Our primary finding was that cortisol exerts a U-shaped effect on neurophysiological activity in the amygdala during exposure to emotional stimuli. Low doses of HC suppressed the hemodynamic responses to all emotional face categories, including fearful faces, while high-dose HC infusion (similar to severe stress cortisol levels) significantly increased right amygdala response to all faces compared to low-dose infusion. Although right amygdala activation to fearful faces as compared to fixation in the low-dose condition only trended toward significance, this difference may become significant in a larger sample. Such a finding would indicate that the right amygdala becomes selectively responsive to fearful stimuli when cortisol levels are moderately high.

54. Schematic Faces Evoke Exaggerated Regional Activation Within the Amygdala in Social Anxiety Disorder
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Sponsor: Travel Awardee, PMRTP, 2005

Background: The amygdala has been consistently implicated in the processing of human emotional facial expressions in neuroimaging studies of healthy subjects. Interestingly, recent imaging studies using contemptuous or angry (contrasted with happy or neutral) facial expressions have suggested abnormalities in amygdalo-cortical function in social anxiety disorder (SAD). Photographs of human facial expressions are complex, and recent neuroimaging studies demonstrate that these stimuli may introduce a number of confounds (e.g., race and or gender bias). We previously reported that line drawings of emotional expressions (schematic faces) evoke amygdala responses in healthy individuals. Given the likelihood that this approach may reduce the variance that could otherwise be introduced by photographs, the objective of the present study was to determine if schematic emotional expressions evoked exaggerated amygdalar responses in SAD patients compared to healthy control subjects (HC) using fMRI.
Methods: Eleven right-handed patients with a primary diagnosis of SAD (4 male, 7 female; ages 22-45, mean 29.0) and eleven age- and gender-matched HC subjects underwent fMRI scanning at 1.5 Tesla. All subjects viewed overt schematic emotional faces during scanning. The facial stimuli were simple line drawings of the happy, angry and neutral expressions, presented for 200ms with a 300ms inter-stimulus interval. Imaging data were pre-processed and analyzed with SPM99. Random-effects, voxel-wise tests of condition x diagnosis were performed to assess an a priori prediction of hyperresponsivity within the amygdala in SAD patients vs. HC.
Results: Compared to HC subjects, SAD patients failed to demonstrate exaggerated amygdala responses in the contrast of angry > happy schematic faces. However, in the contrast of angry > neutral, SAD patients did demonstrate exaggerated responses in the right amygdala (peak Talairach coordinates; x = 26, y = -6, z = -6). Consistent with previous neuroimaging reports in SAD, patients in the present study also exhibited differential activation of additional limbic regions (common to both contrasts): insular cortex, parahippocampal, superior temporal and fusiform gyri.
Discussion: We have previously shown that the amygdala is responsive to emotionally valenced schematic faces, as well as to both masked and overtly presented emotional facial photographs, in healthy individuals. The finding of exaggerated amygdala activation in response to angry (vs. neutral) schematic emotional expressions in SAD patients converges with results from prior studies. Moreover, the identification of hypothesis-driven differences between a patient and control cohort illustrates the potential utility of using schematic faces in future clinical studies. By reducing the number of potential confounds, schematic faces may also decrease the variance of fMRI responses, leading to more consistent patterns of signal changes across subjects as well as between studies.

55. Medial Prefrontal Cortical Maturation: An fMRI Study of Interference Processing in Healthy Children
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Sponsor: Bernard Agranoff

Background: Evidence from functional neuroimaging studies of both children and adults demonstrates a key role for the posterior medial prefrontal cortex (pMFC, including dorsal anterior cingulate cortex) in response interference tasks; however, the neurodevelopmental trajectory of pMFC engagement by interference is not well-defined. We sought to map the functional development of the pMFC over the course of childhood and adolescence by using an fMRI paradigm designed to maximize the intensity of interference. We predicted that pMFC activation would increase with age, based on the improvements of inhibitory processing that occur through childhood and into adolescence (Luna and Sweeney, 2004).
Methods: 14 youth, ages 8-17 years, performed the Multisource Interference Task (MSIT), an fMRI paradigm shown to elicit single subject activation of the dorsal anterior cingulate in adults (Bush et al, 2004). Interference and control trials were presented in an event-related design. 470 T2* spiral GRE volumes were acquired in 5 runs on a 3T GE scanner (TR = 2000, TE = 30). Data were realigned, normalized, and then analyzed using random effects models (SPM2) to examine the interference-related activations for older compared to younger subjects, as well as for the group of subjects as a whole. Correlations between age, accuracy and the magnitude/extent of pMFC activation were examined using SPSS.
Results: There were no correlations between age and accuracy or response latency on either interference or control trials. There was a significant correlation between accuracy and response time for incongruent trials (r = .666, p=.009), suggesting that the better performing subjects slowed their responses in order to achieve greater accuracy. Single subject pMFC activations were demonstrated in most (n=12), but not all of the subjects (n=2). Greater activation occurred in the 7 oldest subjects compared to the 7 youngest (Z=3.72;-3,15,51;k=85) in the same pMFC region that was activated by the group as a whole (z=4.08;-3,15,48). Older subjects also exhibited more activation deep in the motor strip (z=4.89; 24,9,48 and z=4.67, -27,3,51). Age tended to positively correlate with the magnitude of pMFC activation (r=0.431,p=.07), and accuracy on incongruent trials was negatively correlated with the extent of pMFC activation (r=-0.619, p=0.032).
Discussion: Posterior medial frontal cortical involvement in interference processing increased with age, suggesting functional maturation

of this region from childhood through adolescence. The inverse relationship between pMFC activation and performance suggests that inefficient use of this region may be linked to failures of interference processing.

56. Increased Dopamine D2/D3 Receptor Binding After Recovery from Anorexia Nervosa

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Sponsor: Travel Awardee, Young Investigator Memorial, 2005

Background: Disturbances of dopamine function may contribute to alterations of motor activity, food reward and weight in anorexia nervosa (AN). Previously, our group showed reduced CSF homovanillic acid concentrations in recovered AN, suggesting altered dopamine brain-activity. We hypothesized that recovered AN (REC AN) would have increased availability of dopamine auto-receptors in reward related brain regions. Such a finding could be a trait disturbance related to anhedonic behavior and treatment resistance in AN.
Methods: In order to avoid the confounding effects of malnutrition, and to assess possibly trait related disturbances, we studied 10 women recovered from AN (REC AN) compared to 12 healthy age-matched control women (CW). Brain imaging using positron emission tomography (PET) with [11C]raclopride was used to assess dopamine D2/D3 receptor binding. The Reference Tissue Model (SRTM, Lammertsma and Hume 1996) was used for PET data modeling. In addition, in subjects who could have arterial blood sampling, the Logan Graphical Method (LGM, Logan et al, 2001) was applied.
Results: Subject groups were of similar age (CW 27±6 years, REC AN 24±5 years, p=0.2) and body mass index (BMI, CW 23±2, REC AN 22±3, p=0.3). REC AN had significantly higher [11C]raclopride binding potential in the antero-ventral striatum (CW 1.98±0.4, REC AN 2.33±0.3, p=0.036, SRTM). SRTM and LGM were comparable. Cerebellar (LGM) and other striatal regional binding values (SRTM/LGM) were similar between groups. There was a trend toward higher binding in REC AN without history of binge eating behavior compared to REC AN with such a history. However, this was not statistically significant. The trait anxiety measure Harm Avoidance correlated with dorsal caudate [11C]raclopride binding potential in REC AN (rho=0.9, p=0.0004, p=0.008 Bonferroni corrected).
Discussion: These data lend support to the possibility that altered dopamine D2/D3 receptor binding is associated with AN and may contribute to the characteristically increased physical activity found in AN. Most intriguing is the possibility that AN may have a dopamine-related disturbance of reward or motivational mechanisms. This may contribute to altered hedonics of feeding-behavior and might play a role in the ascetic, anhedonic temperament in AN. We are currently expanding our sample in order to test the hypothesis that restricting and non-binge eating REC AN have greater dopamine D2/D3 receptor binding than REC AN with binge eating history. Preliminary results support this hypothesis. Recently, a polymorphism of the dopamine transporter gene has been found in Eating Disorder subjects with binge eating behavior (Shinohara et al, 2004). Such a disturbance could be related to different dopamine receptor expression across Eating Disorder sub-groups. Increased dopamine D2/D3 receptor binding in AN could be consistent with a continuum of reduced dopamine D2/D3 receptor binding found in substance use and obese subjects with behavioral under control and increased dopamine D2/D3 receptor binding in REC AN who present with an extreme capability of self denial and little hedonic experiencing.

57. PET Imaging of the Serotonin 2a Receptor (5-HT2a) and Sertonin Transporter (SERT) in Personality Disordered Subjects with Impulsive Aggressivity

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Sponsor: Suzanne Haber

Background: Reduced activity of the serotonin system has been implicated in impulsive violence and aggression using a variety of paradigms. Studies of brain lesions and metabolic imaging studies point to the oribitofrontal cortex (OFC) and the anterior cingulated gyrus (ACC) as key areas regulating the generation of aggressive behaviors. Using PET imaging with [11C]McN 5652 we recently reported a decrease in SERT in the ACC in subjects with impulsive aggressivity (subject meeting criteria for intermittent explosive disorder-revised, IED-R). This study describes the measurement of the postsynaptic 5-HT2A receptors in this population using the radiotracer [11C]MDL 100907. We also report the confirmation of our previous finding of reduced SERT in a new cohort of subjects using a more recently developed radiotracer for the SERT, [11C]DASB.
Methods: 5-HT2a Receptors: Eighteen patients (35±9 years, 13M/5F) and eighteen healthy controls (34±11, 13M/5F) underwent a 90 min PET study after injection of [11C]MDL 100907. Regions of interest (ROI) included the dorsolateral, medial and orbital prefrontal cortices (DLPFC, MFC, OFC), the temporal, parietal and occipital cortices (TEM, PAR, OCC), the amygdala (AMY), entorrhinal cortex (ENT), hippocampus (HIP), parahippocampal gyrus (PHG) and the anterior cingulate cortex (ACC). SERT: Six patients (39±14 years, 4M/2F) and ten healthy controls (33±5, 7M/3F) underwent a 100 min PET study after injection of [11C]DASB. ROIs included the midbrain (MID), thalamus (THA), dorsal caudate (DCA), dorsal putamen (DPU), ventral striatum (VST), AMY, ENT, HIP, PHG and the ACC. For both radiotracers regional distribution volumes (VT, mL/g) were derived with 2 tissue compartment (2TC) kinetic analysis. VT in the cerebellum was used to estimate the nondisplaceable distribution volume, V2. Two parameters of sites availability were derived: BP (= VTROI-V2, mL/g) and V3" (= BP/V2, unitless).
Results: 5-HT2A receptors: No significant differences in 5-HT2a receptor availability were noted in the sample as a whole. Examination of a subset of IED-R subjects exhibiting current physical aggression (n= 8, 4M/4F, defined as physical aggression towards other people, animals, or property occurring 2x/week on average or 3 episodes involving physical assault against other people or major destruction of property over 1-year), revealed significantly higher 5-HT2a receptor availability in the ENT compared to controls. 5-HT2A receptor binding in the ENT was also found to be significantly correlated with higher irritable assault scores (measured using the Buss-Durkee Hostility Inventory, BDHI) in patients with IED and controls ($r = 0.492$, $p<0.05$). SERT: SERT availability was significantly reduced in the ACC in individuals with IED-R compared with controls. This reduction was noted in V3" (IED-R subjects, 0.26±0.03; control subjects, 0.31±0.04, $p = 0.04$). No significant differences in BP or V3" were observed in other ROIs.
Discussion: These results confirm our previous finding, in a new cohort, using a different radiotracer, of reduced SERT availability in the ACC in IED-R subjects. The 5-HT2A data demonstrates a significant correlation between degree of impulsive aggression as reflected in BDHI scores. Thus, while SERT binding appears to be reduced in our IED-R personality disordered patients and uncorrelated with severity of aggression, 5-HT2A binding appears associated with degree of aggression. If confirmed, these results may provide the basis for developing treatment strategies in pathological aggressivity.

58. Subcortical Asymmetries in Bipolar and Attention Deficit/Hyperactivity Disorders

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Background: Youths with Bipolar Disorder (BPD) are diagnostically complex and a significant percentage have comorbid attention deficit hyperactivity disorder (ADHD). Magnetic Resonance Imaging (MRI) technology may afford a method for disentangling BPD and ADHD. Given reports of a reversal of caudate asymmetry in ADHD, this study sought to assess the morphometric asymmetries of subcortical structures, particularly the basal ganglia, in a sample of youths with ADHD, BPD without ADHD, BPD with ADHD, and healthy controls as measured on MRI scans. We hypothesized that if BPD ADHD youths had severe ADHD, then they would have morphometric findings similar to youths with ADHD; if the BPD ADHD group represented a disorder of two comorbid conditions, they would have neuroanatomic findings similar to youths with ADHD and to youths with BPD alone; if BPD ADHD youths had BPD, then their neurobiologic correlates would be similar to those with BPD alone.
Methods: Youths with DSM-IV BPD, ADHD and healthy controls, similar in age and sex, were enrolled in an anatomic MRI study. All youths underwent a direct abbreviated diagnostic structured and clinical interview, neurological examination, and cognitive testing. Youths and parents answered questions on syndromic rating scales. In addition, parents underwent a structured diagnostic interview-parent version. Imaging data were acquired at McLean Hospital on a 1.5 Tesla, General Electric Signa Scanner. All volumetric analyses were performed using the current methods of MGH Center for Morphometric Analysis. A symmetry index for each subcortical structure of interest (caudate, putamen, hippocampus, amygdala, ventral diencephalon and thalamus) was calculated as: (Right Volume - Left Volume) / [(Right Volume Left Volume)/2]. Linear regression modeling of these asymmetry indices, controlling for the effects of age, sex, and diagnosis, were performed using a two-tailed alpha level of 0.05.
Results: This analysis included data from 62 right-handed subjects including 21 girls: BPD youths with (n=16) and without (n=12) comorbid ADHD, ADHD youths (n=10), and healthy volunteers (n=24). The mean age of the sample was 11.0 ± 2.6. Significant between-group differences in asymmetry existed for the thalamus, caudate, and putamen. Specifically, youths with ADHD had left-sided thalamic asymmetry that differed from each of the other 3 groups ($p<0.1$), all of whom had right-sided thalamic asymmetry. The most pronounced thalamic asymmetry difference was observed between the ADHD and Bipolar (no ADHD) groups ($t=3.073$, $p=0.003$). There were also other differences in basal ganglia asymmetry between the ADHD and control groups: putamen ($t=2.111$, $p=0.039$), caudate ($t= -1.970$, $p=0.053$), and ventral diencephalon ($t=-2.245$, $p=0.029$).
Discussion: Our findings support the findings of other groups indicating that youths with ADHD have a reversal of the normal asymmetry of the caudate. In addition, the ADHD group had a reversal of normal asymmetry of the putamen and ventral diencephalon. Neither the BPD alone group nor the BPD ADHD group showed a similar pattern of subcortical asymmetries to the ADHD group, particularly in the basal ganglia. These data suggest that the morphometric subcortical asymmetry findings of youths with BPD ADHD are more consistent with the findings of youths with BPD alone, and are similar to those found in healthy controls. In addition, these findings may indicate that a reversal of asymmetry of the basal ganglia structures in particular may constitute a risk factor for ADHD. More work is needed with greater numbers to confirm these initial findings.

59. Increased GABAergic Activity Modulates MR-Visible Glutamate and Glutamine: Studies with High Resolution Magic Angle Spinning Proton Magnetic Resonance Spectroscopy (HR-MAS ^{1}H-MRS)

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Background: Clinical proton magnetic resonance spectroscopy (^{1}H-MRS) provides an unprecedented non-invasive assessment of glutamate (GLU), glutamine (GLN), and GABA; however, the neurobiological mechanisms responsible for changes in these neurotransmitters remains to be determined since the MR-visible concentration represents a unique measure distinct from either microdialysis or a tissue extract. Therefore, using HR-MAS ^{1}H-MRS at 11.7T with intact tissue from rat brain, we determined the acute effect of increasing GABAergic tone *in vivo* on the MR-visible neurochemical profile.
Methods: Endogenous GABAergic tone was enhanced in male S-D rats (n=5-8/group) by treatment with the GABA transaminase inhibitor gabaculine (100 mg/kg i.v. 3 hrs), the GABA transporter inhibitor NO711 (5mg/kg , i.p.1 hr), ethanol (6 m/kg, p.o. 6 hrs), or the GABA-A receptor ligand propofol (15m/g kg i.v. x5, 75 min). After sacrifice, tissue punches were rapidly obtained then frozen until ^{1}H-MRS analysis. Acquisition of MRS spectra consisted of high resolution, magic angle spin spectroscopy using standard CPMG pulse sequences at 11.7T, followed by automated quantification (nmol/mg) of neurochemicals using LCModel.
Results: Inhibition of GABA transaminase by gabaculine was evident by a significant ($p<0.05$) 2-3 fold increase in striatal, cortical, and hippocampal GABA. In contrast, gabaculine decreased GLN ($p<0.05$) and GLU (ns, $p>0.05$) as well as the GLN/GLU ratio. Pretreatment with the GABA-A antagonist bicuculline (0.5 mg/kg i.v) partially reversed the GLN/GLU decrease. Inhibition of GAT decreased GABA and increased cortical glutamine levels, consistent with an autoreceptor mediated decrease in GABA synthesis. Propofol treatment significantly decreased MR-visible GLU in cingulate and prefrontal cortices and medial dorsal thalamus; the GLU/GLN ratio was consistently decreased in the majority of brain regions. In the same animals, propofol increased striatal dopamine levels, consistent with on-going tyrosine hydroxylation in the absence of impulse dependent release subsequent to GABA-A mediated inhibition of DA cell firing. Similarly, ethanol significantly decreased GLU/GLN in the thalamus, hippocampus, and striatum, an effect that was driven primarily by increases in GLN.
Discussion: The results suggest that direct potentiation of GABA-A receptor mediated inhibition decreases MR-visible GLU. Increasing GABA transmission via presynaptic mechanisms (i.e. inhibition of catabolism or reuptake) primarily affects MR-visible GLN. The results also highlight the importance of measuring appropriate metabolic ratios when studying GABA-ergic agents with mixed pharmacological properties (e.g. vigabatrin). Supported by NIDA R01 DA-16736 (MPG) F31 AA015224 (SOL).

60. Computational Anatomy to Assess Growth Pattern of Early Brain Development in Healthy and Disease Populations

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Sponsor: John Gilmore

Background: Imaging studies of early brain development get increasing attention as improved modeling of the pattern of normal development might lead to a better understanding of origin, timing and nature of morphologic differences in neurodevelopmental disorders.

It is our goal to model the trajectory of early brain development, primarily focusing on the most challenging group of very young children in the age range from birth to 6 years, as a 4-dimensional atlas represented by a time series of 3-D images and quantitative description of local growth. In addition, the same technique is applied to generate representative group-specific atlases, e.g. for female/male populations and for healthy controls and patients.
Methods: The new computational anatomy tool is based on the concept of unbiased atlas building. A group of 3-D images is simultaneously deformed to build a new average center image, which is a sharp MR image encoding the average structures of the whole population. Longitudinal change is assessed by quantifying local deformation between pairs of atlases at consecutive time points. Morphological differences between groups are analyzed by the same concept but comparing group-specific atlases. This new method is not limited to the analysis of the cortex, e.g., but extends to a fully volumetric description of the growth pattern, including subcortical structures, fluid spaces, and white matter. This project is driven by the needs of several clinical pediatric studies at UNC Chapel Hill. This includes a longitudinal study of neonatal brain development in high risk children and controls (N total =134), with follow-up at 1 year of age, and an autism study (51 autistic (AUT) and 25 control individuals (TYP, DD)) with baseline scans at 2 years and follow-up at 4 years. So far, the new method has been applied to a subset of subjects from the autism study. We have selected 5 subjects each from the TYP and AUT groups, with MRI at 2 and 4 years. We applied the unbiased atlas building procedure to these 4 groups and computed image deformation longitudinally (comparing the 2yrs and 4yrs atlases for AUT and TYP) and cross-sectionally (TYP versus AUT at 2yrs and 4yrs).
Results: The most striking result of the longitudinal growth analysis between 2 and 4 years is the apparent cerebral asymmetry. There is a consistent right frontal > left frontal and a left posterior parietal/occipital > right posterior parietal/occipital pattern, commonly called torque or brain torsion. This growth trajectory finding is consistent for the TYP and AUT groups. The temporal lobes also show a right temporal > left temporal growth pattern. Local growth is mostly evident in cortical gray, which seems to account for the major brain growth. Lateral ventricles are stable, but the third ventricle illustrates a significant width reduction. Group tests between TYP and AUT subjects reveal a strong size difference of the cerebellum, which is much more pronounced at age 2 and lessens towards age 4. These exploratory findings need to be confirmed with independent samples.
Discussion: Our preliminary findings indicate that the new methodology shows excellent potential to explore longitudinal change, difference between groups, and differences between growth trajectories between groups. The simultaneous analysis of the whole volumetric brain is a major strength, as it will reveal morphometric changes of structures with embedding context, e.g. studying cortical growth in relationship to adjacent white matter, and examining groups of subcortical structures and even whole circuits.

61. Altered Pain Processing in Veterans with Posttraumatic Stress Disorder

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Sponsor: James Douglas Bremner

Background: PTSD is a chronic and invalidating anxiety disorder. In patients with PTSD, the ACC, which is involved in affective pain processing, is morphologically and functionally altered, and thus there is reason to believe that PTSD patients not only perceive, but also process pain differently than healthy individuals. As of yet, no study has discussed whether PTSD patients experience and process pain in a different way than healthy controls.
Methods: Ten male Dutch veterans with PTSD, and 10 male Dutch veterans without PTSD, were recruited, and matched for age. The experimental procedure consisted of a pain threshold determination, and neuroimaging with fMRI. During the fMRI acquisition, sensory blocks of 30 seconds in length were applied on the dorsal hand either with a temperature equalling 40% of the subjective pain intensity, or a fixed temperature of 43 °C.
Results: In the 43°C condition, patients with PTSD revealed increased activation in the superior and medial frontal gyri, and left parahippocampal gyrus, and decreased activation in the bilateral insula compared to controls. In the subjective temperature condition patients with PTSD showed increased activation in the right postcentral gyrus, left middle frontal gyrus, and left middle temporal gyrus. Stimuli subjectively experienced as more painful result in increased activation of the caudal ACC, whereas less painful stimuli result in increased activation of the rostral ACC in both groups.
Discussion: Patients with PTSD reveal altered pain processing in the insular cortex, medial, and dorsolateral prefrontal regions. Rostral ACC activation appears to be related to less painful stimuli, whereas more painful stimuli results in increased activation of the caudal ACC.

62. Frontal Dopamine D2 Receptor Binding in Neuroleptic-Naive First-Episode Schizophrenic Patients Correlates with Positive Psychotic Symptoms and Predicts Treatment Outcome

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Sponsor: Svein Dahl

Background: The aim of the study was to investigation extrastriatal D2 receptor binding potentials (BP) and psychopathology in neuroleptic naive schizophrenic patients. Additionally, we wanted to examine whether extrastriatal BP values in the neuroleptic-naive state could predict treatment outcome with regard to positive and negative psychotic symptoms - and, finally, to relate extrastriatal and striatal D2 receptor occupancy to the effect of antipsychotic treatment on positive and negative psychotic symptoms after 3 months of treatment with either a typical or an atypical antipsychotic compound.
Methods: Twenty-five neuroleptic-naive first-episode schizophrenic patients and 20 matched healthy controls were examined with psychopathological ratings and single-photon emission computerized tomography (SPECT) using the D2/3-receptor ligand [123I]epidepride and a previously validated bolus/infusion approach. Positive and negative psychotic symptoms were assessed with the PANSS-positive and PANSS-negative subscales. After baseline examinations the patients were randomized to treatment with either risperidone (mean dose 3.8 mg) or low doses of the typical antipsychotic drug, zuclopenthixol (mean dose 9.6 mg, comparable to haloperidol 3 mg). All examinations were repeated after 3 months of treatment.
Results: In the hitherto largest study on extrastriatal D2 receptors we found a significant correlation between frontal D2 BP values and positive schizophrenic symptoms. No significant differences in BP values were observed between patients and controls; the patients, however, had significantly higher BP in the right compared to the left thalamus, whereas no significant hemispheric imbalances were observed in the healthy subjects. The data did not reveal significant between-group differences in receptor occupancy in any of the examined regions (frontal cortex, temporal cortex, thalamus, caudate nucleus, and putamen) following 3 months of treatment nor did the relative distribution differ between the typical and the atypical drug.

In the total group of patients and in the group randomized to treatment with risperidone we found a highly significant positive correlation between frontal D2 receptor BP in the neuroleptic-naive state and treatment outcome with regard to positive schizophrenic symptoms whereas high D2 BP in the left thalamus predicted outcome regarding negative symptoms. The data further confirmed a negative correlation between treatment-effect on negative symptoms and blockade of frontal as well as thalamic D2 receptors. In contrast, we observed a negative correlation between striatal D2 receptor occupancy and treatment outcome with regard to negative symptoms in the (smaller) subgroup of patients treated with low, uniform doses of zuclopenthixol.
Discussion: The study is the first longitudinal with-in group trial of neuroleptic-naive schizophrenic patients to measure the relation of extrastriatal D2 receptor activity to psychopathology. The data strongly supports that schizophrenic symptomathology is influenced by frontal and thalamic D2/3 receptor activity. The implications and possible explanations will be discussed i the presentation.

63. White Matter Integrity in Kleptomania: A Pilot Study
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Sponsor: Past Travel Awardee, Bristol-Myers Squibb, 2003

Background: Kleptomania is characterized by the impulse to steal objects not needed for personal use or their monetary value and the inability to control that impulse. Although there have been no brain imaging studies of kleptomania, the literature suggests that damage to orbitofrontal-subcortical circuits may result in kleptomania.Studies of white matter microstructure in impulsive schizophrenia patients using diffusion tensor imaging (DTI) showed that lower fractional anisotropy (i.e. axonal disorganization) and higher trace (increase in extracellular space) in the right inferior frontal area was associated with greater impulsivity. Because frontal brain circuits, particularly the orbitofrontal circuit, are important in behavioral regulation, we examined inferior frontal white matter in kleptomania subjects compared to controls using DTI. We hypothesized that kleptomania subjects would show compromised white matter integrity (i.e. increased Trace and decreased FA) in inferior frontal regions compared to a healthy comparison group.
Methods: 10 females with DSM-IV kleptomania and no other psychiatric comorbidity and 10 healthy, nonpsychiatric females, matched to the kleptomania group on key demographic variables, underwent diffusion tensor imaging. Inferior frontal white matter was the a priori region of interest. An experienced rater, blind to group assignment, analyzed images. Trace and fractional anisotropy (FA) were calculated. Group differences were compared using students t-test and analysis of covariance.
Results: The kleptomania group had higher mean frontal Trace ($F(1,14) = 24.90$, $p < .001$; effect size = .640) and lower mean frontal FA ($F(1,14) = 13.22$, $p = .003$; effect size = .488). Group differences remained significant when right and left frontal Trace and FA were analyzed (all $p < .01$).
Discussion: These findings of compromised white matter microstructure in the inferior frontal regions of kleptomania subjects using DTI are consistent with results reported previously in other impulsive behaviors and with the hypothesis that the inferior frontal brain region is involved in impulsive behaviors that involve poor decision-making, such as stealing unnecessary items. Shoplifting may reflect an inability to balance the desire for immediate reward with punishment, an activity thought to involve prefrontal cortical function. These DTI findings in the inferior frontal regions may therefore reflect impaired connectivity in the tracts running from the limbic region to the thalamus and to the prefrontal region. These findings may also have clinical and forensic implications.

64. Prevention of Relapse in MDD: An Investigation of the Neural Basis of Self-Regulation of Emotion
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Sponsor: Richard Shelton

Background: Findings suggest prior treatment with cognitive therapy (CT) is associated with a decreased risk of relapse when compared with prior antidepressant use (ADM) and is as effective as continuation ADM. It has been hypothesized that the reduction of risk following CT is due to improved self-regulation of emotion associated with the acquisition of compensatory reappraisal strategies. The goal of the current study was to identify the neural substrate of this experience-induced change in modulation of emotion and cognitive control in patients treated to remission with either CT or ADMs.
Methods: Medication-free previously depressed subjects (n=5) who completed a randomized 16-week study of CT or ADM (paroxetine augmented with lithium or desipramine if non-responsive) followed by a 12 month follow up were recruited for the study along with matched controls (n=5). We used an fMRI paradigm to assess efficiency of self-regulation of emotion in an event-related design to determine both spatial localization and temporal dynamics of reappraisal processes. All subjects were taught to up-regulate or down-regulate their response to IAPS scenes (negative or neutral) through the use of structured reappraisal strategies that involved reinterpretation. Subjects then returned to perform the scan session where they were presented with 200 randomly intermixed trials. The trials consisted of an instruction cue to either increase or decrease their emotions or simply look at the stimulus. This was followed by the presentation of the image, a rating period and the instruction to relax prior to the next trial. Behavioral data were also acquired assessing post-trial ratings for each scene. Thirty-three axial slices were acquired on a Philips Intera Achieva 3T scanner using a spiral in/out pulse sequence.
Results: Preliminary analysis in our control subjects partially confirmed prior findings in healthy volunteers that the circuitry involved in self-regulation of emotion includes dorsal lateral PFC, dorsal anterior cingulate, dorsal medial PFC and amygdala. Findings from the current replication set found up-regulation of negative affect was associated with medial and superior frontal gyrus activity ($p<0.05$). In contrast, down-regulation of negative affect was associated primarily with increased hippocampal and cingulate activity ($p<0.05$) when controlled for the false discovery rate. Further analysis will be presented including the spatial and temporal dynamic comparisons with remitted depressives.
Discussion: Identifying the neural mechanism(s) underlying experience-induced modulation of emotion in depression will have important implications for understanding both the basic pathophysiology of depression, as well as mapping long-term changes in prefrontal-limbic dynamics.

65. What Is the "Therapeutic Window" of Risperidone Long-Acting Injectable (RLAI)? A Meta-Analysis of Published and Unpublished Data
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Sponsor: Dean F. Wong

Background: Positron emission tomography (PET) is now a valuable tool in the process of finding dosing regimens for antipsychotic agents. Relationships have been established between receptor occupancy and/or drug plasma concentrations with clinical/side effects for antipsychotics. However, it is presently unclear whether depot formulations of antipsychotics follow the same relationships as their

oral analogs. Here we present a systematic analysis of published and unpublished data on the association between D_2 receptor occupancy/plasma concentrations and clinical/side effects for oral risperidone (RIS) and risperidone long-acting injectable (RLAI). We hypothesized that RIS and RLAI are characterized by the same relationship between plasma and brain concentrations.
Methods: We analyzed all published (PET) studies on the relationship between striatal D_2 receptor occupancy/plasma concentrations and antipsychotic/extrapyramidal side effects both for oral (RIS) and long-acting injectable risperidone (RLAI).
Results: Plasma concentrations of RIS and its active metabolite 9-OH-risperidone (the "active moiety") in patients on long-term oral therapy could not demonstrate a correlation with dosage, but there was a curvilinear relationship between plasma concentration and clinical improvement (Olesen et al., 1998; Mauri et al., 2001). Patients who improved most on the PANSS had plasma-active-moiety concentrations of 15-30 ng/mL. At a daily oral dosage of 6 mg/day 90% of patients had plasma active moiety concentrations of 21-62 ng/mL. PET studies show that at that dose a significant proportion of patients have striatal D_2-like occupancies sufficient to cause EPS, while a daily oral dose of RIS of 3 mg produces a striatal D_2-like occupancy in the range 70-80% in most patients (Farde et al., 1995; Nyberg et al., 1996). At the end of an open-label, 1-year study (Kane, et al. 2003), the mean pre-dose plasma concentrations of the active moiety ranged from 18.1 ng/mL for the 25-mg dose to 47.4 ng/mL for the 75-mg dose (Johnson & Johnson, data on file). At the end of a 12-week double-blind, placebo-controlled study (Fleischhacker et al., 2003), the mean pre-dose plasma concentrations of the active moiety ranged from 18.7 ng/mL (25 mg) to 44.7 ng/mL (75 mg, data on file). Striatal D_2-like occupancy was 25%, 40% and 48% in three patients given 25 mg of RLAI (Gefvert et al., 2005). 50 mg RLAI led to occupancies of 59%, 71% and 83%, and 75 mg to 62% and 72%. The corresponding active-moiety concentrations were 5.2-7.4 ng/mL, 15.0-37.0 ng/mL, and 20.9-22.5 ng/mL, respectively. Farde et al. reported plasma active-moiety concentrations of 5.0-46.6, 13.4-92.6 and 13.3-93.4 ng/mL at the same doses, respectively (Farde et al., 2002).
Discussion: Oral RIS and RLAI can be described by the same relationship between plasma concentration and striatal D_2 receptor occupancy. The available data suggest that the 80% threshold which is associated with a higher probability of EPS is reached with approximately 40 ng/mL of both RIS and RLAI, respectively. A plasma concentration of approximately 15 ng/mL of both formulations is associated with 60% striatal D_2 occupancy. The likelihood to be treated within the "therapeutic window" increases for patients on the 25 mg dose to the 50 mg dose. The 75 mg adds no benefit in most patients. Thus, the lower EPS incidence of RLAI compared to RIS which is observed in clinical studies might be attributed to a smoother pK profile (with less fluctuation between peak and trough plasma concentrations) of the RLAI formulation.

66. MAOA Polymorphism Affects BOLD Responses During Behavioral and Emotional Regulation

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Sponsor: Jon-Kar Zubieta

Background: A common functional polymorphism in the promoter region of the gene encoding the enzyme monoamino oxidase A (MAOA) has been found to modulate the risk of developing antisocial behavior in male children, a risk factor for substance use disorders (SUDs), interacting with childhood maltreatment (Caspi et al 2002). Low functional variants were associated with a higher likelihood of antisocial problems in male children subject to maltreatment, while the higher function forms provided higher levels of resiliency. Since this enzyme is capable of metabolizing catecholamines (dopamine, noradrenaline, and adrenaline) as well as the indolamine serotonin, the brain nuclei mediating these variations in risk, and stress by risk interactions are presently unknown. They may include both impulse control mechanisms (for example, associated with dopaminergic function) and affective responses (more prominently modulated by serotonin).
Methods: The present study investigated the effect of MAOA genotype on blood oxygen level dependent (BOLD) responses to an impulse control task and to positive and negative stimuli, using whole-brain voxel-by-voxel analyses. Fourteen males and females between the ages of 15 and 20 years were scanned during the go-no-go task and while passively reading positive, negative and neutral words from the Affective Norms for English Words (ANEW) list from the NIMH Study of Emotion and Attention (University of Florida). Six volunteers had the low functioning variant and 8 had the high functioning variant.
Results: Statistical Parametric Mapping (SPM) analysis revealed an increase in prefrontal cortex and basal ganglia activation during the reading of negative versus neutral words in those volunteers with the high activity variant. A similar pattern was found for positive versus neutral words. During impulse control, BOLD activation was increased in those with the low functioning variant in the brainstem and extended amygdala.
Discussion: These findings suggest that MAOA genotype influences risk factors for SUDs broadly, affecting both affective and behavioral regulation.

