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Poster Session III - Wednesday

1. Intense Cocaine Self-administration in Submissive, but not Dominant Animals: HPA Axis and NMDA Receptors

Klaus A Miczek*, Herbert Covington and Jasmine Yap

Psychology, Tufts University, Medford, MA, USA; Pharmacology, Tufts University, Boston, MA, USA

Glucocorticoid activation characterizes both the dominant and the submissive individual during and after an aggressive confrontation. These stress responses have enduring effects as seen by behavioral and neural sensitization in response to stimulant challenge. Dominant and submissive individuals diverge in terms of hippocampal neurogenesis and in vulnerability to intense cocaine taking (i.e. submissives take more cocaine). Separate groups of Long-Evans rats or CFW mice were investigated after an initial ten-day period of social stress during brief aggressive confrontations either once a day or every four days, either as resident or as intruder. Blood samples were taken during the initial and last aggressive confrontations. Both social defeat in the intruder and aggressive behavior by the resident rapidly increased levels of plasma corticosterone after the first and last aggressive confrontation without sign of habituation or sensitization. Behavioral sensitization was assessed 10 days after the last confrontation in response to an amphetamine challenge (1.0 mg/kg, followed by intravenous self-administration of cocaine during limited and extended, binge-like access periods. Socially defeat stressed animals displayed a sensitized locomotor activation and accumbal dopamine release relative to dominant and control animals. When compared to non-stressed controls, socially defeated animals self-administered cocaine more intensely, as evidenced by a significantly higher "break-point" when cocaine was available after progressively higher response requirements. Moreover, socially defeat stressed animals take more drug and self-administer for longer time when cocaine is available continuously for a 24-h "binge." By contrast, aggressive dominant animals stop self-administering cocaine during the continuous access period. These results provide evidence for a complete dissociation between closely similar corticosteroid responses to social stress in dominant resident and submissive intruder animals relative to the divergent changes in cocaine self-administration. Pretreatment with NMDA (MK-801) or mGluR5 (MPEP) receptor antagonists before each aggressive confrontation that resulted in social defeat, significantly attenuated the subsequent expression of behavioral sensitization. Immunoblot analysis detected increased levels of GluR1 expression in the VTA of social defeat-sensitized rats. These data suggest a significant role for glutamate receptors in the enduring effects of social defeat stress, but the interactions between glutamate receptor subtypes have to await further characterization.

2. 5-HT1B Receptor Agonists Lower Corticolimbic Serotonin and Reduce Impulsive Aggressive Behavior

Sara Faccidomo, Makoto Bannai, Eric W Fish, Joe F DeBold and Klaus A Miczek*

Psychology, Tufts University, Medford, MA, USA; Pharmacology, Tufts University, Boston, MA, USA

A significant minority of individuals engages in excessive impulsive aggressive behavior after consuming alcohol. Both excessive alcohol drinking and fighting have been associated with deficiencies in brain serotonin, based primarily on data from low CSF 5-HIAA levels in clinical samples and from deletions of genes that encode for 5-HT receptor subtypes or MAO-A in mice. Novel experimental models have been developed for the study of serotonergic mechanisms that are critical for alcohol-heightened aggressive behavior, particularly involving fighting after alcohol self-administration and concurrent on-line monitoring of serotonin prior, during and after aggressive and drinking bouts. We investigated the apparent paradox of 5-HT1B receptor agonists which potently lower aggressive behavior while also decreasing corticolimbic 5-HT. Separate groups of CFW mice, housed in breeding pairs, followed a protocol that consisted of an initial phase of self-administering alcohol and a second phase of aggressive behavior toward an intruder into their home cage. During Phase One the animals were conditioned to respond on an active operandum in a panel that was inserted into their home cage. Responding was reinforced with a delivery of 50 microliter of 6% alcohol, initially sweetened with sucrose that was gradually faded out. Fifteen min after each animal self-administered 1 g/kg alcohol or water within 2-3 min, it confronted an intruder. The resident-intruder confrontation lasted for 5 min after the first attack. 5-HT receptor agonists (CP 94,253 or anpirtoline) were administered immediately after alcohol self-administration either systemically or microinjected into the prefrontal cortex or into the dorsal raphe n. After the 240 sec microinjection the injector remained in situ for another 60 sec. An additional group of mice were implanted with CMA/7 guide cannulae into the mPFC. One week later, a 1 mm probe was lowered and 10-min samples were collected and analyzed for monoamines. In about one third of the animals, self-administered alcohol (1 g/kg)led to very large increases in aggressive behavior relative to the level of fighting after water consumption. These increases exceeded the 2 standard deviation statistical outlier criterion and allowed categorization of these individuals as "alcohol-heightened aggressors" (AHA). Administration of 5-HT1B agonists reduced aggressive behavior in a dose-dependent manner without altering concurrently measured non-aggressive motor activities. Microinjections of 1 microgram of CP-94,253 into the prefrontal cortex increased aggressive behavior. In vivo microdialysis of mice injected systemically with CP-94,253 showed a modest but significant 20-40% decrease in 5-HT in prefrontal cortex. Importantly, the execution of aggressive behavior in itself led to a decrease in accumbal and prefrontal cortical 5-HT. Since alcohol increases corticolimbic 5-HT, the inhibitory effects of 5-HT1B receptor agonists on aggressive behavior are most likely due to action at post-synaptic receptor sites in limbic structures. Increased aggressive behavior after CP-94,253 into the mPFC may be due to action at presynaptic receptor sites.

3. Interactions between the Reinforcing Effects of Cocaine and Heroin in Rhesus Monkeys: A Dose-addition nalysis

S. S Negus*

Alcohol & Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA, USA

Concurrent abuse of cocaine and heroin is a common form of polydrug abuse, but the interactions between the reinforcing effects of cocaine and heroin are poorly understood. It has been proposed that the reinforcing effects of cocaine and heroin may interact in a synergistic manner, resulting in especially high abuse potential for this drug combination. Dose-addition analysis is a tool for the quantitative assessment of drug interactions that has been useful in other domains of pharmacology; however, this analysis has not been applied to evaluation of the reinforcing effects of cocaine and heroin. Accordingly, the purpose of this study was to evaluate interactions

between the reinforcing effects of cocaine and heroin in rhesus monkeys using dose-addition analysis. Rhesus monkeys (N=4) were trained under a concurrent-choice schedule of food delivery (1 gm pellets) or drug injections. Two monkeys were initially trained to choose between food and cocaine injections (0-0.1 mg/kg/injection), and two other monkeys were initially trained to choose between food and heroin injections (0-0.1 mg/kg/injection). The primary dependent variables were Percent Drug Choice and Response Rate, and an advantage of this choice procedure is that Percent Drug Choice provides a measure of drug reinforcement than is relatively independent of response rates. Initially, full dose-effect curves were determined for cocaine alone and heroin alone in each monkey. Subsequently, full dose-effect curves were determined for two fixed-proportion mixtures of cocaine and heroin (fixed proportions of 1:1 and 3.2:1 cocaine/heroin). Dose-addition analysis was used to assess whether cocaine/heroin interactions were super-additive (i.e. synergistic), additive, or sub-additive. It was hypothesized that interactions would be super-additive. Cocaine, heroin, and both cocaine/heroin mixtures maintained dose-dependent and monotonic increases in drug choice and dose-dependent decreases in response rates. Choice dose-effect curves for cocaine/heroin mixtures were shifted to the left of dose-effect curves for cocaine or heroin alone, but dose-addition analysis indicated that cocaine/heroin interactions on drug choice were only additive. Cocaine/heroin interactions on response-rate measures were additive (1:1 cocaine/heroin) or sub-additive (3.2:1 cocaine/heroin). The effects of cocaine, heroin and the cocaine/heroin mixtures were similar in the cocaine-trained and heroin-trained monkeys. These results confirm that mixtures of cocaine and heroin produce reinforcing effects in rhesus monkeys; however, cocaine/heroin interactions were only additive. Thus, these results do not support the hypothesis that cocaine and heroin produce super-additive or synergistic reinforcing effects. Rather, the effects of adding cocaine to heroin were functionally similar to the effects of adding cocaine to itself or heroin to itself. One implication of these findings is that interactions between the reinforcing effects of cocaine and heroin do not provide a compelling rationale for the use of cocaine/heroin mixtures as opposed to cocaine or heroin alone. However, concurrent use of cocaine and heroin may be favored under conditions when exclusive use of one or the other drug is constrained by either pharmacological or environmental factors. Supported in part by P01-DA14528 and RO1-DA02519 from NIDA/NIH.

4. Aggregation of Multiple Clinical Disorders in Relatives of Alcohol Dependent Probands—Possible Relationship to Single Genes

John I Nurnberger*, Ryan Wiegand, Kathleen Bucholz, Sean O'Connor, Eric T Meyer, Tatiana Foroud, John P Rice, Alison Goate, Marc Schuckit, Lucy King, Theodore Petti, Laura Bierut, Anthony L Hinrichs, Samuel Kuperman, Raymond Crowe, Victor Hesselbrock, Bernice Porjesz, Jay Tischfield, Howard J Edenberg and Henri Begleiter

Psychiatry, Indiana University, Indianapolis, IN, USA

We analyzed data from the family collection of the Collaborative Study on the Genetics of Alcoholism (COGA) in order to quantify familial aggregation of alcohol dependence and related disorders. Diagnostic data were gathered by semi-structured interview (SSAGA), family history, and medical records when possible. Rates of illness were corrected by validating interview and family history reports against senior clinicians' all sources best estimate diagnosis. We included initial assessment diagnostic data from 8296 first-degree relatives of 1269 alcohol dependent probands and 1654 similarly assessed comparison subjects. Risk of alcohol dependence in relatives of probands compared to controls is increased about twofold, the exact prevalence figures depending on the criteria employed. Significant aggregation of ASPD, multiple forms of substance dependence, several anxiety disorders, and major depressive disorders in relatives is also seen, even after controlling for gender, ethnicity, birth cohort/age, ascertainment site, and comorbidity in probands and relatives. This suggests shared vulnerability factors for these disorders and alcohol dependence within some families. New findings regarding specific gene variants associated with alcohol dependence and related phenotypes (e.g. GABRA2 on chromosome 4p, CHRM2 on chromosome 7q) will help elucidate these mechanisms.

5. Efficacy of Disulfiram for Cocaine Abuse in Methadone Patients: Relevance of Dopamine Beta-hydroxylase

Alison Oliveto*, James Poling, Rhonda Pruzinsky, Kishorchandra Gonsai, Joseph Cubells, George Anderson, mehmet Sofuoglu, Kathleen Carroll, Gerardo Gonzalez and Thomas R Kosten

Psychiatry, UAMS, Little Rock, AR, USA; Psychiatry, Yale School of Medicine, New Haven, CT, USA

Sponsor: Thomas Kosten

Disulfiram has shown some efficacy in treating cocaine dependence and inhibits dopamine beta-hydroxylase (DBH), which converts dopamine to norepinephrine. Thus, this 14-wk, double blind, placebo-controlled clinical trial examined the dose-related efficacy of disulfiram in individuals dually opioid and cocaine dependent and the prognostic relevance of DBH activity. Opioid- and cocaine-dependent individuals (N=123; mean age=36.5 yrs; 57% male; 15H/14AA/ 93Cauc/1Other) were inducted onto methadone (wks 1-2) and randomized to receive disulfiram (wks 3-14) at either 0, 62.5, 125, or 250 mg/day. In addition, all participants received weekly 1-hour individual CBT. Thrice-weekly urine samples were tested for the presence of cocaine metabolites. Blood samples were drawn at wk 2 and/or 6 to assess DBH enzyme activity. At the end the study, participants were tapered off study medications over a 4-wk period. Medication groups generally did not differ on subject characteristics or retention. The proportion of cocaine-positive urines was significantly greater overall and increased over time in patients with minimal DBH activity relative to those with low to normal DBH activity ($p<0.00001$). Cocaine-positive urines increased over time in the 62.5 and 125 disulfiram groups and decreased over time in the 250 disulfiram and placebo groups ($p < 0.00001$). These results suggest that 1) patients with minimal DBH activity may have a greater severity of cocaine dependence that is more resistant to treatment, 2) disulfiram at doses lower than 250 mg/day may exacerbate cocaine use, and 3) disulfiram at doses higher than 250 mg/day may be necessary to facilitate cocaine abstinence.

6. Comorbid Psychopatic Traits in Spanish Male Alcoholic Patients are Associated to the Additive Effect of Allelic Forms of the *DRD2*, *CNR1*, and *FAAH* Genes

Tomas Palomo*, Janet Hoenicka, Guillermo Ponce, Israel Ampuero, Roberto Rodriguez-Jimenez, Gabriel Rubio, Maria Aragues, Jose A Ramos and Miguel A Jimenez-Arriero

Servicio de Psiquiatria, Hospital Universitario 12 Octubre, Madrid, Madrid, Spain

Sponsor: Peter Kalivas

Alcoholism and Antisocial Personality Disorder (ASPD) are psychiatric diseases with high genetic load. Research on clinical population supports there is a frequent co-occurrence of the two disorders although little is known about the factors that underlie this comorbidity. A common malfunctioning central aminergic system had provided a link between antisocial traits and the observed increased vulnerability to develop addictive behaviours, specifically, alcohol use disorder. Because of that, we studied in a sample of Spanish male alcoholic patients the presence of ASPD, psychopathic traits and some candidate genes related to the mesolimbic dopaminergic system, a

key system involved in reward processes and the reinforcing effect of abuse drugs. The study included 137 alcohol dependent males recruited from the *Hospital 12 de Octubre*, Madrid, Spain and 98 control individuals free of psychiatry disorders. The patients were defined according to DSM- IV criteria. A diagnosis of ASPD was made by applying the International Personality Disorder Examination and the psychopathic traits were evaluated in the patients by the Hare Psychopathy Checklist revised. The genetic analysis was performed using Polymerase Chain Reaction methods to amplify the following polymorphisms: the Single Nucleotide Polymorphism (SNP) *Taq*IA of the dopamine receptor D2 gene (*DRD2)*, the SNP C385A of the gene that codes for the fatty acid amide hydrolase (*FAAH*), the SNP A118G of the mu-opioid receptor gene (*HMOR1)*, the 10-repeat allele of a variable number tandem repeat (VNTR) of the dopamine transporter gene (*DAT1*) and the 3-UTR microsatellite of the CB1 receptor gene (*CNR1*). We found a relationship between *DRD2* (OR=2.333 CI: 1.07-5.09; p=0.033) and *FAAH* (OR=2.375 CI: 1.04-5.4; p=0.039) genes and antisocial personality disorder diagnosis in our patients. With regard to the evaluation of psycopathic traits, a significant relationship was unveiled between the factor 1 of the PCL-R and *DRD2* (t135=2.192; p=0.031), *FAAH* (t135=2.356; p=0.013) and *CNR1* (t135=2.216; p=0.029) genes. The above genetic associations were observed neither for the factor 2 of the PCL-R nor for the total score in the PCL-R scale. This relationship seems to be additive and independent and might be responsible for 11.4% of the variance in this PCL-R subscale in our sample. The finding of an association between specific genes related to the dopaminergic and cannabinoid systems and ASPD and psycopathic traits suggests the possible implication of the dopaminergic and endocannabinoid systems in those processes leading to the comorbidity of alcoholism and antisocial behaviour. These genes occupy a relevant position in the reward cerebral system function that has been supposed to be the basis of the changes that would determine both, the vulnerability to addictions and the development of psychopaty traits. Currently, we are extending our analysis in patients and control individuals and we are genotyping other *DRD2 g*ene polymorphisms, among them, the functional SNPs C957T and G1101A that could affect striatal dopaminergic receptor D2 availability. The replication of the relationship between ASPD/psychopathic traits and these additional *DRD2 S*NPs, could help us to identify the relevant *DRD2* variant that is related to the comorbidity of alcoholism and ASPD.

7. Accumbal Neural Activity during Repeated Cocane Self-Administration Sessions: Evidence for the Differential Neuroplasticity and Differential Hypoactivity Hypotheses of Drug Addiction

Laura L Peoples* and Daniel J Cavanaugh

Psychology, University of Pennsylvania, Philadelphia, PA, USA

It is proposed that drug-induced neuroadaptations within the accumbens contribute to drug addiction. Given that the accumbens influences multiple reward-directed behaviors, it is necessary to ask how adaptations in such a region might contribute to a disorder that is characterized by a selective increase in drug-directed behavior. One possible answer to this question is that at least some neuroadaptations critical to the development of addiction are activity dependent and thus occur differentially amongst neurons that are differentially activated in relation to drug self-administration (JD Berke and SE Hyman, Neuron, 25, 515-532, 2000). Based on several lines of evidence we hypothesized that, at least for cocaine, this differential neuroplasticity includes a differential drug-induced hypoactivity. Specifically, it was proposed that neurons that are excited in relation to drug self-administration events are less susceptible to the lasting inhibitory effects of repeated drug exposure than are neurons that are not activated in relation to self-administration events. (LL Peoples and DJ Cavanaugh, J Neurophysiology 90:993-1010, 2003; LL Peoples et al., J Neurophysiology 91:314-323, 2004). The present experiment used chronic electrophysiological techniques in animals self-administering cocaine (daily 6-hr sessions; Fixed-Ratio 1 schedule of cocaine reinforcement) to test whether we could observe changes in accumbal neural activity consistent with an activity-dependent pattern of neuroplasticity. Moreover, we tested the hypothesis that the differential neuroplasticity may include a differential drug-induced hypoactivity. Neurons were sorted into two categories, those that showed an excitatory response to one or more self-administration-related event (Excitatory neurons) and neurons that showed no such excitatory response (Non-Excitatory neurons). Across a 30-day period, the average basal firing rate of the Excitatory neurons showed a non-significant increase. However, the average basal firing rate of the Non-Excitatory neurons showed a significant decrease. A comparable differential pattern of change was observed for firing rates during the drug self-administration session. The differential changes in firing were associated with an increase in the ratio between the average firing rates of the Excitatory neurons and the average firing rates of the Non-Excitatory neurons. These findings are consistent with the proposal that accumbal neurons may undergo activity-dependent neuroadaptations, and that the differential neuroplasticity includes differential drug-induced hypoactivity. The differential changes in firing are expected to be associated with a relative increase in the impact of drug-reward-related signals on thalamo-cortical circuits, and hence response selection. Such changes in signaling could contribute to the differential changes in drug- and non-drug reward-related behavior that define drug-addiction. Research supported by DA06886, DA05186, and DA13401.