67. Brain Glycine Increases Detected During Oral Glycine Supplementation with TE-Averaged Proton Spectroscopy

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Background: Pharmacological agents are being developed to target the Gly regulatory (co-agonist) site on NMDA receptors, to treat disorders involving glutamatergic N-methyl-D-aspartate (NMDA) signaling abnormalities. These include addictive disorders, which are associated with NMDA hyperactivity[1], and schizophrenia, which may involve NMDA receptor hypofunction[2]. Recent work indicates that cortical synaptic Gly levels are maintained at equilibrium by glycine transporters. Thus, pharmacological attempts to regulate NMDA receptors via glycinergic mechanisms may be limited by synaptic compensation. Brain Gly dynamics are difficult to study in vivo because of a lack of suitable noninvasive methods. Conventional proton magnetic resonance spectroscopy (1HMRS) is limited in its ability to measure brain Gly, because the chemical shift of the 1HMRS Gly resonance is coincident with dominant *myo*-inositol (mI) resonances[3]. Accordingly, we developed a novel, noninvasive Gly detection method based on echo time (TE)-averaged (TEAV) 1HMRS, which involves averaging of multiple 1HMRS spectra acquired at different TEs[4]. Our method capitalizes on the fact that mI resonances are strongly *J*-coupled and, when averaged from spectra acquired at multiple TEs, their signals are reduced by destructive interference. By contrast, the Gly resonance is not *J*-coupled and is relatively unaffected by TEAV. Our initial phantom studies showed a direct correlation between Gly concentration and TEAV 1HMRS Gly signal[4]. Presently, we acquired TEAV spectra from occipital cortex in healthy young subjects to determine a) test-retest stability of the brain Gly signal and b) whether oral Gly loading increases the brain Gly resonance.
Methods: All studies were conducted on a 4.0 Tesla Varian scanner, using TEAV 1HMRS[4]. Spectra were analyzed using LC-Model v. 6.0-1. Healthy adults were recruited either for test-retest scans or for Gly loading studies. Gly loading was accomplished with a modification of a paradigm shown previously both to increase plasma Gly levels (3.5- to 6.5-fold) and to improve negative symptoms of schizophrenia[5-7]. Our 13-day protocol involved BID consumption of a Gly-enriched lemon drink. Initial Gly doses were 10 g/day for 2 days, followed by

0.2, 0.4, and 0.6 g/kg/day each for 2 days, with the terminal dose of 0.8 g/kg/day (~60 g) maintained for 5 days.
Results: In repeat scans from 6 subjects, brain Gly levels averaged 99.4±8.8% (mean±SE) of initial scan levels indicating good test-retest reliability. For the 2 subjects to date who completed the Gly loading protocol, brain Gly levels increased to 152±33% baseline levels (mean±SD, $F_{1,6}$=7.3, P<0.04 versus test-retest variation). Studies in additional healthy subjects are underway.
Discussion: These data suggest that TEAV 1HMRS may be useful for quantifying treatment-induced brain Gly changes. They also suggest that there may be substantial variation in the degree of brain Gly increase induced by oral Gly loading, which may in part account for variability in the clinical response to Gly therapy in schizophrenia[5-7].
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68. DTI of Cerebellar and Basal Ganglia Pathways in OCD

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Sponsor: Wayne Goodman

Background: Few diffusion tensor imaging (DTI) studies have yet examined cerebellar pathways, despite recent fMRI evidence for cerebellar dysfunction, in OCD individuals. Although the cerebellum is possibly best known for its involvement in motor control, evidence suggests that the cerebellum also modulates a wide range of cognitive functions. Using DTI, this study aims in part to investigate the possibility that cerebellar connections as well basal ganglia connections are disrupted in OCD. Another prominent regional finding in OCD subjects was an enlarged prefrontal cortical volume relative to controls. However, the finding derived mostly from larger prefrontal regions in younger children. In fact, age correlated inversely with prefrontal volume in OCD patients, so that by adulthood OCD patients had smaller prefrontal volumes than did controls. We also aim to use DTI to identify a structural basis for functional compensation that may be shown in fMRI studies. Based on the previous fMRI findings suggesting that the prefrontal area is strongly activated when suppressing tic symptoms, it was suggested that the larger prefrontal volumes in children probably represented an activity-dependent plastic change of prefrontal tissues that helped individuals with tics to suppress and compensate for their symptoms. It was speculated that the relatively smaller prefrontal volumes in older OCD patients represent a marker for symptom persistence into adulthood. OCD children who have relatively small prefrontal volumes may be likely, if followed into adulthood, to have enduring symptoms. Reduced prefrontal volumes in OCD subjects would then signal a decreased capacity or limited reserve in their neocortical neuromodulatory systems that presumably help to compensate for the presence of tics.
Methods: Using high angular resolution diffusion imaging (HARDI) techniques, we have reconstructed the white matter fibers in four patients with OCD and gender- and age-matched healthy controls. In these adults with OCD, three of them are without tics and one with tics (male, age 33, not on medication). We have employed an ROI analysis method for comparing the focal fractional anisotrosopy (FA), ADC, and R2 ratio (our newly developed HARDI measurement for fiber complexity, i.e. in the region having fiber crossing or branching).
Results: We found that all these OCD patients show an enhanced R2 ratio as well as FA (but not ADC) in the left prefrontal cortex. But only the increase in R2 ratio (not FA) in OCD (n = 4) reached a statistical significance (P < 0.05) compared to the healthy controls (n =12), indicating a possible higher sensitivity of our R2 measurement relative to FA. There are no significant differences in FA, R2 or ADC at the corpus callosum and cerebellum between the OCD group (n =4) and healthy group (n = 12) when data were analyzed collectively. However, the ADC value in the OCD patient with tic is significantly larger (by 3SD) than the mean of ADC in the healthy group at the corpus callosum and cerebellum. There is also a trend of increases in R2 ratio and FA at the basal ganglia (especially at the internal capsules) in this patient (but not in other OCD patients) compared to the healthy group.
Discussion: These preliminary results may implicate region-specific and symptom-specific abnormalities regarding the white matter changes measured by DTI. Future studies will examine a larger number of subjects with different but specific subtypes of OCD.

69. The Old Drug Scopolamine Offers New Promise as a Potent Antidepressant Agent: A Randomized, Placebo-Controlled Clinical Trial

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Sponsor: Phillip Gold

Background: The need to develop improved therapeutic agents that more quickly and effectively treat depression is critical. Here we introduce a highly promising new treatment capable of inducing rapid antidepressant effects. In a pilot study we evaluated the role of the cholinergic system in cognitive symptoms of depression using the antimuscarinic, scopolamine (n= 8). Unexpectedly, we observed significant reductions in depression severity during scopolamine (4 ug/kg) versus placebo (p= 0.002), suggesting antidepressant responses. A second experiment was designed to more specifically evaluate scopolamine as a potential antidepressant agent.
Methods: Nineteen currently depressed individuals with major depressive disorder or bipolar disorder (thirteen with poor prognoses) entered a double-blind, placebo-controlled, cross-over clinical trial, involving multiple sessions with i.v. infusions of placebo or scopolamine (4 ug/kg). Individuals were randomized into either a P/S or S/P sequence (P= three placebo sessions; S= three scopolamine sessions). Psychiatric interviews utilizing the Montgomery & Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HARS) occurred prior to each infusion.
Results: Eighteen patients completed the protocol. The P/S group showed no significant change during placebo versus baseline; significant reductions in MADRS (p< 0.0001) and HARS (p< 0.0001) scores were observed following the administrations of scopolamine versus placebo. The S/P group also showed significant reductions in MADRS (p<0.0001) and HARS (p<0.0001) scores following the administration of scopolamine, relative to placebo. In both groups, improvement was significant at the first evaluation after the administration of scopolamine (p< 0.002).
Discussion: These results provide three independent samples each showing rapid, robust antidepressant responses to the antimuscarinic, scopolamine. Importantly, these responses occurred in patients with predominantly poor prognoses.

70. Genetic Analysis of Dorsal Raphe Tph2 Expression: Potential Interaction with Antidepressant Responsive Gene Kf1 (Rnf103)

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Background: The goal of this investigation was to use BxD recombinant inbred mice to conduct quantitative trait genetic mapping of dorsal raphe Tph2 expression. Tph2 is the gene that encodes the neuron specific isoform of tryptophan hydroxylase. The ultimate objective of the project is to identify the trans elements that regulate expression of this gene in the CNS.

Methods: The general phenotype that we are quantifying is abundance of the transcript that encodes a gene of interest in total RNA isolated from a brain region of interest. Transcript abundance is quantified with real time RT-PCR in a relative abundance assay and the read-out measure is detection threshold cycle (Ct), which is the PCR cycle in which the transcript is detected. Our standard method is to quantify transcript levels from six individual, male animals from each line and then establish the strain mean transcript abundance by averaging the Ct values prior to conducting the genetic analysis, so the actual phenotype is strain mean Ct value for that particular transcript and brain region. Genetic analysis is conducted with the QTX computer program and the genetic marker set is from Dr. Robert Williams at the University of Tennessee Health Science Center, School of Medicine (Memphis, TN).
Results: QTL analysis of Tph2 transcript data revealed a highly significant association ($p<0.001$ genome wide) on chromosome 6 at D6Mit16 and a significant association ($p<0.05$ genome wide) on chromosome 9 at S09Gnf007.700. Scrutiny of the genes on chromosome 6 at D6Mit16 revealed the Kf1 structural gene (also known as Rnf103) residing at this same location. Expression of the Kf1 gene has been shown to be responsive to the SSRI type of antidepressants, ECT and repeated transcranial magnetic stimulation. We therefore generated transcript abundance data for this target and the SDP was clearly biallelic. QTL mapping of Kf1 data revealed significant associations at D6Mit16 on chromosome 6 and at S09Gnf007.700 on chromosome 9. Even at the low stringency, point significance of $p<0.001$ only these two associations were returned in marker regression of Kf1 transcript data.
Discussion: Kf1 is a member of the RING-H2 family of molecules and may be part of the ubiquitin-mediated proteolysis pathway and we believe that this is a very high probability candidate gene for the chromosome 6 QTL impacting Tph2 transcript levels.

71. Genetic Analysis of Dorsal Raphe 5-HT1A, SERT and Glucocorticoid Receptor Expression: Potential Shared Genetic Regulation

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Background: The goal of this investigation was to use BxD recombinant inbred mice to conduct quantitative trait genetic mapping of dorsal raphe 5-HT1A and SERT expression. The 5-HT1A receptor is the autoreceptor that resides on serotonergic neurons in the DR and the SERT is the specific serotonin reuptake pump that clears 5HT from the synapse. The ultimate objective of the project is to identify the trans elements that regulate expression of these genes in the CNS.
Methods: The general phenotype that we are quantifying is abundance of the transcript that encodes a gene of interest in total RNA isolated from a brain region of interest. Transcript abundance is quantified with real time RT-PCR in a relative abundance assay and the read-out measure is detection threshold cycle (Ct), which is the PCR cycle in which the transcript is detected. Our standard method is to quantify transcript levels from six individual, male animals from each line and then establish the strain mean transcript abundance by averaging the Ct values prior to conducting the genetic analysis, so the actual phenotype is strain mean Ct value for that particular transcript and brain region. Genetic analysis is conducted with the QTX computer program and the genetic marker set is from Dr. Robert Williams at the University of Tennessee Health Science Center, School of Medicine (Memphis, TN).
Results: QTL mapping of 5-HT1A transcript abundance data revealed significant associations ($p<0.05$ genome-wide) on chromosome 12 at D12Mit222 and on chromosome 18 at 20 cM with the marker D18 Mit17. Only suggestive level QTL were detected for SERT transcript abundance, but there was one on chromosome 12, coincident with the QTL detected for 5-HT1A transcript abundance. The addictive regression coefficients of the SERT and 5-HT1A QTL were opposite each other, indicating that high expression of 5-HT1A is associated with low expression of SERT. The Nr3c1 gene (glucocorticoid receptor structural gene) resides at 20 cM on chromosome 18 and we immediately considered this as a potential candidate gene for this QTL, as the GR is known to impact transcription of the 5-HT1A gene. So we generated transcript abundance data for GR and QTL mapping revealed three significant associations, on proximal chromosome 1 at D01Msw003, on chromosome 6 at D6mit16, the location of Kf1 and on chromosome 9 at S09Gnf007.700. Examination of the genes on proximal chromosome 1 reveals that the Ncoa2 (nuclear receptor co activator 2) gene, also known as glucocorticoid receptor interacting protein-1 (GRIP-1) resides at 1 cM on this chromosome. The sequences on chromosome 9 around S09Gnf007.700 contain a number of potential candidate genes including Zfp653, which encodes a zinc-finger, DNA binding protein that interacts with nuclear receptors including the GR, to repress transcription of GR responsive genes.
Discussion: Interestingly, Zfp653 and GRIP-1 appear to oppose each other, with GRIP-1 mediating transcriptional activation and Zfp653 blocking that activation of GR responsive genes. These results seem to indicate a significant amount of shared genetic regulation between the serotonergic system and the glucocorticoid receptor systems in the dorsal raphe.

72. Glucocorticoid Receptor Transgenic Mice as Models for Depression

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Sponsor: Fritz Henn

Background: Altered glucocorticoid receptor (GR) signalling is a postulated mechanism for the pathogenesis of major depression. To mimic the human situation of altered GR function claimed for depression we have generated mouse strains that under- or overexpress GR, but maintain the regulatory genetic context controlling the GR gene.
Methods: We generated: i) GR heterozygous mutant mice (GR+/-) with a 50% GR gene dose reduction; and ii) mice overexpressing GR by a yeast artificial chromosome resulting in a 2-fold gene dose elevation. These strains were subjected to a large battery of basal and stress-related behavioral tests. Furthermore, they were analysed for neuroendocrinological and neurochemical alterations.
Results: GR+/- mice exhibit normal baseline behaviors, but demonstrate increased helplessness after stress exposure, a behavioral correlate of depression in mice. Similar to depressed patients, GR+/- mice have a disinhibited HPA system and a pathological DEX/CRH test. Thus, they represent a murine depression model with good face and construct validity. Overexpression of GR in mice evokes reduced helplessness after stress exposure, and an enhanced HPA system feedback regulation. Therefore they may represent a model for a stress-resistant strain.
Discussion: These mouse models can now be used to study biological changes underlying the pathogenesis of depressive disorders. As a first potential molecular correlate for such changes we identified a downregulation of BDNF protein content in the hippocampus of GR+/- mice, which is in agreement with the so-called neurotrophin hypothesis of depression. Furthermore, these strains may represent a tool to detect pharmacological mechanisms or develop new psychopharmacological principles for the treatment of depression.

73. Integration of Emotion-Laden and Working Memory-Related Information in the Prefrontal Cortex

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Sponsor: Robert Friedel

Background: Emotion is not only central to the quality and range of everyday human experience, but also to the core symptoms of depression and anxiety disorders. An emerging theme is the question of how emotion modulates cognition. Mood symptoms are frequently accompanied by cognitive symptoms, suggesting that emotion-processing limbic circuits may also affect cognitive function through interactions with cortical circuits.
Methods: To investigate this topic, we studied 82 healthy volunteers using event-related fMRI. All subjects performed a working memory and control task using unpleasant, pleasant, and neutral IAPS images. Since the cortex is parcellated into highly-specialized neuronal networks, we hypothesized that it is possible to identify two spatially distinct cortical domains, one for emotional and one for cognitve processing. Further, we wanted to explore to what degree the amygdala is functionally connected with prefrontal areas. To provide the topological accuracy necessary, we used a surface-based fMRI approach.
Results: Differential locales of activation related to cognitive and emotional processing were found in distinct PFC regions, with the cognitive component of task processing primarily activating dorsolateral prefrontal (DLPFC, BA 46), while the contrasts that isolated the emotional component revealed activation primarily in ventromedial and dorsomedial prefrontal cortex (BA 9). Functional connectivity showed a strong inverse relationship between amygdala and DLPFC activation, suggesting top-down regulation of amygdala activity during a resting neuronal network. Consistent with previous studies of memory retrieval, a similar inverse relationship was found between hippocampus and DLPFC. Preliminary data indicate that this principle is reversed during emotion processing.
Discussion: These data suggest spatially distinct cognitive and emotional domains in the PFC. Furthermore, we conclude that a resting neuronal network leads to a top-down control of limbic cortex, whereas emotional engagement of neural networks inverts this principle.

74. Neural Correlates of Anxiety in Serotonin 1A Receptor-Deficient Mice

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Sponsor: Past Travel Awardee, Bristol-Myers Squibb, 2003

Background: Mice lacking the serotonin 1A receptor (5-HT1AR) show increased levels of anxiety-related behavior across multiple tests and background strains. Tissue-specific rescue experiments, lesion studies, and neurophysiological findings all point towards the hippocampus as a potential mediator of the phenotype. Serotonin, acting through 5-HT1ARs, can suppress hippocampal theta-frequency oscillations, suggesting that theta oscillations might be increased in the knockouts.
Methods: To test this hypothesis, local field potential recordings were obtained from the hippocampus of awake, behaving knockouts and wild-type littermates. Tungsten microelectrodes were implanted in the pyramidal layer of the CA1 region of the dorsal hippocampus. Field potential recordings were made while animals explored an elevated plus maze and foraged for food pellets in a familiar environment, as well as during REM sleep. Power spectra from the field potential recordings were used to compare the magnitude of theta frequency oscillations across genotypes and environments.
Results: The magnitude of theta oscillations was increased in the knockouts, specifically in the anxiety-provoking elevated plus maze and not in a familiar environment or during REM sleep. The increase in the knockouts was seen regardless of location within the maze or speed of the animal. The increase persisted on multiple exposures to the maze, suggesting that the increase was not due to novelty. Theta power in the elevated plus maze correlated with the fraction of time spent in the open arms, an anxiety-related behavioral variable, in both genotypes.
Discussion: These experiments demonstrate significant abnormalities in hippocampal activity in awake, behaving 5-HT1AR knockout mice. The findings suggest a role for hippocampal theta oscillations in the expression of anxiety-related behaviors in 5-HT1AR knockout mice. The results form a framework for further study into the consequences of 5-HT1AR deletion on the neurophysiology of the neural circuits underlying anxiety.

75. Mouse Strain Differences in Single Dose Lithium Attenuation of Amphetamine Hyperactivity

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Background: Inbred and outbred mice have historically been utilized to compare effects of variations in biology and genetics in behavioral models. More recent advances in neurobehavioral genetics have increased our awareness of the behavioral patterns of different mouse strains and characterized essential neural processes that are influenced by strain-dependent inheritable traits. As examples, mouse strain differences have been identified in hippocampal-dependent spatial learning behaviors, adult neurogenesis, and the forced swim and tail suspension tests. These studies highlight the utility of studying strain differences to elucidate the molecular/cellular underpinnings of complex behaviors and predictive responses to current medications. We have undertaken a comparison of inbred and outbred mouse strains to delineate the range of performance and pharmacological effects in paradigms that are responsive to lithium. Lithium attenuation of stimulant-induced hyperactivity represents a rodent model for the mechanism of lithiums therapeutic action, the development of novel lithium mimetic compounds, and models a clinical endophenotype.
Methods: We studied activity in 10 (3 outbred) mouse strains that received 1) no drugs, 2) lithium only, 3) amphetamine only, or 4) lithium (100mg/kg) 15 minutes prior to amphetamine (2mg/kg).
Results: There was a large degree of strain variation in the effects of lithium in this model. For example, C57/BL5J mice were among the best responders to lithium while CD-1 mice, which were responsive to amphetamine, showed no response to lithium.
Discussion: These results will allow for biological and genetic studies to determine the molecular and cellular underpinnings of the strain dependent behavioral differences in this lithium responsive model.

76. Prevalence of Metabolic Syndrome in Partial Responders to Selective Serotonin Reuptake Inhibitors with Major Depressive Disorder

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Sponsor: Madhukar Trivedi

Background: Major depressive disorder (MDD) is associated with increased risk for cardiovascular disease (CVD). Emerging evidence also suggests a link between cardiovascular disease, metabolic syndrome and depression. The metabolic syndrome, a strong CVD risk

factor, is characterized by elevated abdominal obesity, triglycerides, blood pressure, and fasting glucose, and by low levels of high-density lipoprotein (HDL) cholesterol. There are limited data evaluating the prevalence of metabolic syndrome in individuals with depression.
Methods: We determined the prevalence of the metabolic syndrome in 71 individuals screened to participate in the TReatment with Exercise Augmentation for Depression (TREAD) study, an NIMH-funded randomized, controlled trial. This trial is investigating exercise as an augmentation strategy in partial responders to an adequate dose and duration of selective serotonin reuptake inhibitor (SSRI) treatment. Participants are sedentary individuals with a diagnosis of Major Depressive Disorder based on a structured clinical interview. Participants have reported improvements with SSRI treatment, but still have residual symptoms, quantified by a score of 14 or greater on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Blood pressure, anthropometry, and laboratory analyses were measured at a screening visit for the TREAD study. Metabolic syndrome was defined by the Adult Treatment Panel III (ATP III) criteria.
Results: While patients reported depressive symptom improvement prior to entry, metabolic syndrome and cardiovascular disease risk factors were still of concern in this sample. Twenty-four percent of the sample with all relevant data points met ATP III criteria for metabolic syndrome (i.e., 3 or more determinants). When assessed by gender, 43% of men met criteria (6/14) compared to 19% of women (10/53), and this difference approached statistical significance (χ^2 = 3.5, p=0.07). When each component of metabolic syndrome was assessed, fifty-seven percent of the sample met criteria for abdominal obesity, 24% had triglyceride levels ≧ 150 mg/dL, 30% had low HDL cholesterol, 38% had blood pressure ≧ 130/ ≧ 85 mm Hg or were taking blood pressure medication, and 13% had fasting glucose ≧ 110 mg/dL. Men were more likely to have elevated blood pressure (or blood pressure medication use) (χ^2 = 5.3, p=0.02) and elevated blood glucose (χ^2 = 6.4, p=0.01).
Discussion: There is a clear need to address CVD risk factors in depressed individuals, as supported by these data, and to further explore the important gender differences in metabolic syndrome that may be present in MDD. Current treatment approaches for depression are not designed to improve determinants of the metabolic syndrome or cardiovascular disease risk factors. Thus, there is need to examine non-pharmacological treatment modalities for depression, such as exercise, that not only effectively treat depressive symptoms, but can also improve CVD risk factors including many of the components of the metabolic syndrome.

77. Surinabant, a New CB1 Receptor Antagonist, Displays Efficacy in Animal Models of Attention Deficit/Hyperactivity Disorder

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Sponsor: Craig Karson

Background: There is growing evidence that CB1 receptor antagonists may be useful for the treatment of hyperkinetic syndrome associated with attention deficit (AD/HD).
Methods: We investigated the effects of the novel CB1 receptor antagonist, surinabant (SR147778) in several experimental situations that have been claimed to model certain aspects of the AD/HD pathology in rodents: spontaneous hyperactivity in mice for the hyperkinetic syndrome, delayed choice paradigm for impulsivity, and distractibility for attention deficit in rats. An EEG profile was performed to compare the electrocortical activity of surinabant with that of the psychostimulant, amphetamine.
Results: Results showed that surinabant (3 mg/kg, ip) was able to normalize spontaneous locomotor hyperactivity of BALB/c mice habituated to their environment, an effect shared by low doses of amphetamine. The effects of surinabant were not due to a non-specific change in muscular tone. In the T-maze model of impulsivity in rats, surinabant (0.3 mg/kg, ip) increased the number of choices for a large but delayed reward vs. a small immediate one, an effect interpreted as an increased capacity to wait for a reward. In a distractibility paradigm, surinabant (0.1-1 mg/kg, ip), like methylphenidate, was found to increase selective attention of adult rats towards a novel juvenile, in the presence of a familiar one. Results from the EEG study revealed that at a high dose (10 mg/kg, ip), surinabant increased wakefulness duration (determined by the theta rhythm in rat), in the absence of other EEG modifications.
Discussion: Together, these findings suggest that the CB1 receptor antagonist surinabant may represent a new therapeutic approach for the treatment of AD/HD, with an efficacy against the three main symptoms of this condition - namely the hyperkinetic syndrome, impulsivity and attention deficit. Furthermore, at high doses, surinabant should be devoid of amphetamine-like side effects, such as agitation.

78. The Dexamethasone/CRF Test in Men with Major Depression: Role of Childhood Trauma

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Sponsor: Charles Nemeroff

Background: The combined dexamethasone/CRF test is generally considered to be the most sensitive measure of hypothalamic-pituitary-adrenal (HPA) axis hyperactivity in patients with major depression. Moreover, this test possesses high sensitivity to detect familial depression risk in asymptomatic first-degree relatives of depressed patients, serves as surrogate marker for treatment responsiveness of depressed patients, and demonstrates variation with polymorphisms of genes involved in HPA axis regulation and depression course. Because stress, especially early in life, is a major risk factor for depression that has been shown to impact on HPA axis activity, we sought to determine the effects of childhood abuse on dexamethasone/CRF test results in depressed patients. We have previously reported that several of the neurobiological alterations of depression indeed are secondary to early-life stress and likely induce the increased vulnerability of victims of child abuse and neglect to develop depression. In the current study, we tested the hypothesis that early-life stress is associated with increased HPA axis activity as assessed in the dexamethasone/CRF test.
Methods: Fifty healthy men, 18 to 60 years of age, with no history of mania or psychosis, no active substance abuse or eating disorder within 6 months, and medication-free were recruited into four study groups: (1) normal volunteers with no history of childhood abuse or psychiatric disorder (n=14); (2) current major depression with a history of child abuse (n=14); a history of child abuse without current major depression (n=16); and (4) current major depression but no history of childhood abuse (n=6). Plasma cortisol and adrenocorticotropin (ACTH) concentrations were measured in response to 1 microgram/kg oCRF administered intravenously at 3 p.m. after overnight pretreatment with oral 1.5 mg dexamethasone.
Results: When comparing depressed versus non-depressed men, regardless of childhood trauma, we observed a trend for increased cortisol secretion in response to dexamethasone/CRF in the depressed group [$F(8,352)=1.927$, $P=0.055$]. Comparison of abused versus non-abused men, regardless of depression, revealed a highly significant effect reflecting increased cortisol responses in the abused group [$F(8,360)=4.251$, $P<0.001$]. Accordingly, when stratifying groups by both major depression and histories of childhood trauma, the four comparison groups significantly differed in terms of responsiveness to dexamethasone/CRF administration [$F(24,344)=2.180$, $P=0.001$], with only abused men with current depression, but not depressed men without childhood trauma, demonstrating increased cortisol responses. Concordant results were found for ACTH concentrations.

Discussion: Our results suggest that childhood trauma has a marked influence on results of the dexamethasone/CRF test in depressed patients. This finding is of interest because the test is generally considered a marker of depression risk in the literature. We suggest that the test is not only sensitive to detect familial or genetic risk, but also detects environmental risk secondary to early-life stress. Previous findings in depression research might have been significantly confounded by lack of consideration of early-life stress history. In addition, our findings represent the first demonstration of persistent HPA axis hyperactivity after childhood abuse in adult male subjects.

79. Regulation of 5-HT1A Receptor Function in Inducible BDNF Knock-Out Mice Following Administration of Fluoxetine or Corticosterone

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Sponsor: David Morilak

Background: Brain-derived neurotrophic factor (BDNF) plays a fundamental role in promoting the structural plasticity of neurons in the adult brain. A variety of types of stress reduce BDNF expression in brain and therefore BDNF may be involved in the pathophysiology of stress-related psychiatric disorders. Antidepressant treatments upregulate the levels of BDNF in specific brain regions, most notably the hippocampus. 5-HT_{1A} receptors, implicated in affective disorders, are found in high density in cortical and limbic structures (e.g. hippocampus), as well as in serotonergic cell body areas where they function as the somatodendritic autoreceptor.
Methods: To examine the interaction between forebrain BDNF and 5-HT_{1A} receptor function, we used an inducible knockout (KO) system to delete BDNF selectively in forebrain regions during embryogenesis. These mice show a 70% reduction in BDNF mRNA in hippocampus, cortex, nucleus accumbens and basolateral amygdala. Using quantitative autoradiography, 5-HT_{1A} receptor function, at the level of receptor-G protein interaction, was assessed by measuring [^{35}S]GTPγS binding stimulated by 8-OH-DPAT (1 μM).
Results: In dentate gyrus of hippocampus, there was a significant decrease in 5-HT_{1A} receptor-stimulated [^{35}S]GTPγS binding in BDNF KO versus control mice. Chronic administration of fluoxetine (10 mg/kg, i.p,, 21 days) to control mice did not alter 5-HT_{1A} receptor-stimulated [^{35}S]GTPγS binding in this brain region. By contrast, chronic fluoxetine treatment of BDNF KO mice resulted in a significant increase in 5-HT_{1A} receptor-stimulated [^{35}S]GTPγS binding in dentate gyrus. In the dorsal and median raphe nuclei where the 5-HT_{1A} receptor functions as the somatodendritic autoreceptor, there was no difference in 5-HT_{1A} receptor-stimulated [^{35}S]GTPγS binding in control vs. BDNF KO mice. Chronic administration of fluoxetine or corticosterone (10 mg/kg, s.c., 21 days) resulted in a significant decrease of 5-HT_{1A} receptor-stimulated [^{35}S]GTPγS binding in the dorsal and median raphe of control, but not BDNF KO mice.
Discussion: These findings suggest that loss of BDNF in forebrain regions during embryogenesis prevents the attenuation of 5-HT_{1A} receptor function in serotonergic cell body areas following chronic corticosterone or fluoxetine treatment, and differentially influences the regulation of 5-HT_{1A} receptor function in hippocampus.

80. Demonstration on PET of a Widespread Deficiency in Serotonin Transporter Binding in Bipolar Depression

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Background: Postmortem brain and platelet studies and the efficacy of serotonin reuptake inhibitors for bipolar depression suggest that the serotonin transporter (5-HTT) plays a key role in Bipolar Disorder (BD). Based on this and the similarities in the presentation of major depressive episode in BD and Major Depressive Disorder (MDD), we hypothesized that depressed BD patients would have lower 5-HTT binding potential in amygdala and midbrain compared with healthy volunteers, as we have shown in depressed subjects with MDD. We also explored 5-HTT BP in anterior cingulate cortex, hippocampus, putamen, and thalamus because of their potential role in mood disorders, as well as the relationship between 5-HTTLPR genotype and BP across regions.
Methods: In vivo brain 5-HTT binding potential was compared in 18 depressed, medication-free bipolar subjects and 41 healthy volunteers. 5-HTT binding potential (BP1 = f1Bmax/KD) was determined using [11-C]McNeil 5652 and positron emission tomography. Each subject had a metabolite-corrected arterial input function and magnetic resonance image for the delineation of regions of interest. We also determined the 5-HTTLPR genotype for all subjects, based on triallelic determination. Data was analyzed using a linear mixed effects model.
Results: As hypothesized, we found that depressed BD subjects had lower 5-HTT BP1 in midbrain (27%) and amygdala (26%) compared with healthy volunteers. 5-HTT BP1 was also lower in BD subjects in hippocampus (23%), thalamus (23%), putamen (16%), and anterior cingulate cortex (23%) ($F = 5.41$, $df = 1, 58$, $p = 0.024$). There was no evidence that the deficit in 5-HTT BP1was different across the studied regions ($F = 1.34$, $df = 5, 285$, $p = 0.247$). There was also no difference between BD subjects who had previously attempted suicide and subjects who had not. There was no effect of 5-HTTLPR genotype on 5-HTT BP1 across regions within the bipolar group.
Discussion: Lower 5-HTT BP1 in Bipolar Depression appears both more extensive and more pronounced compared with MDD. The lack of effect of 5-HTTLPR genotype on 5-HTT BP1 in the bipolar group is in agreement with our findings in suicide victims, MDD and healthy volunteers. Nonetheless, widespread deficits in 5-HTT BP1 in Bipolar Depression suggest that serotonergic dysfunction has a role in its pathophysiology. Whether this effect is state dependent or persists into euthymia or mania remains to be determined. This work was supported by PHS Grants: MH62185, MH59710, Stanley Medical Research Foundation, and American Foundation for Suicide Prevention.

81. Anxiolytic-Like Effects of a DNA Enzyme Targeting the Corticotropin-Releasing Factor 2(a) Receptor ($CRF_{2(a)}$) in the Rat Lateral Septum

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Background: The corticotropin-releasing factor system (CRF) integrates the body's response to psychological stress. The CRF system is composed of the CRF peptide and three urocortin peptides. These peptides can interact with two CRF receptors, termed CRF_1 and CRF_2. Multiple receptor isoforms exist, with the $CRF_{2(a)}$ being the predominate CRF_2 isoform expressed in the brain. While much is known about the biological actions of CRF_1, the CRF_2 is less characterized resulting in part from the lack of a selective small molecule CRF_2 antagonist. To further understand the role of the CRF_2 receptor in mediating the actions of CRF and the urocortins the present study utilized a catalytic DNA enzyme that targets the $CRF_{2(a)}$ receptor mRNA. This enzyme should cleave the $CRF_{2(a)}$ mRNA resulting in mRNA degradation and subsequent decease in $CRF_{2(a)}$ protein levels. The behavioral consequences of the treatment were assessed in the elevated plus-maze, which can measure anxiety-like behaviors. Preliminary studies showed that DNA enzymes directed against CRF receptors produced anxiolytic-like effects.
Methods: A 31 base DNA enzyme was designed to hybridize to 16 bp surrounding the translation start site of the rat $CRF_{2(a)}$ mRNA. The DNA enzyme (20 μg/side) was infused into the lateral septum (LS, 20

μg/μl, 0.65 μl/min), once a day for either two or five consecutive days; control rats were infused with saline. Two hours after the last infusion rats were tested in the elevated plus-maze for 5 min. Studies are currently in progress to identify the biochemical changes that underlie the DNA enzyme-induced behavioral effects.
Results: DNA enzyme treatment for 5 days resulted in an increase in % open arm time in the elevated plus-maze from 32.1±3.4% for vehicle-infused (n=6) to 64.4±3.4% for the DNA enzyme-infused (n=6; t_{10}=6.69; $p < 0.0001$). The number of open arm entries also increased from 4.2±0.5 for the vehicle-infused to 9.8±1.1 for the DNA enzyme-infused (t_{10}=4.59; $p < 0.001$). Similarly, DNA enzyme treatment for 2 days increased % open arm time from 26.7±6.6% for vehicle-infused (n=4) to 62.3±6.0% for DNA enzyme-infused (n=5; t_7=4.00; $p < 0.01$). The 2 day experiment was repeated in a separate study with a similar increase in % open arm time from 19.9±2.8% for vehicle-infused (n=14) to 53.1±3.5% for DNA enzyme-infused (n=12; t_{24}=7.50; $p < 0.0001$).
Discussion: Infusion into the LS of a DNA enzyme targeting the $CRF_{2(a)}$ for 2 or 5 days resulted in a significant increase in % open arm time in the elevated plus-maze that is consistent with an anxiolytic-like effect. This result agrees with previous reports on the anxiolytic-like effects of blocking CRF_2 receptors in the LS with pharmacological antagonists (Bakshi et al, J Neurosci 22:2926-2935, 2002) or decreasing CRF_2 receptor levels with centrally administered antisense oligonucleotides (Ho et al, Molec Brain Res 89:29-40, 2001). In conclusion, these data provide further evidence supporting an anxiogenic role for the $CRF_{2(a)}$ receptor in the rat LS. This research was supported by NIH grants MH070077 (SAN), MH040855 (NHK) and the University of Wisconsin Health Emotions Research Institute.

82. A Randomized Placebo-Controlled Trial of Risperidone Augmentation for Patients with Difficult-to-Treat Unipolar, Nonpsychotic Major Depression

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Sponsor: Martin Keller

Background: 30-50% of patients with major depression fail to respond to an adequate trial of antidepressant pharmacotherapy. Pharmacological treatment options available for nonresponders or partial responders include increasing the dose of the antidepressant, switching to another antidepressant, or augmenting with lithium, thyroid hormone, a second antidepressant, or an antipsychotic medication. This two-site study evaluated the use of risperidone as an augmenting agent in a double-blind placebo controlled design.
Methods: 97 patients (age 18-65 years) who met criteria for unipolar nonpsychotic major depression and failed to respond, or only partially responded, to at least a five week trial of an adequate dose of antidepressant monotherapy were randomized in a 2:1 ratio to receive adjunctive risperidone (n=67) (0.5-3 mg/day) or placebo (n=33) for an additional 4 week treatment trial. Primary outcome (remission status) was determined by a Montgomery-Asberg Depression Rating Scale (MADRS) rating ≤10 to denote remission. Secondary outcome measures included Hamilton Rating Scale for Depression (HRSD) scores, Clinical Global Impression (CGI) ratings, adverse events, and quality of life ratings (Q-LES-Q). Analytic strategies included modified intent-to-treat (i.e., patients received at least one dose of study medication, n=96) and completer analysis (i.e., patients received four weeks of study medication, n=82).
Results: At baseline the severity of depression was comparable between patients receiving risperidone augmentation vs. placebo augmentation, measured by the MADRS (mean, sd = 25.8, 5.7 vs. 25.5, 5.4), the HRSD (19.5, 4.7 vs. 18.6, 4.3), or the CGI ratings (moderate-markedly ill: 92.2% vs. 90.9%). Overall, the modified ITT analysis showed that subjects in both groups improved significantly over time in the MADRS scores, but the odds of remitting were significantly better for patients in the risperidone treatment group (odds ratio = 3.33, 95% CI = 1.303, 8.526, p=.011). At the end of four weeks of treatment 51.6% of the risperidone augmentation group (32/62) remitted compared to 24.2% of the placebo augmentation group (8/33) (CMH (1) = 6.48, p=.011). Results based on HRSD scores showed that at endpoint, 35.5% of the risperidone augmentation group (22/62) remitted (HRSD ≤ 7) compared to 18.2% of the placebo group (6/33) (CMH (1) = 3.10, p=.078). CGI change scores also improved for both groups (Risp: 4.2 to 2.8, Pla: 4.1 to 32.) but did not reach significance (F (1,91) = 2.92, p=.091) in between-group comparisons. There was no significant difference between groups in the overall number of adverse events reported. Patients in the risperidone group were significantly more likely to report increased appetite while patients in the placebo group were significantly more likely to report fatigue and abdominal gas. Overall quality of life and satisfaction with medication improved over time as well as between groups, with patients in the risperidone group reporting significantly higher (better) scores compared to the placebo group (Risp 1.3 to 2.5, Pla: 1.2 to 1.7, F (1,62) = 6.44, p= .014).
Discussion: Augmenting an antidepressant with risperidone for patients with difficult-to-treat depression leads to a significantly higher remission rate, significantly better quality of life, significantly better odds of remission without an increase in overall side effect burden. Augmentation with risperidone appears to be an efficacious treatment option for patients with difficult-to-treat depression.

83. Placebo-Controlled Trial of Venlafaxine ER in Prevention of Recurrence in Patients with Recurrent Unipolar Major Depression

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Background: This was a long-term, 3-phase, double-blind, placebo-controlled study in patients with major depressive disorder (MDD). The 2-year maintenance phase of study evaluated the long-term efficacy and safety of venlafaxine extended release (VEN XR) in preventing recurrence of depression.
Methods: During the double-blind acute treatment phase of this study, 1096 patients were randomly assigned in a 3:1 ratio to receive treatment with VEN ER (75-300 mg/day) or fluoxetine (20-60 mg/day) for 10 weeks. Patients in both treatment groups who achieved a satisfactory therapeutic response (17-item Hamilton Rating Scale for Depression [$HAM\text{-}D_{17}$] total score ≤12 and ≥50% decrease from baseline) entered a 6-month double-blind continuation phase remaining on the same medication. Patients responding at the end of the continuation phase were then enrolled into the maintenance phase of the study, which consists of 2 consecutive 12-month periods. At the start of each maintenance period, VEN ER responders were randomly assigned to receive double-blind treatment with VEN ER or placebo, and fluoxetine responders were continued for each period. We report results from the first 12-month maintenance period, which was designed to compare the time to recurrence of depression with VEN ER versus placebo. The primary definition of recurrence was a $HAM\text{-}D_{17}$ total score >12 and <50% reduction from baseline (acute phase) $HAM\text{-}D_{17}$ for 2 consecutive visits, or for 1 visit if these criteria were met at the last valid visit prior to early discontinuation. An additional definition, based on a consensus of a panel of expert psychiatrists upon review of the blinded data, included patients who met the criteria for the primary definition, as well as those who met the above criteria at 1 visit, and who were determined to have had a recurrence. The primary efficacy measure?time to recurrence?was evaluated using Kaplan-Meier methods and compared between the VEN ER and placebo groups using log rank tests. Secondary outcome measures included rates of response and remission (defined as $HAM\text{-}D_{17}$ ≤7). Safety evaluations included spontaneous adverse event reporting as well as electrocardiographic and laboratory tests.
Results: Patients responding to VEN ER at the end of continuation phase were randomly assigned to treatment with VEN ER (n=164) or

placebo (n=172) for the first 12-month maintenance period; 129 patients in each group were evaluable for efficacy assessments. The mean daily dose of VEN ER in this period was 224.7 mg (SD=66.7). The cumulative probability of recurrence through 12 months, based on the primary definition, was 23.1% (95% CI: 15.3, 30.9) for VEN ER and 42.0% (95% CI: 31.8, 52.2) for placebo (cumulative recurrence comparison P=0.005, log rank test). Based on the alternative definition, the cumulative probability of recurrence was 26.5% (95% CI: 18.4, 34.6) for VEN ER and 53.7% (95% CI: 41.8, 65.6) for placebo (cumulative recurrence comparison P<0.001, log rank test). At month 12, using last-observation-carried-forward analysis, the rate of response or remission was significantly higher in patients who continued treatment with VEN ER (80%) than in those with placebo (69%; P=0.012). Overall discontinuation rates were 49% for VEN ER and 73% for placebo. Rates of discontinuation due to adverse event were 4% for VEN ER and 8% for placebo, and due to unsatisfactory response were 17% for VEN ER and 27% for placebo.
Discussion: The study demonstrated that 12-month VEN ER maintenance treatment was effective in preventing recurrence of depression in patients with MDD who had been successfully treated with VEN ER during acute and continuation therapy.

84. Rapid Cycling Differentially Exacerbates Bipolar II Compared to Bipolar I Disorder: Implications for Adjunctive Antidepressant Therapy

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Sponsor: David Spiegel

Background: Emerging data suggest differential roles for adjunctive antidepressants in patients with bipolar I disorder (BPI) versus bipolar II disorder (BPII), and in patients with rapid cycling (RC) and without rapid cycling (Non-RC). We explored this issue considering both bipolar disorder subtype and illness course.
Methods: In 1,071 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder, measures of depressive burden and antidepressant intolerance were assessed at intake and during 18 months longitudinal monitoring, and compared in patients with BPI versus BPII, in patients with RC versus Non-RC, and considering both disorder subtype and course in patients with RC BPI, Non-RC BPI, RC BPII, and Non-RC BPII.
Results: Depressive burden tended to be greater in patients with BPII compared to BPI and in patients with RC compared to Non-RC. The presence of RC in BPI patients increased depressive burden to a level close to that seen in BPII. Antidepressant intolerance was significantly worse in patients with BPI compared to BPII and non-significantly worse in patients with RC compared to Non-RC. The presence of RC in BPII patients tended to increase antidepressant intolerance to a level close to that seen in BPI.
Discussion: RC may differentially exacerbate subtypes of bipolar disorder, by increasing depressive burden in BPI, and by increasing antidepressant intolerance in BPII. This may yield risk:benefit ratios for adjunctive antidepressants that vary from less favorable in RC BPI and Non-RC BPI, to intermediate in RC BPII, to more favorable in Non-RC BPII.

85. The REVAMP Medication Algorithm for Chronic Depression: Preliminary Results

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Background: REVAMP (Research Evaluating the Value of Augmenting Medication with Psychotherapy) is an NIMH sponsored multi-site study of psychotherapy augmentation (Phase 2) in chronically depressed patients who respond incompletely to an initial antidepressant trial (Phase 1). We have developed a pharmaco-therapy strategy based on a combination of empirical data and expert consensus. The algorithm is designed to be flexible and clinically relevant. This sequenced approach to treatment is consistent with other empirically derived algorithms and the recommendations of the TMAP and STAR-D studies. We will present results of the use of this algorithm in the first 613 patients entering the study.
Methods: Patients must have a current major depressive episode, as defined by DSM-IV, and report depressive symptoms persistent for more than 2 years without periods of remission. Subjects may be included if they meet criteria for double depression or recurrent major depression with incomplete recovery between episodes. Patients are assigned to open-label treatment for a twelve-week period based on prior history of antidepressant response or failure obtained using the ATHF. The treatment sequence includes two SSRIs, sertraline and escitalopram. Sertraline in particular has documented efficacy in chronic depression. Bupropion SR is intended for patients who have a history of failed response to two adequate trials of SSRIs or to augment those who achieved only partial response on an SSRI. Those patients who have not benefited from the above medications move on to dual action antidepressants (venlafaxine XR and mirtazepine) and lithium augmentation. Standard antidepressant dosing strategies are employed. The 24 item HAM-D is done every 2 weeks. . Criteria for defining response categories for purposes of augmentation differ somewhat from traditional treatment outcome category definitions. The rationale for this is that many patients traditionally categorized as "responders" (e.g., 50 % reduction in HAMD) continue to have significant residual symptoms, which could benefit from augmentation and are often so treated in clinical practice. Therefore in the current study definitions of response at the end of phase 1 were as follows: NR = less than 30% reduction of HAM-D from baseline and meets DSM-IV MDD criteria for 2 consecutive visits during weeks 6 to 12; FR= 60% or greater reduction HAM-D and HAM-D <8 and does not meet DSM-IV criteria for MDD for 2 consecutive visits during weeks 6 to 12; PR= not meeting criteria for either NR or FR by week 12.
Results: Of the first 613 patients entering the algorithm, 76% received sertraline, 13% escitalopram, 8% bupropion, 4% venlafaxine and one patient mirtazepine. Eighty percent of the 581 patients who have exited the first phase of treatment completed. ITT outcomes - 21% were FR, 48% were PR and 31% NR. Although unblinded the rate of NR among the first 208 patients completing phase 2 has been 8%.
Discussion: 1) A surprisingly high percentage of patients with chronic forms of major depression have not previously failed treatment with SSRIs; 2) 79% had a less than complete remission after an initial trial of pharmaco-therapy; 3)The vast majority of patients were substantially helped by treatment by the end of phase 2.

86. Olanzapine in the Treatment of Acute Mania in Adolescents with Bipolar I Disorder: A 3-Week Randomized Double-Blind Placebo-Controlled Study

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Background: To date, there is limited data from large-scale controlled trials concerning the efficacy of treatments for bipolar disorder in adolescents.
Methods: In this 3-week, multicenter, randomized, double-blind, parallel trial, patients 13-17 years of age with a diagnosis of bipolar disorder manic or mixed received either olanzapine (2.5-20 mg/day; N=107) or placebo (N=54). The primary efficacy analysis was mean

change from baseline to endpoint in Young Mania Rating Scale (YMRS) total score. Additional efficacy analyses included rates of response (≥50% decrease in YMRS total score and CGI-BP Severity of Mania score ≤3) and remission (YMRS total <12 and CGI-BP Severity of Mania score ≤3), time to response and remission, and baseline to endpoint changes on the Clinical Global Impression Scale (CGI-BP overall, mania and depression severity), Children's-Depression Rating Scale-Revised (CDRS-R), Overt Aggression Scale (OAS), and Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHDRS).
Results: The rates of study completion were 79.4% for patients treated with olanzapine, and 64.8% for those treated with placebo (p=.056). Olanzapine-treated patients experienced a significantly greater baseline to endpoint reduction in YMRS total score relative to placebo (-17.7 vs -10.0, p<.001; Effect Size, 0.84), and a greater proportion of olanzapine patients met response and remission criteria (44.8% vs 18.5%; p=.002 and 35.2% vs 11.1%; p=.001, respectively). Patients in the olanzapine group reached response and remission criteria significantly more rapidly (p=.003 and p=.002, respectively) relative to placebo. For nine of the eleven individual YMRS items, improvements were significantly greater with olanzapine compared to placebo. Significantly greater improvements with olanzapine treatment were also observed relative to placebo on the CGI-BP (overall and mania severity)(-1.6 vs -1.0; p<.001 and -1.7 vs -1.1; p<.001, respectively), ADHDRS (-11.4 vs -7.4; p=.048), and OAS (-3.6 vs -1.9; p<.001) scales. The types of adverse events among adolescent patients appear to be similar to those observed in adults. Somnolence, sedation, increased appetite and weight gain were treatment-emergent adverse events reported significantly more frequently among patients in the olanzapine-treatment group. Mean baseline to endpoint weight change was significantly greater for patients treated with olanzapine relative to placebo (3.7 vs 0.3 kg, p<.001). Significantly more olanzapine-treated patients experienced treatment-emergent weight gain ≥7% of baseline relative to placebo (41.9% vs 1.9%; p<.001). Treatment-emergent hyperprolactinemia was also significantly higher in olanzapine-treated patients. The incidence of treatment-emergent abnormal levels at any time during the study among olanzapine- and placebo-treated patients under fasting conditions was 1.2% vs 0.0%, n.s. for glucose; 1.3% vs 0.0%, n.s. for total cholesterol; 7.7% vs 0.0%, n.s. for triglycerides, or uric acid 7.8% vs 6.8%, ns, respectively.
Discussion: Other safety information including laboratory values and vital signs will be presented in the poster.

87. Paroxetine-Induced Increase in LDL Cholesterol Levels

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Sponsor: Past Travel Awardee, ADAA, 2001

Background: Paroxetine, a selective serotonin reuptake inhibitor, is widely prescribed since it is indicated for multiple psychiatric disorders including major depression and anxiety disorders such as panic disorder. Our objective was to assess the effect of short-term administration of paroxetine on the lipid profile, particularly low-density lipoprotein cholesterol (LDL-C) levels.
Methods: Blood samples for measurement of lipid profile were collected at baseline, after 8 weeks of paroxetine administration, and post-discontinuation in 33 male subjects [24 male healthy controls (HCs) and 9 male patients suffering from panic disorder (PD)].
Results: Paroxetine treatment, both in HCs and PD patients, induced a mean 9.35% increase in LDL-C that normalized post-discontinuation, suggesting causality. Potential confounding factors such as exercise, diet, and body mass index (BMI) did not explain such alterations in LDL-C.
Discussion: The LDL-C levels reached after 8 weeks of paroxetine treatment were above 2.59 mmol/L in 36% of our low cardiovascular (CV) risk subjects. This increase in LDL-C in this subgroup would be associated with a minor increase in coronary heart disease (CHD) risk that would not warrant therapeutic intervention according to the National Cholesterol Education Program (NCEP) guidelines. A similar 9.35% paroxetine-induced increase in LDL-C observed in the large number of psychiatric patients suffering from comorbid established CHD would be detrimental from a CV perspective and would oppose the new NCEP therapeutic goals of decreasing LDL-C levels by 30 to 40% in high and moderately high-risk patients.

88. Reduced Brain Docosahexaenoic Acid Content After a Single Reproductive Cycle in Female Rats Maintained on a Diet Deficient in n-3 Polyunsaturated Fatty Acids

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Sponsor: Salvatore Enna

Background: Low levels of n-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA, 22:6n-3), are implicated in postpartum depression, non-puerperal depression, and schizophrenia and affect the serotonergic and dopaminergic systems in animals. Long-chain polyunsaturated fatty acids (LC-PUFAs; 20+ carbons), are a major component of the phospholipids that form cell membranes, serve as precursors for prostaglandins and other signaling molecules, and affect gene transcription. The phospholipid fatty acid composition of various tissues, including brain, can vary over time depending on the availability of specific fatty acids. In humans, the nutritional demands of pregnancy can deplete maternal plasma DHA levels, but little is known about the effects of reproduction on LC-PUFA composition of the maternal brain. In this study, a rat model was used to determine whether brain phospholipid LC-PUFA composition is altered in female rats after pregnancy and lactation under dietary conditions supplying adequate or inadequate n-3 PUFAs.
Methods: The control diet was prepared from Harlan Teklad Basal Diet (TD00235 with mineral, vitamin, and choline additives) by adding 7% by weight of pure soybean oil (without partial hydrogenation). The n-3 PUFA-deficient diet was prepared by adding 7% by weight of pure sunflower oil to the basal diet. The fat composition of the control diet was 7.4% α-linolenic acid (18:3n-3) and 59.5% linoleic acid (18:2n-6), respectively, whereas the deficient diet contained 0.5% and 67.4%, respectively, of these fatty acids. DHA and other LC-PUFAs were not detectable in either diet. Female Long-Evans rats (14 weeks old; n = 5 per group) were mated and placed on the diets at the time conception was noted. Age-matched, virgin rats maintained on the control or deficient diets for 6 weeks served as no-pregnancy controls. At weaning (postnatal day 21), total phospholipid fatty acids were measured in whole brain by GC as area percent and compared between groups by ANOVA and Tukey's test.
Results: Virgin rats on the deficient diet had no alterations in brain content of any of the major n-3 and n-6 LC-PUFAs compared to virgin rats on the control diet. Likewise, the fatty acid composition of postpartum rats on the control diet was not different from virgin controls. In contrast, postpartum rats on the deficient diet exhibited decreased brain DHA content of 21 and 20% compared to virgin rats on the control and deficient diets, respectively (P<0.01). An increase in brain docosapentaenoic acid (DPA, 22:5n6) content to 243% of that in control virgin rats (P<0.01) was also observed, indicating a substitution of n-6 for n-3 fatty acids in cell membranes.
Discussion: The present findings indicate that, in our animal model, maternal brain DHA content can be reduced after a single reproductive cycle under dietary conditions with reduced availability of n-3 PUFAs. This depletion may alter neuronal function and consequently affect the sensitivity of the postpartum organism to stress. In view of the low levels of n-3 PUFAs, relative to n-6, in the North American diet, this finding identifies a candidate environmental risk factor for postpartum neuropsychiatric disorders.

89. Pooled Analysis of Response and Remission Rates with Venlafaxine ER in Social Anxiety Disorder

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Background: To compare the efficacy of venlafaxine extended release (ER) versus placebo in the treatment of social anxiety disorder (SAD).
Methods: Data were pooled from 5 randomized studies of patients with DSM-IV SAD (N=1459) treated with venlafaxine ER (flexible dose 75-225 mg/day in 4 studies; fixed dose 75 mg/day and flexible dose 150-225 mg/day in 1 study; n=772), or placebo (n=687) for 12 weeks; 1 study lasted 28 weeks. Efficacy assessments included the Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Impressions-Improvement (CGI-I) scale. Rates of response (CGI-I =1 or 2) and remission (LSAS ≤30) were determined at week 12 for the full data set and at week 28 for the single long-term study. Severity of physical symptoms was determined using the sum of the scores on 4 items (sweating, blushing, palpitations, and tremor) from the Social Phobia Inventory (SPIN). Response and remission rates were calculated for the overall population, as well as stratified by gender and level of physical symptom severity at baseline, based on the median split in SPIN physical symptoms score. Response and remission rates were compared between the venlafaxine ER and placebo groups using the Fisher's exact test. Data were from the intent-to-treat population, and the last-observation-carried-forward method was used to account for missing data. The number needed to treat and 95% confidence interval (CI) were calculated based on remission rates at week 12.
Results: In the overall population, response rates were 55% for venlafaxine ER and 33% for placebo (P<0.0001); remission rates were 25% and 12%, respectively (P<0.0001). Women comprised 46% of the population. Response and remission rates among men and women did not differ. Response rates were 55% and 32% among venlafaxine ER- and placebo-treated women, respectively (P<0.0001); remission rates were 26% and 12%, respectively (P<0.0001). Among men, response rates were 52% and 34% for the venlafaxine ER and placebo groups, respectively (P<0.0001); remission rates were 25% and 12%, respectively (P<0.0001). The median baseline SPIN physical symptoms score was 9. Response and remission rates did not differ based on severity of physical symptoms. Among patients with less severe physical symptoms (ie, baseline score ≤9; n=661), response rates were 52% and 32% for venlafaxine ER and placebo, respectively (P<0.0001); remission rates were 27% and 14%, respectively (P<0.0001). Response rates for the population with more severe physical symptoms (ie, baseline score >9; n=794) were 56% for the venlafaxine ER group and 33% for the placebo group (P<0.0001); remission rates were 24% and 11%, respectively (P<0.0001). In the long-term study, response rates for venlafaxine ER and placebo were 53% and 28%, respectively, at week 12 (P<0.0001), and 58% and 33%, respectively, at week 28 (P<0.0001). Remission rates in the long-term study were 23% for the venlafaxine ER group and 11% for the placebo group at week 12 (P=0.005) and 31% and 16%, respectively, at week 28 (P=0.0023). For the overall population, the number needed to treat for remission at week 12 was 8 (95% CI: 6.5, 8.9).
Discussion: The results of this analysis demonstrate that venlafaxine ER is effective in the treatment of SAD, regardless of gender or severity of physical symptoms.

90. Randomized Controlled Trial of the Cognitive Side Effects of Magnetic Seizure Therapy and Electroconvulsive Shock

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Background: Magnetic seizure therapy (MST) is under development as a means of improving the cognitive side effect profile of electroconvulsive therapy (ECT) by inducing more spatially delimited seizures that spare cortical regions involved in memory. Previously we reported fewer acute cognitive side effects following individual MST and ECT sessions. Here we report on cognitive outcomes following a full course of MST and electroconvulsive shock (ECS) in a validated nonhuman primate model for the cognitive consequences of convulsive therapy, and present the first data on the safety of high dose MST.
Methods: We tested whether MST had a cognitive side effect profile distinct from ECS in a nonhuman primate model, using the Columbia University Primate Cognitive Profile, which has been shown to be sensitive to the cognitive effects of ECS. Using a within-subject crossover design, daily ECS, MST, and sham (anesthesia-only) were administered in 5-week blocks. ECS and MST were administered at 2.5 x seizure threshold under general anesthesia (methohexital and succinylcholine). Behavioral training to permit venipuncture in the home cage obviated the need for pre-sedation with ketamine, which represented a confound of prior work. Rhesus macaques were trained on a long-term memory task, an anterograde learning and memory task, and a combined anterograde and retrograde task where learning and memory were evaluated for new and previously learned 3-item lists. Acutely following each intervention, monkeys were tested on the cognitive battery twice daily, separated by a 3-hour retention interval.
Results: Monkeys were least accurate following ECS (p's<0.05) as compared to sham and MST. This effect was most marked for long-term memory of a constant target, short-term memory of a variable target and recall of previously learned 3-item lists. Monkeys were slowest to complete all tasks following ECS (p's=0.0001). Time to task completion following MST did not differ from sham. An additional subject was tested with MST delivered at 6 x seizure threshold using a new device capable of delivering 100 Hz stimulation at maximal output for up to 10 seconds, and advantages of MST were still seen, even when contrasted with ECS at 2.5 x seizure threshold. Intracerebral recordings of ictal EEG induced by ECS and MST in hippocampus are consistent with these results, showing less intense seizure spread to hippocampus during MST.
Discussion: These findings suggest that MST has a more benign acute cognitive side effect profile than ECS in the monkey model, consistent with observations from human MST. These data add to evidence for the safety of MST and support further human testing with this intervention. This work was carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health.

91. The Familial Aggregation Anxiety Disorders Ascertained from the Community versus Clinics

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Sponsor: Kathleen Merikangas

Background: The vast majority of literature on the familial aggregation of mental disorders has focused on probands (and their relatives) recruited from clinical settings. Sparse research exists that examines clustering of psychiatric illnesses among families ascertained from the community. Although family ascertainment from the community is not feasible for rare diseases, systematic recruitment from the community increases the generalizability of the estimates and the validity of the components of familial aggregation. Such observations have important implications in the search and understanding of the etiological role genetic factors play in the pathogenesis of psychiatric illness.
Methods: Probands with panic disorder with or without agoraphobia and/or social phobia were recruited from outpatient specialty clinics for anxiety disorders and from the same community using a random digit dialing procedure. All probands, controls, and their relatives were assessed using the Schedule for Affective Disorders and Schizophrenia (SADS) and the Family History Research Diagnostic Criteria

(FHRDC), both of which were modified for DSM-III-R criteria. Best estimate diagnoses of probands, controls and relatives were made by experienced clinicians. Lifetime prevalence rates of anxiety disorders were obtained among the relatives of probands recruited from anxiety disorder clinics (N=182), from the community (N=171), and controls (N= 267).
Results: The rate of anxiety disorders among the relatives of clinic probands was two-fold that of anxiety rates among relatives of community probands (36.5% vs. 16.2%, p<0.0001). The clinical profile of clinic- versus community-ascertained anxiety probands was not different. To explain what accounted for the difference in the familial aggregation of aggregate anxiety disorders, the differential distribution of specific anxiety disorders between the clinic and community was examined. There was a great preponderance of panic disorder probands from clinic (92.5%, 37/40) compared to the community (27.8%, 10/37) (p<0.0001). Therefore, the source of panic disorder probands was examined as a confounder for the differential anxiety rates among relatives. The relative rate of panic disorder among the clinic- versus community-probands was statistically different - 12% (21/174) versus 10.8% (10/37), respectively (p<0.0008). Sixty-five percent (26/40) of the clinic probands had generalized anxiety disorder (GAD) versus 30.6% (11/36) of the community probands (p<0.003). The relative rates of GAD among the clinic families was 20.3% (37/112) compared to 1.8% (3/48) among community (p<0.007). In contrast, rates of social phobia among the probands were 40.0% (16/40) and 72.2% (26/36) from the clinic and community, respectively (p=0.005) and the corresponding relative rates were 18.6% (13/70) compared 11.5% (15/130) (p=0.149).
Discussion: The familial aggregation of anxiety disorders ascertained from clinics is two-fold that of those families ascertained from the community. The difference is mainly explained by the differential distribution of specific anxiety disorder among the clinics versus the community. There was a greater degree of familial aggregation of panic disorder and generalized anxiety disorder among probands from clinics compared to those from the community. In contrast, the familial aggregation of phobic states including social phobia, agoraphobia and simple phobia did not differ among clinic vs community probands. The source of ascertainment of probands may have major impact on the results of studies investigating the role of genetic factors in the etiology of psychiatric disorders.

92. Increased Neurogenesis in CREB-Deficient Mice is Associated with Antidepressant-Like Behavior

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Background: Chronic antidepressant administration increases hippocampal neurogenesis. To date, the mechanisms involved in antidepressant-induced changes in neurogenesis and related synaptic plasticity are unknown. Pharmacological and molecular studies have identified a role for cAMP response element binding protein (CREB) in the mechanism of action of antidepressant drugs. The role of CREB in antidepressant-induced neurogenesis and behavior, using a CREB-deficient mouse model (CREBαΔ mutant), was examined. In addition, noradrenergic and serotonergic modulation of CREB was investigated in this mouse model.
Methods: In the first set of studies, the role of noradrenergic modulation of CREB on cell proliferation and neurogenesis was studied. 5-bromo-2-deoxyuridine (BrdU) was used to label dividing cells after 21-day desipramine (DMI) treatment. Animals were sacrificed 1 day (proliferation) or 28 days (survival and neurogenesis) after the BrdU injection. In the next set of studies, the role of serotonin in sustaining behavior and cell proliferation in CREBαΔ mutants was studied. Animals were administered PCPA to deplete serotonin. They were subsequently analyzed for immobility behavior on the tail suspension test and injected with BrdU for neurogenesis studies.
Results: In the first set of studies, saline-treated CREBαΔ mutant mice had increased cell proliferation (52% increase in BrdU-positive cells) compared to wild-type controls. DMI treatment increased the number of proliferating cells in wild-type mice compared to saline control by the same magnitude (51%). However, DMI treatment did not alter cell proliferation in CREBαΔ mutant mice. At the 28-day timepoint to study cell survival, the same pattern of BrdU labeling was seen. CREBαΔ mutant mice exhibited a 139% increase in BrdU-positive cells compared to wild-type controls. DMI treatment increased the number of BrdU-positive cells (79%) in wild-type mice compared to saline treated controls. There was no effect of DMI in the CREBαΔ mutant mice at this timepoint. Triple-labeling studies demonstrated that in all genotype and treatment groups, the majority of BrdU-positive cells had a neuronal phenotype (Wild-Type-saline or DMI: 67 and 66% respectively; CREBαΔ-saline or DMI: 70 and 76% respectively), indicating that CREB-deficient mice and DMI-treated wild-type mice had increased neurogenesis. In the second set of studies, animals were analyzed on the tail suspension test for antidepressant activity. CREBαΔ mutant mice had reduced baseline levels of immobility compared to wild-type mice. While depletion of 5-HT with PCPA had no effect on immobility time in wild-type mice, PCPA treatment significantly increased the immobility time of CREB-deficient mice to wild-type levels. In addition, PCPA treatment reduced the level of cell proliferation in CREB-deficient mice to wild-type levels.
Discussion: This data demonstrate a complex interaction of CREB with the noradrergic and serotonergic systems in mediating antidepressant-like behavior and neurogenesis. CREB-deficient mice displayed an antidepressant-like phenotype that is associated with increased neurogenesis. However, an intact CREB system is necessary for DMI-induced increases in cell proliferation and neurogenesis. Moreover, serotonin transmission sustains increases in neurogenesis in CREBαΔ mutant mice and antidepressant-induced behavior, since 5HT depletion prevented both the morphological and behavioral effects in mutant mice but not in wild-type controls. This research was supported by NCDDG program MH 72832 between the University of Pennsylvania and Wyeth Neuroscience.

93. Lithium Increases Gray Matter in the Prefrontal and Subgenual Prefrontal Cortices in Treatment Responsive Bipolar Disorder Patients

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Background: Recent molecular, preclinical, and preliminary clinical studies suggest long term therapeutic effects of mood stabilizers may be mediated by modulating expression of potent neurotrophic and neuroprotective factors having the potential to reverse impairments of cellular resilience, reductions in brain volume, and cell death or atrophy hypothesized to underlie the pathophysiology of bipolar disorder
Methods: To investigate the clinical significance of these findings we performed a longitudinal study exploring neurotrophic effects of the mood stabilizer, lithium, via high resolution volumetric MRI in well characterized bipolar depressed subjects (n=28) at baseline (medication free), and following chronic lithium (Li) administration (4 wks). Total brain gray matter (GM), prefrontal GM, and left subgenual prefrontal GM were determined using validated semi-automated segmentation and region of interest methodology.
Results: Significant increases in total brain GM in bipolar subjects were observed following chronic Li administration, confirming our previous preliminary study. Regional analyses in the bipolar subjects revealed significant differences between responders (>50% decrease

in HAM-D) and non-responders; only responders showed increases in GM in the prefrontal cortex and left subgenual prefrontal cortex. Our finding of an increase in prefrontal gray matter structures in clinical responders to mood stabilizer treatment is of particular interest. Specifically, the data from our longitudinal study suggests a regionally-specific, pharmacologically-induced increase in human gray matter volume, but not white matter, following 4 weeks of treatment with lithium in bipolar depressed patients who clinically respond to treatment.
Discussion: This observation provides the first direct in vivo human evidence that medications with neurotrophic effects are capable of increasing gray matter volumes in the adult human brain in regions implicated in the neuropathophysiology of bipolar disorder. These observed changes occur on a time scale associated with increased bcl-2 expression and GSK-3 inhibition, suggesting that these neurotrophic signaling cascades may be responsible for at least some of lithiums therapeutic effects. The data also support the notion that future development of treatments that more directly target molecules in critical CNS pathways that regulate cellular plasticity and resilience hold promise as novel, improved long-term treatments for severe mood disorders.

94. Vagus Nerve Stimulation for the Treatment of Rapid Cycling Bipolar Disorder

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Sponsor: Trisha Suppes

Background: Background: Vagus nerve stimulation (VNS) delivered by an implantable, programmable pulse generator was recently approved by the United States Food and Drug Administration as an adjunctive long-term treatment for patients with recurrent or chronic depression. We hypothesized that VNS might be effective in the treatment of rapid cycling bipolar disorder.
Methods: Methods: Ten adult outpatients (8 females and 2 males) with treatment-resistant rapid cycling bipolar disorder (BP1= 8; BPII= 2) were implanted with the VNS device following 60 days of prospective observation with stable pharmacotherapy. One patient was found to not meet study criteria post-implantation and was discontinued from the study. The nine other subjects received ongoing treatment with VNS and concomitant psychotropic medications for one year. The primary *a priori* endpoint was the change in severity of symptoms, as assessed by prospective Life Charting Methodology (LCM). Secondary outcomes included the MADRS and YMRS.
Results: Results: Over one year of follow-up, the mean percentage change from the two-month baseline period was found to be statistically significant for overall illness, 32% (±32.3) p=0.02, for depression symptoms, 30% (±31.7) p= 0.02, and for manic symptoms, 32% (±35.9), p=0.03, as assessed by the LCM. Statistically significant improvements were also seen in MADRS scores. Over one year, mean change from the 2-month baseline was 9.3 points (±6.7) p< 0.01, and mean percentage change was 40% (±25.3), p<0.01.
Discussion: Conclusions: This open trial in treatment-resistant patient group suggests that long-term VNS may be a useful treatment in rapid cycling bipolar disorder.

95. A Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose, Trial of Augmentation with OROS Methylphenidate in Treatment Resistant Depression

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Background: About 60% of patients with major depression treated with antidepressants respond at 8 weeks and only 30% achieve remission. Patients who experience partial or no response to antidepressant treatment, are considered to experience treatment resistant depression (TRD). In the first double-blind, placebo-controlled study of stimulant augmentation in TRD, we examined the efficacy and safety of augmenting with OROS® methylphenidate (MPH) for non or partial responders to antidepressants
Methods: 60 subjects with an a priori defined TRD were enrolled in a 4-week double-blind, placebo controlled trial of OROS (18 mg to 54 mg per day). The preexisting antidepressant dose was kept unchanged. The primary efficacy measure was a change in scores on the Hamilton Depression Rating Scale (HAM-D) from randomization to end of treatment. Treatment response was defined as a ≥ 50% reduction in HAM-D scores during treatment. Secondary efficacy measures included changes in Clinical Global Impression- Improvement (CGI-I) and severity (CGI-S) scores and Beck Depression Inventory (BDI) scores. Data was analyzed with Intent to Treat (ITT) with Last Observation Carried Forward (LOCF) approach.
Results: 83% of subjects completed the study. The mean dose of methylphenidate ER was 34.2 ± 16.1 mg/day. There were no statistically significant differences between the OROS MPH (n=30) and placebo (n=30) groups in reduction in HAMD scores (-6.9 in drug and -4.7 in placebo) from baseline to end of treatment (F(1,47)=1.24, p =.22, repeated measure ANOVA). Although there were numerically more responders (≥ 50% reduction in HAM-D) in the drug group (40%) compared to placebo group (23.3%), this difference did not reach statistical significance (chi2= 2.34, p=0.12). On the secondary efficacy measures of changes in CGI-I, CGI-S and BDI, the drug failed to separate from placebo, however the proportion of responders (CGI-I score of 1 or 2) in the drug group (43.3%) were numerically higher than placebo (26.6%) (chi2= 1.32, p=0.32). There were no significant differences in weight, heart rate and blood pressure changes between the drug and placebo groups. The common adverse events were loss of appetite, nausea, headache and anxiety.
Discussion: The study failed to show a statistically significant benefit for augmentation with OROS MPH in patients with TRD. Combination of OROS MPH with antidepressants was well tolerated in the patients. A lack of power due to a small sample size could be one explanation of the negative findings. Suboptimal dosing could be another possible reason because the mean dose of OROS MPH (32 ± 16 mg/day) was less than that shown to be effective for treatment of adults with ADHD (82 ± 22 mg/day) (Spencer et al, 2005). Finally depressed patients were not screened for co-morbid ADHD and it is possible this subgroup could have shown a more favorable response to a combination of antidepressants and OROS MPH (Biederman, 2004). Adequately powered, randomized, placebo controlled trials with comorbid ADHD as a stratifying variable are necessary to fully evaluate the efficacy of OROS MPH in treatment-resistant depression.

96. A Genome-by-Genome Interaction Linkage Scan of Bipolar Disorder

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Background: Bipolar disorder (BPD) is a severe psychiatric illness characterized by pathological swings of mood, from mania to depression. There have been several genome-wide scans of BPD with a number of regions implicated, but no one gene has been consistently implicated in the pathophysiology of BPD. It is highly likely that BPD results from interactions between two or more genes along the genome, and attempts have been made to identify interactions between two genomic regions that associate with BPD.
Methods: The sample consisted of the 644 pedigrees from waves 1-4 of the NIMH Genetics Initiative for Bipolar disorder. Analyses were

performed using a narrow phenotype definition, including BPI and schizoaffective mania. There were 796 all possible sib-pairs and 1,119 all possible relative pairs. Families were genotyped in four separate samples; waves 1 and 2 were genotyped by the collaborating institutions and waves 3 and 4 (77% of the families) were genotyped by CIDR. In total, 685 micro-satellite markers were genotyped in the sample across the genome at an average interval of 5.09 cM. Genotype data were combined from all waves 1-4. Several steps were taken to check the genotype data for quality control; UNKNOWN and PEDCHECK to check for inheritance errors, PREST to check for unlikely relationships, and the output from CRIMAP for unlikely double recombinations. The genetic map was the framework deCode map. We then analyzed the data using an NPL regression approach. This approach is based on the NPLpairs statistics computed in Genehunter. It uses a conditional logistic regression framework in which the family-specific NPL statistic at a locus is modeled as a predictor variable. It can be shown that the score test from the likelihood of such a model is asymptotically equivalent to Whittemore and Halpern's class of tests. The primary advantage of this approach is that it allows us to evaluate simultaneously, either by joint or conditional hypothesis tests, the effects of multiple loci (heterogeneity) and test for interactions among sets of loci (epitasis). We used this approach to first conduct a single-locus genome-wide scan of the combined data, and then systematically test for genome-wide by genome-wide interaction between pairs of loci.

Results: In the initial genome-wide scan analysis there were 5 regions with a LOD > 1.0. They include (in rank order of significance) 17q24 (p=0.0009), 17q25 (p=0.001), 6q21 (p=0.001), 17q12 (p=0.009), and 16q24 (p=0.01); the regions on 17 were all separated by a distance of 50 cM or greater. There were 7 regions with nominally significant evidence (p<10-4) of genetic interaction resulting in the Bipolar phenotype. In rank order of significance they include: 3q25-6p22 (p=.00003), 8q24-13q12 (p=.00005), 10p12-14q22 (p=.00005), 8p21-19q13 (p=.00006), 6q25-11p15 (p=.00007), 10p13-11p11 (p=.00009), 3q13-18p11 (p=.00009).