8. Parietal-Occipital Cortical NAA Deficits in HIV-Infected Men Comorbid for Alcoholism

Adolf Pfefferbaum*, Elfar Adalsteinsson and Edith V Sullivan

Neuroscience Program, SRI International, Menlo Park, CA, USA; Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

Alcoholism comorbidity is highly prevalent in individuals infected with human immunodeficiency virus (HIV). Each condition is known to affect brain structure, function, and metabolism, but the combined effects on the brain have only recently been considered. Single-voxel, proton MR spectroscopy (MRS) has proved to be a sensitive index of early brain deterioration in the progression of HIV: Early in the disease, basal ganglia are affected and show evidence of gliosis and cell membrane turnover, whereas in later stages, marked by AIDS-dementia, neuronal integrity, indexed by the N-acetylaspartate (NAA)/creatine ratio, shows signs of compromise, especially in frontal cortex and subjacent white matter. Here, we used variable density spiral MRS imaging to quantify major proton metabolites, NAA, creatine, and choline, in the superior parietal-occipital cortex. This cortical region is difficult to image in the single-voxel mode and may be a site of early pathology in cases of HIV-alcoholism comorbidity, given the known frontoparietal circuitry that can be disrupted in either disease. In addition, the measured metabolites were expressed in absolute units rather than as ratios, an approach that could increase the sensitivity of the NAA measure if both NAA and creatine were low in a disease state. Metabolite levels were transformed to age-corrected Z-scores to account for the effects of aging. Subjects were 14 men with HIV alcoholism (9 taking HAART), 10 men with HIV alone (7 taking HAART), 7 men with alcoholism alone, and 24 healthy, age-matched controls. The two HIV groups were matched in T-cell count and performance on several cognitive and motor tests and were not demented; the two alcoholism groups were matched in total lifetime alcohol consumption. Analysis of the metabolites revealed significant group effects for NAA and creatine. Only the HIV alcoholism group was significantly affected, exhibiting a 0.8 standard deviation deficit in NAA and a 1.1 standard deviation deficit in creatine. The deficits were not related to HAART status. Neither HIV infection nor alcoholism alone resulted in posterior cortical

metabolite abnormalities, yet each disease appears to carry a liability that puts affected individuals at a heightened risk of neuronal compromise when the diseases are compounded. Further, the use of absolute measures revealed deficits in both NAA and creatine that would have gone undetected if the NAA/creatine ratio were used. [Support: AA12388, AA12999, AA05965, AA10723]

9. Gambling and Treatment Outcome in Dually Diagnosed Alcohol Dependent Patients

Marc N Potenza*, Carolyn Levinson, James Poling, Charla Nich, Kathleen Carroll, Bruce J Rounsaville and Ismene Petrakis

Psychiatry, Yale University, New Haven, CT, USA

Background: Although high rates of pathological gambling (PG) have been observed in association with alcohol dependence and other psychiatric disorders, treatment trials for alcohol dependence have generally not included assessments of gambling pathology. **Methods:** 177 subjects with alcohol dependence and a co-occurring, non-gambling psychiatric disorder participated in a placebo-controlled trial of naltrexone and disulfiram and were assessed for DSM-IV symptoms of PG. **Results:** 11 patients (6.2%) met past-year criteria for PG. 45 patients (25.4%) reported at least one past-year symptom and were designated "at-risk" (RG+). RG+ as compared with RG- patients were more likely to be employed full-time ($p<0.01$) and have cocaine dependence ($p=0.04$). Significant ($p<0.05$) gambling-group-by-time-interactions were seen for drinking-days/week and multiple psychiatric measures (anxiety, phobic anxiety, somatization, paranoid ideation and interpersonal sensitivity). In all cases, RG+ status was associated with less improvement. A gambling-group-by-disulfiram-group interaction was observed for alcohol abstinence, with disulfiram appearing less effective in the RG+ group. **Conclusion:** At-risk/problem gambling behaviors appear associated with poorer psychiatric and alcohol outcomes in a controlled treatment trial of dually diagnosed alcohol dependent patients. Future clinical trials should assess gambling and identify mechanisms underlying poorer treatment outcome associated with gambling problems.

10. Neurotensin Receptor Subtype 1 Null Mice are Hyperactive and More Sensitive To D-Amphetamine

Mona Boules, Paul Fredrickson, Katrina Williams and Elliott Richelson*

Psychiatry, Mayo Clinic, Jacksonville, FL, USA

Controversy has existed on the exact role neurotensin plays in schizophrenia and psychostimulant abuse. Prior studies have relied largely on inferences drawn from observing effects of neurotensin receptor agonists and antagonists. The locomotor effects of acute and repeated (sensitizing) injections of D-amphetamine were tested in neurotensin receptor subtype 1 knockout and wild-type mice. Neurotensin receptor subtype 1 (NTS1) null mice showed higher baseline locomotor activity, an increased sensitivity to acute D-amphetamine, and an enhanced response to the sensitizing effects of D-amphetamine, as compared to wild-type mice. Consistent with our studies of a neurotensin receptor agonist and contrary to studies with a neurotensin receptor antagonist, mice lacking NTS1 showed sensitization to D-amphetamine, which was enhanced compared to that seen in wild-type mice. The potential use of a neurotensin agonist, not an antagonist, for the treatment of schizophrenia and psychostimulant abuse is supported by these data.

11. Substituted Amphetamines Increase the Concentration of Free Serotonin in the Bloodstream of Conscious Rats

Richard Rothman*, Robert D Clark and Michael H Baumann

Clinical Psychopharmacology Section, IRP, NIDA, NIH, Baltimore, MD, USA

Under normal circumstances, plasma serotonin (5-HT) levels are kept low due to transporter-mediated 5-HT uptake into blood platelets and lung endothelium, and by 5-HT metabolism by MAO. Elevations in plasma 5-HT concentrations have been implicated in the etiology of serious medical conditions including pulmonary hypertension and cardiac valvulopathy. Surprisingly few studies have examined the effects of amphetamine-type monoamine-releasing agents on plasma 5-HT in intact animals or humans. In the present study, we determined the effects of the substituted amphetamines (+)-fenfluramine, (+/-)-3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and (+)-methamphetamine, on free 5-HT levels in rat blood. We suspected that amphetamines would increase plasma 5-HT levels via a mechanism dependent upon 5-HT transporters (SERTs). Male Sprague-Dawley rats were fitted with indwelling jugular catheters and allowed one week to recover. Rats received i.v. injections of saline or test drugs (0.1-1.0 mg/kg), and serial blood samples were withdrawn into chilled tubes. Blood samples were immediately dialysed ex vivo, and dialysate samples were assayed for 5-HT using HPLC-ECD. All of the amphetamines tested in this study elicited elevations in 5-HT levels that reached 10-fold above baseline. Our data suggest that amphetamines increase circulating 5-HT via SERT-mediated processes. However, additional studies will be required to: 1) determine the specificity of this effect for SERT substrates, and 2) examine whether plasma 5-HT is persistently elevated by chronic drug administration.

12. Comparison of Zolpidem and Midazolam Self-Administration under a Progressive-Ratio Schedule: Labor Supply Analysis

James K Rowlett* and Snjezana Lelas

New England Primate Research Center, Harvard Medical School, Southborough, MA, USA

Sponsor: Roland Griffiths

Zolpidem is a sedative/hypnotic drug that binds preferentially to GABA-A receptors containing alpha-1 subunits. Previous findings using self-administration procedures in monkeys suggest that zolpidem is a robust reinforcer. We compared the reinforcing effects of zolpidem to midazolam, a non-selective BZ with similar pharmacokinetics to zolpidem, using a behavioral economic model called "labor supply". Four rhesus monkeys were prepared with i.v. catheters and trained under a progressive ratio (PR) schedule of i.v. methohexital injection. After establishing dose-response functions for zolpidem (0.003-0.1 mg/kg/injection) and midazolam (0.03-1.0 mg/kg/injection), doses of the two compounds that maintained peak injections/session were made available with initial response requirements (IRRs) increasing from 10 to 160. The results were analyzed according to the labor supply model, which quantitatively evaluates the relationship between labor (total responses/session) and income (injections/session). For both zolpidem and midazolam, increasing the IRR resulted in a reduction in income, whereas labor initially increased and then declined as a function of IRR. At all IRRs, income and labor after zolpidem availability were reliably higher compared to midazolam availability. The reduction in income induced by increasing IRRs was less pronounced for zolpidem compared to midazolam, i.e., the labor-income relationship was reliably more "inelastic" for zolpidem compared to midazolam. Altogether, these results suggest that zolpidem has greater relative reinforcing effectiveness than midazolam, and that alpha-1 containing GABA-A receptors may play an important role in self-administration of BZ agonists. Supported by DA11792 and RR00168.

13. Stress-Induced Cocaine Craving and Associated Arousal Predicts Cocaine Relapse After Inpatient Cocaine Treatment

Rajita Sinha*, Miguel Garcia, Robert M Malison and Mary Jeanne Kreek

Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Sponsor: Mary Jeanne Kreek

Stress is thought to be one of the key factors that increase the risk of relapse in drug dependent individuals. In previous research we

have shown that laboratory induction of emotional stress increases cocaine craving and neurobiological indices of stress. However, whether these measures are significant correlated with measures of cocaine relapse has not been previously studied. Fifty-four treatment seeking, cocaine dependent individuals involved in inpatient treatment also participated in laboratory sessions examining subjective and biological responses to stress, drug cue and neutral imagery exposure. After discharge from inpatient treatment, subjects were followed for 90 days to assess subsequent drug use and relapse status. Results indicated that laboratory stress-induced cocaine craving was significantly associated with time to cocaine relapse in the follow-up phase ($p<.001$). Individuals with high stress induced cocaine craving were likely to relapse more quickly as compared to those with low levels of stress-induced cocaine craving. In addition, increases in heart rate, plasma ACTH and cortisol during stress exposure relative to neutral exposure was also associated with drug use in the follow-up phase. These findings suggest that stress related drug craving and associated alterations in stress system arousal are associated with an increased vulnerability to cocaine relapse in drug dependent individuals. Implications of these findings for the development of pharmacological and psychosocial treatments that target stress regulation are discussed. (Supported by ROIDA1107 (RS), P50-DA16556 (RS) to Yale University and P60-DA05130 (MJK) to Rockefeller University).

14. Short and Long Term Access to Cocaine Self-administration in Rats: Effects on the Reinstatement of Cocaine-seeking Behavior

Ronald E See*, Tod Kippin, Rita A Fuchs and Jordan M Case

Physiology and Neuroscience, Medical University of South Carolina, Charleston, SC, USA

Previous evidence suggests that prolonged access to cocaine self-administration in rats leads to an escalation of daily cocaine intake, and this has been proposed as a model of the transition from drug abuse to drug dependence. While most research has focused on the escalation of cocaine self-administration, there has been limited examination of the effects of prolonged access on the reinstatement of extinguished cocaine-seeking behavior. In the current study, male rats were trained to self-administer cocaine (0.2 mg/0.05 ml/infusion, i.v.) on an FR1 schedule of reinforcement during 10 daily 1-hr sessions. After the acquisition of cocaine self-administration, the subjects were divided into three self-administration maintenance groups: 1 hr short access (SAc), 6 hr long access (LAc), or noncontingent long access cocaine (1 hr of self-administration followed by 5 hr of yoked cocaine administration). Cocaine was available under these access conditions during an additional 14 daily sessions (i.e., maintenance phase). Subsequently, all animals underwent daily 2-hr extinction sessions, during which no drug or stimuli were presented. Reinstatement of cocaine seeking (i.e., nonreinforced responses on the previously cocaine-paired lever) was then assessed in the response contingent presence of a light+tone stimulus complex paired previously with cocaine infusions (conditioned-cued reinstatement) or following a single cocaine priming injection (7.5 mg/kg, IP). During the first hr of the maintenance phase, the group that received yoked cocaine subsequently showed lower rates of lever responding for cocaine reinforcement in comparison to the SAc and LAc groups. All three groups showed significant conditioned-cued reinstatement of cocaine seeking relative to extinction, but the LAc group exhibited slightly higher rates of responding than the other two groups. Furthermore, the LAc group displayed a significantly higher level of cocaine-primed reinstatement of cocaine seeking relative to the other two groups. These findings suggest that prolonged response-contingent access to cocaine may enhance the propensity for reinstatement of drug-seeking behavior and this is related to the reinforcing as opposed to the pharmacological effects of chronic cocaine self-administration. (Supported by NIH grant DA10462)

15. NIDA's Division of Basic Neuroscience and Behavioral Research: Overview of Current Directions and Future Research Opportunities

David Shurtleff* and Glen Hanson

Division of Basic Neuroscience and Behavioral Research, NIDA/NIH/DHHS, Bethesda, MD, USA

Sponsor: Glen Hanson

The Division of Basic Neuroscience and Behavioral Research (DBNBR) is one of four extramural research divisions within the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH). The division comprises four branches: Behavioral and Cognitive Science Research Branch, Functional Neuroscience Research Branch, Chemistry and Physiological Systems Research Branch, and the Genetics and Molecular Neurobiology Research Branch. DBNBR supported research focuses on the neurobiological mechanisms of addiction, genetic factors in drug abuse and addiction, acute and chronic effects of drugs on behavior and cognition, and drug metabolism. A broad array of effects of all major licit and illicit drug groups with abuse potential, including stimulants (e.g. cocaine and methamphetamine), opioid narcotics (e.g. heroin), depressant sedative/hypnotics (e.g., benzodiazepines) hallucinogens (e.g. LSD and methylenedioxymethamphetamine) and others (e.g. anabolic steroids) are studied across multiple levels of analysis. Supported research includes the study of: (i) mechanisms and regulation of neural pathways and brain structures that mediate drug abuse and addiction; (ii) pharmacokinetics and pharmacodynamics,(iii) cell biology that focuses on mechanisms of drug-induced neuro-toxicity, membrane and protein trafficking, signal transduction pathways, protein-protein interactions, protein complex formation, synaptic vesicle formation and regulation, and ion movements; (iv) molecular genetics and gene expression; (v) genetic model organisms, QTL-based responses, and pharmacogenetics and (vi) critical developmental factors that contribute to addiction vulnerability and its long-term expression. Basic research concerned with understanding the complex interrelationship between HIV/AIDS progression and transmission and drug abuse is also supported. DBNBR funds both human laboratory-based and animal-model experimental research to examine neurobiological, behavioral and cognitive factors associated with drug addiction. Overall, the research supported by DBNBR provides fundamental information for understanding the causes and consequences of drug abuse in order to develop new, effective treatment and prevention interventions for this disorder. An overview of the division's portfolio, initiatives, and research gaps and opportunities will be presented.

16. Reversal of Morphine Tolerant Mice to an Acute Morphine State by the Acute Injection of PKC and PKA Inhibitors

Forrest L Smith*, Ruby Javed, George Dalton and Williwm L Dewey

Pharmacology & Toxicology, Va. Commonwealth University, Richmmond, VA, USA

Sponsor: Louis S. Harris

In every study in which opioid antinociceptive tolerance was prevented or reversed the animals were challenged with opioid on the test day. However, the exogenously administered opioid could mask the ability of these PKC and PKA inhibitors to reverse tolerance to other behavioral and physiological effects of opioids. For the current studies, mice were tested in two tests of heat nocicpetion, as well as for Straub tail and hypothermia 3-h and 72-h after implantation of placebo or morphine pellets. At 3-h, significant antinociception occurred in the tail-withdrawal and hot-plate tests, as well as Straub tail and hypothermia. An acute morphine does of 16 mg/kg, s.c. elecited a smilar behavioral response in drug naive animals. By 72-h after pellet implantation these signs disappeared, indicating the development of

tolerance. Other mice were tested at 72-h following intracerebroventricular (i.c.v.) administration of vehicle, PKC and PKA inhibitors. The PKC inhibitors bisindolylmaleimide I and Go-7874 reverted the morphine tolerant mice into an acute morphine state whereby they exhibited significant antinociception, Straub tail and hypothermia. The PKA inhibitors KT-5720 and 4-cyano-3-methylisoquinoline acted in a similar manner. Thus, morphine tolerant mice after PKC and PKA inhibitor administration exhibited the same behaviors as non-tolerant mice acutely exposed to morphine. Previous studies have shown that the level of morphine in the brain 72-h after pellet implantation is comparable to an acute dose that is equally active in these tests. These results showing that tolerance to morphine analgesia can be reversed have potential important clinical implications. Supported by USPHS Grants DA01647, KO5 DA00480 and T32 DA07027.

17. Dependence prior to, but not Subsequent to, Stimulus-Drug Conditioning Increases Drug Seeking During Protracted Morphine Withdrawal

Gary Aston-Jones, Rachel J Smith* and Glenda C Harris

Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Drug dependence and protracted withdrawal cause long-lasting changes in the brain and impact subsequent drug-seeking. Previously, our lab found that rats made dependent on morphine for two weeks via subcutaneous pellet implantation show an enhanced conditioned place preference (CPP) for morphine as compared to naïve animals when conditioned two weeks after withdrawal (Harris and Aston-Jones, Neuropsychopharm 24, 75-85, 2001). To determine if the expression of enhanced preference is due, in part, to the sequence of dependence and conditioning, here animals were conditioned prior to dependence and then tested for CPP during protracted withdrawal. Animals made dependent after morphine conditioning (n=14) did not show enhanced CPP as compared to non-dependent animals (n=14) when tested at three weeks post-withdrawal. When these same animals were re-conditioned and tested at six weeks post-withdrawal, previously dependent animals exhibited significantly enhanced morphine preference (n=8, $p<0.05$). These results indicate that dependence changes the experience of subsequent drug exposure. We propose that enhanced preference may result when conditioning follows dependence because of compensatory changes in the brain caused by excessive drug exposure. These data indicate that stimulus-drug conditioning subsequent to dependence and withdrawal is a critical factor for the increased drug seeking that characterizes protracted withdrawal. Supported by PHS grants DA06214 and T32-GM007517.