Discussion: The findings in the current analyses represent the first genome-by-genome analyses of the waves 1-4 NIMH. In the initial genome-wide analyses the regions that had been identified in previous analyses of subsets were supported. There were additional regions that were identified when interaction between genomic regions was studied. Several of the regions showing interaction had been identified in independent genome wide scans of bipolar disorder (e.g. 8q24, 13q12, 18p11, and 10p12). Future analyses of BPD will include genomic interactions and study of regional genes.

97. Behavioral and Anatomical Interactions Between Dopamine and Corticotropin-Releasing Factor (CRF)

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Background: The neuropeptide corticotropin-releasing factor (CRF) is believed to play a role in a number of psychiatric conditions including depression, anxiety disorders, and eating disorders. Found in neurons of the paraventricular nucleus of the hypothalamus (PVN), a critical component of the hypothalamic-pituitary-adrenal (HPA) axis, as well as brain structures such as the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BST), CRF is in a position to play an important role in the modulation of mood and emotional affect. As such, dysfunction within CRF brain circuits, a condition that has be linked putatively to chronic stress exposure, may underlie such psychiatric conditions as depression and anxiety disorders. In the present study, we examined the effects of altering dopamine transmission on CRF-enhanced startle, a behavioral assay used as an animal model of anxiety-disorder. In addition, because previous studies have shown that the BST is a critical brain area mediating CRF-enhanced startle, we attempted to identify the extent and source of dopaminergic innervation to this brain area using immunohistochemical and retrograde tracing techniques.

Methods: *Behavioral studies*: Male Sprague-Dawley rats (400 g) were implanted with a single infusion cannula (23-guage) into the lateral ventricle. One week later, rats received subcutaneous injections of the selective dopamine D1 receptor antagonist SCH 23390 (0, .01, .05, .1 or 5 mg/kg) followed by intracerebroventricle infusion of either vehicle (artificial cerebrospinal fluid, aCSF) or CRF (1 μg). Rats were then placed in the test cages and the amplitude of their startle reflex was measured in response to 400 startle-eliciting acoustic stimuli at each of three different intensities (95, 100 and 105 dB; 30-s interstimulus interval). *Anatomical studies*: Fluorescent immunohistochemistry was used to double-label CRF-containing cells and tyrosine hydroxylase (TH, an enzyme involved in catecholamine synthesis)-positive fibers in the dorsolateral BST (BSTld). Intra-BSTld injections of the retrograde tracer Fluorogold were then used to identify the source of the TH-positive fibers from the major dopaminergic (A8-A10) and noradrenergic areas (A5-A7).

Results: Behavioral results showed that the startle-enhancing effect of CRF was dose-dependently blocked by the dopamine D1 receptor antagonist SCH 23390 (.05 and .1 mg/kg) at doses that had no effect on baseline startle. Immunohistochemical studies showed that most CRF-containing cells in the BSTld were covered by a dense plexus of TH-positive fibers. Retrograde tracing studies identified neurons in the major dopaminergic areas, but not the major noradrenergic areas as a significant source of TH-positive innervation to the BSTld; the majority of Fluorogold-filled cells double labeled for TH were found in the A10dc periaqueductal gray area.

Discussion: Our behavioral data suggest that compounds with dopamine D1 receptor antagonist properties may have anxiolytic-like effects that could be useful for treating psychiatric symptoms associated with hyperactive CRF systems. Identification of a heavy dopamingeric input to the BST, a brain area shown to be critical for mediating effects of CRF on behavior, suggests that regulation of neurons in the BSTld by specific dopaminergic pathways (e.g. from the A10dc periaqueductal area) may be an important mechanism for controlling CRF-dependent mood and affective states.

98. Amyloid PET Imaging with Pittsburgh Compound-B in Late Life Depression with Cognitive Impairment

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Background: Cognitive impairment — whether reversible or irreversible by antidepressant therapy — appears to be the single strongest predictor of the development of Alzheimers disease (AD) in late-life depressed patients. Further, cognitive impairment appears to enhance the morbidity, brittleness of treatment response, and risk of relapse associated with depression in late life. Increasing evidence supports the concept that late-life, and particularly late-onset, depression may be a prodrome of AD. The development of Pittsburgh Compound-B (PIB) presents the opportunity to investigate the relationship among cognitive impairment, subclinical AD pathology, and dementia risk in patients with depression of late life. The objective of this study was to investigate the underlying pathophysiology of the empirical link between late-life depression and AD using PET imaging and the beta-amyloid binding agent, PIB.

Methods: We studied 5 subjects with treated major depression (3M:2F, mean age 71.4, sd 4.0) who also qualified for a diagnosis of mild cognitive impairment (MCI). Three of these subjects recently presented to a late-life depression clinic and acutely remitted with citalopram therapy; the remaining two subjects presented to a memory disorders clinic and had a history of mid/late-life-onset depression. PIB-PET data from age matched controls (n=6; mean age 72.5,

sd 6.3), AD disease patients (n=8; mean age 68.3, sd 7.4), and MCI subjects without depression (n=8; mean age 70.9, sd 9.9) were used for comparison. Following injection of 15mCi PIB, dynamic PET imaging (90min) was performed with arterial sampling using a Siemens HR tomograph. Regional time-activity data were generated from magnetic resonance imaging (MRI)-guided regions-of-interest, including the posterior cingulate, prefrontal cortex, mesial temporal cortex, parietal cortex. The Logan graphical analysis was applied to the data for determination of regional PIB retention (distribution volume, DV), normalized to the cerebellar reference region DV to yield DV ratios (DVRs). MRI-based partial volume correction was applied to regional DVR values.
Results: Regional PIB DVR values in cortical areas in the 5 elderly subjects with depression and MCI spanned the range of values from control-like to AD-like; 3/5 subjects demonstrated PIB retention above the range of control subjects, indicative of the presence of amyloid in the posterior cingulate, prefrontal cortex, and parietal cortex. The mesial temporal lob demonstrated low DVR values in all subjects, as expected.
Discussion: We have demonstrated elevated PIB retention reflective of brain beta amyloid in non-demented late-life depressed subjects relative to controls. These preliminary findings are consistent with and supportive of the hypothesis that late-life depression may herald the development of AD. Future studies will further explore to what degree AD pathology may contribute to individual long-term prognosis, as well as the course, and treatment response characteristics of depression in late life.

99. Familial Patterns of Comorbidity of Migraine and Affective Disorders

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Background: Comorbidity between affective disorders and migraine has been well-established in clinical and community studies. However, the cause of this association is still unknown. Prospective studies have shown that the order of onset of these conditions is characterized by anxiety disorders in childhood and adolescence followed by the onset of migraine and the subsequent development of mood disorders. Recent findings have demonstrated that migraine is particularly associate with the bipolar subtype of mood disorders and atypical depression.
Methods: Data from a controlled family study of mood and anxiety disorders and migraine and a prospective high risk study of young offspring of parents with these conditions will be used to investigate the causes of comorbidity of these conditions. There were a total of 260 probands and 1615 first degree relatives who were directly interviewed using standardized diagnostic methods for both migraine and psychiatric disorders.
Results: The results demonstrate that both migraine and mood disorders are highly familial and that they co-aggregate in families. Bipolar disorder is associated with a 3.0-fold increased risk of migraine in relatives, irrespective of the presence of migraine in the bipolar probands. However, there is no concomitant increase in the rates of bipolar disorder among relatives of probands with migraine. 5This suggests that migraine may be an index of a subtype of bipolar disorder. There was also a familial association between panic disorder and migraine; however, this was explained in part by comorbidity between panic disorder and bipolar disorder in probands. Investigation of the high risk sample revealed that there is there is maternal transmission of migraine. Offspring also demonstrate comorbidity between migraine and anmxiety disorders, with an increasing association with mood disorders with increasing age.
Discussion: These findings suggest that there may be a discrete subtype of bipolar disorder that is indexed by migraine. The implications of these results for identifying sources of heterogeneity in genetic studies of bipolar disorder and potential endophenotypes underlying this syndrome are discussed.

100. Emergence of Anhedonia in Laboratory Rats During Continuous Subordination Stress: Relevance to Antidepressants and Stimulant Abuse

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Background: The development of experimental conditions for the study of anhedonia with relevance to affective disorders, drug abuse and schizophrenia remains a challenge for preclinical work. We now report evidence for the gradual emergence of loss of appetite, psychomotor retardation and anhedonic responses to rewards over time and their pharmacological reversal using chronic subordination stress in common strains of laboratory rats.
Methods: Breeding pairs of Long-Evans rats confront an intruder rat who lives in a protective cage with free access to food and water in the residents' home cage. Once a day, the protective cage is briefly removed and the ensueing aggressive confrontation is terminated when the intruder displays a submissive-supine posture and emits ultrasonic distress calls. Subsequently, body weight gain, sucrose intake and preference, exploratory behavior, psychomotor stimulant response to cocaine challenge, intravenous cocaine self-administration, cellular activation via c-fos in mesocorticolimbic areas are studied.
Results: In the course of the second week of continuous subordination stress, decreases in body weight, exploratory behavior and sucrose intake and preference begin to emerge. These behavioral indices of psychomotor retardation, loss of appetite and anhedonia persist for five weeks of continuous subordination stress. When challenged with cocaine (10 mg/kg) 10 days after the end of the continuous subordination stress, the typical motor activation was absent. By contrast, the same stimulant challenge resulted in sensitized locomotion in intruder rats that were intermittently stressed by brief defeat episodes. The intruder rats were subsequently fitted with permanently indwelling intravenous catheters and conditioned to activate a pump for cocaine self-administration. When compared to nonstressed control rats, a smaller proportion of continuously subordinate rats (a) acquired cocaine self-administration, (b) achieved lower break points when cocaine was available after progressively higher response requirements, and (c) stopped taking cocaine when the drug was available continuously for a 24-h "binge." By contrast, animals that experienced social defeat stress intermittently, self-administered cocaine more intensely, as evidenced by a significantly higher "breakpoint". Moreover, intermittently stressed animals take more drug and self-administer for longer time when cocaine is available continuously for a 24-h "binge."
Discussion: These results provide evidence for gradually emerging anhedonia-like responses in continuously subordinate animals, and this pattern contrasts with the sensitized response to cocaine due to intermittent social defeat stress. Both intermittent defeat stress and continuous subordination stress activate the HPA axis. Enduring cellular activation in the VTA, central amygdala and prefrontal cortex characterizes the intermittently stressed animals, as indicated by increased c-Fos immunohistochemistry. Antagonism at NMDA and mGluR5 receptors attenuate the sensitizing effects of intermittent social defeat stress. The physiological and behavioral deficits resulting from continuous subordination stress offer the opportunity to investigate the mechanisms by which antidepressant treatments achieve their effects.

101. The Anxiolytic Opipramol Affects Calcium Signalling via Sigma Receptors

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Sponsor: Peter T. Loosen

Background: While sigma receptors have been found in many neuronal as well as non-neuronal tissues, their molecular mechanisms on

cellular function are still not clear. Increasing evidence suggests that sigma sites are involved in the regulation of cellular calcium signalling where elevations but also reductions of the free intracellular calcium concentrations (Ca2+)i have been found (1,2). Although the final relevance of these effects might be still under discussion, modulation of calcium signalling represents an interesting model to study functional aspects of sigma ligands. An example is the anxiolytic drug opipramol (3), which is structurally related to the tricyclic imipramine, but does not inhibit the reuptake of serotonin and norepinephrine. Unlike imipramine, opipramol is a rather potent sigma ligand in vitro and in vivo and is active in several behavioural paradigms indicative for anxiolxtic activity at doses also needed to occupy sigma sites in vivo (4). However, very little is know about sigma sites mediated cellular effects of opipramol except that opipramol specifically down-regulates sigma2-sites after chronic administration (5).
Methods: Accordingly, we investigated possible effects of opipramol in comparison to other sigma ligands on calcium signalling using PC12 and SH-SY5Y cells.
Results: Similar to other sigma ligands, opipramol affected the elevation of (Ca2+)i induced by depolarization or by the cholinergic agonist carbachol dose dependently. The response was mainly mediated by effects on calcium influx rather than on intracellular mobilazation. In respect to other sigma ligands like haloperidol, (+)pentazocine, and di-o-tolylguanidine, similarities but also distinct differences were observed. Opipramol, like haloperidol strongly reduced the depolarisation (KCl 60mM) induced elevation of (Ca2+)i, while (+) pentazocine was less and DTG nearly not effective . On the other site, all three drugs reduced similarly the carbachol (100mM) induced increase of (Ca2+)i although to a lesser extent.
Discussion: The data are in line with the assumption of sigma receptor mediated responses as part of the mechanism of action of the anxiolytic drug opipramol. 1. Hayashi et al., J. Pharmacol. Exp. Ther. 293:788-798, 2000; 2. Hong and Werling, Eur. J. Pharmacol., 436:35-45, 2002; 3. Muller et al., J. Clin. Psychopharmacol., 21:217-226, 2003; 4. Muller et al., Pharmacopsychiatry, 37:S189-S197, 2004; 5. Holoubek and Muller, J. Neural Transm., 111:1169-1179, 2003.

102. Antidepressant Prescribing Trends Pre and Post-Black Box Warning: A Review of the Medicaid Database

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Sponsor: Richard Rech

Background: Objective: This study examines the effects of black box warning on the frequency of antidepressant prescriptions for Medicaid clients in the state of South Carolina. Childhood and adolescent depression is a serious public health problem given the risk of suicide. The past year has brought much turmoil to child and adolescent psychopharmacology in the form of reports of increased suicidal behavior in children and youth taking antidepressants. Data that was analyzed from all antidepressant trials (n=4400) demonstrated an average risk of suicide for patients' on antidepressants was 4% in the studies, versus a 2% risk on placebo, with no suicides occurring during the medication trials. This resulted in the Food and Drug Administration issuing a black box warning for all antidepressants on October 14th, 2004. Although the mechanisms underlying increased suicidality in those taking antidepressants is unclear, complex interactions between biological and psychosocial factors seem to play a role. The risk of adverse events associated with antidepressant use requires caution when these medications are prescribed to children and adolescents. As mental health providers one also needs to acknowledge the unmet need of treating depression in this population given an inherent 10-15% risk of suicide if patients' are left untreated.
Methods: This study examined the prescribing trends pre and post-black box warning of Medicaid antidepressant prescriptions in South Carolina by comparing the prescriptions written from May 2004 through October 2004 (n=2900) to those from November 2004 to April 2005 (n=2678). This study was approved by the Medicaid review board. Only Medicaid claims with a mental/behavioral diagnosis listed were considered. Age,gender,race,past history of suicide attempt were some of the variables that were looked at. For the purposes of this study, the data was grouped into psychiatry providers versus non-psychiatry providers that included pediatrics, family practice, multiple specialty groups and rural health clinics). The medications were grouped by mechanism of action (SSRIs, SNRIs (venlafaxine and mirtazapine), bupropion and tricyclics.
Results: 1. Preliminary analysis of the six month prescription data showed that the overall number of children who were prescribed antidepressants during the six months pre-black box warning (n=2900) versus the six months post-black box warning (n=2678) decreased by 7.66%. 2. 81.2% of the total reduction was attributable to a decrease in antidepressant prescriptions by the non-psychiatric specialty providers. 3. Overall number of recipients who received one or more antidepressants (SSRIs, SNRIs, bupropion and others (TCA's)) pre-black box warning (n=4622) versus post-black box warning (n=3285) decreased by 33.0% for SSRIs, 35.7% for SNRIs, and 25.4% for buproprion. 4. Data on other variables including age, sex and prior attempts is being analyzed.
Discussion: The preliminary data from these six month is a snapshot that suggests antidepressant prescriptions for children and adolescents has decreased since the black-box warning, both in terms of the number of individuals receiving the medications as well as the number of non-psychiatrists prescribing them. Since suicide occurs commly in untreated depression, accurate diagnosis and treatment of depression needs urgent attention. Clinicians need to be practice prudently weighing the risks and benefits of available treatments. Further analysis will need to be done to determine whether the trend is continuing, leveling off, or reversing.

103. Cognitive Function in Patients with Resistant Depression: Effects of Antidepressant Monotherapy and Risperidone Augmentation

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Background: Neurocognitive function was evaluated in patients with resistant major depressive disorder (MDD) who received standard antidepressant monotherapy followed by risperidone augmentation.
Methods: Data were from a study that included an open-label phase and a double-blind maintenance phase. The open-label phase included 4-6 weeks of citalopram monotherapy to confirm treatment nonresponse and 4-6 weeks of risperidone augmentation of citalopram in patients who did not respond to citalopram. The subjects were aged 18-85 years with a DSM-IV diagnosis of MDD and a score of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) at entry. Computerized cognitive tests evaluated 5-domains of function.
Results: Cognitive data were available for 297 patients assessed at the citalopram monotherapy baseline, risperidone augmentation baseline (monotherapy endpoint), and risperidone augmentation end point. Mean (±SD) doses were 37.6±11.0 mg/day of citalopram during monotherapy and 49.4±12.6 mg/day of citalopram and 0.9±0.4 mg/day of risperidone during augmentation. The patients' mean HAM-D score improved at citalopram monotherapy endpoint ($P<0.0001$) and at risperidone augmentation endpoint ($P<0.0001$ vs augmentation baseline). On Auditory Number Sequencing (attention/working memory), significant improvements were seen from the citalopram monotherapy baseline to the monotherapy endpoint ($P<0.05$) and the risperidone augmentation endpoint ($P<0.0001$), and from the augmentation baseline to endpoint ($P<0.01$). On the Continuous Performance Test (attention–distractibility), significant

improvements (P<0.0001) from the citalopram monotherapy baseline to the monotherapy and risperidone augmentation endpoints were seen in the congruent, incongruent, and neutral conditions. Significant improvement was also seen in the neutral condition with risperidone augmentation (P<0.05). On the Faces Memory Test (secondary memory), improvement (P<0.05) was seen only from the citalopram monotherapy baseline to the monotherapy endpoint. On the Set-Shifting Test (procedural learning/executive function/processing speed), significant improvements were seen on 1 of the 5 measures from the citalopram monotherapy baseline to the monotherapy endpoint (P < 0.01), and on 3 of the 5 measures from the monotherapy and risperidone augmentation baselines to the augmentation endpoint (P<0.05). On the Tapping Speed Test, significant improvements were seen from the citalopram monotherapy baseline to the monotherapy and risperidone augmentation endpoints (P<0.01). Of the 64 correlations tested between depressive symptoms (HAM-D subscales) and cognitive function, few were significant (P<0.05), and these showed generally weak correlations. Data from an ongoing normative study will evaluate baseline cognitive impairment in depressed patients and the extent to which cognitive functions normalize with risperidone augmentation.
Discussion: Improvements on some measures of cognitive function were seen with both citalopram monotherapy and risperidone augmentation in patients with resistant depression. No worsening in cognitive measures was observed during risperidone augmentation. This is a clinically relevant finding given the potential sedative and motor effects of risperidone and the substantial clinical improvements observed with risperidone. Supported by Janssen L.P.

104. Alterations of Cortico-Limbic Responsiveness to Emotional Valenced Stimuli in Alpha2CDel322-325 Carriers with Depression and Controls

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Background: Consistent with the hypothesis that alterations in noradrenaline function characterize patients with major depressive disorder (MDD) are studies showing alterations in receptor/transporter expression and function in depressed people. Current studies have not yet, however, sufficiently addressed the contribution of noradrenaline related genes and their polymorphisms to central noradrenaline transmission. We tested the functional relevance of a common coding polymorphism of the gene for the alpha2C-adrenoreceptor (AR), the deletion of four consecutive amino acids at codons 322-325 of the alpha2C-AR (alpha2CDel322-325), on processing of emotional valenced stimuli in MDD.
Methods: We studied 26 medication-free, fully remitted patients with MDD, and 26 matched healthy control subjects. To measure cerebral blood flow (CBF), 0-15 PET studies were conducted while subjects were exposed to emotionally valenced stimuli (happy, sad and fearful faces). CBF in predefined regions of interest (orbitofrontal cortex, amygdala, hippocampus, ventral striatum, subgenual and pregenual anterior cingulate cortices) was examined using a MANOVA and subsequent Bonferroni-corrected simple effect tests.
Results: In response to fearful faces, healthy controls show blunted CBF activation in the amygdala, subgenual and pregenual cingulate cortices when carrying at least one copy of the alpha2CDEL322-325 relative to wild-type (WT) carriers. MDD WT carriers show blunted CBF activation relative to WT healthy control subjects. In response to sad faces, MDD patients show exaggerated CBF activation in the right orbitofrontal cortex and the left ventral striatum relative to controls. No effects of genotype were noted. MDD alpha2CDEL322-325 carriers show elevated CBF in the pregenual and subgenual anterior cingulate cortices relative to healthy alpha2CDEL322-325 carriers, and relative to MDD WT carriers.
Discussion: These data suggest a functional role of the alpha2CDEL322-325 polymorphism in MDD. Pregenual and subgenual hyperresponsiveness to sad faces appears to be a trait abnormality in MDD alpha2CDEL322-325 carriers. The question remains as to whether there is increased vulnerability to future depressive episodes in these patients. Future studies will determine influences of recently described haplotypes of the alpha2CDEL322-325 polymorphism in MDD to further substantiate the present findings.

105. Fluoxetine and Triiodothyronine Reduce 5-HT1A and 5-HT1B Receptor Activites and mRNA Levels in Male but Not in Female Rats

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Sponsor: Bernard Lerer

Background: There are marked sex differences in the incidence of depression, responses to antidepressant (AD) agents in patients, and parameters of serotonergic functioning as measured in brains of experimental animals. Triiodothyronine (T3) is more effective in potentiating the actions of AD agents in females than in males. SSRIs act by inducing subsensitivity of 5-HT1A and 5-HT1B autoreceptros in brain, but experiments showing this have only been performed in male rats.
Methods: We have used in vivo microdialysis to measure 5-HT1A and 5-HT1B autoreceptor activities in frontal cortex and hypothalamus of rats treated with these agents either alone or in combination. In addition we hve measured mRNA levels for these receptors in various brain areas.
Results: In frontal cortex of male rats, fluoxetine at 5 mg/kg given daily for 7 days reduced 5-HT1B autorecptor activity as measured by the action of the agonist CP 93129 to reduce 5-HT release. In hypothalamus of male rats, 5-HT1B autoreceptor activity was not affected by fluoxetine or by T3 at 20 mcg/kg given daily for 7 days alone, but was reduced after administration of both drugs together. mRNA levels for both 5-HT1A and 5-HT1B receptors in raphe nuclei were slightly reduced after fluoxetine and after T3, and significantly reduced (30%) after the combination treatment.In female rats, neither 5-HT1A nor 5-HT1B autoreceptor activity was affected by fluoxetine, T3 or the combination in either frontal cortex or hypothalamus. Similarly, mRNA levels for these receptors were not reduced, and indeed fluoxetine increased mRNA levels for the5-HT1A and 5-HT1B receptors in raphe nucleus by 32% and 30% respectively.
Discussion: SSRIs do not appear to act by inducing subsensitivity of 5-HT1A and 5-HT1B autoreceptors in female rats. The therapeutic effect of T3, either given alone or together with an SSRI, does not appear to involve 5-HT autoreceptors, nd other mechanisms are presumably involved.

106. Sleep EEG Response to Metyrapone May be a Measure of Hypothalamic CRF Activity: A Study of Women with and Without Posttraumatic Stress Disorder

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Sponsor: Laurence Tecott

Background: Metyrapone blocks the conversion of 11-deoxycortisol to cortisol, leading to a reduction in feedback inhibition of the HPA axis In the absence of cortisol feedback inhibition, CRF and ACTH levels are increased as are levels of 11-deoxycortisol. Metyrapone reduces delta sleep activity in humans (1) and rats (2). The effect in rats is presumably under the influence of CRF as it was reduced by anti-CRF antibodies. We have previously shown that metyrapone reduces

delta sleep in both male PTSD and control subjects, though this effect greater in the control group. The decrease in delta sleep was significantly associated with the endocrine (increased 11-deoxycortisol & ACTH) response. This is supportive evidence that the delta sleep response to metyrapone is a measure of the brain response to a hypothalamic CRF challenge (1). The attenuated delta sleep and endocrine response to metyrapone challenge is consistent with a model of downregulation of CRF receptors in an environment of chronically increased CRF activity in PTSD. Due to gender and age effects on HPA activity and sleep, we aimed to extend these findings to younger women. Based on our results in middle-aged men with PTSD, we hypothesized that 1) compared to controls, women with PTSD would show a diminished ACTH and delta sleep response to metyrapone, and 2) the delta sleep response would be correlated with the ACTH response.
Methods: Three nights of polysomnography were obtained in 17 women with PTSD and 16 controls. On day 3, metyrapone was administered throughout the day up until bedtime. Plasma ACTH, cortisol, and 11-deoxycorticol were obtained the morning following sleep recordings the day before and after metyrapone administration. Delta sleep was measured by period amplitude analysis.
Results: There was a significant effect of metyrapone on reducing total sleep time indicating the arousing effect of metyrapone. The effect of metyrapone was predominantly driven by the drop of total sleep time in controls and not in PTSD. Further, there were significant group by condition effects of metyrapone for total sleep time, minutes of stage 2 sleep, delta integrated amplitude, delta time in band, and delta baseline crossing driven by the larger reduction of stage 2 and delta sleep in controls compared to PTSD. There was a significant effect of PTSD status on the ACTH and 11-deoxycortisol response, in that PTSD subjects had less of an ACTH and 11-deoxycortisol rise compared to controls. The effect of metyrapone on reducing delta integrated amplitude was significantly associated with the magnitude of increase in both 11-deoxycortisol ($r = -.38$, $p = .03$) and ACTH ($r = -.41$, $p = .02$).
Discussion: Consistent with our hypotheses, we found an attenuated increase of ACTH and reduction in delta sleep after administration of metyrapone in women with PTSD compared to controls. The decline in delta sleep after metyrapone was significantly correlated with the increase in ACTH. This study extends our earlier findings in men with PTSD and demonstrates that the sleep EEG can be utilized as a proxy measure of hypothalamic CRF in response to endocrine challenges. References: 1. Neylan TC, Lenoci M, Maglione ML, Rosenlicht NZ, Metzler TJ, Otte C, Schoenfeld FB, Yehuda R, Marmar CR: Delta sleep response to metyrapone in posttraumatic stress disorder. Neuropsychopharmacology 2003; 28:1666-1676; 2. Burade VS, Jain MR, Khan FA, Saha SG, Subhedar N: Involvement of corticosteroid-like neurosteroids in pentobarbital-induced sleep. Neuroreport 1996; 8(1):139-141.

107. CSF 5-HIAA, Suicide Intent and Hopelessness in the Prediction of Suicide in High Risk Suicide Attempters

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Background: Prediction of suicide risk is important for suicide prevention and suicide attempters are the obvious high-risk group. There is a need for predictors among suicide attempters to assist the clinician to focus on those most at risk. The aim of the present study was to assess the predictive value of the Beck Suicide Intent Scale (SIS), the Beck Hopelessness Scale (BHS) and of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid for future early suicide in a group of high risk male suicide attempters.
Methods: Fifteen consecutive male patients not receiving any antidepressant treatment admitted to the department of Psychiatry at the Karolinska Hospital after a suicide attempt were included. Index episode suicide attempts included self-poisoning, asphyxiation, cuts and stabs, incineration and electricity. Most patients fulfilled DSM criteria for mood disorders, two for psychotic disorder, seven patients had comorbidity for alcohol abuse and eight patients for a personality disorder. The patients were assessed with SIS and BHS and submitted to lumbar puncture. All patients were followed up for cause of death.
Results: At follow-up, five out of fifteen patients had committed suicide within two years after the index suicide attempt. Mean CSF 5-HIAA distinguished between suicides and survivors (unpaired t-test two-tailed P value < 0.05). Low CSF 5-HIAA identified all men who committed early suicide. However, neither the Suicide Intent Score nor the Hopelessness Score distinguished suicides from survivors in this sample of high risk suicide attempters.
Discussion: The finding that low CSF 5-HIAA predicts future suicide is in line with previous reports of low post-mortem brain serotonin findings in suicide completers. The study gives further support to the suggested association between CSF 5-HIAA and future suicide. Further, in high suicide risk hospitalized male psychiatric patients CSF 5-HIAA may be a better predictor of early suicide after attempted suicide than SIS or BHS.

108. Association of the Down-Regulation of the Norepinephrine Transporter in Rat Brain with the Persistent Behavioral Effects Observed Following Repeated Treatment with Desipramine

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Background: The actions of antidepressants develop over time with repeated treatment, suggesting the importance of neuroadaptation. For the antidepressants that inhibit the reuptake of norepinephrine or serotonin, down-regulation of the norepinephrine or serotonin transporter (NET, SERT) is one such type of adaptation. However, it has not been demonstrated that this contributes to the behavioral effects of antidepressants.
Methods: Rats were treated repeatedly with the tricyclic antidepressant desipramine (DMI), which is a relatively selective inhibitor of the NET. At different times after the discontinuation of repeated treatment, three indices were measured: 1) plasma concentrations of DMI and desmethyl-DMI (DDMI), the major active metabolite; 2) behavior in the forced-swim test; and 3) the expression of the NET in cerebral cortex and hippocampus.
Results: Two days after discontinuation of repeated DMI treatment (15 mg/kg/day), no residual plasma concentrations of DMI or DDMI were detected. However, at this time, there was a residual antidepressant-like effect on behavior, as indicated by reduced immobility in the forced-swim test. Further, there was a leftward shift in the DMI dose-response function. Coincident with the persistent behavioral effect of DMI following its repeated treatment and withdrawal, a reduction in the NET was observed in preparations of cerebral cortex and hippocampus. This was evidenced by reduced binding of 3H-nisoxetine and reduced density of the NET band observed by immunoblot analysis following SDS-PAGE. Overall, comparison of the dose-response and time-course functions for the effects of repeated DMI treatment and withdrawal on forced-swim behavior and NET expression exhibited a high level of concordance. Further, inhibition of tyrosine hydroxylase with alpha-methyltyrosine, which would be expected to reverse enhanced noradrenergic neurotransmission that would result from DMI-induced down-regulation of the NET, inhibited the persistent effect of this treatment in the forced-swim test.
Discussion: The present data demonstrate that the behavioral effects of DMI persist beyond the time when plasma and brain concentrations of the parent compound or its active metabolite DDMI are detectable. This action appears to be due, at least in part, to reduced expression of the NET, which would have the overall effect of enhancing

noradrenergic neurotransmission, even in the absence of acute pharmacological antagonism of the transporter. Consistent with this interpretation, it was found that blocking the enhanced neurotransmission by inhibiting tyrosine hydroxylase blocked the persistent antidepressant-like behavioral effects that are observed following repeated DMI treatment. The present results are in line with clinical observations showing that, while acute activation of monoaminergic neurotransmission is not sufficient for producing antidepressant efficacy, it is necessary to maintain it following repeated treatment.

109. Transmission of Mood Disorders to the Offspring of Parents with Bipolar Disorder and Major Depressive Disorder

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Background: Mood disorders run in families and offspring of depressed parents have higher rates of depression than offspring of non-depressed parents. The transmission rate has been reported to vary between 5% and 67% in Bipolar Disorder (BD) and 2% and 74% in unipolar major depression. Whether there are differences in the rate of transmission of mood disorders in probands with bipolar and unipolar mood disorders has received scant attention, but Major Depressive Disorder (MDD) may be more likely to occur sporadically than BD.
Methods: We studied 347 parents with severe mood disorders (53% inpatients; 41% suicide attempters) and their 703 offspring. We hypothesized that bipolar spectrum mood disordered parents (BD I, II, NOS and unipolar parents with first degree relatives with BD) would more frequently transmit mood disorders to offspring compared to unipolar depressed parents (MDD).
Results: Most parents had MDD (n=265) and 82 parents had BD. The parents with BD had a total of 137 offspring (mean age: 20 + 10.4; 40% female). The parents with MDD had 566 offspring (mean age: 19.6 + 8.7; 51% female). Among the families with BD, 38% of the offspring had a history of mood disorder (MDD, BD, Depression NOS, Dysthymia), 23% had a history of any substance misuse disorders and 4% had a history of disruptive disorders (conduct or antisocial personality disorders). Among the families with MDD, 39% of the offspring had a history of mood disorder (MDD, BD, Depression NOS, Dysthymia), 21% had a history of any substance misuse disorders and 8% had a history of disruptive disorders (conduct or antisocial personality disorders). Suicidal behavior was present in 8% of the BD offspring and 7% of the MDD offspring.
Discussion: There were no differences in the rates of Axis I or suicidal behavior in the offspring of BD spectrum individuals or MDD subjects. Mood disorders are highly heritable independent of whether the condition in the parent is unipolar or bipolar.

110. Brain Derived Neurotrophic Factor (BDNF) is Decreased in Platelets and Lymphocytes of Pediatric Patients with Bipolar Disorder

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Background: Brain derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors, which are critical for the development and functioning of the nervous system. They promote the growth and development of immature neurons and enhance the survival and function of specific neuronal populations and maintain the structural integrity of neurons. That BDNF may be involved in the pathophysiology of mood disorders is derived from many evidences. Chronic treatment with almost all antidepressants including ECS and mood stabilizing drugs cause an increase in BDNF levels in the rat brain, suggesting that the expression of BDNF may be a common mechanism through which antidepressants and mood stabilizing drugs may produce their therapeutic effects. We have also recently reported that protein and mRNA expression of BDNF is decreased in the postmortem brain of depressed suicide victims. Some investigators have also observed a decreased level of BDNF in the plasma of depressed patients. Whereas, BDNF has been studied in the serum of patients with depression, however BDNF in bipolar patients has not been studied.
Methods: In order to examine the role of BDNF in the bipolar illness, we have determined the protein expression level of BDNF in the platelets and mRNA levels in lymphocytes of drug free patients with bipolar disorders and normal control subjects. The patients were studied in the pediatric mood disorders clinic of the University of Illinois at Chicago with IRB approval. Blood was drawn from drug-free pediatric patients and normal control subjects who were diagnosed according to WASH-U-KSADS and mania was rated according to Young Mania Rating Scale (KYMRS). The mean age for the control group was 12.5 years and the mean age for bipolar patients was 10.5 years. The mean KYMRS score was 27 for bipolar subjects. After blood was drawn, platelets and lymphocytes were separated from the blood according to standard procedures. The protein levels of BDNF were determined in the platelets using the ELISA kit provided by Chemicon International. The mRNA levels of BDNF was determined using a quantitative RT-PCR method.
Results: We found that the mean protein level of BDNF in the platelets of bipolar patients (n = 10) was significantly lower as compared to normal control subjects (n = 10). The mRNA levels of BDNF in the lymphocytes of 10 bipolar patients were significantly decreased as compared to the mRNA levels of BDNF in the lymphocytes of 10 normal control subjects.
Discussion: These studies thus indicate a significant decrease in the protein and mRNA expression levels of BDNF in bipolar patients. The source of BDNF in the platelets and/or serum is unclear at this time. However, some studies indicate that BDNF in serum and platelets are derived from the brain since BDNF has been shown to cross blood brain barrier. A correlation between changes in the serum and brain levels of the BDNF in rats has been reported. It is therefore quite possible that the level of BDNF in platelets or lymphocytes may be an appropriate marker for the BDNF level in the brain and that BDNF could be a suitable marker for pediatric bipolar illness.

111. Resolution of Sleepiness and Fatigue in the Treatment of Major Depressive Disorder: A Comparison of Bupropion and the Selective Serotonin Reuptake Inhibitors

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Sponsor: Travel Awardee, Young Investigator Memorial, 2005

Background: Although the biologic basis of excessive sleepiness and fatigue in patients with Major Depressive Disorder (MDD) has not been fully elucidated, a number of studies suggest that the neurotransmitters dopamine and norepinephrine play a key role in the patho-physiology of these symptoms (1, 2). However, to date, it is unclear whether the treatment of MDD with antidepressants which also possess noradrenergic and/or dopaminergic activity can result in a greater resolution of sleepiness and fatigue than the selective serotonin reuptake inhibitors (SSRIs).
Methods: Data from all double-blind, randomized clinical trials conducted to date comparing the norepinephrine-dopamine reuptake inhibitor (NDRI) bupropion with an SSRI for the treatment of MDD were pooled. Hypersomnia scores were defined as the sum of scores of HDRS items #22, 23 and 24. Fatigue scores were defined as the score of HDRS item #13. Remission was defined as an HDRS-17 score

equal to or less than 7 at endpoint. Resolution of a symptom was defined as an endpoint score of 0, while residual symptomatology was defined as an endpoint score >0. Cochran-Mantel-Haenszel tests for the change in each symptom (hypersomnia, fatigue) adjusting for the baseline level of severity of that symptom were conducted to compare the degree of improvement of symptom scores among groups.
Results: 6 double-blind studies involving a total of 662 patients randomized to bupropion, 655 to SSRIs, and 489 to placebo were included in the pooled analysis. There was a greater improvement in hypersomnia scores among bupropion- than SSRI- ($p<0.0001$) or placebo-treated patients ($p=0.0008$). There was no statistically significant difference in the degree of improvement of hypersomnia scores between SSRI- and placebo-treated patients ($p=0.8320$). Similarly, there was a greater improvement in fatigue scores among bupropion- ($p<0.0001$) and SSRI- ($p=0.0004$), than placebo-treated patients as well as a greater improvement in fatigue scores among bupropion- than SSRI- treated patients ($p=0.0088$). Fewer bupropion-remitters experienced residual hypersomnia (19.9%) than SSRI-remitters (32.0%) ($p=0.005$), and fewer bupropion-remitters experienced residual fatigue (19.4%) than SSRI-remitters (30.2%) ($p=0.0004$).
Discussion: Treatment of MDD with bupropion resulted in a greater resolution of sleepiness and fatigue than SSRIs treatment. Less than one in five bupropion-remitters compared to nearly one-third of SSRI-remitters experienced residual sleepiness and fatigue at endpoint.

112. Proton Magnetic Resonance Spectroscopy Study of the Effects of Lithium on *Myo*-Inositol in Bipolar Depressed Adolescents

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Sponsor: Travel Awardee, NIMH, 2005

Background: Lithium's mood stabilizing effects may result via depletion of neuronal *myo*-inositol (mI) levels through inhibition of inositol monophosphatase. The primary objective was to use proton magnetic resonance spectroscopy (^{1}H MRS) to identify the *in vivo* effects of lithium on mI concentrations in adolescents with bipolar depression. A secondary aim was to identify neurochemical predictors of successful lithium treatment.
Methods: Twenty-seven adolescents (12-18 years old) with a depressive episode associated with bipolar I disorder received open-label lithium 30 mg/kg, which was adjusted to achieve a therapeutic serum level (1.0-1.2 mEq/L). Clinical remission was defined as a Children's Depression Rating Scale - Revised score ≤ 28 and a Clinical Global Impressions Improvement Scale for Bipolar Disorder score of 1 or 2. ^{1}H MRS scans were acquired on a 1.5 T Signa General Electric MR scanner. For each subject, a three plane echo localizer was performed and an axial three-dimensional, inversion recovery prepped, fast spoiled gradient echo (TE=5.4 msec, TR=12.5 msec, TI=300 msec, FOV=24 cm, 1.5-mm thick with contiguous slices) was also acquired for voxel placement. All spectra were acquired using point resolved spectroscopy (TE=35 msec, TR=2 sec with 64 averages) and data were processed using the LC Model program. Medial and left and right lateral ventral prefrontal mI concentrations were measured at baseline, prior to receiving medication, and on days 7 and 42 of lithium treatment. Changes in mI concentrations over the three visits were analyzed. Baseline mI concentrations were compared between remitters and non-remitters of lithium treatment.
Results: The mean±SD age of subjects was 15.6±1.4 years and the majority were female (82%) and white (82%). A significant visit effect in medial and right lateral prefrontal mI concentrations was observed ($F_{2,49.5}=3.7$, $p=0.03$ and $F_{2,65.5}=3.3$, $p=0.04$, respectively). There was no significant difference in medial prefrontal mI concentration at baseline (4.86±0.53) and day 7 (4.70±0.54). A significant increase from day 7 to day 42 (4.96±0.56) was observed ($p=0.01$). There were no significant differences in right lateral prefrontal mI concentration at baseline (4.29±0.65), day 7 (4.04±0.67), and day 42 (4.43±0.71). There was no significant visit effect in left lateral prefrontal mI concentration. Lithium remitters (4.56±0.17) had significantly lower baseline medial prefrontal mI concentration compared to non-remitters (4.98±0.51) ($t_{24.4}=3.2$, $p=0.004$).
Discussion: Acute reductions in mI may represent the initiation of secondary changes in signaling pathways and gene expression that may be associated with the antidepressant activity of lithium in bipolar depressed adolescents. Successful lithium treatment may be able to be identified by baseline medial prefrontal mI concentrations. Additional studies examining lithium's effect on ventral prefrontal mI concentrations in adolescent bipolar depression are needed.

113. Electroconvulsive Seizures Increase Cell Proliferation in the Adult Monkey Cortex

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Sponsor: Past Travel Awardee, Young Investigator Memorial, 2004

Background: New neurons are generated in the hippocampus of adult mammals. Chronic stress and drugs of abuse suppress neurogenesis. In contrast, all classes of antidepressants stimulate neurogenesis and their therapeutic effects in a mouse stress model were abolished when neurogenesis was blocked by the irradiation of hippocampal precursor cells. These findings lead to the view that induction of neurogenesis is a necessary condition for antidepressant effects. We recently showed that electroconvulsive seizures (ECS), the animal analogue of ECT significantly increases neurogenesis and endothelial cell proliferation in the adult monkey hippocampus within a clinically relevant time frame. It is widely accepted that adult neurogenesis occurs in the subgranular zone of the hippocampus and the olfactory bulb-stemming from precursors in the subventricular zone. Neurogenesis outside these regions however, is a controversial topic. While some groups claim evidence of extra hippocampal or cortical neurogenesis, most investigators have not found this to occur either under baseline conditions or after treatment with ECS in rodents. Among antidepressants, ECS is the most robust stimulator of neurogenesis, thus provides the optimal method of ruling in or out the possibility of extra-hippocampal neurogenesis. In this study, we determined whether ECS increases cell proliferation and neurogenesis specifically in the frontal cortex because of its potentially key role in the mechanism of antidepressant action. Our subjects were Old World monkeys because of their similarities to humans.
Methods: Young adult (3-6yrs), age and weight matched, male bonnet macaque monkeys (Macaca radiata) were given 11 treatments of bilateral ECS at 350% above threshold (n=6) or sham (anesthesia only) (n=6), over a 4-week period. A control group received neither ECS nor sham (n=3). After the treatment course, the subjects received 4 daily IV injections of 100mg/kg of bromodeoxyuridine (BrdU), a thymidine analogue that is taken up by newly dividing cells. Four ECS, 4 sham, and 2 control subjects were transcardially perfused 2 hours after the last BrdU injection (immediate sacrifice group) and 2 ECS, 2 sham, 1 control were perfused 4 weeks later (delayed sacrifice group). Brains were post-fixed, cut into 40mm sections, and immunostained. A rater masked to treatment conditions determined the rate of cell proliferation outside the hippocampus by counting BrdU labeled cells and quantified the rate of neurogenesis by determining the percentage of BrdU cells that double labeled with a marker of mature neurons (NeuN) in the delayed sacrifice group. In addition, we assessed gliogenesis by double labeling with CNP (oligodendrocytes) and GFAP (astrocytes), and angiogenesis by labeling with CNP (endothelial cells). StereoInvestigator software was used to count the cells and record their regional distribution. Double labeling was confirmed by confocal microscopy.

Results: There was an approximately 200% increase in the number of BrdU-labeled cells in the extra hippocampal regions in the delayed sacrifice subjects. A few of these cells double labeled for both BrdU and NeuN, and this double labeling is currently being confirmed with by confocal microscopy. We are also assessing the regional distribution of the extra hippocampal proliferating cells and determining if they mature into glial or endothelial cells.
Discussion: ECS robustly stimulates cell proliferation in adult non-human primate cortex. Based on preliminary evidence, most of these cells do not mature into neurons. We are currently confirming the maturational lineage of these cells and their regional distribution.

114. Pharmacological Characterization of the Novel 5-HT_{2C} Agonist SCA-136: Antidepressant-Like Effects

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Background: Selective serotonin reuptake inhibitors (SSRIs) increase levels of synaptic serotonin, which acts at the different 5-HT receptor subtypes (as many as 14 different receptors). The antidepressant effects of SSRIs are likely mediated by one or more of these receptors, but it is unlikely that all 14 play critical roles. One candidate 5-HT receptor for mediating the antidepressant-like effects of SSRIs is the 5-HT_{2C} receptor. The present studies describe the novel 5-HT_{2C} receptor agonist SCA-136 and demonstrate its rapid onset antidepressant-like effects in preclinical models.
Methods: In vitro characterization of SCA-136 was performed in CHO lines stably expressing the human 5-HT_{2C}, 5-HT_{2A} or 5-HT_{2B} receptors. In binding studies, the ability of SCA-136 to displace [^{125}I]-DOI (5-HT_{2C} and 5-HT_{2A} cell lines) or [^{3}H]5-HT (5-HT_{2B} cell line) was investigated and Ki values were determined. In functional studies, the ability of SCA-136 to mobilize intracellular calcium in a FLIPR assay was evaluated in all 3 cell lines. In vivo characterization of SCA-136 was conducted in animal models of antidepressant activity. In the forced swim test, day 1 consisted of a 15 min swim pretest and day 2 consisted of a 5 min swim test session. SCA-136 was administered 23.5, 5, and 1 hour prior to the test session and immobility time was measured in the test session. In the resident-intruder model, the effects of SCA-136 were evaluated on the observable behavior of the resident rat following the placement of an intruder in the residents home cage. In the olfactory bulbectomy (OB) model, removal of the olfactory bulbs results in hyperactivity (2 weeks post surgery). The effects of SCA-136 on OB-induced hyperactivity were assessed.
Results: SCA-136 is a novel compound that displaces [^{125}I]-DOI binding from human 5-HT_{2C} receptor sites in CHO cell membranes with a Ki value of 3 nM. Binding affinities determined for the human 5-HT_{2A} and 5-HT_{2B} receptor subtypes were 152 and 14 nM, respectively. In functional studies, SCA-136 stimulated the mobilization of intracellular calcium in CHO cells stably expressing the human 5-HT_{2C} receptor with an EC_{50} value of 8 nM, and Emax relative to 5-HT of 100%. SCA-136 failed to stimulate calcium mobilization in cells expressing the human 5-HT_{2A} or 5-HT_{2B} receptor subtype (EC_{50} >> 10 μM). In the rat forced swim test, SCA-136 produced dose-dependent decreases in immobility. In the resident-intruder model, acute administration of SCA-136 decreased aggression at doses lower than those required for decreasing total behavior. Chronic administration of SCA-136 showed rapid onset effects with antidepressant-like increases in aggression observed by Day 3. In the olfactory bulbectomy model, SCA-136 was administered to Sham and OB rats for a 3 day to 3-week period starting 2 weeks post surgery. SCA-136 produced a dose-dependent decrease in olfactory bulbectomy-induced hyperactivity in rats, consistent with antidepressant-like effects. Importantly, the effects of SCA-136 were evident following (3-21 days) of administration, indicative of rapid onset effects without tolerance.
Discussion: The present studies identify SCA-136 as a novel and potent 5-HT5-HT_{2C} selective receptor agonist with rapid onset antidepressant-like effects.

115. Constitutive Activation of the G-Protein Subunit G αs Causes Behavioral and Biochemical Deficits Due to a PKA-Dependent Upregulation of PDE Activity

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Background: Abnormalities within the cAMP/PKA pathway, along with changes in G-protein signaling, have been noted in patients with schizophrenia. Our laboratory has developed transgenic mice that express a constitutively active isoform of the G-protein subunit Gs (Gαs *) within forebrain neurons (driven by the CaMKII|α promoter), to test the hypothesis that altered G-protein signaling contributes to specific endophenotypes associated with schizophrenia, including deficits in sensorimotor gating and memory. Previously, G αs* transgenic mice showed impaired sensorimotor gating, as measured by prepulse inhibition of acoustic startle (PPI; Gould et al., Neuropsychopharmacology, 2004, v29, p494), which was rescued by treatment with the antipsychotic haloperidol. G αs* transgenic mice also showed impaired memory for conditioned fear. These behavioral deficits appear to be due to decreases in cAMP levels within cortex and/or hippocampus that are caused by a compensatory upregulation of phosphodiesterase (PDE) activity. Given evidence in the literature that upregulation of PDE activity is dependent on PKA signaling, we tested the hypothesis that inhibition of PKA in our G αs* transgenic mice would rescue both the behavioral and biochemical deficits exhibited by these mice.
Methods: To inhibit PKA activity within the same forebrain neurons that express G αs*, we crossed G αs* transgenic mice with another line of transgenic mice expressing R(AB), an inhibitor of PKA activity (Abel et al., Cell, 1997, v88, p615).
Results: Co-expression of G αs* and R(AB) rescued the PPI deficits caused by expression of G αs*. Co-expression of G αs* and R(AB) also rescued the decrease in cAMP levels measured in cortex of G αs* transgenic mice, but did not attenuate the increase in cAMP levels measured in striatum. This suggests that inhibition of PKA activity rescued the PPI deficits caused by G αs* expression by specifically blocking the upregulation of PDE activity, not the increase in adenylyl cyclase activity caused by the transgene. In fact, pharmacological inhibition of PDE activity by rolipram (0.66 mg/kg) also rescued the PPI deficits exhibited by G αs* transgenic mice. PKA signaling also appears to contribute to the memory deficits caused by G αs* expression. Co-expression of G αs* and R(AB) rescued the impairments in pavlovian fear conditioning caused by Gαs* expression and fully restored expression of activity-regulated cytoskeleton-associated protein (Arc), a memory-related immediate-early gene.
Discussion: Together, these results suggest that constitutive activation of G αs* results in behavioral endophenotypes associated with schizophrenia due to a PKA-dependent upregulation of PDE activity, and point to a novel therapeutic application of phosphodiesterase inhibitors as antipsychotics. Supported by: Merck Foundation, NIH, the Packard Foundation, the University of Pennsylvania Research Foundation, Whitehall Foundation, and the Tourette's Syndrome Association. The authors affirm that this work has been carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and was fully approved by the IACUC of the University of Pennsylvania.

116. Does Maintenance Treatment with Atypical Antipsychotics Worsen Quality of Life Among Stable Patients with Schizophrenia?

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Sponsor: David Pickar

Background: Some controversy continues to exist over whether patients with schizophrenia should be maintained on continuous long-term antipsychotic treatment. We assessed whether maintenance treatment with an atypical antipsychotic agent worsens quality of life (QOL) relative to placebo treatment among stable, minimally symptomatic patients with schizophrenia.
Methods: This was a post-hoc analysis of our 52-week double-blind trial, which consisted of 4 phases: 1) 4- to 9-day screening and evaluation phase, 2) 6-week conversion to open-label olanzapine 10-20 mg/day, 3) 8-week stabilization on olanzapine 10-20 mg/day, and 4) 52-week randomized (2:1), double-blind maintenance with olanzapine 10-20 mg/day (N=224) or placebo (N=102). Baseline-to-endpoint mean changes on the Heinrichs-Carpenter Quality of Life scale (QLS) Total were analyzed for olanzapine- or placebo-treated patients during the maintenance phase. Relapse criteria included a pre-specified increase in positive symptoms, as measured by the BPRS Positive; hospitalization due to positive psychotic symptoms; or a completed suicide or serious attempt. An exacerbation criterion was a ≥10% increase in PANSS Total score (≈4 points, on average). An analysis of covariance was performed between treatment groups for non-relapsing patients and a non-inferiority test was performed for QLS data collected while patients were non-exacerbating. QLS change scores in the non-exacerbating non-inferiority analysis were computed based on the QLS scores collected 1 visit before exacerbation of psychotic symptoms, or endpoint, whichever was sooner. A 2-sided 95% confidence interval (CI) for treatment difference in change in QLS scores was computed from these changes. A delta of 6 points was specified (5% of maximum possible score), thus setting a lower limit of the 95% CI for the olanzapine-placebo treatment difference of > -6.
Results: The study was terminated early (longest double-blind treatment ≈35 weeks). For non-relapsing patients, QLS scores improved for those treated with olanzapine (4.9 ± 10.1; N=203) and worsened for those given placebo (-3.3 ± 11.1; N=70); these differences were significant ($p<0.001$). When restricting consideration to non-exacerbating periods, QLS scores were improved for both olanzapine (5.7 ± 8.9; N=174) and placebo (2.7 ± 11.0; N=40) groups. The 95% CI for QLS mean change treatment differences was (-0.2, 6.2), thus non-inferiority was demonstrated. During the non-exacerbating period, both the olanzapine- and placebo-treated groups showed slight, but similar, improvement in psychopathology (0.2-point greater PANSS Total improvement among olanzapine-treated patients), suggesting no bias against the placebo group on the basis of psychopathology. These findings were supported by a path analysis for all patients over the entire study period, which indicated a partial direct effect of treatment (29%) on QOL that was not accounted for by differential changes in psychopathology.
Discussion: This report showed no worsening of QOL among stable, minimally symptomatic patients with schizophrenia who were continued on antipsychotic treatment relative to those who were discontinued from active medication and maintained a relatively minimally symptomatic state over a maximum duration of approximately 35 weeks. These data suggest that to preserve the QOL of patients with schizophrenia, who have had their illness for a significant period of time and have received chronic antipsychotic medication, treatment with antipsychotic medication should continue, even when symptoms are under control.

117. Dopaminergic Modulation of Excitatory and Inhibitory Transmission in the Basolateral Amygdala-Prefrontal Cortex Pathway

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Background: Projections from basolateral amygdala (BLA) and dopamine (DA) inputs converging in the medial prefrontal cortex (PFC) form a neural pathway implicated in a number of cognitive and emotional processes. Perturbations in these neural circuits are thought to underlie emotional and learning disturbances in diseases such as schizophrenia and drug addiction. Activation of the BLA can evoke two distinct types of electrophysiological responses in subpopulations of PFC neurons; a monosynaptic, excitatory response and a presumably polysynaptic inhibition of spontaneous firing. However, the role that DA plays in modulating these differential effects is currently unknown.
Methods: The present study assessed the effects of intravenous administration of selective DA receptor agonists on inhibitory and excitatory responses in PFC neurons evoked by BLA stimulation, using extracellular single-unit recordings in urethane-anesthetized rats. Single pulse stimulation of the BLA (0.2-0.8 mA) revealed two distinct responses in PFC neurons. In the majority of PFC neurons (>75%), activation of the BLA caused an 80% reduction in the spontaneous firing rate of these cells, with a complete suppression of firing occurring ~30 ms after stimulation and lasting ~170 ms. In a separate population of cells, BLA stimulation evoked a robust, monosynaptic excitatory response with an onset latency of ~15 ms.
Results: For PFC neurons inhibited by BLA stimulation, administration of either the D2 agonist bromocriptine (0.5 mg/kg), the D2/D4 agonist quinpirole (0.2 mg/kg) or the D4 receptor agonist PD168,077 (1 mg/kg) dramatically reduced the inhibitory influence that BLA inputs exerted over PFC neural activity. This was indexed by an increase in onset latency and decreases the magnitude and duration of the suppression of spontaneous firing following BLA stimulation. Moreover, in some neurons, administration of quinpirole revealed a monosyaptic excitatory response that was not apparent prior to drug administration. In comparison, the D1 receptor agonist SKF81297 (0.5 mg/kg i.v.) caused only a slight reduction in the duration of the inhibition. For PFC neurons excited by BLA stimulation, D1 receptor stimulation caused a significant (>40%) reduction in spike firing evoked by single-pulse stimulation of the BLA, but did not alter spontaneous activity. However, the inhibition of BLA-evoked firing by SKF 81297 was frequency dependent. Firing evoked by stimulation of the BLA with a 20 Hz train of pulses was less affected by D1 receptor stimulation as compared to firing evoked by single-pulse stimulation. In contrast to these findings, administration of quinipirole or PD168,077 produced no reliable effect on evoked firing, but caused a slight increase in spontaneous activity.
Discussion: Taken together, the present findings highlight the dissociable DA receptor mechanisms that regulate excitatory and inhibitory transmission in the BLA-PFC pathway. Activation of D2/D4 receptors attenuates inhibitory transmission in this pathway, promoting an increase in the activity of PFC neurons. On the other hand, D1 receptors reduce the excitatory responses that BLA inputs exert on PFC neural firing, but do so in a frequency-dependent manner. These data suggest that perturbations in these DA receptor mechanisms may disrupt in the normal inhibitory influence that BLA inputs exert over PFC neural activity, leading to an aberrant increase in frontal lobe activity. Alterations in the dopaminergic regulation of BLA-PFC circuits may underlie some of the disturbances in decision making and emotional processing observed in schizophrenia. (Conducted in accordance with the Guide for the Care and Use of Laboratory Animals, supported by CIHR).

118. Schizophrenia, Diabetic Ketoacidosis and Atypical Antipsychotic Agents

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Sponsor: Donald Goff

Background: There have been several reports of diabetic ketoacidosis (DKA) associated with treatment with atypical antipsychotic agents, most notably clozapine and olanzapine. DKA is the result of an absolute or relative insulin deficiency usually associated with increased levels of counter-regulatory hormones such as catecholamines, glucagon, cortisol, and growth hormone.
Methods: We conducted a retrospective epidemiological study assessing the incidence of new onset DM presenting as DKA in schizophrenia patients treated with atypical antipsychotic agents. The patient population studied included patients that attended Massachusetts General Hospital (MGH) between January 1, 1995 and December 31, 2001. Following Institutional Review Board (IRB) approval, identification of the patients was achieved by using the Research Patient Data Registry (RPDR), an electronic database linking administrative and clinical laboratory data following.
Results: 819,308 attended the hospital during the seven year period with 51% female and 53942 (6.6%) received the diagnosis of diabetes mellitus. There were 4,850 patients with the diagnosis of schizophrenia that attended the hospital during this time period and represented only 0 .6% of the general hospital population. 893 (18.4%) of patients with the diagnosis of schizophrenia were also diagnosed with DM, compared to 6.6% in the general hospital population ($p<0.001$). There were 1132 of 819,308 (0.138%) patients in the general hospital population that received the diagnosis of DKA, while 1.1% (51 of 4850) of patients with schizophrenia received the diagnosis of DKA. Of 23 schizophrenia patients identified with DKA, eleven were new onset DM presenting as DKA; eight were DKA in patients with known DM two were HHS without prior history of DM; and two were HHS with a known history of DM. Thus, the incidence of DKA in schizophrenia patients was 19/1132 or 1.67% during the 7 year period. Three patients with new onset DM presenting as DKA went on to have additional episodes of DKA within the 7 year period of follow-up. Of the 11 patients with new onset DM presenting as DKA, the mean age was 42 +/- 12 years (range 26-64), the mean BMI was 29.9 +/- 4.5 (range 24-35), six (55%) were female, 73% were white, 18% black, and 9% Hispanic. Eight (73%) were diagnosed with chronic schizophrenia and three (27%) with schizoaffective disorder. The mean glucose at the time of presenting with DKA was 795 +/-328 mg/dl; the bicarbonate was 13.1 +/- 5.4 mmol/L (range, 5-21); anion gap 20.1 +/-4.6 (15-30), pH was 7.22 +/- 0.17; HbA1c 13.3 +/- 1.9% (10.4-16.9). There was a known family history of DM in 27%. The incidence of DKA in schizophrenia patients without a prior diagnosis of diabetes was more than ten fold higher than that reported in the general population: 14.93 per 10,000 patient years (schizophrenia) vs. 1.4 per 10,000 patient years ($p<.000001$). The incidence of DKA for each drug over the seven year period was clozapine 2.2%, olanzapine 0.8%, risperidone 0.2%, quetiapine and ziprasidone, none. If HHS cases were included then incidence with olanzapine rose to 1.0%. After up to six years of follow-up, three of 11 new onset DM-DKA and one of two new onset DM-HHS the DM resolved completely upon switching antipsychotic agents.
Discussion: The incidence of DM and new onset DM presenting as DKA in schizophrenia patients is much higher than in the general hospital population and differs across atypical antipsychotic agents. The most striking finding was consistent, grossly elevated hemoglobin A1c in patients with new onset DM-DKA. This suggests that these patients had undiagnosed DM for at least several weeks before experiencing a DKA episode.

119. DISC1 Polymorphism in Schizophrenia: Associations with Cognition and MRI Brain Morphology

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Background: Cytogenetic studies and linkage studies have implicated disrupted-in-schizophrenia 1 (DISC1) as a candidate gene for schizophrenia. Although the functions of DISC1 remain unclear, allelic variations at or close to the DISC1 locus have been associated with working memory and visual span performance and with reduced P300 amplitudes; all of which are endophenotypic features of schizophrenia. Association studies investigating DISC1 SNPs have also found over-transmission of specific alleles in schizophrenia and relationships with hippocampus cognitive functions and gray matter (GM) volumes. The aim of this study is to systematically examine the effects of DISC1 Cys704Ser polymorphism on neurocognition and MRI brain morphology in schizophrenia.
Methods: A comprehensive battery of standardized neuropsychological tests was administered to 150 healthy volunteers and 302 schizophrenia patients. Approximately 60% of the sample also received multi-spectral MRI brain scans. Using general linear models, we examined the effects of genotype (Ser homozygotes versus Cys carriers) on five cognitive domain scores (covariates: FSIQ, gender and age), and on MRI lobar GM volumes (covariates: intracranial volume and age).
Results: There were significant genotype effects on language domain scores ($F=3.91$, $p=0.05$), such that Ser homozygous patients had poorer language scores than Cys-carrier patients. Healthy volunteers did not differ across genotype groupings on language test performance. No statistically significant genotype effects were observed with regard to full scale IQ, or with the other 4 cognitive domain scores. Again, when component neuropsychological tests within the language cognitive domain were examined, only Ser homozygous patients had significantly lower WAIS Vocabulary subtest and Shipley Institute of Living Scale Vocabulary scores than Cys-carrier patients ($F's \geq 4.02$, $p's \leq 0.04$). Consistent with being associated with language abilities, there was a significant main genotype effect on MRI frontal lobe GM volumes ($F=8.13$, $p=0.005$). Ser homozygous patients had significantly smaller frontal GM volumes than Cys-carrier patients ($p=0.02$). The differences in frontal GM volumes across healthy volunteer genotype groupings approached but did not achieve statistical significance ($p=0.07$). No statistically significant genotype effects were seen with temporal, parietal or occipital lobar GM volumes.
Discussion: The associations between DISC1Ser variant with poorer language abilities and with smaller frontal lobar GM volumes appear to be specific to schizophrenia patients. Our findings provide additional support for DISC1 as a candidate gene that mediates particular phenotypic features of schizophrenia.

120. Temporal and Prefrontal Cortex Gray Matter Abnormalities in Patients with Schizophrenia and Their Unaffected Siblings; An Optimized Voxel-Based Morphometry Study

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Sponsor: Jack Durell

Background: Patients with schizophrenia have known decreases in volume in gray matter, most often in the lateral and medial temporal lobes, as well as frontal and anterior cingulate cortices. These alterations in structure are not only related to clinical phenotype, but also may be endophenotypic markers of liability. First-degree relatives are useful in this search for endophenotypes, as there is evidence that unaffected siblings of patients with schizophrenia share ventricular enlargement as well as selective decreases in the temporal and frontal

cortices. Optimized voxel-based morphometry (VBM) has the advantage of facilitating whole brain, unbiased analyses on a large group of subjects. The aim of this study was to compare the gray matter volume in a large cohort of patients with schizophrenia and their unaffected siblings to normal controls using VBM.
Methods: Magnetic resonance images and optimized voxel-based morphometry (VBM) were used to measure relative gray matter volumes in 169 patients with schizophrenia (mean age 36 ± 9; 78% male), 213 of their siblings (mean age 36 ± 10; 42% male), and 212 control subjects (mean age 33 ± 10; 49% male). All subjects were Caucasian of European ancestry, and normal controls had no current or prior history of psychiatric or neurological illness, while siblings had no current psychiatric illness. T1-weighted SPGR MRIs were acquired on a 1.5T GE scanner with a voxel resolution of 0.975 x 0.975 x 1.5 mm3. For data processing, VBM was performed in SPM2 using an optimized VBM protocol with customized apriori templates. Data were analyzed using the General Linear Model, as implemented in SPM2, with linear and nonlinear age expansions, as well as sex and total gray matter volume, used as covariates.
Results: Significant group differences in gray matter volume were seen between the patients with schizophrenia and control subjects (voxel-level, $p<.001$ corrected), with decreased volume in the thalamus, left insula, right superior and bilateral middle temporal cortices, prefrontal and frontal cortices, and the parahippocampal gyrus. Siblings of patients shared significant decreases (voxel-level, $p<.005$ uncorrected) in the left thalamus, left insula, left middle temporal, prefrontal and frontal cortices, and the right parahippocampal gyrus. Patients also had significantly increased volume (voxel-level, $p<.001$ corrected) in the cerebellum, lentiform nucleus, caudate, medial prefrontal cortex, and left amygdala. There were no increases in gray matter in the siblings relative to the control group.
Discussion: These regional decreases in patients with schizophrenia are compatible with and extend the relevant findings of previous volumetric analyses. Unselected siblings of patients with schizophrenia have gray matter abnormalities in the prefrontal and temporal cortices, revealing a familial element to brain structure abnormality in schizophrenia. Thus gray matter loss as seen using imaging and VBM may add another element to genetic studies in schizophrenia. Further investigation using whole brain analysis of relative risk will further elucidate the significance of these shared structural abnormalities.

121. Identification of a Novel Genetic Locus at 7q36.1 in Strong LD with Schizophrenia and the Differential Expression of the Flanking Genes, NOS3 and KCNH2

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Background: Increases in the level of nitric oxide synthase (NOS) activity and products of NO synthesis in the brains and periphery of individuals with schizophrenia have previously been reported. While NOS1 has been investigated at the protein and mRNA level, finding slight increases in patients with schizophrenia, increases in NOS3 were only recently observed using microarray technology.
Methods: Using TaqMan assays we genotyped SNPs in the region of KCNH2 and NOS3 in individuals from 297 affected families as well as in 712 case/control samples (including 329 affected individuals). Quantitative real-time PCR was performed using RNA isolated from the dorsolateral prefrontal cortex of 114 post-mortem brain samples (including 39 schizophrenia patients).
Results: We confirmed significantly increased levels of NOS3 mRNA in post-mortem brains of schizophrenia patients. Furthermore, genetic screening of SNPs in the area surrounding this gene found highly significant association within the families of schizophrenic individuals. Interestingly, this signal is located 16.7 Kb upstream of NOS3 in a neighboring gene, KCNH2. Nonetheless, an effect of genotype on NOS3 mRNA expression was observed suggesting that the region of association may, in part, elicit effects on the regulation of NOS3 expression. Changes in KCNH, or the ERG family, potassium channels have not previously been investigated with relation to neuropsychiatric illnesses. Here we describe significantly decreased levels of KCNH2 mRNA within the post-mortem schizophrenia brain.
Discussion: These findings provide both genetic and expression level evidence of two new genes previously unreported as being involved with schizophrenia. Though it is unclear what precise mechanisms might cause or be affected by these changes, the possibility of their functional involvement in glutamatergic signaling and neuronal regulating activities offers interesting avenues of further investigation for their involvement in the development and prognosis of schizophrenia.

122. Allelic Variations in NRG1 Affect Region-Specific Expression of Low Affinity Nicotinic Acetylcholine Receptors in the Human Brain

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Sponsor: Joel Kleinman

Background: The prevalence of cigarette smoking in schizophrenic patients is much higher than that in the general population. While an ongoing debate exists on the underlying etiology for nicotine addiction among schizophrenics, a neuronal basis is suggested by evidence of a decrease in high and low affinity nicotinic acetylcholine receptors (CHRNA4 and CHRNA7, respectively) in brains regions implicated in the pathogenesis of schizophrenia. Rodent studies suggest that the expression of CHRNA7 is regulated by neuregulin-1 (NRG1), a putative susceptibility gene for schizophrenia. In this study, we tested the hypothesis that allelic variations in NRG1 will lead to altered mRNA expression of CHRNA7 in the human hippocampus and dorsolateral prefrontal cortex (DLPFC).
Methods: The NRG1 SNPs examined in this study are in a tight LD block in the 5′ region of the gene and are contained within the region spanned by the original at-risk haplotype identified by Stefansson, et al. (2002); thus, an effect of haplotype on mRNA expression was also explored. Using postmortem hippocampal (N= 62 normal controls; N=29 schizophrenics) and DLPFC (N=63 normal controls, N=35 schizophrenics) tissue samples, we measured the common transcript of the CHRNA7 subunit using RT-PCR.
Results: In the hippocampus, there was a main effect of genotype on single SNPs (SNP8NRG221533 and SNP8NRG243177) with those alleles initially found to be associated with the disease having a lower CHRNA7 mRNA expression. In the same brain region, normal controls who carry the disease associated haplotype have a significantly lower expression of CHRNA7 ($p=0.007$) but when schizophrenics are included in the analysis, only a trend for significance remained ($p=0.08$). In contrast, neither an effect of genotype nor haplotype was observed on mRNA expression in the DLPFC.
Discussion: Our studies provide evidence, for the first time in human brain tissue, that polymorphisms in the NRG1 gene are associated with region specific alterations in CHRNA7 expression and add to other evidence that the deCode risk haplotype identifies a functional element controlling NRG1 expression.

123. Treatment of Patients with Acute Schizophrenia Using Paliperidone Extended-Release Tablets: A 6-Week Placebo-Controlled Study

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Background: Future therapies for schizophrenia need to address efficacy and tolerability, as well as functioning to ensure progress in the

treatment of this disease. The objective of this study was to evaluate the efficacy, tolerability and effect on functioning of three fixed doses of the investigational psychotropic agent, paliperidone extended-release tablets in patients with schizophrenia.
Methods: In this international, 6-week, multicenter, double-blind, randomized, placebo- and active-controlled, parallel-group, dose-response study, patients with schizophrenia (n=630, age ≥18 years) were randomized to receive daily doses of paliperidone ER 6mg, 9mg, or 12mg, placebo or olanzapine 10mg. Patients enrolled were experiencing an acute episode of schizophrenia (Positive and Negative Syndrome Scale [PANSS] score=70—120) and agreed to protocol-specified hospitalization for the first 14 days. The Intent-to-Treat (ITT) analysis set=patients who received ≥1 dose of double-blind study medication and had ≥1 post-baseline efficacy measurement. The primary efficacy measure=change from baseline to endpoint in total PANSS score in the ITT group. The olanzapine group was included for assay sensitivity and was not included in the statistical model. Other efficacy analyses included responder rates (RR=improvement at endpoint in PANSS total score by ≥30%) and change in baseline to endpoint score on the Personal and Social Performance (PSP) scale. Safety assessments included treatment-emergent adverse events (TEAE) and vital signs including bodyweight.
Results: The ITT population (n=628) was 86% white, 52% male, age=37.1±10.9 years and had a baseline PANSS total score of 93.9±11.0. There was a significant reduction in mean PANSS total score at endpoint for all paliperidone ER doses vs placebo (6mg=—17.9±22.2, 9mg=—17.2±20.2, 12mg=—23.3±20.1, placebo=—4.1±23.2; p<0.001). The change in mean PANSS total score at endpoint in the olanzapine group=—19.9±19.0. A significant improvement in mean PANSS total score for paliperidone ER vs placebo was evident at every post-baseline time point from Day 4 for paliperidone ER 12mg (p<0.01), and from Day 8 for the 6mg and 9mg groups (p<0.05). RR were significantly higher in all treatment groups vs placebo (6mg=56%, 9mg=51%, 12mg=61%, placebo=30%; p≤0.001). RR for olanzapine was 52%. PSP scale scores improved significantly from baseline to endpoint vs placebo for the 3 paliperidone ER groups (6mg=9.1±15.5, 9mg=8.1±14.5, 12mg=11.5±16.0, placebo=0.5±15.5; p<0.001). TEAE were observed in 63%, 60%, 63%, 73% and 63% of patients treated with placebo, paliperidone ER 6mg, 9mg and 12mg and olanzapine, respectively. TEAE that occurred >3% more frequently than with placebo were tachycardia, extrapyramidal disorder and hyperkinesia for paliperidone ER, and somnolence, tachycardia and postural hypotension for olanzapine. TEAE-extrapyramidal symptom rates were comparable for paliperidone ER 6mg, olanzapine and placebo with dose-related increases for paliperidone ER 9mg and 12mg groups. The mean change in bodyweight (kg) at endpoint with placebo, paliperidone ER 6mg, 9mg and 12mg and olanzapine groups were —0.7±2.4, 0.2±2.4, 0.6±2.7, 0.5±2.6 and 1.3±2.8, respectively.
Discussion: This study shows that paliperidone ER is an effective psychotropic in the treatment of schizophrenia, which also results in functional improvements and is generally well tolerated.