18. Striatal Volume Deficits in Alcoholism with and without Korsakoff's Syndrome

Edith V Sullivan*, Anjali Deshmukh, Eve De Rosa, Margaret J Rosenbloom and Adolf Pfefferbaum

Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

Sponsor: Adolf Pfefferbaum

Structures of the striatum harbor candidate cerebral mechanisms of drug and alcohol reward. Numerous animal and human studies implicate these dopaminergically rich sites in the reinforcing effects of alcoholism. For example, a recent functional MRI study revealed that strong activation of the ventral putamen in abstinent alcoholics predicted relapse over the following three months. Positron emission tomography metabolic and ligand studies also provide convincing support for the role of striatal dopamine, especially in nucleus accumbens, in responsivity to alcohol. Despite the likely role of the striatal structures in the development and maintenance of alcohol dependence and the known damaging effect that chronic alcoholism has on many brain structures, few in vivo studies have measured volumes of striatal structures in chronic alcoholics. One of the few published reports identified volume deficits of the caudate nucleus in individuals with fetal alcohol syndrome (FAS), but FAS differs in many respects from classic, self-induced alcoholism. Even though neuropathological studies of brains of adult alcoholics have reported a lack of volume loss in caudate, putamen, and globus pallidus, a recent retrospective study of ischemic stroke indicated a disproportionately high incidence of putaminal infarct in patients diagnosed with alcohol use disorder compared with social drinkers, suggesting a vulnerability of the putamen to alcoholism. Further, some in vivo brain volume deficits elude autopsy study because of myriad postmortem changes. Here, we acquired high resolution MRI to measure volumes of the putamen, caudate nucleus, and nucleus accumbens and a neighboring subcortical comparison structure, the cholinergically-rich medial septum/diagonal band (MS/DB). The subjects were 25 alcoholic men, 6 men with alcoholic Korsakoff's syndrome (KS), and 51 healthy men. The KS patients served as pathological controls, assuming that volume deficits, if present, would be particularly severe in this group. Structures were manually outlined; volumes were corrected for normal variation in intracranial volume and age, expressed as standardized Z-scores, and tested with 2-tailed, nonparametric statistics. Both the alcoholic and the KS groups had significant volume deficits in the left and the right caudate nucleus and putamen ($p<.03$ to .003). Both alcoholic groups showed a trend deficit for the MS/DB ($p<.08$). The nonamnesic alcoholic group also showed a trend towards a deficit in the nucleus accumbens ($p<.10$). On average, the caudate and putamen volume deficits ranged from ~.8 to 1.1 standard deviation in both alcoholic groups, indicating striatal shrinkage commonly overlooked in chronic alcoholism. Such dysmorphology in these dopaminergic structures should be taken into account in functional imaging studies. Further, the shrinkage in the MS/DB may contribute to the amnesic syndrome characteristic of patients with KS. [Support: AA12388, AA12999, AA05965, AA10723]

19. Delineation of a Role for Long Homer Isoforms in the Expression of Cocaine-induced Neural Plasticity

Karen K Szumlinski*, Kenneth E Abernathy, Erik B Oleson, Kevin D Lominac, Matthias Klugmann, Simone Buckman, Matthew T During and Peter W Kalivas

Physiology and Neuroscience, Medical University of South Carolina, Charleston, SC, USA

Sponsor: Travel Awardee, BMS, 2004

A down-regulation of long Homer protein isoforms in the nucleus accumbens is implicated in mediating the long-term behavioural and neurochemical consequences of repeated cocaine exposure. To address this hypothesis, an adeno-associated virus (AAV) strategy was employed to up-regulate Homer protein expression in the nucleus accumbens of rats following repeated cocaine treatment. Cocaine-induced changes in behaviour and extracellular glutamate were assessed at 3 weeks withdrawal. AAV-mediated over-expression of the long Homer isoforms Homer1c and Homer2b reversed the cocaine-induced reduction in basal extracellular glutamate in the nucleus accumbens and prevented the expression of locomotor and glutamate sensitization in response to a cocaine challenge. In contrast, AAV-mediated over-expression of the truncated, IEG product of the Homer1 gene Homer1a produced no observable effect upon sensitized behaviour or accumbens glutamate. The observed effects of long Homer isoform expression upon cocaine sensitization depended upon cocaine treatment, as AAV-mediated over-expression of Homer2b prior to repeated cocaine administration did not influence the development of cocaine locomotor sensitization. These data provide compelling evidence that the down-regulation of long Homer protein isoforms by withdrawal from repeated cocaine is a necessary

molecular event contributing to certain long-term neural consequences of repeated cocaine exposure.

20. Activator Protein 1 Acts as a Activator of the N-Methyl-D-aspartate Receptor 2B Subunit Gene in Basal and Ethanol-induced Gene Expression

Maharaj K Ticku*

Pharmacology, UTHSCSA, San Antonio, TX, USA

Activator protein 1 (AP1) has been reported to regulate the gene expression in a variety of cells in response to a stimulus. However, its role in regulating on the N-Methyl-D-aspartate receptor 2B subunit (NR2B) gene is still not understood. In this study, we investigated the DNA-binding activities of AP-1 proteins in normal and following ethanol treatment. Five constructs from 5'flanking region of the NR2B gene extended from -5319 to 30 relative to the reported transcription start site of the mouse NR2B gene were prepared by PCR. Functional analysis of these constructs by transient transfection of neurons revealed that the highest level of activity (approximately 48-fold increase over pGL3-Basic control) was observed with the construct -1224bp. There is an AP-1 binding motif (TGACTAA) in this region. The identity of AP-1 as the functional binding factor is suggested by the specific binding of cell lysate derived from primary cultured cortical neurons to the labeled probes and the specific antibody-induced supershift. The Bands of complexes were supershifted by addition of antibody to c-FOS and c-Jun. Mutations of two nucleotides in the core sequences resulted in significantly reducing promoter activity, and on EMSA, abolished the ability of the mutated probes to compete with the wild type DNA. Treatment of cultured cortical neuron with 100_M ethanol for 5 days caused a significant increase in the NRSF/NRSE binding activity. Therefore, our study suggests that AP-1 is an active regulator of NR2B expression and may contribute to the ethanol-induced up-regulation of the NR2B gene.
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21. Hepatitis C in Treatment Seeking Alcoholics: A Comparison of High-risk Behaviors and Biologic Markers in Cohorts with and without Cocaine Dependence

Carlos Tirado*, David Oslin, Helen Pettinati, Kyle Kampman and Joseph Volpicelli

University of Pennsylvania, Philadelphia, PA, USA

Sponsor: Travel Awardee, PMRTP, 2004

Hepatitis C (HCV) is the most common blood borne infection in the United States. HCV is also the leading cause of chronic liver disease and cirrhosis. Population based studies have shown that persons with HCV and co-morbid alcoholism have rates of cirrhosis, and hepatocellular carcinoma far higher than populations with either diagnosis alone. HCV and alcoholism are therefore thought to relate synergistically in predicting poor clinical outcomes. Although alcoholism is not considered an independent risk factor for HCV, persons with alcoholism have higher lifetime rates of drug use and high-risk sexual behavior, which are associated with HCV infection. Since HCV does not cause clinically significant illness until the second or third decade of infection, persons seeking treatment for alcoholism may present without clinically significant hepatic illness and a distant history of high-risk behaviors. Chronic elevations in serum transaminases are seen in approximately 70% of persons with sub clinical HCV infection. It is unknown whether sub clinical HCV infection in persons with alcoholism has a significant effect on the interpretation of biomarkers for alcohol consumption. This study was conducted to examine the prevalence of HCV infection, risk factors for HCV infection and the effect of HCV infection on biologic markers typically used for assessing alcohol dependence in a treatment seeking population. Results are presented for 345 subjects who were enrolled in either a treatment study for patients with alcohol dependence in the absence of cocaine dependence (n=212) or in a study of alcohol and cocaine dependence (n=133). Both studies excluded patients with other illicit drug dependence and are designed to test the efficacy of naltrexone. Among alcohol dependent only patients 12.3% presented with HCV infection whereas in alcohol and cocaine dependence 21.1% were infected (p=0.029). Lifetime use of cocaine was higher in the current cocaine dependent group (p<0.001). However, the lifetime use of injected drugs (overall 16.7%), ever having a blood transfusion (overall 20.1%), and having more than 3 sexual partners (overall 87.5%) were not different in the two study populations. Liver dysfunction was assessed using transaminase levels (GGT, AST, or ALT) and assessment of the presence of Carbohydrate Deficient Transferrin (CDT). In patients with HCV infection, the average transaminase value and the percentage of subjects with an elevated level was significantly greater than in subjects without HCV infection. The effect on CDT values was less apparent and in the opposite direction with mean CDT levels lower in those with HCV infection. The linear increase in transaminase and CDT levels with increasing levels of drinking was preserved with all 4 measures. These data emphasize the importance of evaluating HCV infection in alcohol dependent populations. In treatment seeking alcoholics with and without cocaine dependence, the rate of HCV infection was roughly 8 times the general population rate. A substantial percentage of treatment seeking alcoholics engaged in high-risk behaviors for HCV infection. Moreover, the data raise questions regarding the use of transaminase levels and CDT as biologic markers of alcohol use in patients when HCV status is unknown. These data suggest that knowledge of HCV status may be important to prevent misinterpretation of transaminase levels as markers of alcohol consumption. It is unclear if chronic HCV infection has an effect on transaminase or CDT levels following a period of abstinence.

22. Naltrexone and 6-beta-naltrexol Differ in Ability to Exert Aversive Effects during Acute Morphine Dependence

Alice M Young*, Awanti Deshmukh, Evelena Muhammad and Brandi Walker

Pharmacology & Neuroscience, Texas Tech University Health Sciences Center, Lubbock, TX, USA; Psychology, Texas Tech University, Lubbock, TX, USA

The multiple effects of precipitated opioid withdrawal include subjective or stimulus effects that are perceived as aversive by humans and other species. The place aversion procedure in rats provides a useful animal model for studies of the biological bases of such aversive effects. In rats, work from several laboratories has established that naloxone-precipitated withdrawal from both chronic and acute morphine dependence supports rapid conditional place aversion learning. Pharmacological studies have shown that the strength of such aversion varies as a direct function of the doses of both morphine and naloxone, and as a function of the time between morphine and naloxone treatment. The present experiment examined the place aversion established by two additional opioid antagonists in male Sprague-Dawley rats (N=122) treated acutely with morphine (5.6 or 10 mg/kg SC, -4 h, with a maximum of four exposures separated by at least 48 h). Naltrexone, a second classical opioid antagonist, and 6-beta-naltrexol, a putative neutral antagonist, were studied at doses able to exert at least a 3 to 10-fold-antagonism of the acute behavioral effects of morphine. Neither antagonist evoked aversion 4 h after saline treatment. After 5.6 mg/kg morphine treatment, 0.32 mg/kg naltrexone evoked substantial place aversion, whereas 0.1 mg/kg naltrexone did not. When the dose of morphine was increased to 10 mg/kg, both doses of naltrexone produced substantial aversion. In all cases, the aversion elicited by naltrexone following morphine pretreatment was susceptible to extinction. In contrast to the effects of naltrexone, doses of 1.0 and 3.2 mg/kg 6-beta-naltrexol, which are capable of exerting equivalent antagonism of the agonist effects of morphine, did not evoke aversion following treatment with either 5.6 or

10 mg/kg morphine. Taken together, these results suggest that the aversive effects of naltrexone in acutely dependent rats may arise from actions that are not shared by 6-beta-naltrexol. On the basis of work from other laboratories that suggests that 6-beta-naltrexol may lack the inverse agonist effects exerted by naltrexone, we suggest that these differences in aversive effects may arise from differences in inverse agonist actions. (Supported by DA-03796.)

23. Responses to D-amphetamine in Humans Related to a Polymorphism in the BDNF Gene

Brody Flanagan, Edwin Cook and Harriet De Wit*

Psychiatry, University of Chicago, Chicago, IL, USA

Responses to stimulants like d-amphetamine (AMP) vary across individuals (de Wit et al., 1986; Mattay et al., 2000), perhaps because of genetic variations that interact with the effects of AMP (Lott et al, 2003; Mattay et al., 2003). In this analysis we examined a common valine to methionine missense mutation (val66met) in the gene encoding brain-derived neurotrophic factor (BDNF) in relation to acute responses to AMP in healthy volunteers. Preclinical studies suggest that BDNF plays a role in mediating the acute effects of stimulant drugs (Guillin et al., 2001; Horger et al., 1999; Meredith et al., 2002; Lu et al., 2004; Thomas et al., 2004). In humans, the BDNF val66met polymorphism studied here has been shown to be associated with obsessive-compulsive disorder (OCD), mood disorders, and memory and hippocampal function (Hall et al., 2003; Green and Craddock, 2003; Hariri et al., 2003). We hypothesized that subjects with the val/val genotype would exhibit greater behavioral and subjective response to AMP than heterozygous or met/met subjects. Healthy volunteers (n=100) received either placebo or oral AMP (10, 20 mg) on three separate occasions and completed subjective ratings over 3 hours. The effects of AMP on heart rate and self-ratings of Arousal (POMS) and BG (ARCI) were greater in subjects who were homozygous for the val allele compared to the other groups. This suggests that BDNF plays a role in the acute behavioral effects of AMP in humans.

24. A Voxelwise Study of White Matter Integrity and Neurocognitive Function in Patients with Schizophrenia

Kelvin Lim*, Isaac Schechter, Dongsoo Kim, Babak A Ardekani, Pamela D Butler, Jay Nierenberg, Daniel C Javitt and Matthew J Hoptman

Psychiatry, University of Minnesota, Minneapolis, MN, USA

Background: Few studies have examined the relationship between white matter (WM) integrity and neurocognitive function in patients with schizophrenia. Deficits in verbal declarative memory have been reported in schizophrenia, which appear to involve left-lateralized temporal regions. **Methods:** Diffusion tensor images (DTI) were acquired from 17 patients with schizophrenia. Fractional anisotropy (FA) derived from these images was transformed into Talairach space. Correlations between FA and recall performance on the WMS-III logical memory subtest (LM) were examined on a voxelwise basis, with a minimum extent threshold of 50 contiguous voxels and a minimum alpha level of .05. **Results:** LM performance was associated with higher FA in parahippocampal WM, as well as in the fusiform WM and posterior cingulate. These patterns were far more pronounced on the left than the right side. **Conclusions:** Performance on this task appears to involve distinct networks, consistent with those identified from lesion and imaging studies. This association of WM integrity with cognitive performance supports the potential value of combined DTI and fMRI studies to further elucidate involved networks.

25. Neural Patterns to Expressive Faces and Complex IAPS Pictures

Israel Liberzon*, Jennifer C Britton and Stephan F Taylor

Psychiatry, Univ. of Michigan, Ann Arbor, MI, USA; Psychiatry, Ann Arbor VAMC, Ann Arbor, MI, USA

Background: Emotion has been studied using either expressive faces or complex IAPS (International Affective Picture System) pictures. Due to inherent differences between stimuli, it is not known whether these paradigms activate similar emotional circuitry. Thus, we tested whether common or differential brain regions mediate processing of these two types of emotional stimuli. **Methods:** In a 3T fMRI setting, healthy subjects (n=12, 6 male, age: 21.4?2.2 years) passively viewed 16-second blocks of faces and pictures, interspersed by fixation images. Stimuli sets were matched in discrete emotional content (happy, neutral, sad, anger, fear, mixed negative). Oblique fMRI images were acquired using reverse spiral, gradient echo acquisition. Preprocessing and whole-brain, voxel-by-voxel analysis was examined using random effects analysis in SPM99 using a $p<0.005$ uncorrected, 5 contiguous voxel threshold. **Results:** Both expressive faces and complex emotional pictures activated a common network relative to fixation: left amygdala [faces: Z=4.18, pictures: Z=3.81], right amygdala [faces: Z=4.05, pictures: Z=3.06], bilateral posterior hippocampus [faces: Z=3.73 and Z=2.90, pictures: Z=4.57], ventromedial prefrontal cortex [faces: Z=4.55, pictures: Z=3.65], and visual cortex [faces: Z=5.68, pictures: Z=5.79]. Happy faces activated the nucleus accumbens [Z=3.08]. Sad and anger faces activated the ventromedial prefrontal cortex [sad: Z=3.21, anger: Z=2.95]. Ventromedial prefrontal cortex and insula were more activated by faces than pictures. In happy and sad conditions, the amygdala was more activated by pictures than faces. **Conclusions:** Preliminary findings suggest common brain circuits process emotions conveyed by faces and complex pictures; however, different neural patterns to specific emotions, compared to neutral, emerge depending on modality. The divergent patterns between expressive faces and complex IAPS pictures may be due to differences inherent to each type of stimulus: recognized vs. evoked emotion, contextual, or arousal differences.

26. Preservation of Cortical Metabolic Function by Donepezil in Patients with Mild to Moderate Alzheimer's Disease: A 24-week Clinical Trial with Placebo Control

James R Moeller*, Henry Rusinek, Manuel F Casanova, John M Hoffman, Larry M Tune, Carlos Perdomo, John R Ieni, R D Jewart and Thomas B Cooper

Department of Psychiatry, Columbia University, New York, NY, USA

Sponsor: Thomas Cooper

Background: Donepezil hydrochloride, a piperidine-based selective acetylcholinesterase inhibitor, has consistently demonstrated clinical benefits for patients with Alzheimer's disease (AD). **Objective:** To evaluate the brain response of AD patients to donepezil therapy using positron emission tomography with [18F]-fluorodeoxyglucose (FDG/PET) and a multivariate analysis with high regional statistical sensitivity. **Methods:** In a double-blind, 24-week study, patients with mild to moderate AD (mean MMSE 21.0 $\pm$3.9) were randomized to donepezil (10 mg/day) or placebo (n=14 per group). Resting-state FDG/PET scans were acquired to quantify grey matter glucose metabolism in 27 regions-of-interest [ROI] per hemisphere at baseline, Week 12 and Week 24. ROI metabolism was corrected for patient differences in regional brain atrophy based on individual structural MRIs. A brain-wide, multivariate statistical analysis (Canonical Variates Analysis) was performed on corrected regional metabolic activity to quantify the ROI responsiveness to donepezil therapy compared with placebo. The primary outcome measure was the change in regional metabolic activity from baseline to Week 24. Cognitive function was assessed at 6-week intervals using the Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-

cog). **Results:** The donepezil and placebo groups did not significantly differ on demographic factors; nor did they differ at baseline on cognitive function or in atrophy-corrected regional metabolic activity. Post baseline, corrected metabolic activity revealed significant group differences in the following ROI: the temporo-parieto-occipital, visual associative, and calcarine areas in the posterior cortex; and Broca's area, superior and middle frontal, and premotor areas in the prefrontal cortex. At Weeks 12 and 24, metabolic activity was maintained in donepezil-treated patients, but showed a marked decline from baseline in placebo-treated patients ($P<0.005$). ADAS-cog scores improved in both groups, albeit to a greater extent in donepezil-treated patients. In the donepezil group, the changes in the most responsive regions at Week 24 were correlated with patient improvement in ADAS-cog scores ($r=0.84$; $P<0.05$). In the placebo group, metabolic decline in these regions was not correlated with change in clinical status. **Conclusions:** Donepezil treatment appeared to preserve metabolic function in temporo-parietal and prefrontal regions of patients with mild to moderate AD, where the changes in the most responsive regions correlated significantly with neuropsychological assessments of enhanced cognitive function. Research supported by Eisai Inc., Teaneck, NJ and Pfizer Inc., New York, NY.

27. Serial Vagus Nerve Stimulation Functional Mri (VNS/fMRI) in Treatment-Resistant Depression

Ziad Nahas*, Charlotte Teneback, Jeong-Ho Chae, Qiwen Mu, Chris Molnar, Frank A Kozel, John Walker, Jejo Koola, Mikhail Lomarev, Daryl E Bohning and Mark S George

Psychiatry, Medical University of South Carolina, Charleston, SC, USA

Sponsor: Travel Awardee, Memorial, 2004

Background: Vagus nerve stimulation (VNS) showed antidepressant effects in open acute and long-term studies of adults in a treatment-resistant major depressive episode. Long-term VNS may be associated with lower relapse rates than expected with conventional psychopharmacology. The mechanisms of action of VNS are not known. **Method:** 18 depressed subjects enrolled a double-blind placebo controlled study assessing the efficacy of VNS in treating depression (D-02) were implanted with Vagus Nerve Therapy in an MRI-compatible fashion and scanned serially 9 times (at baseline and up to 20 months of VNS therapy) with interleaved VNS/fMRI using a send-receive head coil. To investigate the effects of several clinical parameters on VNS response, a multiple regression model was designed using the following covariates: 1) Hamilton Depression Rating Score at the time of scanning (HDRS); 2) time since activation of VNS therapy in weeks (TIME); 3) the intensity of VNS stimulation at each scanning session, adjusted independently based on clinical parameters (INTENSITY); and 4) a measure of severity of illness, based on the interaction between each subject baseline ATHF score and the current Hamilton Depression rating (HDRSxATHF). **Results:** VNS therapy over time is associated with dynamic rCBF changesincluding a deactivation of medial prefrontal and subgenual cingulate. We will report on more detailed results. **Conclusion:** Interleaved VNS and fMRI may help understand the regional neurobiological effects of VNS in patients with treatment-resistant depression including its postulated delayed time of onset and guide future dosing.

28. Amygdala/Frontal Circuitry Dysfunction in Borderline Personality Disorder

Antonia S New*, Monte S Buchsbaum, Erin A Hazlett, Randall Newmark, Serge Mitelman, Marianne Goodman, Harold W Koenigsberg, Janine Flory and Larry J Siever

Psychiatry, Mount Sinai School of Medicine, New York, NY, USA; Psychiatry, Bronx VAMC, Bronx New York, NY, USA

Sponsor: Larry Siever

Background: Evidence suggests that patients with borderline personality disorder (BPD) have decreased brain glucose metabolism in orbitofrontal cortex (OFC) and anterior cingulate gyrus (ACG) at rest and in response to serotonergic stimulation compared to controls as measured by ^{18}FDG-PET. Studies employing fMRI BOLD response show that borderline patients have heightened activation in the amygdala in response to negatively valenced emotional stimuli. However, no studies to date have explored the relationship between amygdala and OFC activity. These correlations are potentially interesting as OFC may be an important brain region in modulating amygdala activity; disturbances in this relationship may correspond to the emotional disinhibition seen in BPD. **Methods:** The present study examined correlations between relative brain glucose metabolism (rGMR) in the amygdala and frontal Brodmann areas (BAs) at baseline and in response to m-CPP. Using ^{18}FDG-PET, rGMR was examined in 27 DSM-IV BPD patients and 24 age and sex-matched controls. All PET scans were coregistered to MRIs. Brain edges were visually traced on all MRI axial slices and the amygdala was visually traced on all coronal MRI slices and divided between dorsal and ventral by bisecting the slice containing the amygdala. rGMR was obtained for the ventral and dorsal amygdala and for all 13 prefrontal Brodmann areas in the right and left hemisphere. Correlation coefficients were calculated between the metabolic rates of the dorsal and ventral amygdala with all ipsilateral prefrontal BAs. **Results:** In ***normal controls*** at ***baseline***, the ventral amygdala had significant positive correlations with BA 11, 12, 25, 44, 47 (right), 44 (left), while the dorsal amygdala had only one significant negative correlation with area 6 (right). In contrast, ***borderline patients*** showed only negative correlations between the dorsal (BA: 6,8,9,10,32, 46-left and right) and ventral areas (BA: 6,8,9,10,32, 46-left and right) of the amygdala, with no distinction between dorsal and ventral amygdala. There were highly significant differences in the pattern of correlations between patients and controls, when subjected to Kullback test for correlational matrices($p<.0001$). ***In response to m-CPP***, ***normal controls*** showed positive correlations between the dorsal amygdala and orbital BAs (11,12, 25-right and left) and between ventral amygdala and orbital BAs (11, 12, 25-left); controls showed negative correlations between dorsal amygdala and BA 8 (left and right), and BA 6 (right). ***Patients*** showed *positive* correlations between the dorsal and ventral amygdala and *dorsolateral* BAs (44 R+L and 45L), but *negative* correlations between the top of the amygdala and *orbital* BAs (11,12,25) on the right but not left. There were also high significant differences in patterns of correlations between patients and controls in response to m-CPP ($p<.0001$). **Conclusions:** This suggests at baseline a loss of functional specificity between dorsal and ventral amygdala in BPD, and supports a model of disinhibition through the failure to activate OFC in response to amygdala activity in BPD. It also suggests that the activation of OFC in response to a serotonergic probe which occurs in normal subjects, does not occur in borderline patients. BPD patients appear to activate alternative areas in dorsolateral PFC; the positive correlation with dorsolateral PFC and amygdala suggests that they may be using conscious processing to control amygdala activity. The implications of this neuroanatomical model of disinhibition in BPD will be discussed.

29. PET Study of 5HT1A Serotonin Receptors at Different Phases of the Menstrual Cycle in Premenstrual Dysphoria

Anna-Lena Nordstrom*, Hristina Jovanovic, Asta Cerin, Per Karlsson and Christer Halldin

Dept of Clin Neuroscience, Psychiatry, Karolinska Institutet, Stockholm, Sweden

Sponsor: Goran Sedvall

Three to eight percent of women of reproductive age suffer from severe premenstrual symptoms of irritability, tension, dysphoria and mood lability which seriously interfer with their usual activities or relationships. Research criteria for the symptoms labelled Premenstrual Dysphoric Disorder (PMDD) are listed in DSM-IV. The etiology of PMDD is still largely unknown. It has been hypothesized that normal hormone secretion during the menstrual cycle trigger PMDD related

biochemical events within the brain and that serotonin plays a major role. The hypothesis is supported by indirect biochemical findings, the fact that PMDD shares common features with other serotonin related disorders (mood and anxiety) and the observation that selective serotonin reuptake inhibitors (SSRIs) are effective in the treatment of PMDD. In the present study we used positron emission tomography (PET) and [11C]WAY-100635 to examine serotonin 5HT1A receptors in healthy women and in women with PMDD. Five women were examined in each group. Two PET examinations were performed in each subject, one before (follicular phase) and one after ovulation (luteal phase). PET scans were scheduled based on the individual menstrual cycle characterized by ultrasonography of the ovaries as well as with hormone levels in blood and urine. The binding potential for [11C]WAY100635 was calculated according to the simplified reference tissue model. The regions of interest included in the analysis were dorsolateral prefrontal cortex, orbito-frontal cortex, anterior cingulate cortex, amygdala, hippocampus and raphe nuclei. In the raphe nuclei a high variation in the 5HT1A binding potential was observed between the follicular and luteal phase in the healthy controls. This menstrual cycle related variation was significantly lower in the PMDD patients (Mann-Whitney, $p<0.05$). To our knowledge this is the first report of receptor changes in the brain during the menstrual cycle demonstrated with PET. Further, the result gives support to the view that PMDD patients may have a blunted response or are subsensitive to challenges of the serotoninergic system induced by normal hormone secretion. The results urge for replication in an extended series of patients.

30. Response to Emotionally Salient Faces and Glutamate Concentrations in the Rostral Anterior Cingulate Cortex in Social Phobia: Preliminary Combined Spectroscopic and Functional Magnetic Resonance Imaging Studies at 4 Telsa

K. Luan Phan*, Daniel A Fitzgerald, Bernadette M Cortese, Navid Seraji-Bozorgzad, Laura Jelsone, Manuel E Tancer and Gregory J Moore

Psychiatry, University of Chicago Pritzker School of Medicine, Chicago, IL, USA

Sponsor: Daniel Luchins

Introduction: Functional neuroimaging studies implicate hyperactivity in limbic circuitry (e.g., amygdala, rostral anterior cingulate cortex [rACC]) in response to negative /harsh faces, public speaking tasks, and aversive conditioning in patients with social phobia (also known as social anxiety disorder [SAD]). However, few studies have sought to ascertain the neurochemical mechanisms that modulate these responses. While preclinical studies suggest that these processes may be driven by increased glutamatergic output or neurotransmission, the role of glutamate has been relatively understudied in human anxiety disorders, including social phobia. **Methods:** BOLD-sensitive functional magnetic resonance imaging (fMRI) and single-voxel 1H-proton magnetic resonance spectroscopy (MRS) were performed on ten subjects with DSM-IV generalized SAD and ten age- and sex-matched healthy controls (HCs), historically free of other Axis I or neurologic disorders and naive to psychotropic medication. Data were collected on a 4Tesla MRI scanner using a multi-echo echoplanar imaging (EPI) sequence for fMRI and stimulated echo acquisition mode (STEAM) sequence for MRS. During fMRI, subjects viewed alternating blocks of photographs of faces and radios, while evaluating the emotional expression of each face and the color of each radio, respectively. During MRS, baseline glutamate (Glu) concentrations were measured in 2cm isotropic voxels localized at the rACC and occipital cortex (OC) along the center of the inter-hemispheric fissure. Group differences in fMRI responses (Faces > Radios) data were analyzed based on a random effects model with Statistical Parametric Mapping (SPM2). MRS data were analyzed with LC-Model software, and group differences in Glu concentrations (relative to creatine [Cr]) in the rACC and OC were evaluated using analyses of covariance (ANCOVA) controlling for GM-WM-CSF content. **Results:** Generalized SAD patients had greater activation to emotional faces in rACC (maximum foci at [x=-4, y=40, z=-4], Z-score=3.11, $p<0.05$, SVcorrected) relative to HCs. Patients with social phobia also a 13.2% higher Glu/Cr ratio in the rACC (but not OC) than their comparison subjects ($F=9.03$; $p=0.01$). Intensity of social anxiety symptoms was also correlated with Glu/Cr in the ACC (Pearson $r=0.52$, $p=0.03$). **Conclusion:** These preliminary findings provide new evidence of a potential association between an enhanced response to emotionally salient faces and elevated glutamate levels in the anterior cingulate cortex in social phobia, consistent with an excitatory/anxiogenic role for the glutamatergic system in limbic activity. Combining multi-modal brain imaging methodologies may elucidate an integrative model of brain function and mental illness.

31. Frontal Subsystems Implicated in Dysregulation of Attention in Panic Disorder: An fMRI Pilot Study

Srinivasan S Pillay*, Staci A Gruber, Jadwiga Rogowska, Norah Simpson and Deborah Yurgelun-Todd

Harvard Medical School, Brain Imaging Center/McLean Hospital, Belmont, MD, USA; Harvard Medical School, Boston, MD, USA

Sponsor: Travel Awardee, ADAA, 2004

Background: This study investigated how frontal systems mediate a task of selective attention and working memory in patients with panic disorder (PD) using the interference component of a color-word naming Stroop test and BOLD functional magnetic resonance imaging. **Methods**: Eight patients with PD and eight age- and sex matched controls were recruited for the study. Scanning was performed on a GE 1.5 Tesla scanner retrofitted with a whole body echo planar coil. Using a quadrature head coil, echo planar images and high-resolution MR images were acquired. **Results**: Examination of group differences revealed greater frontal activation in patients with PD compared to controls. Within the frontal lobe, significantly greater frontal activation was observed in the cingulate and prefrontal cortices of patients with PD at a statistically significant level. This occurred in the context of a greater number of errors in the PD population that did not reach statistical significance when compared to controls. **Conclusion**: This is the first study to our knowledge that demonstrates hyperfrontality in response to a task of selective attention and working memory in patients with PD. This project was supported in part by a grant from Harvard Medical School (Kaplen Award) and a NARSAD Award (2002-3) to Dr. Pillay. This paper was also supported in part by a NIDA Grant R01 12483 (to Dr. Yurgelun-Todd).

32. Amyloid Imaging in Alzheimers Disease and Mild Cognitive Impairment using Pittsburgh Compound-B (PIB)

Julie C Price*, William E Klunk, Brian J Lopresti, Carolyn C Meltzer, Scott K Ziolko, Jessica A Hoge, Steven T DeKosky and Chester A Mathis

Radiology, Psychiatry, and Neurology, University of Pittsburgh, Pittsburgh, PA, USA

Introduction: Previously we reported the first positron emission tomography (PET) imaging studies of the amyloid-binding radiotracer, Pittsburgh Compound-B (PIB). These semi-quantitative studies were performed in Uppsala, Sweden in 16 Alzheimers disease (AD) patients and 9 healthy control subjects and showed robust group differences in PIB retention consistent with amyloid deposition in AD (parietal; $p=0.0002$). Quantitative PET PIB imaging studies have now been performed in Pittsburgh in three subject groups: AD, mild cognitive impairment (MCI), and healthy controls. The present study reports on the status of these PIB PET imaging studies. **Methods:** High specific activity PIB PET studies were performed over 90 min (ECAT HR , 13±3 mCi) in 11 patients (5 mild-moderate AD: 68±10yrs; 6 MCI: 70±10 yrs) and 7 controls (64±16 yrs). Arterial

blood samples were collected and metabolite-corrected input functions were determined. Magnetic resonance images were acquired and co-registered to the PET data for region-of-interest (ROI) definition and atrophy correction of the PET data. Regional PIB distribution volume (DV) values were determined using Logan graphical analysis. ROIs included cortical areas (posterior cingulate: PCG; parietal: PAR; anterior cingulate: ANC) and cerebellum (CER). The regional DV measures were normalized to the cerebellar (reference region) value to yield DV ratios (DVRs) as measures of PIB retention. **Results:** The greatest PIB retention was observed in the PCG (2.60±0.39) and PAR (2.55±0.46) of the AD subjects with high retention also in ANC (2.53±0.46). On average, lower values were observed for the MCI subjects (PCG: 1.86±0.58; PAR: 1.79±0.54, ANC: 1.81±0.72), while controls demonstrated uniformly lower DVR values across cortical areas (PCG: 1.23±0.20; PAR: 1.28±0.22, ANC: 1.30±0.27). Similar levels of non-specific PIB retention were observed across subject groups (AD CER DV: 3.27± 0.88; MCI CER DV: 3.65±0.50; Control CER DV: 3.42± 0.30). Subjects within the MCI group tended to be either "control-like"or "AD-like" with respect to the observed PIB retention. Similar group differences were observed using cerebellar data in place of the arterial input. **Conclusion:** These results support the validity and feasibility of performing in vivo assessments of amyloid deposition in AD and MCI subjects. This work was supported by MH070729, NIA, Alzheimers Association, GE Health Care.

33. Diffuse Cortical and Sub-Cortical Over-Activation During Source Monitoring in Schizophrenia

J. Daniel Ragland*, Jeffrey Valdez, James Loughead, Ruben C Gur, Mark Elliot and Raquel E Gur

Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Patients with schizophrenia often have difficulty identifying the source of remembered information despite relatively intact recognition memory performance. In a previous multinomial analysis we investigated source monitoring in patients utilizing a levels-of-processing (LOP) word encoding paradigm. During encoding, subjects made either uppercase vs. lowercase (shallow) or concrete vs. abstract decisions (deep), and source monitoring was tested by presenting subjects with these targets mixed with new foils and requiring them to decide if each word was a previously presented target that had undergone shallow processing, a target that had undergone deep processing, or a new foil word. Although there was no group difference in recognition or source memory parameters, patients did not show a significant LOP effect on source monitoring, suggesting subtle problems in the relational binding of semantic information. The current study was designed to examine whether or not these subtle performance differences are accompanied by differences in brain activation measured by BOLD fMRI. 13 patients with schizophrenia and 13 demographically matched healthy controls were studied on a 3 Tesla Siemens scanner while performing the source monitoring task. The task consisted of 60 words (40 targets, 20 foils) presented in a pseudo-random order for 3 sec. each with a jittered ISI ranging from 0-12 sec. to permit event-related analysis. Images were pre-processed in SPM2 using standard motion correction, normalization and smoothing procedures, and events were modeled using a canonical hemodynamic response function. SPM2 contrasts examined signal change during correct source identification of target words. Healthy controls activated an established fronto-parietal network including the left dorso- and ventrolateral prefrontal cortex (PFC), bilateral sensori-motor areas, bilateral superior parietal cortex, and right cuneus. Patients activated right dorsolateral PFC, bilateral frontal pole, left sensori-motor, and multiple sub-cortical areas including bilateral insula, left thalamus and caudate, bilateral posterior cingulate, and right anterior cingulate. When groups were directly contrasted there were no areas of greater activation in healthy controls. Patients, however, showed greater bilateral activation in a large network of regions including sensorimotor cortex, middle temporal gyrus, thalamus, visual association areas, and superior parietal cortex and precuneus. These preliminary results indicate that although patients can successfully perform a source monitoring task following a LOP encoding paradigm, they must recruit a much broader network of brain regions than healthy controls who can rely on a focal fronto-parietal network. This less efficient pattern of activation along with subtle performance differences suggests that there is a fundamental difference in the way that patients utilize semantic information even when strategic memory demands are reduced.