124. A Comparison of the Effects of Olanzapine, Quetiapine, and Risperidone on Neurocognitive Function in First-Episode Psychosis

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Background: Patients with schizophrenia and first-episode psychosis perform poorly (one to two standard deviations below the baseline of control participants) on a variety of neurocognitive measures. Interventions that may reduce these deficits are crucial, as neurocognitive improvement may enhance patients' recovery and functional life outcomes. While olanzapine and risperidone have been shown to improve cognition more than haloperidol in first-episode patients, the effect of quetiapine on cognition is unknown in this population. Furthermore, no comparisons have been made among atypical antipsychotics.
Methods: In this 52-week, randomized, double-blind, multicenter study, patients with first-episode psychosis were randomized to treatment with olanzapine (2.5 to 20 mg/d), quetiapine (100 to 800 mg/d), or risperidone (0.5 to 4 mg/d). Patients completed neurocognitive assessments at baseline and at 12 and 52 weeks of treatment. Neurocognitive composite scores were calculated from a battery of tests compiled for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia clinical trial and from the Brief Assessment of Cognition in Schizophrenia (BACS), and these two composite scores were averaged for the summary analyses.
Results: The mean (SD) modal prescribed daily dose of medication in the 400 patients randomized to treatment was 11.7 (5.3) mg for olanzapine, 506 (215) mg for quetiapine, and 2.4 (1.0) mg for risperidone. At Week 12, there was significant improvement in cognitive measures for each of the treatments (P<0.01), with mean composite score improvements of 0.18 for olanzapine, 0.34 for quetiapine, and 0.27 for risperidone. There was no significant overall difference between the treatments. However, pairwise comparisons of between-group differences suggested trends for quetiapine to improve cognition more than olanzapine on the CATIE composite score (P=0.080) and on the BACS composite score (P=0.059) after 12 weeks of treatment. The magnitude of improvement in the mean of the two composite scores was slightly smaller for patients who stayed in the study through to Week 52 (0.13 for olanzapine, 0.28 for quetiapine, and 0.30 for risperidone), and the within-group treatment effects were no longer statistically significant. Quetiapine improved cognition more than olanzapine on five of the 15 individual measures (P<0.05) and more than risperidone on four of the 15 measures at 12 weeks (P<0.05). Risperidone improved cognition more than olanzapine at 12 weeks on one measure (P<0.05). Cognitive improvement was not significantly related to anticholinergic treatment, sleepiness, akinesia, Abnormal Involuntary Movement Scale scores, or Barnes Akathisia Scale scores, but correlated with Simpson Angus Scale scores (r=-0.16, P=0.020). At Week 52, statistically significant relationships emerged between the BACS composite score and vocational outcome in patients treated with quetiapine (r=0.49, P=0.012), and between the CATIE composite score and social outcome in patients treated with olanzapine (r=0.61, P=0.002).
Discussion: Atypical antipsychotics significantly improve neurocognitive function in patients with first-episode psychosis. These improvements are related to changes in functional outcome after one year of treatment. While overall composite scores did not differentiate treatments, individual measures appeared more sensitive to quetiapine treatment.

125. Relationship of Paternal Age to N-Acetyl-Aspartate in the Prefrontal Cortex in Schizophrenia

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Background: Recent epidemiologic and genetic studies have shown that increasing paternal age is an independent risk factor for sporadic or nonfamilial schizophrenia. A proton magnetic resonance spectroscopy (1H MRS) measure of neuronal functional integrity, the ratio of N-acetyl-aspartate (NAA) to creatine-containing compounds (Cr), has been found in some but not all studies in schizophrenia to be in deficit in the dorsolateral prefrontal cortex (DLPFC), consistent with a possible deficit of glutamatergic function in that region. In this study, we investigated the relationship between paternal age and this MRS measure in a group of hospitalized patients with schizophrenia.

Methods: We studied 34 patients with DSM-IV schizophrenia and 34 group-matched healthy control subjects using MRS to determine NAA/Cr in the DLPFC. Twenty-five of the 34 patients had sporadic illness. The acquisition protocol consisted of a multislice spin-echo sequence with outer volume suppression. A DLPFC region of interest (ROI) was defined, and the ROI mean of the ratio of NAA/Cr was computed as outcome measure. We examined the effects of paternal age on this outcome measure, controlling for maternal age and subject age, using multiple regression analysis within the sporadic and familial patient groups separately.
Results: The patients with sporadic illness (n=25) showed a significant decline in DLPFC NAA/Cr with increasing paternal age (df = (3,20), F=3.94, p=.017, after controlling for subject age (p=0.436) and maternal age (p=0.550)). The effect of paternal age was not significant among the familial cases of schizophrenia. DLPFC NAA/Cr did not differ between the patients and control subjects by two-tailed t test.
Discussion: These data show that among sporadic cases of schizophrenia, advancing paternal age is associated with decreased DLPFC NAA/Cr, even after accounting for the effects of subjects' age and maternal age. While the familial group may be underpowered to detect this relationship, the data suggest that sporadic, paternal age-related schizophrenia may involve distinct neurochemical alterations. Support: NIMH, NARSAD, Irving Center, Lieber Center

126. Cardiac-Related Mortality in People with Schizophrenia

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Background: Deaths from cardiovascular-related events are believed to occur more frequently in patients with schizophrenia than in the normal population and the risk may be up to 5x greater than in the general population. Others have reported this risk to be rising annually, possibly due to newer second-generation antipsychotic (SGA) medications. Thus, we examined cardiovascular mortality associated with a sample of patients with chronic schizophrenia receiving clozapine to a sample with chronic schizophrenia who have never received clozapine and who were identified as having risperidone treatment.
Methods: Between 1994 and 2000 we included 1122 people with schizophrenia treated with clozapine and 915 treated with risperidone and never receiving clozapine treatment. We eliminated 274 subjects in the risperidone group who had received olanzapine also during treatment thus, producing a sample of 641 subjects on risperidone during this time period
Results: The sample was 62% male and this did not differ by drug group. Among all deaths on clozapine, 51% (18/35) were cardiovascular as were 38% (8/21) on risperidone. The mean age of death for those dying from cardiovascular disease was 54.1 +/- 10.0 years for those who were treated with clozapine vs. 68.9 +/- 16.6 years (p=0.0094), however, the mean age of starting risperidone was older (41.5 +/- 15.3 [82% under age 55] vs. 38.8 +/- 10.8 years [92% under age 55]; p<0.001). The risk for cardiovascular death was driven primarily by age (p<0.01) and male sex (p=0.04) and antipsychotic treatment was not found to be significant. In treating people younger than 55 years the five-year estimated rate of death from cardiovascular disease is 3.7% on clozapine and 2.1% on risperidone. (P=NS). Additionally, in a random sample of clinical charts audited, 104/378 (27.5%) of all patients had a comorbid diagnosis of cardiovascular disease/cardiac condition at the time of drug initiation. Also, 20/379 (5.3%) had diabetes mellitus (DM)/glucose dysregulation and 33/328 (10.1%) had a family history of DM. A significantly larger proportion of those who died from a cardiac-related death on risperidone had preexisting cardiac disease (50%) as compared to the clozapine group (13%) (p<0.019). People who died from a cardiac-related death in either drug group did not have higher BMI or lipids as compared to those who did not die.
Discussion: It is well known that weight and cardiovascular disease is highly related to increased mortality. However, the risk of cardiovascular mortality associated with schizophrenia may be maximized by disease-related risk, poor lifestyles and high rates of preexisting obesity. The risk of cardiovascular-related mortality does not appear to largely differ by antipsychotic treatment, including an agent (clozapine) that is known to be associated with changes in weight and metabolic status. We are currently adding data on another 364 deaths from this sample for a longer follow-up (through 2004) that will increase the power of this study to detect any differences in mortality between these two drug groups.

127. Cognitive Remediation and Social Cognition in Early Schizophrenia: Preliminary fMRI Data

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Background: Schizophrenia patients frequently have impairments in social cognition, i.e. the mental processes by which people make sense of themselves, others, and their social situations. Remediation approaches such as Cognition Enhancement Treatment (CET) can potentially improve such deficits, by comparison with Enriched Supportive Therapy (EST) (Hogarty et al, 2004) and may lead to superior and more efficient processing of socially-relevant information. The neurobiologic correlates of treatment related improvements in these domains have not been investigated. We report preliminary results of the first fMRI study to examine the efficacy of CET or EST, and their effects on the neural circuitry underlying social cognition. Social cognition was assessed using the Baron Cohen "eyes" task in a series of stable early-course patients with schizophrenia following treatment with either EST or CET.
Methods: Subjects were scanned using a 3T G.E. MRI Scanner at the University of Pittsburgh's MR Research Center. For each subject, 283 axial images were collected over 26 slices using a T2* spiral sequence (TE=18 ms, TR=1500 ms, flip angle=70°, size: 3.125 x 3.125 x 3.2 mm, 0 gap). The pictures were sampled from the data set used to study "theory of mind" in autism (see: www.autismresearchcentre.com; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Pictures were presented in 36 sec epochs (5 sec/face, inter-stimulus interval=1 sec) organized by condition (judging conveyed emotion vs. gender). Each picture was seen in a given condition only once. Response for the emotion condition was two-alternative forced choice (modal response vs. a randomly picked alternative based on the original study). Subjects signaled responses using a response glove. Fixation epochs (30 sec) were used as a baseline control. Stimuli were rear projected through a two-way mirror system using E-prime. Data from fourteen subjects following a year of randomization to EST (n=5) or CET (n=9) were analyzed. fMRI images were processed using SPM2. Volumes were realigned and resliced and slice acquisition was time-corrected. Volumes were normalized to the standard Montreal Neurological Institute (MNI) template for group analysis and smoothed by voxel dimensions (FWHM=3.125 x 3.125 x 3.2 mm). The fMRI response was modeled separately for each condition used SPM's basic haemodynamic response function (HRF). Individual contrasts (Emotion > Gender; Emotion > Fixation) for each subject were analyzed in group analysis and clusters were identified using directional contrasts (CET vs. EST) using preset thresholds (p<01; extent=25 voxels).
Results: Behavioral performance for the gender task between the two groups was comparable (>90%, n.s.). CET subjects performed more accurately on the emotions task than their EST counterparts (82.9% vs. 67.5%, $t_7 = 2.44$, p<.05) indicating superior ability to assign emotion to faces. Importantly, CET subjects performed the task more efficiently than their EST counterparts: Comparing fMRI activation during the emotion vs. the gender conditions, EST subjects needed

significantly more activation (t>2.68, p<.01), particularly in the dorsolateral prefrontal cortex to complete the task.
Discussion: These preliminary results are consistent with behavioral data using social cognition measures, and suggest increased accuracy and efficiency of social processing following CET than EST in our sample of early course schizophrenia patients.

128. Factorial Structure of the Schedule for Deficit Syndrome in Schizophrenia
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Sponsor: Dolores Malaspina

Background: Deficit Schizophrenia (DS) is considered a distinct subtype within the diagnosis of schizophrenia and is characterized by the presence of negative symptoms that are primary, enduring, and at least moderate in severity. DS patients have been reported to differ from non-deficit (ND) schizophrenia patients with regard to risk factors, symptom profiles, neuropsychological functioning, family history, course of illness, treatment response, and structural and functional neurobiology. While the common assumption is that the DS represents a single, cohesive domain of psychopathology, the factorial structure of the DS has not been investigated. Thus, our aim is to investigate the factor structure of the DS. We hypothesized that the DS may have two distinct factors: one factor relating to volition and a second factor relating to affect. A clear delineation of specific areas of psychopathology will facilitate discovery of links between symptoms and putative neurobiological mechanisms, possibly indicating that these phenomena are separate targets for treatment studies.
Methods: We assessed 52 individuals with DSM-IV diagnosis of schizophrenia with DS as assessed by the Schedule for the Deficit Syndrome (SDS). A Principal Component Analysis (PCA) with varimax rotation was conducted on the six symptoms of the SDS.
Results: On average, participants had 4.19 symptoms (S.D.=1.39) that were primary, enduring and at least moderate in severity. The mean severity of all symptoms was 2.25 (S.D.=1.06), indicating a predominance of symptoms with moderate severity. The only symptom with a mean smaller than two was poverty of speech, which was also the least prevalent symptom (41% of participants). Diminished emotional range was the most prevalent symptom (80% of participants). The PCA resulted in two distinct factors explaining 73.8% of the variance. Factor 1 (Avolition; 37.1% of variance) comprised by symptoms of curbing of interests, diminished sense of purpose, and diminished social drive. Factor 2 (Emotional Expression; 36.7% of variance) comprised by symptoms of restricted affect, diminished emotional range, and poverty of speech. Fourteen participants (26%) had all six SDS symptoms meeting DS criteria as primary, enduring, and at least moderate in severity. Four participants (8%) had only Emotional Expression symptoms and three participants (6%) had only Avolition symptoms that met DS criteria. Post-hoc analyses of the relationship between the obtained factors and neuropsychological and clinical variables hypothesized to be associated with each factor's construct supported the validity of the factors. The Avolition factor was strongly correlated (r= -.49, p=.03) with University of Pennsylvania Smell Identification Test (UPSIT) scores, a measure associated with disturbances in volition. Similarly, the Emotional Expression factor was associated (r = .37, p=.04) with The Stroop Color-Word Test (SCWT) scores. The SCWT measures the ability to regulate responses and to focus attention which is consistent with the neural mechanisms of top-down control of emotionally laden information.
Discussion: To our knowledge, this is the first study of the factor structure of DS. The results indicate that DS is best characterized by two factors - Avolition and Emotional Expression. Our hypothesis is also supported by the unique relationships of each factor to neuropsychological and clinical variables (UPSIT and SCWT) linked with each factor's construct. The authors discuss possible links between the obtained factors and putative neurobiological mechanisms.

129. Association of Depressive Symptoms and Discontinuation from Schizophrenia Treatment: A Post-hoc Pooled Analysis of 4 Controlled Atypical Antipsychotic Treatment Trials
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Sponsor: Richard Mohs

Background: This research was conducted to better understand the phenomenon of antipsychotic treatment discontinuation. Treatment discontinuation data from controlled clinical trials were utilized to explore the association between distinct positive, negative, and depressive symptom domains of schizophrenia and treatment discontinuation.
Methods: This was a post hoc, pooled analysis of 4 randomized, double-blind clinical trials that had duration of 24-28 weeks, enrolling 1627 patients with schizophrenia or a related disorder. Analyses were conducted combining all atypical antipsychotic treatment groups (olanzapine, risperidone, quetiapine, and ziprasidone) in the studies. Positive, negative, and depressive symptoms were compared between completers and non-completers at each visit using the Positive and Negative Syndrome Scale (PANSS) and the PANSS Depression Cluster (PDC). A Cox regression model was implemented to examine whether treatment discontinuation was predicted by baseline positive, negative, or depressive symptoms and/or by their changes from baseline. Finally, a logistic regression model was used to examine whether a 20% response in PANSS positive, negative, or PDC scores at two weeks was associated with an increased likelihood of study completion.
Results: A majority of patients (53%; 866/1627) discontinued early from their antipsychotic treatment. Poor response or symptom worsening was the most frequent reason for treatment discontinuation (36%; 315/866), which was substantially more common than discontinuation due to medication intolerability (12%; 106/866). A retrospective analysis of patients who discontinued showed less depressive symptom improvement compared to completers based on the PDC scores by Week 2 of treatment and at each of the remaining weeks of the study (p<.025). Significantly less positive and negative symptom improvement was also seen in patients who discontinued compared with completers based on PANSS positive and negative scores beginning at Week 2 (p<.01), except at Week 24 for negative symptoms. Patients with lower baseline PDC (hazard ratio 0.95; 95% CI 0.93, 0.97; p<.001) and PANSS positive (hazard ratio 0.97; 95% CI 0.95, 0.98; p<.001) scores were significantly less likely to discontinue treatment. In addition, patients with improvement in PDC (hazard ratio 0.94; 95% CI 0.92, 0.96; p<.001) and PANSS positive (hazard ratio .95; 95% CI 0.93, 0.96; p<.001) scores were significantly less likely to discontinue treatment at a subsequent visit. A 20% improvement in depressive and positive symptoms during the first 2 weeks of treatment was associated with a 50% (odds ratio 1.52; 95% CI 1.22, 1.90) and 70% (odds ratio 1.71; 95% CI 1.35, 2.16) greater likelihood of study completion, respectively. Baseline PANSS negative or change in PANSS negative scores did not significantly predict treatment discontinuation.
Discussion: In these studies, poor response or symptom worsening was the most frequent reason for antipsychotic treatment discontinuation. Poor improvement of depressive symptoms in addition to positive and negative symptom domains was associated with treatment discontinuation. Our findings suggest that treatment adherence may be enhanced by effective control of a broad range of symptoms.

130. Increased Brain Activation During Eye Gaze Discrimination in Schizophrenia
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Sponsor: Ruben Gur

Background: Functional brain imaging studies of healthy individuals show fusiform and superior temporal gyri activation during eye gaze

discrimination. Early studies of individuals diagnosed with schizophrenia reported gaze discrimination impairment for patients, particularly misidentification of averted gaze as making eye contact. However, two later studies failed to replicate these findings. Gaze detection is localized to the superior temporal sulcus, an area strongly implicated in the pathophysiology of schizophrenia. Testing of eye gaze discrimination may represent a suitable cognitive challenge for temporal lobe function.
Methods: Seven stable schizophrenia subjects and seven healthy controls underwent a novel task of gaze discrimination, which included 24 face stimuli at 0, 4 and 8 degree deviation from head-on, presented in random order. Subjects were asked to identify whether a face was making eye contact. fMRI was acquired with BOLD imaging using a 15 slice, single-shot gradient-echo (GE) echo-planar (EPI) sequence (TR/TE=1000/32 ms, FOV=240 mm, matrix= 64 X 64, slice thickness/gap=3/0mm). fMRI data are preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool) Version 5.1 using standard procedures.
Results: Speed and accuracy did not differ between groups. A Group (Patient, Control) by Orientation (0, 4, 8 degrees) mixed effects ANOVA showed a main effect for Group. Patients showed increased activation in the IFG (bilateral), right STG, left fusiform gyrus, left amygdala, left inferior occipital gyrus, right caudate, and brainstem.
Discussion: Our findings indicate that despite similar gaze discrimination performance, schizophrenia subjects exhibit increased brain activation, as indicated by blood flow, in areas of visual processing and gaze detection. This preliminary finding may relate to common symptoms in acute schizophrenia, such as paranoia and ideas of reference. Future studies, using more subtle degrees of gaze deviation and in larger and more symptomatic patient groups are needed.

131. Abnormal Expression of NMDA Receptor Subunits and Interacting PSD Molecules in the Endoplasmic Reticulum in Schizophrenia

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Background: Abnormal expression of molecules involved in glutamatergic signaling is a key finding in postmortem tissue from psychiatrically ill patients. Expression of the N-methyl-D-aspartate (NMDA) receptor and in particular its interacting proteins of the postsynaptic density (PSD) is altered in various cortical and subcortical regions in schizophrenia. The cellular changes of the neuronal circuitry reported in schizophrenia likely are not exclusively a matter of molecular expression levels but additionally reflect abnormal execution of cellular processing. The tetrameric NMDA receptor, which consists of an obligatory NR1 subunit in combination with various NR2A-D subunits, is assembled in the endoplasmic reticulum (ER) in a tissue specific manner. Dependent on the particular NR1 subtype, the NMDA receptor is trafficked in intracellular vesicles to the PSD in a fast or slow manner, bound to either PSD-95 or SAP-102. When the NMDA receptor associates with PSD-95, trafficking to the PSD is carried out by the KIF17/CASK/mLin10/Veli complex whereas NMDA-binding to SAP-102 confers trafficking to the PSD through the Sec6-Sec8 complex. We hypothesize that aspects involved in translation, assembly and trafficking of the NMDA receptor complex are compromised in schizophrenia, resulting in abnormal localization of the NMDA receptor and its interacting PSD molecules in subcellular compartments including the ER.
Methods: In the present work we have used the ER specific protein calnexin attached to superparamagnetic polymer beads to isolate a subcellular fraction enriched in ER-linked proteins from postmortem brain tissue from schizophrenic patients and matched control subjects.
Results: In this ER enriched subcellular fraction we have analyzed expression of the NR1, NR2B subunits of the NMDA receptor and the NR2B interacting proteins of the PSD, SAP-102 and PSD-95. Whereas no changes in overall expression for any of these proteins were found in total brain homogenates, expression of NR2B, PSD-95 and SAP-102 were significantly decreased in the purified subcellular ER-related fraction in schizophrenic subjects. The NR1 subunit, which is normally expressed in excess in the ER, was not altered in this fraction.
Discussion: Based on the functional role interaction of PSD-95 and SAP-102 plays in ER-exit and dendritic trafficking of the NMDA receptor, our findings suggest that early cellular processing of newly synthesized NMDA receptor is altered in schizophrenia. This work was supported by MH53327 and by the Stanley Foundation.

132. Functional Effects of Haloperidol and Olanzapine over a 6-Week Treatment Period: Relation to Clinical Response

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Background: Using PET with ^{15}O, we characterized the rCBF changes induced by haloperidol and olanzapine after 1 and 6 weeks of treatment during resting and task activated conditions. We sought to (1) characterize the neuronal networks activated in association with these drugs and (2) evaluate if drug-induced rCBF changes correlated with or predicted treatment response. Based on our previous work, we had hypothesized that drug-induced rCBF changes in ventral striatum, anterior cingulate cortex (ACC) and hippocampus would correlate and predict treatment response. We further hypothesized that activation of the dorsal ACC (dACC) during cognitive task would be related to olanzapine beneficial effect on cognition.
Methods: After a two-week medication withdrawal, schizophrenia volunteers (SV) were blindly randomized to treatment with haloperidol (n=12) or olanzapine (n=17). Each SV was scanned off-medication and after 1 and 6 weeks of treatment. They were scanned at rest and during an effortful auditory discrimination task. To evaluate the effect of drugs on resting rCBF, contrasts were made between the Off-drug and Week 6 scans, and the Off-drug and Week 1 scans. In these contrasts, rCBF values were extracted from significant ACC and hippocampal clusters and correlated with changes in BPRS Psychosis scores. To test the proposition that dACC activation during the discrimination task was related to the degree of cognitive improvement obtained with olanzapine, we generated pixel by pixel correlations between the Week 6 task-activated scans and changes (Week 6-Off) in Digit Symbol (DS) scores. We focus on the DS because performance on this task was significantly better in the olanzapine group than in the haloperidol group ($p=0.04$). This is consistent with the results of other studies (Bilder, 2002; Keefe, 2004).
Results: Cortico-subcortical and limbic neuronal networks were activated in association with both haloperidol and olanzapine. Consistent with its greater incidence of motor side effects, haloperidol treatment was associated with greater dorsal striatum activation compared to olanzapine. For haloperidol and at a trend level for olanzapine, decrease rCBF in ACC as the result of 6 weeks of treatment correlated with psychosis improvement. Increase rCBF in ventral striatum and ACC and decrease in hippocampus as the result of one week of treatment were found to predict a favorable response to treatment. In these regions, important drug-induced modulation differences between good and poor drug responders were observed. In the Week 6 task-activated scans, rCBF activation in the dACC (x, y, z: 4, 12, 46) was significantly correlated with DS change scores ($r=0.67$, $p<0.0001$).
Discussion: Three published studies have now reported that treatment with second-generation antipsychotic drugs (APDs) increases dACC activity during tasks engaging the ACC (Honey, 1999, Lahti,

2004; Snitz, 2005). However these studies did not relate this functional gain to a therapeutic benefit. In this study, the magnitude of the dACC response to a discrimination task correlated with treatment-induced cognitive benefit. Conclusion: Resting rCBF patterns in ACC and hippocampus may provide early markers of treatment response to APDs. We propose that the dACC pattern seen during the task-activated scans may account for the superior (albeit small) therapeutic effect of olanzapine on cognition and represents a surrogate marker of this action.

133. Prefrontal Cortical"UP" States in Adult Rat Brain Slice: Role of Glutamate Spillover and 5-HT_{2A} Receptors

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Background: 5-HT_{2A} receptor stimulation with psychedelic hallucinogens (e.g., DOI and LSD) is known to promote a late wave of glutamate release onto layer V pyramidal neurons in prefrontal cortical slice in response to local electrical stimulation. These results are consistent with microdialysis studies in vivo showing that hallucinogens can increase extracellular levels of glutamate (Scruggs et al., Neurosci Lett, 2003; Muschamp et al., Brain Res, 2004). The hallucinogen-enhanced late excitatory postsynaptic currents (EPSCs) closely resemble the "UP" states in prefrontal neurons observed in ferret slice by Shu et al., Nature, 2003. Such depolarized, hyper-responsive states are found in the alert waking state and result from sustained activity in balanced excitatory and inhibitory recurrent networks.
Methods: We use whole cell electrophysiological recording from layer V pyramidal neurons in brain slice of adult rat prefrontal cortex. Local electrical stimulation is delivered to the slice through bipolar platinum irridium electrodes. Drugs are applied in the bath.
Results: Here, we show that spontaneous and electrically-evoked UP states occur in layer V pyramidal neurons in brain slice of adult rat prefrontal cortex. These UP states can be enhanced by application of the 5-HT_{2A} partial agonists, LSD and DOI. We show that glutamate spillover is involved in the generation of UP states. For example, they can be suppressed selectively by raising the viscosity of the extracellular solution with addition of the inert macromolecule dextran (~1 mM) that is known to retard overflow of synaptic glutamate into the extracellular space. The addition of dextran does not reduce fast evoked transmission, traditional polysynaptic transmission, nor a synaptic form of 5-HT5-HT_{2A}-mediated transmission (serotonin-induced spontaneous EPSCs). Consistent with previous work showing that extrasynaptic glutamate transmission in adult depends on NR2B-containing NMDA receptors, we also found that NR2B-selective antagonists, ifenprodil and Ro25-6981, suppressed UP states. Interestingly, the effect of psychedelic hallucinogens is different from simply blocking glutamate uptake. Application of the glutamate transporter inhibitor TBOA is known to increase tonic glutamate through a TTX-insensitive mechanism (Melendez et al., JPET, 2005). However, we find that strong UP states are observed in the presence of TBOA only after additionally inactivating group 2/3 metabotropic glutamate mGlu2/3 receptors. By contrast, psychedelic hallucinogens appear to enhance UP states through increasing glutamate spillover in a manner that does not incur strong activation of mGlu2/3 receptors. One explanation is that psychedelic hallucinogens mainly increases the overflow of phasically released glutamate.
Discussion: We conclude that phasic glutamate spillover contributes to the generation of UP states. Understanding the mechanisms underlying the generation and modulation of UP states is important for appreciating normal brain processes during active waking and ways the brain can be perturbed by hallucinogenic drugs or in illnesses such as schizophrenia.

134. Schizophrenia is Associated with Increased Synaptic Dopamine in Associative Rather than Limbic Regions of the Striatum

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Background: Over the last decade, a convergent body of imaging studies have documented that schizophrenia is associated with increased dopamine (DA) function in the striatum. A limitation of previous studies is that DA function was measured at the level of the striatum as a whole. The striatum is divided into limbic, associative and sensorimotor subregions, based on the origin of cortical projections. We previously documented that high resolution PET imaging with ECAT HR Plus enables valid measurement of the radioactive signal generated in these striatal subregions.
Methods: We report here the results of a new imaging study, performed in 18 untreated patients with schizophrenia (SCH) and 18 matched controls (CTR). Subjects were scanned with [11C]raclopride at baseline and after acute DA depletion induced by alpha-methyl-para-tyrosine (AMPT). The difference in D2 receptor availability between the baseline and DA depleted scans provided an index of occupancy of D2 receptors by DA at baseline. Five regions of interest were analyzed: ventral striatum (VST), precommissural dorsal caudate (preDCA), precommissural dorsal putamen (preDPU), postcommissural caudate (postCA) and postcommissural putamen (post PU).
Results: AMPT-induced increase in D2 receptor availability was significantly higher in SCH compared to CTR in preDCA [Mean (SD): SCH: 15.1 (8.1) %; CTR: 9.0 (7.6) %, $p = 0.03$], but not in the VST [SCH: 11.5 (9.7) %; CTR: 9.8 (6.7) %, ns) or in other striatal subregions. This result suggests that SCH is associated with increased D2 receptor transmission in the preDCA (i.e.the head of the caudate), the area of the striatum that receives the most dense projections from the dorsolateral prefrontal cortex (DLPFC).
Discussion: Two implications will be discussed: 1) This result questions the widely accepted view that the therapeutic effects of antipsychotic drugs derive from D2 receptor blockade in the limbic striatum (i.e. nucleus accumbens in rodents) while D2 receptor blockade in the dorsal striatum is only responsible for motor side effects; 2) While subcortical DA dysregulation has historically been conceptualized as consequence of DLPFC dysfunction, these findings suggest that alterations of subcortical DA transmission in SCH might in turn negatively impact on DLPFC function, by preventing glutamate mediated flow of information in DPLFC-preDCA-thalamic-DLPFC loops.

135. *DRD2* Promoter Region Variation Predicts Sustained Response to Antipsychotic Medication in First Episode Schizophrenia

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Sponsor: Past Travel Awardee, Memorial, 2003

Background: Dopamine D2 receptor blockade is critical to antipsychotic efficacy, yet the relationship between allelic variants of *DRD2* and antipsychotic response remains unclear. The present study employed several design features, not previously utilized in *DRD2* pharmacogenetic studies, to improve detection of genetic signal: (1) examination of first episode (FE), predominately antipsychotic-naive patients; (2) use of prospective, longitudinal data to examine response time-course; (3) strict, clinically-relevant criteria for sustained response; (4) focus on single nucleotide polymorphisms (SNPs) in the *DRD2* promoter region (A-241G and -141C Ins/Del).

Methods: Sixty-one FE patients (74% male; mean age 24±5) with schizophrenia, schizoaffective, or schizophreniform disorder were randomized to olanzapine or risperidone. Most subjects were antipsychotic-naive (79%); none had more than 12 weeks prior exposure. Masked raters conducted weekly, then biweekly assessments for 16 weeks. Sustained response criteria were: two consecutive assessments ≤3 (mild) on SADS-C+PD positive symptom severity items, and CGI ≥ much improved. Patients were genotyped by 5'-exonuclease fluorescence assay. For data analysis, patients were dichotomized as homozygous wildtype vs. carriers of the rare variants for each SNP. Differences between groups in time to response were examined using Kaplan-Meier curves (log-rank statistic).
Results: Carriers of the -141C Del allele showed significantly longer time to respond (p=.025) relative to Ins/Ins homozygotes; -241 G carriers showed significantly faster rate of response compared to A/A homozygotes (p=.0038). Diplotype analysis revealed similar results.
Discussion: Genetic variation in the promoter region of *DRD2* may influence sustained treatment response in FE schizophrenia. The first episode population may provide improved power in pharmacogenetic studies of antipsychotic treatment response. Given prior functional studies of *DRD2* promoter region variation, our findings suggest the possibility that the timing of clinical response may be related to variation in density or binding potentials of D2 receptors.

136. Clozapine Effects on Memory Function are Reversed by Hippocampal Damage

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Sponsor: Cynthia Kuhn

Background: Clozapine as well as other antipsychotic drugs such as haloperidol have been found to significantly impair working memory function as measured by choice accuracy in the radial-arm maze in intact rats. Given that antipsychotic drugs are most often given to people with neurobehavioral dysfunction, is important to determine the effects of these drugs in animal models of cognitive dysfunction. This could also add to the understanding of the neural mechanisms of antipsychotic drug effects on cognition. We have begun this line of research with studies of the role of hippocampal function since the hippocampus has been shown to be critically important for memory function and hippocampal function has been found to be impaired in schizophrenia. We have conducted a series of studies of clozapine effects on memory in intact rats and compared with rats with compromised hippocampal function.
Methods: Sprague-Dawley rats were trained in the win-shift procedure in an 8-arm radial maze. After they had passed the learning phase and achieved asymptotic performance levels in which working memory could be determined they were given the experimental manipulations, which included bilateral transections of the fimbria-fornix in the first study and chronic bilateral local ventral hippocampal infusion of the high affinity nicotinic antagonist DH-beta-E via osmotic minipump in the second study. Sham treated rats served as controls. The rats were then tested under acute challenge with clozapine (0, 1.25 and 2.5 mg/kg of clozapine) in a repeated measures counterbalanced design.
Results: Lesions of the fimbria-fornix, which carries acetylcholine-containing fibers to the hippocampus, cause significant memory impairments in rats on the radial-arm maze. The same doses of clozapine, which cause significant impairment in intact rats, significantly improved memory performance in rats with impaired memory after lesions of the fimbria-fornix. In a subsequent study, we examined the roles of nicotinic acetylcholine receptors in the hippocampus for clozapine effects on memory function. Chronic local ventral hippocampal infusions of DH-beta-E a high affinity nicotinic receptor blocker caused significant memory impairment of rats in the radial-arm maze. Clozapine, at the same doses that caused impairments in vehicle infused animals significantly improved memory performance in the rats with memory impairments, caused by chronic local infusions of DH-beta-E.
Discussion: Clozapine has a wide variety of mechanisms of action. The hippocampus may be a target for the memory impairing effects of clozapine. Hippocampal impairment may serve to remove this structure from the set of targets for clozapine actions leaving unopposed actions, which cause a net improvement in memory function. These results may help explain why clozapine can provide improved cognitive function in people with schizophrenia in which there is hippocampal dysfunction. The recognition that the hippocampus is a likely site of action for the cognitive-impairing effects of clozapine and more specifically that hippocampal circuits involving high affinity alpha4beta2 nicotinic receptors blocked by DH-beta-E are likely circuits for clozapine actions impairing memory should help in identifying which of the many clozapine actions underlie its cognitive impairment. Development of successor drugs which do not have the those actions which cause cognitive impairment may unmask the full efficacy of this class of drugs for improving cognitive improvement and broaden their therapeutic use in conditions where there is not substantial hippocampal damage.

137. Synergetic Effects of Quetiapine and Venlafaxine in Preventing the Decrease in Cell Proliferation and BDNF Expression in Rat Hippocampus Caused by Chronic Restraint Stress

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Sponsor: Alan Boulton

Background: Quetiapine is an atypical antipsychotic drug (APD). In previous studies, quetiapine elevated brain-derived neurotrophic factor (BDNF) levels in the hippocampi of rats subjected to chronic restraint stress (RS) or with reduced NMDA receptor activity. Venlafaxine is an antidepressant agent with dual noradrenergic and serotonergic actions that increased BDNF levels in rats, as well as in patients with a major depressive disorder, and reversed the decreased hippocampal cell proliferation and BDNF expression caused by chronic RS. These studies suggest that quetiapine and venlafaxine may be combined to regulate hippocampal cell proliferation and BDNF expression.
Methods: To test this assumption, three experiments were conducted using adult male rats.
Results: In the first experiment, we corroborated that chronic RS (6 h/day for 14 days) suppressed hippocampal cell proliferation and decreased BDNF expression. In the second and third experiments, we found that (1) chronic administration of quetiapine or venlafaxine dose-dependently prevented the stress-induced lower levels of hippocampal cell proliferation and BDNF expression; (2) the lower doses of quetiapine (5 mg/kg) and venlafaxine (2.5 mg/kg) exerted no effects, but when used in combination, they completely prevented the decrease in hippocampal cell proliferation and BDNF expression shown in stressed rats, indicating a synergetic effect of the lower doses.
Discussion: These results suggest that these two drugs may share hippocampal neurogenesis and BDNF expression as their common targets, thus enhancing brain resilience. This explanation may help us to understand the augmented therapeutic effects of antidepressants by atypical APDs in patients with depression or schizophrenia.

138. Remission in Schizophrenia: A Comparison of 2 Dose Regimens of Ziprasidone versus Haloperidol Treatment in a 3-Year Double-Blind Extension Study

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Background: The efficacy and tolerability of atypical antipsychotics in comparison with conventional agents have not been well studied in the long-term treatment of schizophrenia. We present the results of a

double-blind, parallel, continuation study (up to 4 years) of 2 dose regimens of ziprasidone (BID or QD) versus haloperidol in schizophrenic subjects, based on the recently proposed remission criteria for schizophrenia.
Methods: This is a double-blind, randomized, continuation study in subjects who completed the core 40-week trial of 2 dose regimens of ziprasidone, 40-80 mg BID (N=72) or 80-120 mg QD (N=67), and haloperidol 5-20 mg/d (N=47). Efficacy evaluation was based on recently proposed remission criteria for schizophrenia1 which require maintenance, over a 6-month period, of simultaneous ratings of mild or less (< 3) on all PANSS remission criteria items (P1, G9, P3, P2, G5, N1, N4, and N6). In addition, we evaluated the response rate observed (OC) at each visit (week 6, months 4, 7, 10, 17, 23, 31, 37, 43, and 49) using both the traditional definition of > 20% PANSS total improvement and an alternative definition using the cross-sectional remission criteria as defined above. Response rates over time and the significance of treatment-by-time interaction effects were evaluated using the longitudinal Generalized Estimating Equation (GEE) method.
Results: Baseline severity was comparable among treatment groups (PANSS total score 70-71.6, PANSS negative score 21-22, and GAF 49-50). Subject discontinuation rates (up to 4 years) were 65% and 58% for ziprasidone BID and QD groups and 66% for the haloperidol group. The proportion of patients who achieved at least 1 period of symptomatic remission (during core and blinded continuation study) was 57% for both ziprasidone BID and QD groups, compared with 45% for the haloperidol group (p=NS). In the last 6 months of the study, the proportion of subjects experiencing remission in the ziprasidone groups (BID 41% and QD 43%) was numerically higher than the haloperidol group (23%). Responder analysis (>20% PANSS total improvement from baseline) over time (up to 4 years) showed ziprasidone BID 61% to 83%, QD 50% to 69%, and haloperidol 50% to 68% (p=NS). In contrast, response rates using cross-sectional remission criteria at years 1, 2, and 3 in the extension phase were: ziprasidone BID 48%, 59%, and 69%, respectively; QD 45%, 69%, and 57%, respectively; and haloperidol 41%, 40%, and 32%, respectively. There was a significantly greater increase in these response rates over time when comparing ziprasidone BID (p=0.004, treatment-by-time interaction) and QD (p=0.03, treatment-by-time interaction) with haloperidol.
Discussion: The results of this double-blind, parallel, continuation study (up to 4 years) support the effectiveness of both ziprasidone BID and QD dose regimens in the long-term treatment of patients with schizophrenia. Observed response and clinical remission rates were consistently higher among subjects treated with ziprasidone compared to haloperidol.

139. Probing the Cognitive, Clinical, and Functional Impairments of Schizophrenia Patients with Mismatch Negativity

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Sponsor: Travel Awardee, Young Investigator Memorial, 2005

Background: Schizophrenia patients have widespread deficits ranging from abnormalities in sensory processing to impairments in cognition and daily living. Mismatch Negativity (MMN) is an EEG waveform that is automatically elicited by infrequent, oddball stimuli that occur during the presentation of more frequent, standard stimuli. The MMN represents a pre-attentional probe of the earliest stages of cognition and can be elicited in the absence of directed attention. Schizophrenia patients have robust MMN deficits that are both highly stable over time (ICCs>0.90) and associated with everyday functional impairments. In normal subjects, age-related progressive reductions in MMN have been observed across adulthood. The aim of the present study was to determine if MMN deficits in schizophrenia patients are associated with cognitive, clinical and functional impairments in a large sample of schizophrenia patients.
Methods: Schizophrenia Patients (n=150) and normal comparison subjects (n=108) underwent MMN and extensive cognitive, clinical, and functional assessments.
Results: Schizophrenia patients had significantly reduced MMN. Decreased MMN was also observed with increased age in both schizophrenia patients and normal comparison subjects. Thus, ANOVAs were performed using age-corrected MMN values. MMN deficits in schizophrenia patients were selectively associated with impaired performance on tests of working memory ($p<0.01$) and verbal recall ($p<0.01$). MMN deficits were also associated with more severe negative symptoms ($p<0.01$), reduced performance ($p<0.05$) on a comprehensive functional skills assessment battery (e.g., ability to perform basic financial tasks), and significantly ($p<0.001$) lower ratings on several measures of functional status (e.g., independence in living situation, managing personal finances, Scale of Functioning, Global Assessment of Functioning Scale). These effects were significant even after controlling for age effects. In contrast, MMN deficits were not associated with performance on other cognitive measures ($p>0.05$) or positive symptoms ($p>0.50$).
Discussion: MMN deficits reflect neural dysfunction associated with the core cognitive, clinical, and functional deficits of schizophrenia patients. MMN deficits may have multiple applications including use as a biomarker in drug development and as an endophenotype in genetic studies of schizophrenia.

140. Role of Catechol-O-Methyltransferase Val/Met Polymorphism on P50 Sensory Gating in Schizophrenia

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Background: P50 pair-click sensory gating is commonly used to investigate the neurophysiological basis of impaired stimulus filtering in schizophrenia. In schizophrenia patients, P50 amplitude evoked by the second of the paired auditory stimuli (S2) is little reduced compared to that by the first (S1). Also evident in first-degree relatives of schizophrenia patients, deficit in P50 sensory gating is regarded as an endophenotype of schizophrenia. Studies have implicated dopamine and prefrontal cortex in modulating gating, and recent findings suggest that prefrontal dopamine modulates cortical signal-to-noise information processing. Thus, we hypothesize that the Val(158)Met polymorphism of the Catechol-O-methyltransferase (COMT) gene predicts the degree of sensory gating. In COMT, the higher activity Val allele is believed to be associated with higher prefrontal dopamine degradation as well as inefficient and poor prefrontal-related tasks.
Methods: Control and schizophrenia subjects of European descent underwent COMT genotyping and an EEG P50 auditory paired-click paradigm. The paired clicks (S1 and S2) were identical in intensity and separated by 500 milliseconds. Evoked S1 and S2 responses (40-80 milliseconds post-stimulus, P50) were measured at the Cz electrode. At least one hundred trials were averaged for amplitude calculation. Gating ratio is computed as S2 amplitude divided by S1. Because the distribution of gating ratios was positively skewed, the raw ratios were first reported and then logarithmically transformed for ANOVA analysis.
Results: 42 schizophrenia patients (9 Met/Met, 16 Met/Val, and 17 Val/Val) and 25 age, gender, and education-matched controls (6 Met/Met, 12 Met/Val, and 7 Val/Val) have been enrolled. Chi-Square analyses detected no significant group difference in allelic frequency or genotypic distribution. Within the schizophrenia group, there was no genotype-specific difference in gender, antipsychotic use (conventional vs. novel), or smoking status. Schizophrenia subjects demon-

strated worse gating, or higher gating ratios (ave=.73) than controls (ave=.40, p=.020). There was a main effect of genotype on gating (ave Met/Met=.48, Met/Val=.42, Val/Val=.73, p=.012), with Val/Val gating significantly worse than Met/Val (p=.004). Such Val/Val-associated poor gating appeared to be much pronounced in the schizophrenia group, as a one-way analysis with contrasts showed that only Val/Val schizophrenia patients (ave=.83) gated significantly worse than either the control Met/Val (ave=.34, p=.001) or the schizophrenia Met/Val (ave=.47,p=.006). There was no apparent linear relationship between gating and Val allele load, with Val/Met heterozygotes having the best gating averages and the Val/Val with the worst.
Discussion: This study suggests that deficient prefrontal dopamine, as predicted in the Val/Val group, leads to gating deficit in the primary auditory cortex, especially in the schizophrenia group. These results strengthen the model of a prefrontal dopamine-mediated signaling homeostasis in regulating information load in other cortical areas. Also, few explanations exist to account for the persistence of the Val allele in humans, given its putative association with inefficient prefrontal functioning. Given that sensory gating assesses how passively received redundant stimuli are attenuated, our results suggest that the Val/Met heterozygotes are the most efficient in doing so. How these links between genetic variation and a neurophysiological endophenotype of schizophrenia lead to differences in the phenomenology of schizophrenia warrants further investigation.

141. The Prospective Study of Cannabis Use, Symptoms and Functioning in Patients Prodromal to Psychosis
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Background: Cannabis use has been implicated as a risk factor for psychosis and schizophrenia, particularly in individuals with enhanced genetic (COMT) and clinical (attenuated positive symptoms) risk. Cannabis use and psychotic disorders are highly comorbid, and both have their antecedents in adolescence, a critical period characterized by profound changes in circuitry underlying incentive salience. We have begun to study the co-evolution of cannabis (and other drug) use with psychotic (and other) symptoms in a prodromal or clinical high risk sample, who have attenuated positive symptoms.
Methods: There were 19 patients, ages 14-25, with IQ>= 70, who fulfilled criteria for >=1 of 3 categories of psychosis prodrome, using the Structured Interview and Scale of Prodromal Symptoms (SIPS/SOPS): 1) attenuated psychotic symptoms, 2) brief psychotic symptoms, and/or 3) genetic high risk and decline in functioning. Exclusion criteria included substantial risk for suicide or violence, major medical illness, and history of psychosis. Prodromal patients had baseline and quarterly (q3 month) assessments of drug use for up to 2 years (self-report for cannabis and other drugs, with # of days of use), symptoms (SOPS positive and SOPS negative, HAM-D depressed and HAM-A anxious), and modified GAF (1-100). Patients also had baseline assessment of diagnosis, including substance use disorders (DIGS and K-SADS). Among prodromal patients, drug users and nonusers were compared at baseline. We also evaluated associations of cannabis use and symptoms prospectively (quarterly) in patients with cannabis abuse or dependence. (Self-reported interval use of other drugs was too low to determine associations with symptoms and functioning).
Results: Nineteen prodromal patients were enrolled, mean age 19 (sd 3.750). Nine of these 19 subjects (47%; 7 males and 2 females) endorsed use of any drugs or alcohol, and all nine had at least tried both alcohol and cannabis. Abuse and dependence were limited to cannabis and alcohol, except for one woman with comorbid cocaine abuse. 4 patients had cannabis dependence (2 with comorbid alcohol abuse), 2 had cannabis abuse (and also tried alcohol, hallucinogens and/or cocaine), and 3 tried cannabis (+/- tried hallucinogens, amphetamine). Drug users were older than nonusers (22 +/- 2.3 vs. 17 +/- 3.4; p = .003), though did not differ by sex (male = 80%) or ethnicity (40% white). Drug users had more positive symptoms, especially unusual thought content (p = .005), even adjusting for age, as well as more suspiciousness and grandiosity. Drug users had equivalent levels of hallucinations, disorganization, negative symptoms, functioning (serious impairment with mean GAF ~45), depression and anxiety. Cannabis use fluctuated over time with positive symptoms (hallucinations), depression, anxiety and poor function.
Discussion: Consistent with studies in patients with schizophrenia, drug users had more positive symptoms than nonusers. Further, among prodromal patients with cannabis abuse or dependence, cannabis use was temporally associated with increases of psychotic-like and affective symptoms, as well as fluctuations in functioning. Future studies with more frequent assessments and/or use of experience sampling can begin to clarify the causal directions of these associations.

142. Symptomatic Remission in Schizophrenia Patients Treated with Aripiprazole or Haloperidol for up to 52 Weeks
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Sponsor: John Kane

Background: Schizophrenia is a debilitating, life-long disease for which full recovery is typically not considered as a realistic treatment endpoint. Symptomatic remission, however, may be an objectively attainable treatment goal. We studied symptomatic remission rates within a 52-week period for patients diagnosed with schizophrenia and randomized to double-blind treatment with either aripiprazole or haloperidol.
Methods: Remission rates were calculated using data from a 52-week trial in which patients diagnosed with acute schizophrenia were stabilized and randomly assigned in a 2:1 ratio to aripiprazole (n= 851; dose=30-20 mg/d) or haloperidol (n=430; 10-7 mg/d). For this analysis, remission was operationalized according to the consensus-based symptomatic remission criteria established by the Remission in Schizophrenia Working Group (Andreasen et al, 2005). Accordingly, patients were required to achieve scores ≥ 3 on eight specific Positive and Negative Syndrome Scale (PANSS) items (delusions, unusual thought content, hallucinatory behavior, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity) and to maintain the item score threshold for at least six consecutive months. We also evaluated differences between remitters and non-remitters on the Clinical Global Impressions-Improvement (CGI-I) scale. In order to assess whether tolerability issues might be affecting remission, we examined discontinuation rates due to adverse events and use of concomitant medication to treat EPS.
Results: Thirty-two percent of aripiprazole-treated patients and 22% of haloperidol-treated patients satisfied the criteria for symptomatic remission within the 52-week trial period. These rates were significantly different in favor of aripiprazole ($p < 0.001$). In both groups, mean time to achieve the PANSS item threshold was 2.9 months, and on average, patients on maintained remission status for similar lengths of time (aripiprazole 9.8 months; haloperidol 9.4 months). Approximately 6% of aripiprazole-treated patients and 7% of haloperidol-treated patients subsequently lost their remission status prior to the trial end, with mean time in remission of 7.5 months. Forty-six percent of patients on aripiprazole never met the PANSS item threshold compared to 51% of patients on haloperidol ($p > 0.05$). In both the aripiprazole and haloperidol groups, patients who achieved remission showed significant improvement on the CGI-I at endpoint compared to those who did not remit ($p < 0.0001$ for both). During the 52-week trial, significantly fewer aripiprazole-treated patients discontinued the study for adverse events other than worsening of symptoms (8%) or received concomitant EPS medication (23%) compared to haloperidol-treated patients (17% and 57% respectively; $p < 0.001$ for both).

Discussion: Nearly one-third of the patients treated with aripiprazole achieved remission status within a one-year period, a significantly higher rate than for patients treated with haloperidol. Most patients who achieved remission also remained in remission for more than nine months until trial termination. Overall clinical impressions of these patients were significantly better than for patients who did not remit. Compared to haloperidole, aripiprazole was associated with a higher remission rate, fewer adverse events, and less EPS medication use, suggesting that both efficacy and tolerability may have accounted for group differences in remission rates.

143. Inhibition of the Glycine Transporter (GlyT1) Potentiates the Effect of Risperidone, but Not Clozapine, on Glutamatergic Transmission in the Rat Medial Prefrontal Cortex

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Sponsor: Past Travel Awardee, ECNP-ACNP Fellow, 2003

Background: Dysfunctional glutamatergic transmission has been postulated to play a role in the pathophysiology of schizophrenia. Clinical studies indicate that glycine site agonists of the NMDA receptor may reduce negative, and to some extent cognitive symptoms, in treatment-resistant schizophrenia when used as adjuvants to conventional antipsychotic drugs (APDs). Recent clinical results also suggest that the efficacy of the atypical APD risperidone, but not clozapine, can be augmented by adjunctive glycine treatment. Our previous data show that atypical, but not typical, APDs facilitate NMDA-induced currents in pyramidal cells of the rat medial prefrontal cortex.
Methods: By using intracellular recording, we have now investigated the effect of the glycine transporter (GlyT1) inhibitor NFPS on the NMDA-induced currents in pyramidal cells of the rat medial prefrontal cortex, both when given alone and in combination with either risperidone or clozapine.
Results: Both risperidone and clozapine augmented the NMDA-induced responses. The concentration-response curves were biphasic, and the maximal effects on the NMDA-evoked currents were produced by 20nM risperidone and 100nM clozapine, respectively. NFPS (1μM) alone did not augment the NMDA-induced currents. However, NFPS (1μM) augmented both the effect of a maximal (20nM), and a submaximal (10nM), concentration of risperidone. In contrast, NFPS did not potentiate either the effect of a maximal or a submaximal concentration of clozapine on the NMDA-induced currents.
Discussion: These experimental data parallel previous clinical results using direct glycine site agonists, and thus propose that also GlyT1 inhibitors may be used to enhance the effect of APDs, with the exception of clozapine, on negative and cognitive symptoms in treatment-resistant schizophrenia.

144. Efficacy and Tolerability of Two Fixed Dosages of Paliperidone Extended-Release Tablets in the Treatment of Acute Schizophrenia: A 6-Week Placebo-Controlled Study

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Background: Efficacy and tolerability are primary considerations in the treatment of patients with schizophrenia while aspects of patient function are increasingly important. The objective of this study was to evaluate the efficacy and safety of 2 fixed doses of paliperidone extended-release tablets a potentially new psychotropic medication for the treatment of patients with schizophrenia.
Methods: In this 6-week US-based multicenter, double-blind, placebo- and active-controlled, parallel-group, dose-response study patients with schizophrenia (n=444, age ≥18 years) were randomized to receive daily doses of paliperidone ER 6mg or 12mg, placebo or olanzapine 10mg. Patients were experiencing an acute episode of schizophrenia (total Positive and Negative Syndrome Scale [PANSS] score=70—120) and agreed to protocol-specified hospitalization for the first 14 days. The Intent-to-Treat (ITT) analysis set=patients who received ≥1 dose of double-blind study medication and had ≥1 post-baseline efficacy measurement. The primary efficacy measure=change in total PANSS score in the ITT analysis set. The olanzapine group was included for assay sensitivity and was not included in the statistical model. Other efficacy analyses included responder rates (RR=improvement at endpoint in PANSS total score by ≥30%) and change on the Personal and Social Performance (PSP) scale. Safety assessments included report of treatment-emergent adverse events (TEAE) and vital signs including bodyweight.
Results: The ITT set (n=432) was 55% black, 74% male, mean age=41.6±10.7 years and had a baseline total PANSS score=93.7±11.9. There was a significant reduction in mean PANSS total score at endpoint for both doses of paliperidone ER vs placebo (6mg=—15.7±18.9 [p=0.006], 12mg=—17.5±19.8 [p<0.001], placebo=—8.0±21.5). RR were significantly higher in paliperidone ER treatment groups vs placebo (6mg=50% [p=0.025], 12mg=51% [p=0.012], placebo=34%). The change in mean PANSS total score at endpoint for olanzapine group was —18.4±19.9 and the RR was 46%. Although PSP scores improved for each paliperidone ER group vs placebo, only the 6mg group reached statistical significance at endpoint (6mg=8.8±13.9 [p=0.008], 12mg=6.6±13.1 [p=0.214], placebo=2.9±13.0). TEAE were observed in 77%, 73%, 79% and 72% of patients treated with placebo, paliperidone ER 6mg and 12mg, and olanzapine, respectively. TEAE that occurred >3% more frequently than placebo were headache and dry mouth for paliperidone ER and somnolence, anorexia and increased serum glutamic oxaloacetic transaminase for olanzapine. TEAE-extrapyramidal symptom rates were comparable in the paliperidone ER 6mg, olanzapine and placebo groups, while they were higher with paliperidone ER 12mg. Study discontinuation due to TEAE was low and comparable between placebo, paliperidone ER and olanzapine (range 4—6%). Mean change in bodyweight (kg) at endpoint with placebo, paliperidone ER 6mg and 12mg and olanzapine were 0.4±3.6, 1.0±3.9, 2.0±3.5 and 2.7±4.4, respectively.
Discussion: The results of this 6-week study show that 6mg and 12mg paliperidone ER provide symptomatic improvements in patients experiencing an acute episode of schizophrenia and are generally well tolerated.

145. ERP P300 and Mismatch Negativity Abnormalities in Prodromal and Early Illness Schizophrenia: Predicting Conversion to Psychosis

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Background: Most patients with schizophrenia experience a prodromal phase before psychosis onset, characterized by attenuated psychotic symptoms and functional deterioration. Current diagnostic criteria for this prodromal syndrome show promising predictive validity, with estimated 12-month psychosis conversion rates ranging from 35 to 54%. However, this still leaves 46 to 65% of patients identified as prodromal who are not at imminent risk for psychosis and who, therefore, may not require or benefit from targeted preventive interventions. Thus, enhancing predictive validity of prodromal criteria by incorporation of neurobiological measures is a major research imperative. Two electrophysiological measures known to be abnormal in schizophrenia are the mismatch negativity (MMN) and P300 components of the event-related brain potential (ERP). These components reflect auditory sensory memory and allocation of attentional resources to infrequent events, respectively. We present data

from an ongoing study examining these ERP components in prodromal and early-illness schizophrenia patients, relative to age-matched controls. Clinical correlations of these ERP components with concurrent prodromal symptom severity and subsequent conversion to psychosis during a 12-month follow-up period are also examined.
Methods: ERPs were assessed by electroencephalogram (EEG) recording in 28 prodromal patients (12-25 years old, 17 males), 18 early illness (i.e., within five years of first hospitalization) patients (17-37 years old, 16 males) with schizophrenia, and 44 healthy controls (12-37 years old). The MMN paradigm consisted of a frequent (90%) tone (633 Hz, 50 ms duration) and a pitch/duration deviant (10%) tone (1000 Hz, 100 ms duration) presented randomly every 510 ms while subjects read a book. P300 was elicited in auditory and visual oddball tasks in which subjects were presented with task-relevant targets (10%) requiring a button press response, task-irrelevant but salient novel stimuli (10%), and frequent standard stimuli (80%). Twelve-month clinical follow-up data were available from a subset of 15 prodromal patients, yielding 5 patients who converted to a psychotic disorder.
Results: Early illness patients showed expected reductions, relative to age-matched controls, in MMN (p=.03) and P300 amplitudes in both auditory (target P3b, p=.02; novelty P3a, p=.02) and visual (target P3b, p=.03; novelty P3a, p=.03) modalities. Prodromal patients showed reduced P300 amplitude, relative to age-matched controls, for auditory targets (p=.03) and visual novels (p=.03), but the other P300 and MMN measures were not significantly reduced. Correlations with symptom severity in prodromal patients showed smaller auditory novelty P3a to be related to more severe positive, negative, and disorganization symptoms. Auditory target P3b and visual novelty P3a amplitude reductions were associated with more severe concurrent negative symptoms and predicted subsequent conversion to psychosis during a 12-month follow-up period.
Discussion: These data indicate that P300 to auditory targets and visual novels are compromised in prodromal patients and predict subsequent conversion to psychosis. This suggests that compromise of attentional neurocircuitry involved in auditory target detection and orienting to visual novelty may identify prodromal patients who are particularly at high risk for developing psychosis. Auditory novelty P300 was associated with prodromal symptom severity but did not predict conversion to psychosis. MMN was not compromised in prodromal patients, but its reduction was evident in early illness patients, suggesting that its amplitude declines early in the illness.

146. Comparison of Atypicals in First-Episode Psychosis (CAFE): A Randomized, 52-Week Comparison of Olanzapine, Quetiapine, and Risperidone

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Sponsor: Jeffrey Lieberman

Background: To evaluate the overall effectiveness of olanzapine, quetiapine, and risperidone in patients experiencing a first psychotic episode.
Methods: This was a 52-week, randomized, double-blind, multicenter study of first-episode patients with a DSM-IV diagnosis of schizophrenia, schizophreniform or schizoaffective disorder and psychotic symptoms that had persisted for 1 month to 5 years. Patients were randomized to olanzapine (2.5 to 20 mg/d), quetiapine (100 to 800 mg/d), or risperidone (0.5 to 4 mg/d) in a twice-daily dosing regimen. Clinicians were encouraged to lower the antipsychotic dose to relieve extrapyramidal symptoms (EPS). The primary outcome measure was the rate of all-cause treatment discontinuation up to 52 weeks. Secondary outcome measures included change from baseline in Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) Scale, and Calgary Depression Scale for Schizophrenia (CDSS) scores. Safety and tolerability assessments included elicited adverse events (AEs) and Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) scores. All assessments were conducted at baseline and at 12 and 52 weeks. Statistical analysis tested for non-inferiority in all-cause treatment discontinuation rates between quetiapine and olanzapine or risperidone based on a 20% equivalence margin.
Results: Four hundred patients were assigned to olanzapine (N=133), quetiapine (N=134), or risperidone (N=133) treatment, with a mean age (±SD) of 24.5 (±5.8) years. The majority of patients had a diagnosis of schizophrenia (57.8%). The mean modal prescribed daily doses for olanzapine, quetiapine, and risperidone were 11.7 mg, 506 mg, and 2.4 mg, respectively. At endpoint, the all-cause treatment discontinuation rates were 68.4%, 70.9%, and 71.4% for olanzapine, quetiapine, and risperidone, respectively, which did not exceed the 20% equivalence margin between treatments. All treatments showed reductions in mean PANSS total, CGI severity, CDSS total subscale scores at Week 52, with no significant differences between treatments. Common AEs among all groups were sleepiness and weight gain. At endpoint, 80%, 50%, and 57.6% of olanzapine-, quetiapine-, and risperidone-treated patients had gained >7% of their baseline weight (olanzapine versus quetiapine: P=0.01). EPS rating scale scores did not differ significantly between treatments, but fewer quetiapine-treated patients received concomitant medications for parkinsonism or akathisia compared with olanzapine (P=0.02).
Discussion: Olanzapine, quetiapine, and risperidone, at mean modal doses of 11.7 mg/d, 506 mg/d, and 2.4 mg/d, respectively, demonstrate similar rates of all-cause treatment discontinuation and produce similar improvements in psychopathology.

147. Novel Targets of Quaking: A Gene Essential for Myelination That is Severely Reduced in Schizophrenia

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Background: QUAKING (QKI), has 3 major splice forms, QKI-5, QKI-6 and QKI-7, encoding 3 RNA splicing and processing proteins (RSPPs) essential for normal myelination. In addition to strictly regulated temporal splicing of myelin genes, QKI also binds to the 3′UTRs of target genes to control translation. For instance QKI binds Cyclin-dependent kinase inhibitor 1B to increase its translation, resulting in cell cycle arrest and oligodendrocyte differentiation. QKI was recently found to be the most significantly decreased gene in the largest and most comprehensive gene expression study of SCZ brain performed to date (Haroutunian et al. 2005). Furthermore, QKI is located on chromosome 6q26 making it a strong candidate gene for SCZ. QKI is known to influence splicing and/or processing of 6 oligodendrocyte/myelin-related genes decreased in SCZ brain in the same cohort of samples (Katsel et al. 2005) and is predicted to bind the transcripts of 7 RSPPs that are also significantly decreased in SCZ (Katsel & Haroutunian personal communication). As expression of QKI is largely restricted to oligodendrocytes in the postnatal brain, our hypothesis is that abnormal RNA splicing and processing of myelin genes is a major factor contributing to oligodendrocyte dysfunction and white matter damage in SCZ. Therefore, our goal is to determine whether these RSPPs are true targets of QK.
Methods: MBP is a well studied QKI target and contains Quaking Star Binding Elements (QSBEs). QSBEs are high affinity binding sites for QK as determined by Ryder et al. 2004. A.Bioinformatics approaches are used to identify putative QSBE consensus sites in target transcripts of interest, in this case RBBP4, SFRS1 and SF3B1. B.Competition fluorescence polarization binding experiments are performed using short (12mers) chemically synthesized RNA targets to compare the affinity of each site to that of QKI binding to its best site in the 3 ′UTR of MBP mRNA. C.For the most interesting targets, longer sequences (30mers) are prepared and direct titration binding experiments are performed, both by fluorescence polarization and by

gel mobility shift assay. D.Qk1-RNA co-immunoprecipitations are performed using a bead binding assay followed by RT-PCR to confirm in vivo targets of QKI. E.Follow-up findings with quantitative immunoblotting in SCZ brain.
Results: Competition fluorescence polarization assays were performed with target sequences from RBBP4, SFRS1 and SF3B1 and compared with the highest affinity QSBE binding site in MBP (Kd= 10±2 nM). An RBBP4 QSBE binds as well as the highest affinity binding site in MBP (Kd= 11±1.5 nM) and SFRS1 sequences also bind tightly as well (Kd=22±4 nM and Kd=60±15 nM). SF3B1 binding was negligible. Gelshift assays with purified recombinant QKI confirmed binding to RBBP4 and SFRS1 RNA target sequences and show that QKI actually binds the QSBE in RBBP4 with slightly higher affinity (Kd=18±5 nM) than MBP (Kd= 23nM ±4 nM).
Discussion: The RSPP QKI was found to be severely decreased in a recent large scale SCZ gene expression study and 6 myelin-related genes, also decreased in SCZ, are proven QKI targets. Additionally, all 7 RSPPs found to be significantly decreased in SCZ in the same cohort of samples are predicted to be QKI targets. Of the first three of these RSPPs we tested, RBBP4 and SFRS1, but not SF3B1, may be real in vivo targets of QKI. Interestingly, RBBP4 binds a complex with CREB and is involved in activation of transcription so the effects of reduced RBBP4 could be manifold. In addition to continuing this work, we are also in the process of identifying abnormally spliced transcripts in SCZ brain to help illuminate the role of decreased RSPPs in the pathology of SCZ.

148. Comparison of Clozapine and High Dose Olanzapine in Treatment Resistant Schizophrenia in a Double Blind, Randomized, 6 Month Clinical Trial

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Sponsor: Roger Meyer

Background: There is extensive evidence that clozapine (CLZ) is more effective than typical antipsychotic drugs (APDs) in treatment-resistant (TR) schizophrenia (SCH) . Most but not all controlled trials report that other atypical (APDs), including olanzapine (OLZ), are not more effective than typical APDs in TR SCH. However, case reports and some small series of open treatment with high dose OLZ indicate greater efficacy in some TR patients. We hypothesized that high dose OLZ might be not significantly different from CLZ in TR SCH.
Methods: Forty six patients with TR SCH by historical criteria and current assessment, mean age 37, with an average of 6.4 prior hospitalizations, a baseline total PANSS score of 92, and PANSS positive score of 23 were randomly assigned to either CLZ or OLZ for a six month double blind trial at four sites. All patients had blood drawn on a weekly basis throughout the study. Ten of the 22 CLZ-treated and 14 of the 24 OLZ-treated patients completed the study. The mean dose of CLZ at 6 months was 564+/-SD243 mg/day; of OLZ, 33.6+/-SD11 mg/day. Side effects or apparent maximum response were factors limiting higher doses. The maximum dose of OLZ was 40 mg/day. Psychopathology and cognition were assessed with PANSS, SANS, SAPS, CGI, GAFS and a comprehensive neurocognitive battery at baseline, 6 weeks, and 6 months by trained raters who were blind to drug treatment. Data were analyzed by a mixed model analysis of covariance with baseline levels as covariates.
Results: There were significant time effects, signifying not significantly different improvements in PANSS total, general, and cognition subscale scores, as well as SANS Global, SAPS Global, and CGI Severity rating for both treatments. There was a trend for lower PANSS positive ratings at six months in the CLZ-treated patients compared to the OLZ-treated patients (p =0.07). The GAFS score was significantly higher in the CLZ-treated patients at 6 months (p= 0.01; 62.4 vs 54.8, compared to baseline LS mean scores of 45.1 in both groups). There was significant improvement in secondary memory, as measured by Verbal Immediate Recall, in verbal fluency, and in attention/motor performance at 6 months with both drugs. Performance on the WISC-R Maze, a measure of executive function, and Verbal-Delayed Recall at six months was significantly better in the OLZ-treated patients. OLZ-treated patients also had higher baseline adjusted weight at 6 months (p=0.01). There were significantly higher Barnes Akathisia scale scores in the OLZ-treated patients at 6 months.
Discussion: These results must be considered preliminary because of the small size of the sample, the absence of a placebo group, and the relatively high drop out rate. However, the fact that these patients did improve in psychopathology and cognition to the extent noted with both drugs is suggestive that these two treatments are useful in patients with TR SCH. These results suggest the need for a large scale study of higher dose OLZ vs CLZ. Further study is also indicated as to the mechanism by which higher doses of both CLZ and OLZ, which are chemically and pharmacologically similar, might be more effective in TR than non-TR patients. Supported, in part, by an investigator-initiated grant from Eli Lilly and by grants from the William K Warren Foundation and the Ritter Foundation.

149. Comparative Effects of Ziprasidone and Olanzapine on Markers of Insulin Resistance: Results of a 6-Week Randomized Study in Patients with Acute Schizophrenia

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Sponsor: Henry Nasrallah

Background: The metabolic syndrome is an entity used to identify individuals with underlying insulin resistance who are thereby at risk for future type 2 diabetes mellitus and cardiovascular mortality; however, not all patients who meet metabolic syndrome criteria manifest levels of insulin resistance in the upper tertile, a level associated with increased cardiovascular risk. The commonly used NCEP ATP III criteria for metabolic syndrome have a sensitivity of only 52% for those with the highest levels of insulin resistance. Serum triglyceride (TG):high density lipoprotein cholesterol (HDL) ratio > 3.0 has emerged as a simple and useful marker of significant insulin resistance in nondiabetics, with 64% sensitivity for those in the upper tertile, while the more difficult to obtain fasting insulin measure achieves only 57% sensitivity.
Methods: Using data from a randomized, double-blind 6-week trial where laboratory measures were obtained on a fasting basis, analysis of changes in TG:HDL ratio and fasting serum insulin levels was performed for subjects treated with olanzapine or ziprasidone.
Results: Baseline and endpoint data on fasting TG and HDL were available for 110 ziprasidone-treated subjects, and 118 olanzapine-treated subjects. At baseline, both drug cohorts had TG:HDL ratios > 3, indicative of high risk of significant insulin resistance (ziprasidone 3.50±2.88, olanzapine 4.69±6.91). At endpoint, there was a significant increase in TG:HDL ratio for the olanzapine-treated subjects (5.99±7.37; p=.0001), but no significant change in TG:HDL ratio for the ziprasidone cohort (3.67±3.23; p=.435). After adjustment for baseline differences, the increase in TG:HDL ratio was significantly greater for those randomized to olanzapine (p=.0062). Fasting insulin values at baseline and endpoint were available for 114 olanzapine-treated subjects and 108 ziprasidone-treated subjects. The median change from baseline in fasting insulin was also significant for the olanzapine group (3.30 μU/ml, p<.0001), but not for ziprasidone-treated subjects (0.25 μU/ml, p=0.33).
Discussion: The TG:HDL ratio has been proposed as a sensitive marker of insulin resistance and risk related to the metabolic syndrome. In this short-term study, ziprasidone was associated with no significant change in the TG:HDL ratio, in contrast to olanzapine which was associated with a significant increase in this parameter. Olanzapine treatment also significantly increased fasting insulin values, while no significant effect was seen in the ziprasidone cohort. These findings are consistent with the ADA/APA Consensus State-

ment regarding the greater risk for diabetes and hyperlipidemia during olanzapine treatment relative to ziprasidone. Future research will help elucidate the mechanisms related to the differential liability for metabolic effects between atypical antipsychotics. References: 1. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Annals of Internal Medicine 2003; 139(10):802-9. 2. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. Diabetes 2004; 53(5):1195-200.

150. Aripiprazole Effects on Highly Agitated Patients with Alzheimers's Disease and Associated Psychosis

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Sponsor: Lindsay DeVane

Background: Patients with Alzheimers's disease and associated psychosis often experience severe and disruptive behavioral disturbances such as agitation in addition to their core cognitive symptoms. In this analysis, patients treated with either aripiprazole or placebo were separated into high and low agitation groups, and analyses were performed to evaluate the association between baseline agitation status and treatment improvement.
Methods: Data from two 10-week, randomized, placebo-controlled aripiprazole trials in psychosis associated with Alzheimers's disease were pooled, and patients were dichotomized according to their level of agitation (i.e., high agitation and low agitation). High agitation was defined as a score ≥ 4 on the agitation/aggression item of the Neuropsychiatric Inventory (NPI). Treatment outcomes were compared between aripiprazole (2-10 mg/day) and placebo within the high (ARI n=335, PLA n=168) and low (ARI n=150, PLA n=70) agitation groups, by analyzing change from baseline in four separate measures: the NPI psychosis subscore (NPI-P: sum of delusions and hallucinations items), the Clinical Global Impressions-Improvement score (CGI-I), the Cohen-Mansfield Agitation Inventory score (CMAI), and the NPI agitation/aggression item score. Additional analysis also adjusted for baseline differences in baseline NPI-P, CGI-Severity, CMAI, and NPI agitation/aggression scores.
Results: Analyses of the NPI-P revealed significant decreases from baseline in psychosis for patients in both the high and low agitation groups (mean decreases: ARI high = -9.6, ARI low = -4.9, PLA high = -7.4, PLA low = -3.5; $p < 0.05$ for all), although there were no differences between aripiprazole and placebo. In the high agitation group, however, CGI-I analyses showed significant improvement in patients treated with aripiprazole compared to placebo-treated patients during the initial three study weeks ($p \leq 0.004$), as well as during weeks 8 through 10 ($p \leq 0.0016$; mean difference at endpoint = -0.4, $p < 0.05$); an effect not seen in the low agitation group. Adjustments for baseline CGI-I score did not alter these findings. For both of the agitation measures (CMAI and NPI agitation/aggression item), patients in the high agitation group treated with aripiprazole showed significant decreases in agitation compared to placebo-treated patients beginning at week-4 and continuing through week-10 ($p \leq 0.0003$ and $p \leq 0.0076$ respectively; mean difference at endpoint: CMAI = -0.4, NPI agitation/aggression = -1.2, $p < 0.05$ for both). These effects were not seen in the low agitation group. Results were maintained when adjusting for baseline dependent measure score.
Discussion: Highly agitated patients with Alzheimers's disease and associated psychosis who were treated with aripiprazole demonstrated overall clinical improvement and significant decreases in agitation compared to patients treated with placebo. Group differences were evident only in patients with high baseline agitation. These findings suggests that aripiprazole may reduce agitation symptoms and improve overall clinical impression in patients with psychosis associated with Alzheimer's disease who are experiencing marked agitation.