34. Levels-Of-Processing Effect on Source Monitoring in Schizophrenia

J. Daniel Ragland*, Erin McCarthy, Jeffrey Valdez, Colleen Brensinger, Warren B Bilker, Ruben C Gur and Raquel E Gur

Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Reducing strategic memory demands by providing semantic encoding strategies through levels-of-processing (LOP) paradigms can normalize recognition and left prefrontal activation in schizophrenia. However, normalized recognition does not necessarily imply an unimpaired memory trace as patients may rely more on a sense of familiarity during word retrieval. The current study is designed to test the strength of the memory trace through a LOP source monitoring paradigm. 16 patients with schizophrenia and 15 demographically matched healthy controls received a source monitoring task following word encoding and recognition. Subjects were presented with 60 words (40 targets, 20 foils) and asked to determine if they were old words that had undergone shallow processing (i.e., uppercase, lowercase decision), old words that had undergone deep processing (i.e., concrete, abstract decision), or new words (foils) that had not been previously presented. A two-high threshold multinomial model was used to obtain independent measures of item recognition, source memory, and response bias. A bootstrapping technique was used to obtain a variance-covariance matrix for these multinomial parameters so that two-sample t-tests could be used to assess within- and between-group differences. Goodness-of-fit tests revealed that the multinomial model adequately fit the data of both groups. As in our previous studies there was a robust LOP effect on recognition memory, with both patients and controls recognizing more words that had undergone deep processing. Although source memory was also better for deeply processed words in healthy controls, this effect was only a trend ($p<.10$) in the patient sample. However, there were no group differences in source memory when patients and controls were directly compared. These results indicate that providing patients with semantic encoding strategies normalizes recognition performance but does not fully restore source monitoring. Less robust source memory improvement with deep processing suggests residual difficulties in the relational binding of semantic information in schizophrenia. Nevertheless, teaching semantic encoding strategies holds promise for future remediation efforts.

35. Enhanced Dorsal Medial Prefrontal Cortex Reponses to Social Threat Perception in Schizophrenia: A Preliminary fMRI study at 4 Tesla

RP Rajarethinam*, Rahul Peethala, Matcheri Keshavan, David Rosenberg, Vaibhav Diwadkar and Luan Phan

Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

Sponsor: David Rosenberg

Introduction: Enhanced threat perception in schizophrenia may be an important component of the affective and social deficits observed in patients with schizophrenia. Neuropsychological and neuroimaging studies implicate a primary role for the amygdala and medial prefrontal cortex (MPFC) in the evaluation of danger signs from facial expressions and other social stimuli, and more generally, in emotional arousal and vigilance. In an ongoing functional magnetic

resonance imaging (fMRI) study, we examined brain activity during the processing of faces expressing fear (as well as other discrete emotions), and hypothesized that patients with schizophrenia would excessively activate the amygdala and prefrontal cortex relative to healthy comparison subjects. **Methods:** Seven male patients with schizophrenia and seven age- and sex-matched normal controls participated in this study. BOLD fMRI images were obtained using a 4T MRI scanner with a multi-echo echoplanar imaging sequence while the subjects viewed alternating 20sec blocks of photographs of faces (obtained from the Section of Neuropsychiatry, University of Pennsylvania) and identified the emotion (Fear, Angry, Sad, Happy, Disgust, Neutral) expressed in each face. BOLD-responses between each emotion type (F, A, S, H, D) versus non-emotional (Neutral, N) faces were contrasted initially in each subject and then entered into a second-level random effects analysis to examine within-group activations and between-group differences. The data were analyzed using statistical parametric mapping (SPM 99) and activations exceeding a threshold of $T>5.21$ ($p < 0.001$, uncorrected) were considered significant. **Results:** The initial results show that schizophrenia patients activated the dorsal MPFC ([x=0, y=52, z=30], $Z>3.58$) in response to fearful faces, while controls showed no activation in this area (even at a lowered threshold, $p<0.05$ uncorrected); this activation difference was significant in between-groups analysis ([x=6, y=52, z=28], $Z>4.33$). The dorsal MPFC activation was absent in both groups in response to other emotionally salient faces. Amygdala activation was not detected in either group to each discrete emotion vs. neutral face contrast, but present when all face conditions (including neutral) were included in the analysis. **Conclusions:** These preliminary data suggest enhanced activation in the dorsal MPFC specifically in the processing threat-related emotions among patients with schizophrenia compared to normal controls. Further studies with a larger sample are needed to better elucidate the role of social threat perception in the neural pathophysiology of schizophrenia, in particular in those with paranoid symptomatology.

36. Rapid Effects of Intensive Cognitive-Behavioral Therapy on Brain Glucose Metabolism in Obsessive-Compulsive Disorder

Sanjaya Saxena*, Eda Gorbis, Susanna Chang, Joseph O'Neill, Stephanie K Baker, Karron M Maidment, Jeffrey M Schwartz and Edythe D London

Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute, Los Angeles, CA, USA

Functional neuroimaging studies of obsessive-compulsive disorder (OCD) have found elevated glucose metabolism in the orbitofrontal cortex, striatum, and thalamus that decreases with response to serotonin reuptake inhibitors (SRIs) or cognitive-behavioral therapy (CBT). Intensive, daily CBT using exposure and response prevention (ERP) produces improvement in 60-80% of OCD patients in as little as four weeks. However, it has been thought that at least 10-12 weeks of treatment were needed to produce the changes in brain function associated with improvement in OCD. We sought to elucidate the brain mediation of response to intensive CBT in OCD, and to determine whether intensive CBT could rapidly induce the brain metabolic changes that have been seen after much longer trials of pharmacotherapy or standard, weekly CBT. [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans were obtained on ten OCD patients before and after four weeks of intensive CBT. All patients received 90 minute, individual CBT sessions, five days a week for four weeks, combining ERP with cognitive techniques and homework exercises. Ten normal controls received FDG-PET scans several weeks apart, without treatment. Pre- to post-treatment, glucose metabolic changes were measured by MRI-based region-of-interest analysis and Statistical Parametric Mapping. OCD patients responded well to treatment, with significant improvements in OCD, depression, anxiety, and overall functioning. Pre- to post-treatment changes in cerebral glucose metabolism differed significantly between OCD patients and controls. OCD patients showed significant metabolic decreases in bilateral thalamus, putamen, and left posterior cingulate cortex, but had significant increases in left dorsolateral prefrontal cortex. Controls showed a slight metabolic decrease in the AC and an increase in left thalamus. The declines in thalamic and striatal activity seen with intensive CBT replicated those seen in previous studies with SRIs in OCD. However, the increases in prefrontal activity were opposite to changes seen with SRIs. These results suggest that CBT shares some common subcortical mechanisms of anti-obsessional action with SRIs but has different effects in the prefrontal cortex. Our results also indicate that significant changes in both brain activity and symptom severity can be achieved after just four weeks of intensive CBT, much faster than with SRIs or standard, weekly CBT.

37. A PET Study Examining Pharmacokinetics, Likability, and Dopamine Transporter Receptor Occupancy of Methylphenidate Formulations in Adults

Thomas J Spencer*, Jerrold F Rosenbaum, Alan J Fischman, Joseph Biederman, Patrick Ciccone and Darin Dougherty

Harvard Medical School, Boston, MA, USA; Massachusetts General Hospital, Boston, MA, USA

Sponsor: Jerrold Rosenbaum

Introduction: Both the abuse potential and the likability of stimulant medications are associated with the rapid onset of presynaptic dopamine transporter (DAT) blockade in the brain. Previous studies of this association have compared intravenous and oral administration of stimulant medications. The primary objective of this study was to compare immediate- and extended-release oral formulations of methylphenidate (MPH) with respect to the relationship between likability and kinetics of DAT blockade. **Methods:** Twelve healthy adults were randomized to single doses of either immediate-release (IR) MPH or OROS® MPH. Doses were chosen to yield a similar C_{max} for each treatment (40 mg IR MPH, 90 mg OROS MPH). Subjects underwent a baseline PET scan and then repeated the experiment on two separate days. Serum d-MPH levels were obtained, and likability questionnaires were completed hourly for 10 hours. DAT occupancies were obtained at 1 and 3 hours post-dose on Day 1, and at 5 and 7 hours post-dose on Day 2 using C-11 altropane PET. **Results:** Although the dose of OROS MPH was more than twice that of IR MPH, OROS MPH had a slower velocity of association on the brain dopamine transporter. Because CNS uptake of MPH is a function of serum MPH concentrations, it was expected that the CNS uptake of OROS MPH would be slower than that of IR MPH. However, evidence indicated that CNS kinetics were altered beyond predictions based on individual serum concentrations. The rate of increase in DAT occupancy, which occurred with increasing serum MPH concentrations, was greater in the IR group than in the OROS group. In addition, the likability questionaires indicated a greater subjective response to IR MPH than to OROS MPH despite similar C_{max} and maximum DAT occupancies; subjective response to OROS MPH was negligible after 4 hours. **Conclusion:** These results support the hypothesis that subjective liking is associated with the kinetics of each MPH formulation. These results have important implications for the clinical characteristics of the 2 formulations of MPH, including their substance abuse potential.

38. GRM3 Genotype is Associated with Reduced N-Acetyl Aspartate Levels in the Frontal Cortex

Sonya U Steele*, Stefano Marenco, Alan S Barnett, Jan Willem Van der Veen, Terry E Goldberg, Richard E Straub, Michael F Egan and Daniel R Weinberger

Clinical Brain Disorders Branch, NIMH, NIH, Bethesda, MD, USA

Sponsor: ACNP Secretariat

Background: The A allele of a SNP (hCV11245618) in intron two of the gene for the metabotropic glutamate receptor 3 (GRM3)

may confer added risk for schizophrenia and has been associated with reduced prefrontal cortical NAA and poorer cognitive test performance in a prior study by our group (Egan et al *PNAS* 2004). The purpose of this study was to examine the effect of genotype at this SNP in a new cohort with higher spatial resolution on a 3T scanner. **Methods:** We studied 47 carefully screened healthy Caucasian controls of European descent (mean age 32.7 ±9.29) genotyped at this SNP (hCV11245618). Subjects were also tested on measures of frontal function that included a letter and category fluency task, which also had shown association in the earlier study. Proton magnetic resonance spectroscopic imaging ^{1}H-MRSI) was performed at 3T (4 slices; spin echo slice selection; TR/TE: 2300/280ms; 7.5x7.5x7.5mm voxels). Metabolite signals were reported as ratios of the area under the peaks for NAA/Creatine + Phosphocreatine (CRE), NAA/Choline (Cho) and Cho/CRE. Regions of Interest (ROIs) were drawn on the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate, the hippocampal formation, and the occipital cortex. We collapsed the A/G (N=23) and G/G (N=1) subjects into a ″G carrier″ group in the analysis and computed the group differences in metabolite ratios by unpaired t-tests. A comparison of the letter and category fluency task scores between the two genotype groups was done by unpaired t-tests. Spearman′s Rho was used to test for correlations between the metabolite ratios for the DLPFC and neuropsychological performance. **Results:** The A/A genotype group exhibited a significant reduction of NAA/CRE in the right DLPFC ($p<0.013$, one-tailed) compared to the G carriers, a trend that was also apparent in the left hemisphere. No other metabolite ratios were significantly different between groups. The A/A group generated significantly fewer words in the category fluency task ($p<0.0033$, one-tailed) than the G carrier group. Performance on this task was significantly correlated with the NAA/CRE levels in the right DLPFC ($p<0.029$). Performance on the letter fluency task, on the other hand, significantly correlated with the NAA/CRE levels in the left DLPFC ($p<0.041$). **Conclusions:** These results are consistent with prior findings from our group. Egan et al. (*PNAS*, 2004) reported that NAA/CRE levels were reduced bilaterally in the DLPFC of Caucasians homozygous for the A allele of this SNP. Those findings were obtained on a 1.5T scanner with double the voxel size than the current study (0.84 vs.0.42 cc). The A/A homozygotes in this sample also did significantly worse as compared to the G-carriers in a test that relies heavily on the integrity of the DLPFC. NAA/CRE levels in the DLPFC were also predictive of neuropsychological performance on tasks that index prefrontal function. The current results, obtained with more sophisticated technology in an entirely different cohort of normal controls, strengthen the evidence indicating that GRM3 may be an important gene in regulating prefrontal function and via this mechanism increased risk for schizophrenia. Based on evidence that GRM3 modulates synaptic glutamate, the prefrontal NAA reduction may reflect an alteration in glutamate neurotransmission or innervation patterns.

39. Functional Brain Imaging and Psychology of Human Parent-Infant Attachment

James E Swain*, James F Leckman, Linda C Mayes, Ruth Feldman and Robert T Schultz

Child Study Center, Yale University, New Haven, CT, USA

Sponsor: Past Travel Awardee, NIMH, 2003

Background: The transforming emergence of parental behavior, around the birth of a child, appears to be a governed by a cascade of genetic and epigenetic events that reorganize hypothalamic and limbic brain circuits. Many of these critical circuits are involved in physiological and cognitive aspects of stress response, salience determination, and anxiety response. Indeed, as part of an array of peripartum changes, behaviors and thoughts are manifest that bear a striking similarity to obsessive-compulsive disorder (OCD). Among others, these include: preoccupations and anxious intrusive thoughts regarding the well-being of the infant and a compulsive need to check the infant repeatedly and arrange things until they are "just right". **Hypotheses:** We hypothesize that a functional overlap in the neural substrates that mediate both OCD and the human capacity to form parental attachment, such that: 1. Parental preoccupations involving anxious, intrusive, OCD-like thoughts are related to neural activation in striato-thalamo-cortical circuits, and baby cry stimuli; 2. Parental preoccupations involving intrusive, but positive idealizing thoughts and joys are related to expected neural activation in the ventral striatum, midbrain and hypothalamus by infant visual stimuli; 3. Parental brain responses to stimuli from their own infants will be more robust than stimuli from control infants; 4. There will be correlations between psychometric assessments of parenting behaviors, cortisol response, and brain activity in parenting circuits. **Methods:** We are studying parental attachment with psychological and physiological assays at 2-weeks and 3 months postpartum. First we are administering interview and self-report versions of the Yale Inventory of Parental Thoughts and Actions. Variables derived from these interactions describe parental attachment, preoccupation, care, level of anxious and intrusive thoughts, and degree of perceived transformation by the parenting experience. Questionnaires also assess parents' perception of their own parenting and depressive/anxious symptoms. Second, we are performing functional magnetic resonance imaging of the brains of both parents using a 3T scanner. Brain activation maps are generated from blood oxygenation level dependent magnetic measurements taken while listening to baby stimuli, which consist of cries of their own baby, another baby, control noises, as well as pictures of their own baby, another baby, baby toys, and houses. Salivary cortisol is obtained before and after each scan. All data are acquired at the two postpartum times. **Results:** Analysis of brain imaging data shows that baby cries stimulate frontal, cingulate, auditory and visual cortices, as well as midbrain, mygdala, hypothalamus and ventral striatum. Baby pictures activate more visual processing areas. Differences are also emerging in the pattern of responses between moms & dads and between early and later postpartum times in brain activations as well as interview responses. Psychometric data indicate significantly higher preoccupations in moms compared to dads ($p<0,001$), and correlations of preoccupations with intrusive worries and checking ($p<0.01$), depression ($p<0.001$), baby-centric behaviors ($p<0.01$), positive parenting ($p<0.05$), hedonic transformation ($p<0.01$), and brain activity in OCD circuits. Conclusions: This work constitutes the first study to combine neuroimaging of brain regions that we expect to be involved in normal attachment as well as psychopathology in both mothers & fathers, with concurrent psychometric & endocrine measures using both auditory and visual stimuli. Our results fit with human and animal work on affiliative behaviors and may lead to biological models for protective & vulnerability factors in human family attachments.

40. Correlations between Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (1H MRS) in Schizophrenic Patients and Normal Controls

Cheuk Y Tang*, Joseph Friedman, Linda Chang, Thomas Ernst, Dikoma Shungu, Xiangling Mao, Patrick Hof, Jonathan Osowski, Arash Hajianpour, Monte S Buchsbaum, Kenneth Davis and Jack Gorman

Radiology, Mt. Sinai School of Medicine, New York, NY, USA; Psychiatry, Mt. Sinai School of Medcine, New York, NY, USA

Sponsor: Jack Gorman

N-acetylaspartate (NAA) is a neuronal marker and is decreased in white matter lesions and regions of axonal loss. It has also been found to be reduced in the prefrontal and temporal regions in patients with schizophrenia. Diffusion Tensor Imaging (DTI) allows one to measure the orientations of axonal tracts as well as the coherence of axonal bundles. DTI is thus sensitive to demyelination and

other structural abnormalities. Significant differences in 1H MRS as well as DTI data have previously been reported between patients with schizophrenia and normal controls. There are limited reports comparing MRS results with DTI in white matter. In this study we sought to correlate the results of these two imaging modalities in the same patient groups. **Methods:** Schizophrenic subjects (n=31) between the ages of 20-80 were recruited from outpatients psychiatric facilities. Normal Controls (n=24). The diagnosis of schizophrenia was confirmed by a structured diagnostic interview (Comprehensive Assessment of Psychiatric Symptoms and History; CASH) as was the absence of any significant axis I psychopathology in the healthy comparison subject group. Drug testing and medical screening was performed to exclude patients with substance abuse and cardiovascular disease which might affect MRI results. Whole brain Diffusion Tensor data was obtained and fractional anisotropy (FA) indices were computed. 2D CSI data was obtained in two slices containing DLPF white matter, Medial Temporal white matter and Occipital White matter. MRS metabolites (NAA, Cho, Cr, Ins1 & Ins2) were obtained from these regions of interests (ROIs). Relative Anisotropy values were obtained in from the same ROIs from matched imaging planes. **Results:** Significant differences were found in the NAA/Cr ratios in the Medial Temporal regions ($p<0.00023$). Relative Anisotropy values in the same region were found to be statistically significant as well ($p<0.014$). Correlation analysis between NAA/Cr ratios with RA values in the same regions was also significant ($p<0.047$). **Conclusion:** The implications of these results are twofold: 1) there is a white matter abnormality in patients with schizophrenia and 2) the biochemical abnormality as detected in MRS is consistent with the DTI results. The biochemical abnormalities likely precede the structural defects. The current results may reflect a disease state that is already in an advanced stage in which both metabolic as well structural abnormalities are present.