151. A New Approach to Assessing Objective Functional Outcomes in Schizophrenia: A Validation Study

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Background: Background: Cognitive impairment associated with schizophrenia negatively affects functional ability (Addington and Addington 2000; Bell and Bryson 2001; Bryson and Bell 2003; Bryson et al. 1998; Green et al. 2000; Kasckow et al. 2001; McGurk et al. 2003; Palmer et al. 2002; Sharma and Antonova 2003). Evaluation of the efficacy of new treatments in enhancing function is limited because there is no psychometrically validated objective measure of functioning. The Schizophrenia Objective Functioning Instrument (SOFI) was developed to address this unmet need for measuring change of functionality in clinical trials, quantifying observable functioning in four domains: living situation, instrumental activities of daily living, productive activities, and social functioning. The SOFI is administered via trained interviewers to either patient informants or patients themselves. Interviewers use specific probes to elicit information for open-ended items and then rate closed-ended items on a Likert scale. Each domain concludes with a global score rating by the interviewer (0-100, description of anchors is provided at 10 point increments, with higher scores indicating better functioning).
Methods: Objective: To assess the reliability and validity of both the patient and the informant version of the SOFI, the patient-informant concordance, and the easy of use of the SOFI. Method: The SOFI was validated across 9 geographically distributed CATIE clinical centers in the US between January and June 2005. Relatively stable individuals with schizophrenia or schizoaffective disorder and a patient-identified informant were recruited from 3 levels of living situation: restricted, semi-restricted, and unrestricted. Informants were typically family members, friends, or paid caregivers. A total of 104 patient/informant dyads participated; 25 dyads were randomly assigned to a test-retest reliability condition (8-12 days) and 26 dyads were randomly assigned to same-day inter-rater reliability testing. Known-group validity was based on PANSS scores (below vs. above median for positive, negative, and general score), Brief Assessment of Cognition in Schizophrenia score (below vs. above mean), and living situation. A survey was conducted among participating sites to assess the easy of use of SOFI.
Results: Results: Test-retest reliability was good; patient values ranged from r=0.66 (productive activities) to r=0.89 (living situation); informant reliability was higher, ranging from r= 0.87 (social functioning) to r=0.94 (living situation). Inter-rater reliabilities were acceptable (patient r=0.54 — 0.73 across domains; informants r = 0.51 — 0.79). Patient-informant intra-class correlation coefficients exceeded 0.65, indicating acceptable agreement. SOFI global scores for patients were significantly different when categorized by PANSS score (high vs. low) for positive, negative, and general scale (all p less than 0.05). All 4 SOFI domain scores differentiated between patients scoring above mean BACS score and below (p less than 0.05). All SOFI global domain scores differed by living situation (p less than 0.05). Interviewers spent approximately 30-45 minutes to administer SOFI, and both probes and close-ended items were helpful in establishing global ratings. Although overall the SOFI did a very thorough job in assessing function, it is recommended to increase the number and specificity of probing items.
Discussion: Conclusion: Based on cross-sectional data, psychometric performance of the SOFI is acceptable, suggesting it can provide a previously unavailable method for objectively quantifying the functioning of patients with schizophrenia.

152. Error Feedback Negativity During a Learning Task in Schizophrenia

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Sponsor: Alan Bellack

Background: The purpose of this study was to examine changes in brain activity that accompany learning in schizophrenia using the error-related negativity (ERN) component of the event-related brain potential recorded during a probabilistic learning task.
Methods: We recorded feedback-related ERNs while schizophrenia outpatients and normal comparison subjects performed a task in which they learned picture-response pairs via trial-by-trial feedback consisting of a small financial reward or penalty. The stimuli varied in the consistency with which they were mapped to a response. For stimuli in the 100% condition, correct responses were invariantly rewarded. In the 80% condition, correct responses were rewarded on 80% of trials and penalized on the remaining trials. In the 50% condition, rewards and penalties were given on a random basis.
Results: Response accuracy did not differ between the two groups. When response accuracy was uncertain (i.e., in the 50% condition), both groups exhibited a larger ERN following feedback indicating that an incorrect response had been made than when feedback indicated that a correct response had been made. In contrast, when negative feedback was unexpected (i.e., following invalid error feedback in the 80% condition), schizophrenia patients failed to generate an ERN.
Discussion: These results suggest that although patients process feedback appropriately when response accuracy is entirely uncertain, they fail to detect discrepancies between the accuracy of executed responses and feedback when response accuracy is more certain. Interpreted in the context of the reinforcement learning theory of the ERN, this finding may reflect a failure of the ERN to signal prediction errors in schizophrenia patients, possibly due to disturbance in the function of the midbrain dopamine system.

153. Prefrontal Activity in Schizophrenia: An Interleaved TMS/fMRI Study

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Sponsor: Travel Awardee, PMRTP, 2005

Background: Knowledge about Schizophrenia's pathophysiology is still incomplete. Some evidence exists that the dorsolateral prefrontal cortex (DLPFC) may be dysfunctional in schizophrenia. Neuroimaging studies have reported both hypoactive and hyperactive DLPFC in subjects with schizophrenia involved in a cognitive task. These apparent contradictions may be due in part to the skills, performance and the difficulty of each task. Transcranial Magnetic Stimulation (TMS) is a non-invasive technique that does not depend on compliance or effort by the subject. Here, we report on the use interleaved TMS/fMRI in schizophrenia subjects to investigate if DLPFC is truly hypoactive.
Methods: So far, we enrolled 18 schizophrenia neuroleptic free subjects (for at least 2 weeks) and 5 healthy matched controls (recruitment is ongoing). They underwent a high resolution structural scan and an automated determination of left middle frontal gyrus (Brodmann Area 9) which guided TMS placement. In the same session they underwent an interleaved TMS/fMRI session over the left middle frontal gyrus in a single event paradigm with random 4 different intensities delivered in 10Hz triplets at 0%, 80%, 100% and 120% of motor threshold (intensity necessary to move the thumb) [Philips 1.5T with synergy coils]. Analyses were performed with SPM2.
Results: ANOVA results shows higher activation underneath the coil with 120%MT compared to 100% or 80%MT. 10Hz triplet stimulation over the left DLPFC leads to limbic deactivations which are also intensity dependent. We will also report on comparison between schizophrenia subjects and matched healthy controls.
Discussion: Preliminary data support a parametric modulation of LDPFC with TMS at sub, supra and at motor threshold intensity. It is unclear how does this pattern compares to health matched controls athough data sugggest that TMS induced BOLD activation is less pronounced in non-medicated schizophrenia subjects than in matched controls.

154. Low Rates of Treatment for Metabolic Disorders in the CATIE Schizophrenia Trial at Baseline

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Background: A growing body of evidence suggests that metabolic disorders, such as obesity, diabetes, hyperlipidemia, and hypertension, are quite prevalent in persons suffering from chronic schizophrenia. The most recent data from the large (N=1460, mean age 40.6 years) NIMH sponsored CATIE schizophrenia trial indicate that the metabolic syndrome (NCEP updated definition) is present in 42.7% of the CATIE sample at baseline (McEvoy et al, 2005) which is nearly twice the prevalence in the general population ages 40-49 years. We examined the proportion of the CATIE schizophrenia subjects who met criteria for one of the major metabolic disorders (diabetes, hyperlipidemia, and hypertension) and were or were not receiving treatment at the time of enrollment into the study.
Methods: We analyzed the baseline data from the 57-site CATIE schizophrenia trial for the number of patients meeting clinical and laboratory diagnostic criteria for diabetes, hyperlipidemia, and hypertension, and calculated the percentage of those subjects at enrollment who were receiving a hypoglycemic agent, a statin, or an antihypertensive agent respectively. We also examined the relationship of sex, race, and ethnicity to the rates of treatment for those disorders.
Results: a) Diabetes: 11.0% of the subjects with fasting serum glucose had diabetes. 45.3% of the diabetic schizophrenia patients were not receiving treatment. b) Hyperlipidemia: Of the 471 subjects with elevated fasting lipid levels, 89.4% were not receiving a statin. c) Hypertension: of 550 patients who met criteria for hypertension, 62.4% were not receiving any antihypertensive. Gender and racial/ethnic breakdowns will be presented at the meeting.
Discussion: A high proportion of the CATIE Trial schizophrenia sample was not receiving appropriate and standard treatment for their metabolic disorder at the time of enrollment. These data are suggestive of health disparities reflected in the low rates of access to standard medical treatments, despite the high prevalence of the metabolic disorders observed in this schizophrenia sample. These findings have serious implications for the morbidity and mortality of persons with schizophrenia in the U.S.

155. An Integrative Approach to Investigate Molecular Mechanisms Underlying Schizophrenia Using both Rat and *Drosophila Melanogaster*

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Sponsor: Elaine Sanders-Bush

Background: Many psychiatric disorders, such as schizophrenia, are believed to have a significant developmental or genetic component. Both human and animal studies have implicated the involvement of specific neurotransmitter systems, including dopamine, serotonin, glutamate, and GABA. We have developed a novel approach that integrates functional genomic studies of gene response in mammalian

prefrontal cortex with the powerful genetics of Drosophila melanogaster to elucidate molecular cascades and events that may contribute to the development and behaviors of schizophrenia. Because schizophrenia is a uniquely human disorder, it cannot be modeled per se in animals, but animal models can be used to recapitulate certain molecular events relevant to the disease and study their role in behavior. Our overall hypothesis is that the molecular and gene expression events initiated by a pharmacological model of schizophrenia that contribute to behavioral effects represent candidates for involvement in the development and etiology of schizophrenia in humans, and importantly, targets for new avenues of discovery for therapeutics.
Methods: Microarray screens, RNase protections, and real time PCR were used to examine gene expression levels. In flies, locomoter, visual processing, and circadian behavioral tests were performed to examine LSD and DOI induced behaviors. Standard histochemical techniques were used to visualize 5-HT_2Dro receptor circuitry.
Results: In contrast to our earlier studies investigating acute LSD administration, where we described several genes that were upregulated, in rats treated chronically with LSD we have identified new genes whose expression is down-regulated. These include the transcripts for *Neuregulin 1*, and *Grin1*, both having previously been shown by others to have reduced expression in human schizophrenia brains. Remarkably, LSD produced robust quantifiable behaviors in the fly not unlike those observed in mammalian systems. These include severe deficits in visual processing, changes in overt locomotor activity, and parallel alterations in gene expression. Significantly, these LSD-induced behaviors were blocked by antipsychotic drugs. Furthermore, both agonists and antagonists of 5-HT_2 receptors influence various aspects of the circadian cycle in the fly, suggesting that 5-HT_2 receptor circuitry is involved in these behaviors. Using an enhancer trap expression system we show that 5-HT_2Dro receptor mRNA is expressed throughout large areas of both the larva and adult brain.
Discussion: Recent studies have indicated that chronic administration of LSD to rats produces a persistent behavioral state that may bear certain neurochemical similarities to psychosis. Although the behavioral effects of LSD involve serotonin receptor activation, LSD is also a powerful dopaminergic agent, and dramatically alters both glutamate and GABA function within the prefrontal cortex of the brain, pathways that are all implicated in schizophrenia. Gene identification is only the first step toward elucidating molecular events underlying schizophrenia. The most effective approach to reveal complex signaling cascade components is to perform genetic studies that can identify interacting factors. Therefore, we have developed the fruit fly, Drosophila melanogaster, to serve as a powerful model system to study molecular events underlying the action of LSD. 5-HT systems in drosophila brain may be extremely useful in modeling the orthologous systems in mammalian brain, but with the significant advantage of being genetically-tractable. Supported in part by: NIH grants DA05993, DA05181, and the Heffter Research Institute

156. Association of the $5HT_{2C}$ Gene Polymorphism and Antipsychotic-Induced Weight Gain

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Sponsor: Travel Awardee, PMRTP, 2005

Background: Single nucleotide substitutions in the promoter region of serotonin receptor, type 2C ($5HT_{2C}$) could be associated with antipsychotic-induced weight gain and metabolic abnormalities. We examined the relationship of this gene to weight gain in an adolescent, predominantly antipsychotic naive, group of subjects undergoing treatment with the second generation antipsychotic medications (SGAs).
Methods: We genotyped three loci in the $5HT_{2C}$ gene (1→2 at -759, 1→2 at -697 and 1→2 at -995) of 157 patients (Age 14.1 years±3.2yrs, 40% Females, 63% antipsychotic naive) who received treatment with SGAs for three months and were monitored for metabolic and weight parameters. Baseline parameters of the subjects did not differ by genotype.
Results: We detected an association between the -995 single nucleotide polymorphism (snp) and weight gain. The "2" allele carriers gained more weight than non-carriers at 4 weeks of treatment (mean change ± s.d was 7.15±6.3 vs 2.13±3.2; $p<0.037$) and at 12 weeks (mean change from baseline ±s.d was 13.8±11.6 vs 4.95 ±5.3). In addition, the leptin levels (ng/ml) were significantly increased among the "2" carriers than non-carriers at 4 weeks (mean change± s.d was 3.25±5.6 vs -3.1±9.5; $p<0.015$) and at 12 weeks (mean change±s.d was 3.7±6.3 vs -4.2±7.7; $p<0.006$). The -759 and -697 snps were not associated with weight gain in this cohort.
Discussion: Data supports earlier reports of an association between antipsychotic-induced weight gain and $5HT_{2C}$ gene. Our sample was ethnically heterogeneous and a larger study of specific SGAs in weight gain is underway.

157. Genetic Analysis Supports a Primary Abnormality in Oligodendrocyte Function in Schizophrenia

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Sponsor: Joseph Buxbaum

Background: Oligodendrocyte abnormalities have been implicated in schizophrenia by a diverse range of experimental approaches including gene expression analysis, neuropathology, and neuroimaging. One critical component of the Silvio O Conte Centre For The Neuroscience of Mental Disorders led by Mount Sinai Medical School (NY) is the analysis of genes relevant to oligodendrocyte function for association with schizophrenia, in order to establish whether such abnormalities are likely to be of primary aetiological relevance.
Methods: Candidate genes are being examined in large case-control and family based association samples using a combination of direct association analysis based upon de novo mutation detection and also by indirect association analysis based upon dense maps of database markers.
Results: We have previously reported evidence for association between schizophrenia and the neuregulin receptor erbB4 and also the gene encoding 2',3'-Cyclic Nucleotide 3'-Phosphodiesterase. As these genes have respectively multiple and unknown functions, it is unclear to what extent these findings support the fundamental hypothesis under investigation. However, more recently acquired data provide strong evidence for association between Oligodendrocyte lineage transcription factor 2 (Olig2) and schizophrenia. As the function of this gene is very clearly related to oligodendrocyte development, these data provide more robust support for the hypothesis. Moreover, we have also strong statistical evidence (corrected $p<0.001$) for interactions between Olig2 and CNP, and between Olig2 and erbB4.
Discussion: Our data now increasingly point to abnormal oligodendrocyte function as a primary aetiological mechanism in schizophrenia. Moreover, recently acquired genetic data will also be presented that suggests this mechanism may also be of relevance to bipolar disorder.

158. The Consortium on the Gentics of Schizophrenia (COGS): The P50 Auditory Evoked Potential as an Endophenotype in a Large Multi-Site Study

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Background: COGS is a seven site consortium studying the genetics of schizophrenia using six different endophenotypes including the

P50 auditory evoked potential. Examination of the feasibility and reliability of obtaining P50 data as part of a larger research battery at multiple sites is crucial for the COGS project to succeed. Documentation of endophenotype quality is important if these endophenotypes are to be used to study the genetics of schizophrenia.
Methods: The P50 auditory evoked potential was recorded using the LEA 2003 system. Subjects were reclining. Sweeps were rejected online if they contained large muscle artifact or eye blinks. Five trials were collected for each subject that contained 20 acceptable sweeps. Averages with conditioning P50 waves <0.5 mV or with the EOG>EEG at the same latency were excluded. If the average was excluded, the individual sweeps were then reexamined by the quality assurance site to eliminate sleep activity. The sweeps were then averaged and the one trial with the largest P50 conditiong amplitude EEG/EOG ratio and with a conditioning amplitude of >0.5 mV was selected. An additional criteria was that trials with less than 12 sweeps were excluded. A one way-analysis of variance determined if the conditioning amplitude, test amplitude, test/conditioning ratio and conditioning latency were affected by diagnosis.
Results: Data from 149 normal subjects, 119 probands and 259 first degree relatives of probands have been analyzed. Of the 7 sites, 6 recorded mean P50 ratios in the normal sumbjects within the previously reported range of below 0.5. The P50 ratio of all combined sites significantly discriminated probands (mean 0.55, S.D. 0.52) from normal subjects (mean 0.38, S.D. 0.32). The P50 ratio of the relatives(mean 0.45, S.D. 0.40) fell between the probands and the normal subjects.
Discussion: The P50 auditory evoked potential is a difficult endophenotype to record, however, in this multisite study, the COGS collaboration was able to distinguish normal subjects from probands.

159. Learning to Relax with MRS: Altered NAA T2 Relaxation Times in Schizophrenia

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Background: Magnetic resonance imaging (MRI) and spectroscopic (MRS) investigations in schizophrenia have reported decreased volume in many cortical regions as well as evidence of altered neurochemistry such as decreased N-acetyl aspartate (NAA) which is generally considered to be a marker of neuronal density/integrity. These MRS studies, to date, have assumed that the T2 (transverse) relaxation rates of brain metabolites such as NAA are constant between experimental and control groups and do not need to be independently measured. The current study was undertaken to determine the validity of this assumption by measuring NAA T2 relaxation times and T2 corrected concentrations in the anterior cingulate. If metabolite T2 relaxation rates do differ between groups then explicit correction factors must be included in order to obtain unbiased concentration levels. Brain metabolites are typically quantified by measuring the integrated area under the spectral curve of the metabolite of interest. This "raw" number is then normalized using one of several standard techniques in order to facilitate inter-subject and inter-study comparisons. One common normalization technique is to report the ratio of the metabolite of interest to a reference metabolite such as creatine. Absolute quantitative techniques may also be applied with the advantage that metabolite concentrations may be reported in laboratory units such as milligrams per deciliter. The T2 relaxation correction, when needed, is an additional factor.
Methods: 20 Schizophrenic subjects ages 18-49 and 15 healthy controls ages 21-37 were recruited. Subjects underwent structural imaging and spatially localized 2D J-resolved proton spectroscopy (2D MRS) on a 1.5T GE Signa scanner. A 2.5cm x 2.5cm x 3cm voxel was centered on the anterior cingulate cortex. Spectra were acquired at 64 echo times (48-678 msec) in 10 msec steps. T2 relaxation times for NAA and Cr were calculated by a two parameter exponential fit to the peak amplitude as a function of TE. In the 2D MRS protocol data undergo a second Fourier transform in the echo time domain which allows spectral peaks to be resolved (in a second dimension) as a function of coupling strength. NAA and Cr peak areas were measured from the J=0 Hz spectra and T2 relaxation correction factors were applied to measured NAA/Cre ratios.
Results: NAA T2 relaxation rates were found to be significantly lower in schizophrenic subjects compared to healthy controls (300.5 msec vs. 357.0 msec; $p < 0.005$). Uncorrected NAA/Cr concentrations were also significantly lower in schizophrenic subjects compared to controls (1.74 vs 1.98; $p < 0.01$). T2 corrected NAA/Cr concentrations were not significantly different between groups (1.63 vs. 1.77; $p < 0.20$).
Discussion: T2 relaxation times for NAA were found to be significantly decreased for schizophrenic subjects compared to healthy controls. The net effect of the lower NAA T2 relaxation times was to enhance between group differences in the uncorrected NAA/Cr concentration measurements. These differences were no longer statistically significant when individual T2 corrections were applied. Metabolite T2 relaxation times are sensitive to changes in the intracellular environment such as decreased cell volume. These findings are therefore consistent with morphometric and post mortem studies indicating reduced cingulate volume in schizophrenic subjects. Previously MRS reports of decreased NAA concentration may reflect actual concentration shifts but may also be mixed with the effects of signal/peak area changes due to altered metabolite transverse relaxation (T2) times. Supported by MH60450.

160. Sleep Spindle Abnormalities in Schizophrenia

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Sponsor: Burr Eichelman

Background: Abnormalities in sleep electroencephalographic (EEG) activities have been reported in several psychiatric disorders including schizophrenia (Feinberg, 1964). The recent development of high-density (hd) EEG systems holds promise for a more precise mapping of these rhythm abnormalities. We present an initial investigation of sleep patterns in schizophrenia using a 256-channel hd-EEG.
Methods: EEG recordings used a 256-channel hd-EEG Geodesic Net (EGI, OR). The first sleep episode was recorded in subjects with schizophrenia (n=13, all taking antipsychotics), subjects with major depression (n=11), and age-matched non-psychiatric controls (n=13). Subjects were placed in a shielded, soundproof room and allowed to sleep at their customary bedtime. EEG signals were digitized at 500 Hz together with electromyogram and electrooculogram, filtered (0.5–50 Hz), artifact-rejected, average-referenced, and sleep-staged. Recordings were analyzed by power spectral analysis and topographic mapping of signal strength at frequencies of interest.
Results: This report focuses on changes in the spindle frequency range (12–15 Hz). Compared to both depressed and control subjects, subjects with schizophrenia had slightly but non-significantly reduced spectral power in the spindle range. However, the topographic distribution of power in the spindle frequency range was clearly different. Both control and depressed subjects had a well-defined centroparietal peak of spindle frequency power, whereas in subjects with schizophrenia this peak was missing and power in the spindle range was widely distributed. The lack of a centroparietal peak was especially prominent in the high frequency spindle range (14–15 Hz). A preliminary analysis of the morphology of individual spindle oscillations indicated a statistically significant reduction in spindle amplitude and duration in schizophrenic subjects compared to control or depressed subjects.
Discussion: These changes may reflect dysfunction in the thalamocortical circuits involved in the generation and synchronization of spindle-frequency oscillations during sleep. Further studies are

needed to determine whether such changes represent potential trait or state markers and to rule out possible confounding factors.

161. A Double-Blind Placebo Controlled Trial of Modafinil for Negative Symptoms in Schizophrenia

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Background: Negative symptoms of schizophrenia (affective flattening, alogia, avolition) are functionally debilitating, refractory to treatment, and associated with poor overall outcome. Despite advances in the pharmacotherapy of schizophrenia, there are still no treatments proven to be effective for primary negative symptoms. Modafinil is a wakefulness promoting agent approved by the FDA for the treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. Case reports and clinical trials have demonstrated efficacy in conditions associated with fatigue, as an adjunctive treatment of depression, and in open-label therapy of negative symptoms in schizophrenia. We hypothesized that modafinil would be effective as an adjunctive treatment for patients with schizophrenia and prominent negative symptoms.
Methods: 20 subjects were randomized to placebo or modafinil 200 mg/day for 8 weeks of double-blind treatment in addition to existing antipsychotic therapy. Inclusion criteria were 1) age 18-65 2) DSM-IV schizophrenia or schizoaffective disorder, 3) clinical stability, with no medication changes in the past month, 4) SANS Total > or = 20 and alogia or affective flattening > or = 2, 5) BPRS Psychosis Cluster < or = 14. Exclusion criteria included 1) Active substance abuse, 2) Patients taking MAOI's, 3) Significant medical or neurological illness, or 4) Unable to give informed consent. Outcome measures were the SANS, BPRS, CGI, Quality of Life (QOL), as well as neurocognitive measures (CVLT, DS-CPT, Trails B), and effects on sleep, weight, and metabolic labs. For the major outcomes, statistical analyses were performed using analyses of variance (ANOVA) and data from the last observation carried forward (LOCF).
Results: Modafinil treatment was associated with a significantly greater rate of improvement at endpoint (CGI-change < or = 3) compared to placebo (chi square=7.5 df=1, p=0.006). Mean CGI-change scores were also significantly lower (reflecting greater improvement) at endpoint among subjects treated with modafinil compared to placebo. In this sample of subjects, of whom 50% had the deficit syndrome, treatment with modafinil did not yield significant improvements in negative symptoms compared to placebo. Modafinil did not significantly worsen psychopathology or positive symptoms (BPRS total, BPRS psychotic cluster) compared to placebo. Compared to placebo, modafinil did not significantly improve neurocognitive deficits associated with negative symptoms in schizophrenia. Modafinil was well-tolerated with few side effects.
Discussion: Adjunctive treatment with modafinil may result in global clinical improvement in patients with schizophrenia who have prominent negative symptoms. In contrast to published open-label reports, this small, exploratory double-blind study did not demonstrate any significant benefit for modafinil in the treatment of core negative symptoms in schizophrenia. For these symptoms, there remains no treatment with proven efficacy. Modafinil was well-tolerated and did not worsen psychosis, as has been reported elsewhere. The study's main limitation is its small sample size. Larger controlled trials are warranted to further explore a role for modafinil in the treatment of negative symptoms of schizophrenia.

162. PCP- and Cocaine- Induced Changes in White Matter- Comparison with DTI Findings in Schizophrenia and Cocaine Dependence

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Background: Structural brain abnormalities in Schizophrenia (SZ) and Cocaine Dependence (CD) are well known and include pathology in white matter (WM). However, animal models of WM changes are lacking. Psychosis associated with psychostimulants is a model of positive symptoms in SZ, but administration of N-methyl-D-aspartate (NMDA) antagonists mimics the negative symptoms and cognitive deficits of SZ, as well as positive symptoms. We have used DTI to study WM changes in patients with SZ and CD and in animal models. DTI provides information about WM structure by measuring water diffusion parallel to axon fibers (axial diffusivity, Dax) as well as diffusion perpendicular to fibers (radial diffusivity, Dra). Fractional anisotropy (FA) reflects the ratio of Dax to the root mean square of the combined diffusivities. FA ranges from zero to one and is high in WM since Dax is much greater than Dra. In gray matter, Dax and Dra are similar and FA is lower. Our DTI studies in patients with SZ and CD indicate that patterns of WM change have similarities and differences. Consistent with other reports, we have reported decreased FA throughout the brain in SZ, including the corpus callosum (CC). More recently, we have found elevated Dra in cortical WM in SZ and decreased Dax in thalamus and internal capsule. Increased Dra has been associated with developmental and drug-induced myelin lesions, and decreased Dax has been associated with axonal degeneration. Our studies in CD inpatients showed increased FA in frontal WM, relative to matched controls (in contrast to SZ). Patients also showed decreased FA in temporal lobe WM (similar to SZ). Briefly abstinent CD subjects scanned longitudinally showed decreased frontal FA relative to their initial scan. This suggests that drug-induced increase in FA can also represent a pathological state in humans. No studies have evaluated effects of PCP or cocaine on WM structure using DTI in rodents.
Methods: Imaging studies used fixed tissue, which eliminates the need for anesthesia and motion artifacts. Our study in the myelin basic protein knockout, shiverer (Nierenberg et al., 2005), and the work of others suggest that anatomic features giving rise to the DTI signal remain intact following fixation, and relative indices of water diffusion anisotropy remain equivalent. Dosage regimens (10 mg/kg/day i.p. for cocaine and 15 mg/kg/day i.p. for PCP) have been shown to result in behavioral, structural and neurochemical changes. Controls were treated with saline. Imaging data were acquired on a 7T MRI system. DTI was obtained using a standard 6-direction pulse field gradient spin-echo sequence that is free of distortions. 40-400μm coronal slices covering the entire cerebrum were acquired. ROIs were placed in the CC, anterior commissure, internal and external capsules. DTI scans were acquired using fixed brains from rats treated with 15 mg/kg/day PCP or saline.
Results: PCP-treated animals reduced FA in the CC (p=.009) relative to controls. The reduction in FA was associated with reduction in Dax and increase in Dra, although neither effect was statistically reliable in this limited sample. Maps of the color-coded directional information in the principal diffusion vector illustrated preservation of WM anatomy in fixed brain. Studies with cocaine are ongoing.
Discussion: These data demonstrate the feasibility of exploring NMDA and dopamine-mediated change in WM structure using DTI in fixed tissue in which histological analyses can be performed. Potential mechanisms and relationships between animal models and patient findings will be discussed. Results may provide important insight into the basis of DTI changes in SZ and CD and in neuropsychiatric disorders in general.

163. A Post-Marketing Observational Study of the Effects of Donepezil on Patients with Alzheimer Disease

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Background: The objective of this study was to examine the 1-year clinical effectiveness of donepezil in a prospective, non-randomized, observational study of patients with Alzheimer disease (AD) and to compare these effects with those found in a published Nordic 1-year randomized AD trial.
Methods: Patients (n = 502; mean age = 77.5 years; SD = 7.5) with probable or possible AD from 11 clinical sites in California were identified. Their treatment, including prescription of donepezil, was determined by their individual physician according to his/her usual criteria. Outcomes were cognitive and functional change scores over one year. The 11 study sites included a consortium of eight university-based Alzheimer Disease Research Centers of California (ARCCs) and three Veteran Affairs Mental Illness Research and Education Centers (MIRECC). All sites have been closely collaborating and using common research data collection protocols for over five years.
Results: The 112 California patients who completed one year of donepezil treatment had an average 1-year decline of 1.4 (3.6 SD) points on the 30-point Mini-Mental State (MMS) scores in contrast to a decline of 3.2 (4.3 SD) in the 143 AD patients who completed the one year trial and received no donepezil, other cholinesterase inhibitors, or memantine during the study period ($p < .0007$). The MMS decline in Nordic sample was ~ 0.25 for the 91 patients receiving donepezil and ~ 2.2 for the 98 patients receiving placebo. The effect sizes of these treatment-associated differences were essentially the same in the two studies: .43 in the California non-randomized study and about .49 in the Nordic randomized clinical trial. Advantages of donepezil over no-donepezil treatment were also found in the Blessed-Roth Dementia Rating Scale scores, which assess functional activities of daily living (~ 0.8 decline vs. 2.0 on 17-point scale; $p < .0003$). Detailed analyses were completed on the California data to assess the possibility of biases being introduced by patients who did not complete the study. These assessments indicated it was unlikely that factors related to non-completers significantly impacted the California results. We further analyzed the California data using propensity methods to determine if biases were introduced by non-random factors generated by each patients' physician deciding by his/her own criteria whether to prescribe donepezil. The pattern of results did not significantly change; the lack of randomization did not bias the outcome results.
Discussion: Taken together, our results suggest that observational studies can provide useful information on what a typical physician can expect in his/her clinical practice if appropriate analyses are conducted to assure that non-random factors do not significantly bias the findings. When we completed these analyses, our one-year California study indicates that donepezil treatment does have modest effectiveness in AD patients having racial-ethnic and clinical characteristics similar to those of the Nordic study sample. However, somewhat faster decline with donepezil treatment should be expected than those found in randomized clinical trials, especially when the AD patients are Hispanic or non-white.

164. Alterations in Sensorimotor Processing in Mice with Hyperdopaminergic or Hypomonoaminergic Tone

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Background: Although psychiatric disorders are characterized by a broad spectrum of behavioral dysfunction, some of these conditions may be accompanied by cognitive abnormalities. As cognition is a complex phenomenon that relies upon many different interdependent processes, deficiencies in early processes — such as attention — may contribute to perturbations in higher function. A critical feature of attention involves the ability to filter or "gate" sensory and motor information so that the most salient features in the environment can be selected and processed. This process can be studied by prepulse inhibition (PPI) and deficits in PPI occur in a number of psychiatric conditions that include schizophrenia, attention deficit - hyperactivity disorder, Tourette's syndrome, obsessive-compulsive disorder, Parkinson's disease, post-traumatic stress disorder, and autism.
Methods: We have varied the interstimulus interval (ISI) between the prepulse and startle stimulus from 5 to 200 msec to examine PPI performance. PPI was studied in mice where dopaminergic tone was increased by dopamine receptor agonists or by genetic deletion of the dopamine transporter (Dat1), or where monoaminergic tone was decreased through disruption of the vesicular monoamine transporter 2 (Vmat2) gene.
Results: Apomorphine and amphetamine disrupt PPI in C57BL/6 mice by shifting optimal processing of sensorimotor stimuli from 100 msec to very short ISIs. Optimal ISI is shifted also to shorter ISIs in Dat1 homozygous mutants. PPI performance of Dat1 mice was restored with sulpiride, as well as with methylphenidate or atomoxetine. Hence, pharmacologic- or genetic-induced hyperdopaminergia increase the speed of gating sensorimotor stimuli and drugs used to treat the conditions normalize it. Mice heterozygous for the Vmat2 mutation are deficient also in PPI. In this case, optimal processing of sensorimotor stimuli is shifted to very long ISIs and is rescued by the antidepressants, fluoxetine and reboxetine.
Discussion: These findings suggest that changes in the speed of processing sensorimotor stimuli may represent a fundamental aspect of cognitive dysfunction in subjects with altered monoaminergic tone and that studies in Dat1 and Vmat2 mice may reveal novel aspects of cognition that may be amenable to pharmacotherapy in these and, perhaps, other behavioral or psychiatric conditions. [Supported in part by a grant from the National Alliance for Research on Schizophrenia and Depression and NIH grant MH60451]

165. Candidate Gene Polymorphisms and Birth Weight (BW) in the National Longitudinal Study of Adolescent Health (Add Health)

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Background: Persons with lower BW, including weights within the normal range, are at increased risk of both cardiovascular disease and depression in adulthood. Poor maternal nutrition, race/ethnicity and prenatal stress contribute to reduced BW. Genetic factors also contribute, as shown by a recent association between BW and a polymorphism in the angiotensin converting enzyme gene. (J Clin Endrocrinol Metabol 2004;89:5738). We conducted exploratory analyses evaluating associations between BW and six candidate gene polymorphisms that have been genotyped in the sibling subset of the large population of individuals participating in the Add Health study.
Methods: We analyzed BW (parent report) and genotype data from 261 unrelated non-hispanic African American (AA, 53% female) and 1265 unrelated non-hispanic Caucasian (C, 53% female) individuals. Six polymorphisms were genotyped within the following genes: dopamine transporter (DAT1-40bp VNTR in 3' UTR), serotonin transporter (44 bp insertion/deletion polymorphism in promoter; 5HTTLPR), dopamine D2 receptor (DRD2, TaqIA polymorphism), dopamine D4 receptor (DRD4, 48bp VNTR in exon 3), monoamine oxidase A (MAOA-uVNTR) and cytochrome P450-A6 (T479A substitution). GLM was used to evaluate associations between BW and genotypes, controlling for race (AA vs C) and sex, as well as their interactions with genotype.

Results: Of the 6 genes evaluated, polymorphisms in 3 showed significant associations with BW. For the serotonin transporter there was a significant race X gene interaction (p=0.007) such that AA subjects with the s/s genotype had higher BW (7.33 Lb, p=0.008) than l carriers (6.48 Lb). In contrast, C subjects, with the l/l genotype had higher BW (7.26 Lb, p=0.007) than s carriers (7.04 Lb). Because MAOA is on the X chromosome, we analyzed the sexes separately. We observed in males, but not females, those with the active (3.5,4 and 5 repeats) alleles had higher BW (7.05 Lb, p=0.03) than those with the less active alleles (6.81 Lb). For CYP2A6 those with the A/A genotype had lower BW (6.82 Lb, p=0.02) than T carriers (7.20 Lb). DRD4 showed a trend toward a race X gene interaction (P=0.058) such that AA subjects with at least one 7-repeats allele had higher BW (6.72 Lb, P<0.05) than those with no 7-repeats (6.34 Lb).

Discussion: These findings suggest that, even in utero, genetic variation contributes to lower BW. The race x 5HTTLPR interaction for BW reported here parallels a similar effect of 5HTTLPR genotype on CSF 5HIAA (Neuropsychopharmacology 2003; 28:533-541), such that the s allele has opposite effects on both BW and 5HIAA in AA (higher BW and 5HIAA) vs. C subjects (lower BW and 5HIAA). The MAOA effect on BW was restricted to males, possibly due to the differing biology, in that females have two copies of the MAOA gene that are subject to X inactivation. Alternatively, the association observed with males may be a false positive. The CYP2A6 A/A genotype produces a leucine for histidine substitution at codon 60 that results in a catalytically inactive protein product (Toxicol 2003;183:151), suggesting that the lower BW in those with the A/A genotype could be related to reduced metabolic breakdown of environmental toxins or endogenous steroid hormones. This is one of the few studies that has examined the effects of fetal genotype on intrauterine growth and birth weight. Results suggest that the fetus plays an active role in its own development and health. Final determination of the implications of these associations will depend first upon their being replicated and then upon further research to determine the responsible mechanisms, including evaluation of environmental factors that might moderate the genetic effects.