41. Striatal D_2 Receptor Occupancy in Bipolar Patients Treated with Olanzapine

Trawat Attarbaschi, Thomas Geiss-Granadia, Julia Sacher, Nikolas Klein, Nilufar Mossaheb, Georg Wiesegger, Rupert Lanzenberger, Susanne Asenbaum, Sitra Tauscher-Wisniewski, Robert Dudczak, Dagmar Doby, Siegfried Kasper and Johannes Tauscher*

Dept. of General Psychiatry, Medical University Vienna, Vienna, Austria

Sponsor: Past Travel Awardee, ECNP-ACNP, 2003

There is clinical evidence that patients with affective disorders are more vulnerable to extra-pyramidal symptoms (EPS) during treatment with typical neuroleptics. We explored the relationship between striatal D_2 occupancy and EPS in bipolar patients receiving the atypical antipsychotic olanzapine. Seventeen patients with a DSM-IV diagnosis of bipolar disorder, currently manic, depressive, or mixed episode, were enrolled to an open-label treatment with oral olanzapine in doses from 5-45 mg/d for at least 14 days. After this period, striatal D_2 receptor occupancy was quantitatively analysed using [^{123}I]Iodobenzamide (IBZM) and single photon emission computerized tomography (SPECT). Regions of interest (ROI) were drawn manually on the MRI coregistered to the SPECT scan, in areas corresponding to the striatum and the frontal cortex, and subsequently transferred to the SPECT scan. A ratio was calculated between average count-rates in the striata (S) and the frontal cortex (F). This ratio minus one corresponds to the D_2 binding potential, which was compared to an age-corrected control value obtained from a historic, healthy control group. On the day of the SPECT scans, plasma levels of olanzapine were obtained. Side effects were assessed by the Simpson-Angus Scale (SAS) and Barnes-Akathisia Scale (BAS) for EPS, and clinical improvement by the Young Mania Rating Scale (YMRS) and the Clinical Global Impressions (CGI) scale. Striatal D_2 receptor occupancy rates ranged from 28 % to 80%. There was a dose-dependent increase in occupancy: 5 mg (n=5) led to 28-50%, 10 mg (n=4) to 40-68%, 15 mg to 69%, 20 mg (n=5) to 57-66%, 30 mg (n=1) to 66% and 45 mg (n=1) to 80% D_2 receptor occupancy. There was a significant correlation between dose and D_2 occupancy (R^2= .69; *P*= .0001) as well as between plasma levels and occupancy (R^2= .55, *P*= .0014). We also found a correlation between dose and plasma levels (R^2= .56, *P*=.0009). No clinical significant EPS occurred: The mean SAS and BAS scores at endpoint did not differ significantly from baseline values. The CGI scores were significantly reduced from a mean of 4.3 at baseline to 2.8 at the time of the SPECT scan (*P*= .001), and the YMRS score from a mean of 8.0 to 4.2 (*P*= .003). Olanzapine in doses from 5 to 45 mg in bipolar patients led to a D_2 receptor occupancy between 28 and 80%, comparable to that seen in patients suffering from schizophrenia. A dose-dependent increase in D_2 occupancy was observed. No clinical significant EPS occurred during treatment. Similar to schizophrenic patients, bipolar patients did not exhibit EPS at D_2 occupancy levels of 28 to 80%. Our data do not suggest an increased vulnerability for EPS in bipolar patients receiving 5-45 mg/d olanzapine.

42. Incentive Modulation of Performance Monitoring in the Anterior Cingulate Cortex

Stephan F Taylor*, Brian Martis, Robert C Welsh, William J Gehring, Israel Liberzon, Kate D Fitzgerald, Joseph A Himle and James L Abelson

Psychiatry, University of Michigan, Ann Arbor, MI, USA

Specific brain networks monitor ongoing behavior, and characterizing them provides conceptual and experimental handles on psychiatric illness. Brain mapping studies have implicated the dorsal midline frontal cortex, including the dorsal anterior cingulate cortex (dACC, area 32), in performance monitoring, particularly after making errors. The dACC is relevant to many psychiatric disorders, such as obsessive compulsive disorder, where patients focus excessively on potential or imagined errors. Interestingly, experimental work has demonstrated that patients with this illness exhibit an exaggerated electrophysiological marker of error commission. Other work suggests that the greater error-related signal represents a larger emotional response to making a mistake. In order to explore the role of emotional investment in performance monitoring, we used a standard, cognitive interference task and manipulated a monetary performance incentive. Our hypothesis was that when subjects stood to lose money and made an error, they would exhibit greater activation in the ACC, compared to a condition without a monetary penalty. Twelve subjects (5 males, mean age ± S.D.=27.9 ± 8.1 yrs) underwent fMRI BOLD scanning while they performed a modified flanker task, which required subjects to press one of 2 keys to a target letter, appearing amidst distracting, 'flanker' letters, e. g. 'HHSHHHH.' To increase error rates, we required subjects to respond within a deadline (1.2-1.3 times mean response latency). Trials lasted 3 seconds, and began with a 2 sec cue (pictures of hands with thumbs up, down or horizontal) indicating the condition (gain, lose, neutral). If subjects responded correctly and within the deadline, they would, depending upon the condition, gain money ($2, $1 or 5¢), not lose money (the same amounts), or neither. Subjects received feedback for correct/incorrect responses immediately after each trial and a tally of their earnings appeared at the end of each run (6 runs, 60 trials/run). Spiral GRE volumes were acquired at 3.0 T. Data were analyzed in a random effects model after realignment, normalization and temporal filtering. Results were thesholded at $q < 0.005$ (FDR) after small volume correction for frontal midline cortex. The overall error rate for the fMRI experiment was 26.9 ± 15.4 %, and there was no difference in accuracy between incentive conditions ($F=0.15$, $p=0.78$). Analysis of fMRI BOLD signal at the onset of the incentive cue (for correct trials, only) showed a significant signal in the head of the caudate nucleus/ventral striatum, relative to the neutral condition. For

all error trials (analyzed relative to an implicit baseline), we found activation in supplementary motor area (SMA) and pre-SMA/dACC. The BOLD signal was significantly greater for errors committed during the loss condition, relative to the neutral condition, in the most rostral extent of the dACC focus ([9, 33, 39], Z=3.76; $p < 0.003$).
The findings demonstrate that motivation influences activity of regions, such as the dACC, involved in performance monitoring. In addition to demonstrating psychological processes relevant to performance monitoring, this paradigm may also be used to investigate motivational and affective components of abnormal performance monitoring in psychiatric illnesses, such as OCD.

43. Neuronal Risk Markers For Substance Abuse in Youth
Binu P Thomas*, Carol A Tamminga, Monique Ernst and Uma Rao

Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

Sponsor: Uma Rao

This study aims to identify differences in demographic characteristics, cognitive performance, and brain physiology that could predict the risk for development of substance use disorder (SUD) in depressed and healthy adolescents. Adolescents with and without depression are recruited, clinically characterized, and evaluated with cognitive tasks. fMRI with BOLD is collected during a two-choice probabilistic reward task. The task involves probabilistic monetary rewards with varying levels of risk during an event?related design; the event related acquisition provides the opportunity to characterize brain activity during three different phases of the task, i.e., selection, anticipation and feedback. 18 normal (NV) (11M; 7F) and 15 depressed (DV) (8M; 7F) adolescent volunteers have been recruited. Mean age of the NV group (14.7 +/- 1.8 yrs) was not different from that of the depressed youths (13.9 +/-1.8 yrs). During the two-choice probabilistic task, 41.2% +/- 26.4% of the NV and 67.1% +/-38.5% of the DV made a āriskyā selection. The groups did not differ from each other on measures of reaction time during the reward task. Preliminary fMRI results suggest that NVs activate orbitofrontal, anterior cingulate and inferior frontal cortex during the selection component of the task. We will contrast activations between the normal and depressed youths and also assess differences across risk categories. Longitudinal clinical assessments will determine whether these baseline differences in risk taking behavior and brain function are associated with higher vulnerability to SUD in depressed youth.

44. Hippocampal Volume in Neuropsychiatric Disorders
Elbert Geuze, Eric Vermetten* and J D Bremner

Psychiatry, Rudolf Magnus Institute Neurosciences, Utrecht, Netherlands; Military Psychiatry, Central Military Hospital, Utrecht, Netherlands

Sponsor: J. Douglas Bremner

BACKGROUND: The advance of neuroimaging techniques has resulted in a burgeoning of studies reporting abnormalities in brain structure and function in a number of neuropsychiatric disorders. The use of MRI derived hippocampal volume is a proven method with diagnostic value, which is also used in the determination of etiology and course of neuropsychiatric diseases. **METHOD:** We reviewed the literature and selected all English-language, human subject, data-driven papers on hippocampal volumetry, yielding a database of 423 records. From this database the methodology of all original manual tracing protocols were studied. **RESULTS:** These protocols differed in a number of important factors for accurate hippocampal volume determination including magnetic field strength, the number of slices assessed and the thickness of slices, hippocampal orientation correction, volumetric correction, software used, inter-rater reliability, and anatomical boundaries of the hippocampus. In addition, the research findings of these studies were reviewed. **CONCLUSION:** More than 100 segmentation protocols are used that do not allow for one on one comparison across studies. Smaller hippocampal volumes have been reported in a variety of neurological and psychiatric disorders and survivors of low birth weight (10-25%). Larger hippocampal volumes have been correlated with bipolar disorder, autism, and children with fragile X syndrome (10-25%) Optimal determination of hippocampal volume is dependent on a large number of factors related to image acquisition, image processing, and anatomic guidelines.

45. Neuronal Activation in Response to Taste Stimuli - A fMRI Study
Angela Wagner*, Guido K Frank, Howard Aizenstein, Jennifer Figurski, Christopher May, Ursula F Bailer, Shannan E Henry, Claire McConaha, Vickie Vogel and Walter H Kaye

Psychiatry, University of Pittsburgh, Western Psychiatric Institute & Clinic, Pittsburgh, PA, USA; Child & Adolescent Psychiatry, University of Mannheim, Central Institute of Mental Health, Mannheim, Germany

Sponsor: Walter Kaye

It is not known whether appetite disturbances in eating disorders are related to anxious, obsessional preoccupation with weight gain or whether there is a primary disturbance of the regulation of appetite. The orbital frontal, anterior cingulate, antero-medial temporal, and insula regions contribute to the modulation of taste and other aspects of feeding, such as the hedonic or rewarding aspects of food consumption. In order to test the hypothesis that disturbances of the hedonics or rewarding aspects of feeding may contribute to anorexia nervosa, our group (Frank et al 2003) has developed a paradigm that blindly compares a 10 % sucrose solution to distilled water, using a programmable syringe pump, while subjects undergo functional MR imaging. The paradigm consisted of six blocks, four blocks in which the solution was given repeatedly over the whole block and two blocks in which the solutions were randomly alternated. Anatomical and functional imaging was performed using a 3T MR scanner. The data were analysed with a Region of Interest based method using Neuroimaging Software (NIS). A pilot study of 9 healthy women (HW), using a block analysis, showed a significantly lower activation in the medial orbitofrontal cortex (0.024) when sucrose was compared to water. An event-related approach confirmed these results and revealed a sustained activation over the time course. In comparison, other regions, such as the amygdala, showed a higher activation of sucrose in comparison to distilled water (0.08). These preliminary results suggest that HW show a lower activation with sucrose in the secondary taste cortex, where the reward value of taste is represented. The activity levels of the amygdala could reflect the motivational or emotional aspects of this study. These findings are similar to other studies in humans and primates that show activation in brain areas associated with emotional coding of taste experience.

46. [99mTc]TRODAT-1 SPECT Imaging Correlates with Anxiety and Depression Symptoms in Parkinson's Disease
Daniel Weintraub*, Andrew B Newberg, Andrew D Siderowf, Paul J Moberg, Galit Kleiner-Fisman, John E Duda, Matthew B Stern, P D Mosley and Ira R Katz

Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; Neurology, University of Pennsylvania, Philadelphia, PA, USA

Sponsor: Ira Katz

Research in PD and non-PD patients suggests that depression is associated with striatal changes, especially left hemisphere impairment. Depression in non-PD patients is associated with altered basal

ganglia DAT availability, but the relationship between neuropsychiatric symptoms and nigrostriatal DAT availability in PD is unknown. Patients with idiopathic PD (N=76) and age-matched healthy volunteers (N=46) underwent single photon emission computed tomographic (SPECT) brain scans using [99mTc]TRODAT-1, a radiolabeled tropane that selectively binds to the DAT. TRODAT-1 distribution volume ratios, a reflection of DAT availability, were calculated from the SPECT scan data for six regions of interest (ROIs) in the caudate and putamen. The association between neuropsychiatric symptoms (anxiety, depression, and fatigue) and DAT availability was explored for both subject groups. PD patients demonstrated less DAT availability than healthy volunteers (all ROIs P<.001). In PD, higher individual affective measures (anxiety [r=-.30, P=.01] and depression [r=-.24, P=.05]) and total affect score (r=-.31, P=.01) were associated with diminished left anterior putamen DAT availability; no association was found in controls. The association between total affect score and DAT availability in PD was present only in the subset of patients with less severe PD (r=-.35, P=.04). These preliminary findings suggest that affective symptoms are associated with nigrostriatal dopamine system deficits in PD. This is consistent with previous research showing a link between depression and left basal ganglia impairment, and extends this finding to include anxiety. The presence of an association only in less severe PD suggests either a floor effect for the neuroimaging techniques used or that the pathophysiology of anxiety and depression in PD changes with disease progression.

47. Pre, Post and Intrasynaptic PET Measures of the Dopamine and Serotonin System in Tourette Syndrome

Dean F Wong*, James Brasic, Harvey Singer, Anil Kumar, Hiroto Kuwabara, Yun Zhou, Weiguo Ye, Mohab Alexander and David Schretlen

Radiology, Johns Hopkins University, Baltimore, MD, USA; Psychiatry, Johns Hopkins University, Baltimore, MD, USA

Introduction: The dopamine (DA) and serotonin (5HT) systems are important in the pathophysiology of Tourette Syndrome (TS). The DA system is generally considered to be the primary dysfunctional neurotransmitter. This is reinforced by the abnormalities shown both postmortem and by PET studies as well as treatment. TS also has co-morbidity with attention deficit disorder and obsessive compulsive disorder which not only reinforces the role of DA, but also the potential role of 5HT. We report here our preliminary results to examine pre, post and intrasynaptic measurements of D2 DA receptors, DA transporters (DAT) and psychostimulant (iv amphetamine) induced dopamine release as well as serotonin transporters (SERT) and 5HT2A receptors. **Methods:** DA studies consisted of a four-PET scan (GE Advance PET) design. For dopamine day I: scan 1 and scan 2 high specific activity bolus IV [11C] raclopride PET imaging with the second scan preceded by iv amphetamine (0.3 mg/kg) for a measure of dopamine release (DAR). This is followed 3-4 days later with day 2 studies using scan 3 with 11C WIN 35,428 for DAT and low specific activity [11C] raclopride for scan 4. D2 DA receptor density (Bmax) was measured from scan 1 and scan 4, DAT binding potential from scan 3. For 5HT, SERT is measured with 11C McN 5652 and the 5HT2A with 11C MDL 100,907. All studies involved IV bolus injections with radioarterial sampling input and HPLC metabolite correction for the input function. Subdivisions of striatum employing a volume of interest approach (Kuwabara et al 2003) with co-registered SPGR MRI was employed. DA studies for various methods of mathematical modeling are employed. For the DA studies we have carried out 11 TS subjects (DSM IV), average age 31 years ± 9 (SD)(9M, 2F) and 8 healthy controls, average age 26 ± 6 (4M, 4F). Clinician rated measures: YBOCS 8, Yale tic severity 21, AIMS 11, NIMH Global OC 5. All these subjects received 4 PET scans for the 3 outcome measures for dopamine described above. **Results:** The most striking findings with the primary univariate DA findings were with DAR. The Logan method and the Lammertsma simplified reference tissue method yielded significant elevations 101-151% for DAR for right ventral striatum (TS (17-18) vs control (7-8) (p<0.03) after age adjustment. There were trends for elevated DAR in all other basal ganglia subdivisions including anterior and posterior caudate or putamen. Multivariate analyses for TS with D2 Bmax, DAT and DAR are on going, and will be compared with controls. Preliminary studies involving pre/post 5HT included 7 subjects with TS (average age 32 ± 6) (5M, 2F) and 7 control subjects (average age 32 ± 7) (3M, 4F). Clinician rated measures: YBOCS 17, Yale tic severity 55, AIMS 12, NIMH Global OC 5. Preliminary modeling in the binding potentials for both the SERT and the 5HT2A demonstrated a reduction of 19% in midbrain (SERT), putamen (7%), caudate (18%) in SERT using a parametric modeling approach as initially reported elsewhere (Zhou et al 2004). **Conclusions:** These results, employing a newer higher resolution scanner and improved volume of interest and modeling quantification, confirm and extend the original results of DAR elevation or published by our group (Singer et al, Am J Psych 159:1329, 2002) using an older PET scanner, the GE4096+. The addition of analyses with the DAT and D2 Bmax simultaneously with DAR and/or SERT and 5HT2A illustrates the promising opportunity of studying all neurotransmitter changes in the same person to better understand the DA/5HT pathophysiology of TS. Funded by NIH (NS 38927, K24-DA00412) and Tourette Syndrome Association.

48. An fMRI Study Of Cognitive Deficits Following Exposure To A High-Load Working Memory Task

Richard J Yun*, John H Krystal and Daniel H Mathalon

Department of Psychiatry, Yale University, New Haven, CT, USA; Department of Psychiatry, VA Connecticut Healthcare System, West Haven, CT, USA

Sponsor: Travel Awardee, PMRTP, 2004

Background: The N-back is a variable-difficulty working memory task that has been used to demonstrate capacity constraints in healthy individuals. At high loads, subjects have been shown to exhibit a decrease in task accuracy associated with a decrease in activation of dorsolateral prefrontal cortex (DLPFC). High-load working memory tasks are similar to the unsolvable problems used in human "learned helplessness" paradigms in that both involve the experience of response-outcome noncontingency. Thus, we hypothesized that exposure to high-loads in the N-back task could induce a transient learned helplessness-like state, producing impairments in subsequent performance and associated prefrontal brain activity during lower working memory load conditions. **Methods:** Healthy subjects (n=21, age mean +/- SD = 26.6 +/- 7.8) performed blocks of N-back alternating in difficulty between 1-back, 2-back, and 4-back while undergoing BOLD fMRI (Siemens 3T scanner, EPI sequence, TR=2 sec, TE=30, FA=85, FOV=20 cm). Data were analyzed using the general linear model as implemented in SPM2. Accuracy and DLPFC brain activity during blocks of 2-back that immediately followed blocks of 4-back ("2-back/4") were compared to the same measures during blocks of 2-back that immediately followed blocks of 1-back ("2-back/1"). **Results:** As a whole, subjects experienced a decline in accuracy from the 2-back/1 to 2-back/4 conditions (mean percent change +/- SEM = -4.4% +/- 1.5%, p=0.007). Analysis of corresponding fMRI data showed reduced activation on 2-back/4 relative to 2-back/1 in regions including bilateral DLPFC and bilateral medial dorsal thalamus (p<0.002 uncorrected, extent threshold=3). Worse performance on the 4-back was directly related to a decline in performance from 2-back/1 to 2-back/4 (r=0.50, p=0.02). In order to further explore the relationship between performance decline and DLPFC activation, the subjects were divided into tertiles (n=7 each) based on the extent to which performance declined from 2-back/1 to 2/back/4. The group with the greatest performance decline ("the deficit group") was compared to the group with the least performance decline ("the no-deficit group") on the fMRI contrast of 2-

back/1 minus 2-back/4. Compared to the no-deficit group, the deficit group showed greater reduction of bilateral DLPFC activity in the 2-back/4 relative to the 2-back/1 condition ($p<0.01$ uncorrected, extent threshold=3). **Conclusions:** Our data suggest that exposure to a difficult working memory load can induce transient cognitive deficits during subsequent performance at easier loads, and that this effect is associated with decreased brain activation in prefrontal regions including DLPFC. We plan to further explore possible links between vulnerability to this effect and vulnerability to various mental disorders including major depressive disorder.

49. Placebo Activation of Brain Regional Endogenous Opioid Neurotransmission

Jon-Kar Zubieta*, Joshua A Bueller, Lisa R Jackson, David J Scott, Yanjun Xu, Robert A Koeppe and Christian S Stohler

Psychiatry, Radiology, University of Michigan, Ann Arbor, MI, USA

Reductions in pain ratings when administered a placebo with expected analgesic properties have been described and hypothesized to be mediated by the endogenous opioid system. We directly examined in 14 male healthy volunteers, 20-30 years of age, the activity of the endogenous opioid system on mu-opioid receptors during experimentally-induced sustained pain with and without the administration of a placebo. Three PET studies were performed with [11C]carfentanil, a selective mu-opioid receptor radiotracer, incorporating a baseline study, sustained pain, and sustained pain placebo conditions. 10-15 mCi of [11C]carfentanil were administered for each of the studies using a bolus continuous infusion tracer delivery which produced steady-state tracer levels by 40 min post-tracer administration. Binding potential measures (Bmax/Kd) were obtained including data from 40-90 min post-tracer administration with Logan plots and occipital cortex as the input function. Sustained pain conditions with and without placebo were introduced 40 min post-tracer administration, and were randomized and counterbalanced in order between subjects. Significant activation of mu-opioid neurotransmission by pain alone was observed in the rostral, dorsal anterior cingulate and adjacent prefrontal cortex, right (contralateral to pain) insular cortex, medial thalamus, ventral basal ganglia (incorporating the nucleus accumbens and ventral pallidum) bilaterally, right amygdala, left subamygdalar temporal cortex and the periaqueductal gray (z scores from 3.56 to 9.26, $p< 0.05$ after correction for multiple comparisons). Significant placebo-induced activation of mu-opioid receptor mediated neurotransmission was observed in both higher order and subcortical brain regions, which included the rostral anterior cingulate, the dorsolateral prefrontal cortex, insular cortex and the nucleus accumbens (z scores 4.15 to 4.83, $p < 0.05$ after correction for multiple comparisons). Regional activations attributable to placebo were correlated with lower ratings of pain intensity, reductions in its sensory and affective qualities and in the negative emotional state of the volunteers ($p < 0.05$). These data demonstrate that cognitive factors (e.g., expectation of pain relief) are capable of modulating physical and emotional states through the site-specific activation of mu-opioid receptor signaling in the human brain. Supported by grant RO1 AT 001415 to J.K.Z.

50. Microglia Activation in Patients with Schizophrenia: An (R)-[11C]-PK11195 Positron Emission Tomography Study

Bart N Van Berckel*, Ronald Boellaard, Esther Caspers, Wiepke Cahn, Adriaan A Lammerstma and Rene Kahn

Dept of Psychiatry, Rudolf Magnus Institute for Neuroscience, Utrecht, Netherlands; Department of Nuclear Medicine and PET research, VUmc, Amsterdam, Netherlands

Sponsor: Herbert Barry

Schizophrenia is a complex and chronic disease that affects different aspects of cognition and behaviour, including attention, perception, thought processes, emotion and volition. Schizophrenia is a brain disease particularly involving decrement in gray matter as has been supported by findings from many imaging studies. The pathophysiology of these gray matter changes has not been clarified. Microglia activation is the consequence of virtually all conditions associated with neuronal injury. When activated following neuronal damage, microglia show a marked increase in the expression of peripheral type benzodiazepine binding sites, which are particularly abundant on cells of the mononuclear macrophage. (R)-PK11195[1-(2-chlorophenyl)-N-methyl-N-1(1-methylpropyl]-3soquinolinecarboxamide) is a highly selective ligand for the peripheral benzodiazepine binding site. (R)-PK11195, labeled with the positron emitter carbon-11, can be used to monitor the peripheral type benzodiazepine receptors using Positron Emission Tomography (PET). In this currently ongoing protocol, 5 patients with schizophrenia (DSM-IV criteria) and 3 healthy controls have been included to date. All patients were treated with atypical anti-psychotics. PET scans were performed using an ECAT-EXACT HR+ scanner. A dynamic 3D scan, consisting of 22 frames over 60 minutes, was acquired following a bolus injection of 370 MBq (R)-[11C]-PK11195. Arterial whole blood concentration was monitored continiously using an online detection system. In addition, discrete samples were taken in order to derive a metabolite corrected plasma curve. Finally, for each subject a T1 weighted structural MRI scan was acquired using a Philips 1.5 Tesla scanner. For initial analysis, regions of interest were defined on a sum image consisting of the early frames of the (R)-[11C]-PK11195 scan. ROI were defined for frontal cortex, cerebellum and thalamus. These ROI were projected onto the dynamic (R)-[11C]-PK11195 scans, thereby generating time activity curves for each region. A two-tissue reversible compartment model (K1/k2 fixed to values obtained from whole brain) using a metabolite corrected plasma input function was fitted to the data. In addition, the simplified reference tissue model was used with the cerebellum as reference tissue. The primary outcome measure was binding potential (BP). Initial analyses indicate a moderate elevation of (R)-[11C]-PK11195 binding in the thalamus in patients with schizophrenia. More subjects are currently being included.

51. Electroconvulsive Therapy Increases Angiogenesis and Neurogenesis in the Monkey Hippocampus

Tarique D Perera*, Jeremy D Coplan, Cecilia M Lipira, Cristina Carpio, Sarah H Lisanby, Goradsz Rosoklija, Rene Hen, Lenard A Rosenblum, Andrew J Dwork and Harold A Sackeim

Psychiatry, Columbia University, New York, NY, USA

Sponsor: Travel Awardee, BMS, 2004

A plausible, yet speculative hypothesis states that the formation of new neurons (neurogenesis) in the hippocampus is associated with the therapeutic effects of antidepressants. In rodent studies, environmental stress and drugs of abuse suppress neurogenesis whereas all classes of established antidepressants stimulate neuron formation. The hippocampal precursors cells that give rise to neurons also appear to mature into endothelial cells that line new vessels (angiogenesis). Indeed, electroconvulsive shock (ECS), which is the animal analogue of the antidepressant ECT, was reported to stimulate both neurogenesis and angiogenesis in the rat hippocampus. In order to determine the clinical relevance of these antepressant mediated hippocampal changes, non-human primate studies were warranted. We addressed this need by showing that ECS robustly increased precursor cell proliferation in the adult Old World monkey hippocampus and that these cells differentiated into mature neurons and glia. We now report that a fraction of these hippocampal precursors also differentiate into endothelial cells that line capillaries. Thus, relative to sham-treated controls, ECS results in a marked increase in both neurogenesis and angiogenesis in the monkey hippocampus. It is likely that similar structural brain changes occur in humans and may play a

role in the therapeutic actions of ECT and other antidepressant medications.

52. Interaction of SERT & BDNF: Susceptibility for Depression is Reflected in Morphometric Changes of Critical Limbic Circuits in Humans

Lukas Pezawas*, Aaron L Goldman, Beth A Verchinski, Venkata S Mattay, Joseph H Callicott, Bhaskar S Kolachana, Richard E Straub, Michael F Egan, Andreas Meyer-Lindenberg and Daniel R Weinberger

Genes, Cognition and Psychosis Program (GCAP), NIMH, NIH, Bethesda, MD, USA

Sponsor: Daniel Weinberger

Introduction: BDNF and SERT, both of which have been associated with psychopathological states, are important genes in brain development and in functions related to memory and to emotion. Genetic variations of the BDNF (val66met) and SERT gene (5-HTTLPR) affect the function of these proteins in neurons and predict variation in human memory and in fear behavior. We hypothesized that SERT s-carriers would show reduced gray matter volume in limbic regions critical to the processing of unpleasant emotion, especially the subgenual cingulate and bilateral amygdalae (Hariri et al 2002). Additionally, we hypothesized that consistent with the cellular and clinical effects of the BDNF val66met polymorphism and the role of BDNF in cortical development and in hippocampal function (Egan et al 2003), met-allele carriers would have reduced hippocampal gray matter volume. The SERT effect on mechanisms implicated in fear behavior is mediated in part by BDNF and has been explored to a limited degree in animals. This suggests that the SERT effect on susceptibility for depression may be mediated at least in part by BDNF. Thus, we also hypothesized that the mediating effect of BDNF can be tested directly in humans by analyzing the interactions between functional polymorphisms within these two genes, and that the met-allele of BDNF would protect against the adverse implications of s-HTTLPR. **Methods:** We investigated high-resolution anatomical magnetic resonance images (MRI) of 111 normal healthy volunteers (Caucasians of European ancestry) without any psychiatric life-time history using optimized voxel-based morphometry (VBM), a sophisticated fully automated morphological imaging technique, which allows a statistical comparison of gray matter volume on a voxel-by-voxel basis. **Results:** Consistent with our initial hypothesis, we found bilateral reductions of hippocampal gray matter volume (right: $p<0.001$; left: $p=0.013$) in met-BDNF carriers compared with val/val-BDNF subjects. Furthermore, we performed an exploratory analysis of the entire brain and found that, compared to val/val-carriers, met-BDNF carriers exhibited additional loci of reduced gray matter volumes predominately in the lateral convexity of the frontal lobes, with peak values encompassing the dorsolateral prefrontal cortex bilaterally ($p<0.001$). In SERT s-carriers, as hypothesized, we found significantly reduced bilateral gray matter volumes in both the amygdala and the subgenual anterior cingulate. Finally, we found that the SERT s-allele effect on subgenual cingulate volume is dramatically reduced in BDNF met-allele carriers in comparison to val/val carriers ($p<0.001$) in which the effect appears exaggerated.**Conclusion:** The val66met BDNF polymorphism may be a modifying genetic factor for depression, because it affects development and plasticity of critical serotonergic brain systems related to the experience of negative mood and may lead, together with abnormal serotonergic function (s-allele), to an anatomical substrate reflecting an increased vulnerability for depression. Our results also likely explain the increased risk of mood disorder associated with the val-allele of BDNF. The fact that these results were found in normal volunteers demonstrates that these putative developmental differences are a mechanism of genetic susceptibility. References: Egan, M.F. et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257-69 (2003); Hariri, A.R. et al. Serotonin transporter genetic variation and the response of the human amygdala. Science 297, 400-3 (2002).

53. A Preliminary Genetic Investigation of the Relationship Between Body Dysmorphic Disorder and OCD

Margaret A Richter, Subi Tharmalingam, E Burroughs, Nicole A King, Willam E Menard, James L Kennedy and Katharine A Phillips*

Butler Hospital, Department of Psychiatry, Brown Medical School, Providence, RI, USA

Body dysmorphic disorder (BDD) is a relatively common and impairing somatoform disorder that is characterized by a distressing and/or impairing preoccupation with an imagined or slight defect in one's physical appearance. Controlled family studies, phenomenology studies, comorbidity studies, and treatment studies (showing selective response to SRIs) suggest that BDD may be closely related to OCD. Indeed, BDD is widely conceptualized as an OCD-spectrum disorder, although these disorders also have some differences (e.g., poorer insight in BDD). In this study we examined the genetic relationship between BDD and OCD, focusing on previously reported candidate genes. To our knowledge, our study is the only study that has examined the genetics of BDD or its genetic relationship to OCD. We tested polymorphisms in the serotonin, dopamine, and gamma-aminobutyric acid systems, all of which have been implicated previously in OCD. Dopamine system genes were also of interest because BDD symptoms are often psychotic (i.e., delusional). Serotonergic candidates included the 5HT1B and 5-HT1A receptor genes, and both the VNTR and promoter-region (5-HTTLPR) polymorphisms for the serotonin transporter. The dopamine DRD4 and DRD5 receptor genes and the dopamine transporter (DAT1), as well as the $GABA_A$-$\gamma 2$, were also typed. Participants were 50 individuals with BDD (31 with primary DSM-IV BDD and 19 with DSM-IV OCD plus comorbid BDD), 20 individuals with OCD plus comorbid subclinical BDD, and matched healthy controls of similar ethnicity and gender. Genotypes and allelic frequency were tested for all markers using chi-square analysis without controlling for multiple testing, as this was an exploratory study. BDD subjects showed association for $GABA_A$-$\gamma 2$ (5q31.1-q33.2) ($p=0.012$). Association for BDD was demonstrated at a trend level for the 5-HTTLPR (17q11.1-q12) gene ($p=.064$) considering all three genotypes, with the S/S genotype occurring more frequently in BDD subjects than in controls. A more significant result was obtained when comparing individuals with or without the long allele ($p=0.041$). In contrast, in the group with OCD plus subclinical BDD, only $GABA_A$-$\gamma 2$ showed association ($p=0.017$). No association was found for the other genes that were tested. These results must be considered preliminary, because the sample sizes were small and power was limited. Nonetheless, the $GABA_A$-$\gamma 2$ findings were similar in the two diagnostic groups, whereas the BDD group showed association for 5-HTTLPR but the group with OCD plus subclinical BDD did not. These preliminary data suggest that there may be vulnerability genes unique to BDD as compared to subclinical BDD or OCD. Further studies are needed to clarify the genetic relationship of these phenotypically similar disorders.

54. A Prospective Longitudinal Investigation of the Course of Body Dysmorphic Disorder (BDD) and Pharmacotherapy Received

Katharine A Phillips*, Maria E Pagano, William E Menard, Christina Fay and Robert L Stout

Brown Medical School, Butler Hospital, Providence, RI, USA

Body dysmorphic disorder (BDD), a distressing or impairing preoccupation with an imagined or slight defect in one's physical appearance, is a relatively common disorder that is associated with markedly poor functioning and quality of life. To our knowledge, no

previous study has prospectively examined the longitudinal course of BDD, pharmacotherapy received, or the relationship of pharmacologic treatment to course of illness. In this study, weekly BDD symptom status ratings were obtained over 1 year of prospective follow-up for 148 subjects recruited from a wide variety of sources who met full DSM-IV criteria for BDD at the baseline assessment. Probabilities of partial and full remission, as well as predictors of remission, during follow-up were examined. Full remission was defined as minimal or no BDD symptoms for at least 8 consecutive weeks and partial remission as less than full DSM-IV criteria for at least 8 consecutive weeks (assessed by the reliable Psychiatric Status Rating scale). We examined pharmacotherapy received and its relationship to illness course for 111 of the 148 subjects, with a focus on SRIs because they appear selectively efficacious for BDD and are currently the first-line treatment for BDD. Although what constitutes an adequate SRI trial for BDD is not well established, we used recommended guidelines, which are similar to those for OCD. Over 1 year of prospective follow-up, the probability of full remission from BDD was .09, and the probability of partial or full remission was .24. Subjects met full BDD criteria for a mean of 77% of all follow-up weeks, even though 83% received mental health treatment during the follow-up period. More severe BDD at the baseline assessment and the presence of a personality disorder predicted a lower probability of remission (p=.0001 and p=.030, respectively). Subjects who received surgery or nonpsychiatric medical treatment (e.g., dermatologic) for their perceived appearance defects were not more likely to remit. During 1 year of follow-up, 50.5% of the sample received an SRI, but only 9.9% received what is generally considered a minimally adequate SRI trial for BDD, and only 16.2% received an adequate SRI trial. Because so few subjects received an adequate SRI trial, data on the relationship of receipt of an adequate SRI trial to BDD course are presented descriptively. 28% of subjects had improvement in BDD symptoms following initiation of an adequate SRI trial whereas the remainder had no change (no subjects experienced worsening). These findings indicate that BDD is usually chronic. Remission probabilities were lower than those reported for mood disorders, anxiety disorders (except for social phobia), and personality disorders in studies using very similar methodology to ours. However, very few subjects received an adequate SRI trial (doses were generally very low); thus, the chronicity of BDD in this sample is not surprising.

55. Differential Patterns of Neural Response to Sad versus Happy Facial Expressions Distinguish Depressed from Healthy Individuals

Mary L Phillips*, Simon Surguladze, Paul Keedwell, Michael Brammer, Andrew W Young, Vincent Giampietro and Michael Travis

Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

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Background: Accurate recognition of facial expressions is crucial for social functioning. In individuals with major depressive disorder (MDD), cognitive models have emphasized the presence of negative schemata, which are frequently associated with impaired interpersonal functioning. Previous studies have, furthermore, demonstrated unconscious and conscious negative attentional biases towards emotionally-salient stimuli and events within the environment, including facial expressions, and a pattern of predominantly increased activity in neural regions important for the response to emotional stimuli in individuals with MDD. Aim. We wished to examine the neural basis of the reported implicit and explicit attentional biases in depressed individuals. **Methods:** Using event-related fMRI, neural responses to mild and intense happy and sad facial expressions were measured in 14 healthy individuals and 16 individuals with MDD. Linear trends in neural response to facial expressions of increasing intensity of happiness and sadness (neutral to mild to intense emotion) were measured and compared between groups. **Results:** Healthy but not depressed individuals demonstrated linear increases in neural response in bilateral fusiform gyri and right putamen to expressions of increasing happiness, whilst depressed but not healthy individuals demonstrated linear increases in response in left putamen, left parahippocampal gyrus and right fusiform gyrus to expressions of increasing sadness. There was a negative correlation in depressed individuals between depression severity and magnitude of neural response within the right fusiform gyrus to happy expressions. In depressed individuals, higher compared with lower doses of antidepressant medication were associated with decreases in neural response predominantly within fusiform gyri and cerebellum to both types of emotional expression; these findings did not, therefore, account for the significant increases in neural response to sad expressions, nor did they explain the negative correlation between depression severity and right fusiform gyral response to happy expressions in these individuals. **Conclusions:** Our findings indicate preferential increases in neural response to sad but not happy facial expressions in neural regions involved in the response to visually-presented emotional stimuli in depressed individuals. These findings may be associated with the above pattern of implicit and explicit attentional biases in these individuals, and suggest a potential neural basis for the negative cognitions and social dysfunction in MDD.

56. A Comparison of Venlafaxine XR and Paroxetine in the Treatment of Outpatients With Panic Disorder

Mark Pollack*, Timothy Whitaker, Richard Mangano and Bo Gao

Massachusetts General Hospital, Boston, MA, USA; Wyeth Pharmaceuticals, Collegeville, PA, USA

Objective: The primary objective was to compare short-term efficacy, safety, and tolerability of venlafaxine extended release (XR) with placebo in outpatients with panic disorder (PD). Secondary objectives included comparing paroxetine- and venlafaxine XR-treated groups, and paroxetine- and placebo-treated groups. **Methods:** Male or female outpatients aged ≥ 18 years, who met DSM-IV criteria for PD (±agoraphobia) for ≥3 months before study day 1 with score 4 on the Clinical Global Impression-Severity (CGI-S), had ≥8 full-symptom panic attacks in the 4 weeks before the screening visit, had ≥4 full-symptom panic attacks during the 14±3-day placebo lead-in period between screening and baseline (study day 1) visits, and had a Covi Anxiety Scale total score greater than their Raskin Depression Scale total score at screening and baseline were eligible. After the lead-in period, eligible patients were randomly assigned to receive, using titration, venlafaxine XR (75 mg/d or 225 mg/d), paroxetine 40 mg/d, or placebo for up to 12 weeks, followed by ≤14 days of taper. The primary outcome measure was the percentage of patients free of full-symptom panic attacks (≥4 symptoms) at endpoint, analyzed by logistic regression with treatment group and country as factors and baseline severity as covariate. Change in full-symptom panic attack frequency was analyzed by Mann-Whitney U test. The Panic Disorder Severity Scale (PDSS) was analyzed by analysis of covariance (ANCOVA) with treatment and country as factors and baseline score as covariate. The percentage of CGI-Improvement (CGI-I) responders (patients having a score of 1 or 2) was analyzed by Fisher exact test. Additional secondary efficacy variables included frequency of Panic and Anticipatory Anxiety Scale (PAAS) full- and limited-symptom panic attacks, PDSS (mean and response rate [40% reduction in score from baseline]), Phobia Scale (PS), Hamilton Anxiety Scale (HAM-A), CGI-S, and remission rate (no panic attacks and CGI-S score = 1 or 2). For anticipatory anxiety, ANCOVA was applied to log transformed ratios of baseline-to-endpoint changes with logs of baseline values as covariates. **Results:** 624 patients made up the ITT population (placebo, n=157; venlafaxine XR, 75 mg, n=156; venlafaxine XR 225 mg, n=160; paroxetine, n=151). Absence of full-symptom panic attacks was significantly (P<0.01 or better) greater in the venlafaxine

XR 75 mg (64.1%), venlafaxine XR 225 mg (70.0%), and paroxetine (58.9%) groups than in the placebo group (46.5%). The venlafaxine XR 75 mg and 225 mg, and paroxetine groups showed greater (P<0.001) mean improvement in PDSS scores from baseline than placebo (-11.24, -12.72, -11.67 and -8.31, respectively). The percentage of CGI-I responders was greater (P<0.001) in the venlafaxine XR 75 mg and 225 mg, and paroxetine groups than in the placebo group (82.1%, 85.6%, 83.3%, and 59.9%, respectively). All active treatment groups were superior to placebo (P<0.05 or better) on change from baseline in panic attack frequency, CGI-I mean scores, remission rate, percentage of PDSS responders, CGI-S mean change from baseline, median change from baseline in anticipatory anxiety, PS mean change in fear and avoidance factors, PAAS limited-symptom panic attack frequency, and HAM-A adjusted mean change from baseline. The venlafaxine XR 225 mg group had a significantly higher percentage of panic-free patients (P=0.0.32) and greater PDSS score improvement (P=0.0.48) at endpoint than paroxetine. Both drugs were generally well tolerated. **Conclusion:** Results suggest that venlafaxine XR 75 mg and 225 mg are safe, well tolerated, and effective in short-term treatment of PD.

57. Plasma Amyloid Beta 1-42 Levels in Geriatric Depression: A Pilot Study

Nunzio Pomara*, P. Murali Doraiswamy, Lisa Willoughby, Pankaj D Mehta and Bruce G Pollock

Psychiatry, Nathan Kline Institute/ NYU School of Medicine, Orangeburg, NY, USA

Sponsor: David J. Greenblatt

Background: Major depression is a risk factor for Alzheimer's disease (AD) and has been linked to greater brain atrophy and cognitive impairment. Elevated plasma amyloid beta 1-42 (Abeta42) levels have been linked to increased risk for incident AD in cognitively intact elderly. The only prior study that examined Abeta42 in cognitively intact subjects with major depression found elevated CSF levels relative to healthy controls raising the possibility that abnormal regulation of cerebral Abeta42 metabolism, which has been found in AD, could be one hypothetical mechanism to explain the links between depression and AD. **Methods:** In this pilot study we examined plasma Abeta40 and Abeta42 levels in non-demented elderly depressed pts (n=14; HAM-D, mean=21.4, sd=4.2) and in age- and sex-matched controls (n=14; HAM-D mean=0.4, sd=1.3) between the ages of 67 to 79 years (mean=71.9, sd=3.4) and having a MMSE score of 25 or better (mean=28.2, sd=1.5). The 28 subjects were selected from a larger pool of subjects based just on age and gender matching and blinded to Abeta levels. The effect of 6 weeks treatment on plasma Abeta levels in an additional group of non-demented depressed elderly individuals ages 67 to 95 years (HAM-D mean=21.8, sd=4.1; MMSE mean=27.9, sd=1.5) who were treated with either paroxetine (n=19; mean age=76.5, sd=6.1) or nortriptyline (n= 16; mean age=82.5, sd=7.2) was also determined. Abeta40 and Abeta42 levels were determined in properly stored plasma samples using ELISA assays. Analyses were performed on Abeta40 and 42 levels, as well as on the Abeta peptide ratio 42/40, which has been shown to be better in discriminating AD from controls than Abeta42 alone. **Results:** Elderly depressed pts showed a selective elevation in plasma Abeta42 levels (mean=14.3 pg/ml, sd=5.2) relative to controls (mean=8.1 pg/ml, sd=1.4; p<.01). Abeta42/40 ratio values were also increased in elderly depressed (mean=.18, sd=.06) relative to controls (mean=.10, sd=.05; p=.001). Acute treatment with either paroxetine or nortriptyline did not produce any significant change from baseline or differential effect on plasma Abeta40 or Abeta42 or Abeta42/40 ratio levels. Additional analyses using MRI data from the depressed elderly group indicated that higher Abeta42/40 ratios were associated with greater changes in white matter. **Conclusion:** In summary, this is the first study to report elevated plasma Abeta42 and Abeta peptide ratio 42/40 in elderly depressives, their relationship to white matter changes, and the effect of antidepressant treatment. Further studies will be needed to confirm our preliminary findings and to evaluate the role, if any, that alterations in Abeta42 metabolism might have in the development of cognitive and cerebral abnormalities in geriatric depression.

58. Ziprasidone in Bipolar Mania: Efficacy Across Patient Subgroups

Steven G Potkin*, Paul Keck, Earl Giller, Kathleen Ice, Lewis Warrington and Antony Loebel

Neuropsychiatric Center, University of California - Irvine, Orange, CA, USA

BACKGROUND: To evaluate the efficacy and tolerability of ziprasidone in acute bipolar mania, focusing on clinically relevant subgroups. **METHODS:** This was a pooled analysis of two randomized, double-blind 21-day trials comparing flexible-dose ziprasidone (40 to 80 mg BID) to placebo in adults with mania associated with bipolar I disorder. Changes in Mania Rating Scale (MRS) score and CGI-S were calculated for combined study populations and in subgroups of patients with manic episodes or mixed episodes, and with or without psychotic symptoms. **RESULTS:** At last visit (LOCF), mean change in MRS in patients receiving ziprasidone (n=268) was -11.72 (baseline 26.82) vs -6.69 (baseline 26.53) in patients receiving placebo (n=131) (P<0.001). Change in CGI-S for ziprasidone was -1.19 (baseline 4.71) vs -0.66 (baseline 4.76) for placebo (P<0.001). Significant improvement vs placebo was observed from Day 2 for MRS and Day 4 for CGI-S. MRS and CGI-S changes were comparably robust whether the manic episode of subjects was classified as acute or mixed, or was complicated by psychotic symptoms or not. Overall, ziprasidone subjects had a response rate of 48% and a remission rate of 40% (both P<0.01 vs placebo). **CONCLUSIONS:** Ziprasidone rapidly improves symptoms and global illness severity in bipolar mania. It is comparably efficacious in mixed and manic episodes and in the presence or absence of psychotic symptoms, and is well tolerated.

59. Corticostrone Accelerates Extinction Of Conditioned Fear In Rats

Gregory J Quirk*, Patricia Hernandez-Poudevida and Bruce S McEwen

Physiology, Ponce School of Medicine, Puerto Rico, Puerto Rico

People with posttraumatic stress disorder (PTSD) exhibit exaggerated fear responses to stimuli associated with the traumatic event. It has been suggested that this may be due to deficient extinction of conditioned fear (Peri et al., 2000; Charney et al., 2004). Another hallmark of PTSD is decreased cortisol levels (Yehuda et al., 1998). To investigate the possibility that cortisol might modulate extinction learning, we used auditory fear conditioning in rats. On day 1, rats were given 7 tones paired with shocks. On day 2, we administered exogenous corticosterone (10 mg/kg s.c.) or vehicle, one hour prior to 10 extinction trials (tone alone, ITI=4 min). Rats injected with corticosterone extinguished to 12% of their initial freezing level, compared to 59% in vehicle-treated rats ($t(18)=3.2$, $p < 0.01$). On day 3, corticosterone-treated rats continued to show significantly lower freezing to the tone in the absence of drug (21% vs 65%, $t=2.5$, $p < 0.05$). We then asked if reducing plasma levels of corticosterone would inhibit extinction. Low-dose dexamethasone (0.05 mg/kg sc) reduced plasma corticosterone 95% compared to controls, but had no effect on extinction (vehicle: 16%, dexamethasone: 15%, of initial fear). Thus, while not necessary for extinction, corticosterone can accelerate extinction, perhaps by acting on prefrontal-amygdala circuits. These findings support recent studies showing that administration of adrenal corticosteroids reduces the incidence of PTSD symptoms in humans (Schelling et al., 2001; Aerni et al., 2004). Facilitation of extinction by corticosterone suggests that administration of corticosteroids might accelerate extinction-based exposure therapy

for PTSD and specific phobias. Supported by NIH grants R01-MH58883, S06-GM08239, and P50-MH58911.

60. 12-Week, Double-Blind, Placebo-Controlled Study of Ziprasidone vs Haloperidol for Efficacy and Maintained Treatment Effect in Acute Bipolar Mania

Tanya Ramey*, Earl L Giller, Patricia English, Robert Riesenberg, Jitendra K Trivedi, Janardhan Y Reddy, Yuri A Aleksandrovsky, Vladimir A Tochilov and B K Koe

Department of Neuroscience, Pfizer Global Research and Development, Groton, CT, USA

Sponsor: B Kenneth Koe

Objectives: Previous 3-week studies have shown that ziprasidone is effective in the treatment of bipolar mania. The objectives of this 12-week study were to establish superior efficacy of ziprasidone versus placebo in the treatment of bipolar mania at week 3 and to evaluate maintenance of effect for ziprasidone and haloperidol. **Methods:** A total of 438 bipolar patients with current episode manic or mixed were randomly assigned to double-blind treatment with flexibly-dosed ziprasidone (40-80 mg BID), haloperidol (4-15 mg BID), or placebo for the first 3 weeks. At the end of Week 3 of double-blind treatment, placebo subjects were reassigned to ziprasidone for the remainder of the trial and were analyzed for safety only. Subjects randomized to ziprasidone or haloperidol continued to receive the assigned treatment for up to 12 weeks. The primary efficacy measure was mean change from baseline to Week 3 in Mania Rating Scale (MRS) Total score (SADS-CB derived). Maintenance of effect was determined by the percent of Week 3 responders (at least 50% decrease in MRS from baseline) who remained responders at Week 12. **Results:** Ziprasidone was superior to placebo at Week 3 ($P<0.001$) in both LOCF and OC analyses of mean change from baseline on the MRS. The effect of ziprasidone was significant as early as Day 2. The responder rate at Week 3 was significantly higher in the ziprasidone group (36.9%) compared with the placebo group (20.5%). Improvement in the MRS was maintained for ziprasidone: 92.5% of the subjects who responded at Week 3 were still in response at Week 12. The ziprasidone- and haloperidol-treatment groups had similar percentages of responders. In addition, ziprasidone was statistically significantly superior to placebo in CGI-S and CGI-I scores at Week 3. More subjects in the haloperidol treatment group (5.0 %) switched to depression than subjects in the ziprasidone treatment group (3.4 %). **Conclusion:** Ziprasidone was efficacious in the treatment of mania, and this effect was maintained throughout the 12-week study. Ziprasidone was also safe and well tolerated in patients with bipolar mania.

61. Serotonergic Neuroanatomy of the Amygdala in Human, Baboon and Rat: Serotonin transporter, 5-HT1A and 5-HT2A receptors

Sarina M Rodrigues*, Mark D Underwood, J. J Mann and Victoria Arango

Neuroscience, New York State Psychiatric Institute, New York, NY, USA

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Alterations in serotonergic neurotransmission in the amygdala, a brain region critical for regulation of emotion and affect, have been shown to correlate with depression and suicidal behavior. Our laboratory has found that suicide victims exhibit serotonergic dysregulation in brain areas with strong connections to the amygdala, including the prefrontal cortex and dorsal raphe nucleus. We sought to characterize the receptor binding patterns and amount of the serotonin transporter (SERT), the 5-HT_{1A} receptor, and the 5-HT_{2A} receptor in the human amygdala using quantitative receptor autoradiography with [3H]cyanoimipramine, [3H]8-OH-DPAT, and [3H]ketanserin, respectively. We are also in the process of comparing these patterns to those found in the baboon and rat amygdala. The distribution of these receptors at the cellular level was also examined with immunohistochemical staining for these proteins. The lateral (LA), basal (B), and accessory basal (AB) nuclei were examined as they are the principal components for emotional computation in the amygdala. In the human amygdala, SERT binding is extremely robust in all three nuclei. The highest binding is in AB, while L and B have a similar number of sites. In the rat amygdala, however, SERT binding is most robust in B as compared to LA and AB. Immunohistochemistry for SERT in human and baboon tissue reveals a very dense axonal plexus of serotonergic innervation throughout the entire amygdala. 5-HT_{1A} binding in the human and baboon, in contrast, is highest in B as compared to AB and LA, with LA having the lowest level of binding. 5-HT_{1A} binding in the rat is similar throughout LA, B, and AB. Immunohistochemistry in human, baboon, and rat tissue for the 5-HT_{1A} receptor shows that it is primarily localized to the somata and initial axon segment of pyramidal neurons in the amygdala. Finally, 5-HT_{2A} binding in the human amygdala is significantly higher in LA among the three nuclei. Immunohistochemical stains in human, monkey, and rat tissue for the 5-HT_{2A} receptor display immunoreactivity primarily in apical dendrites, cell bodies, and glia. These findings reveal a unique distribution of SERT, 5-HT_{1A} and 5-HT_{2A} receptors in amygdaloid subnuclei essential for emotional computation and provide useful information about serotonergic proteins in these structures. This study provides a framework for subsequent postmortem studies of the amygdala and how it might be altered in individuals who are affected by major depression and suicidal behavior. Supported by MH40210 and MH62185.

62. Amygdala CRF-binding Protein Gene Expression: A Human Post Mortem Brain Study

Pat Roseboom*, Ryan J Herringa and Ned H Kalin

Psychiatry, University of Wisconsin, Madison, WI, USA

Sponsor: Ned Kalin

Stressful life events are commonly associated with the onset and maintenance of psychopathology. Much research has focused on the role of the corticotropin-releasing factor (CRF) system in psychopathology. Since CRF serves to integrate the stress response, the possibility exists that the CRF system is a key mediator of the effects of stress and the expression of psychopathology. Furthermore, a number of studies suggest that depression and perhaps anxiety disorders are associated with increased brain CRF activity. While CRF-binding protein is thought to modulate CRF activity, alterations in this system have not been well studied in relation to psychopathology. The possibility exists that in some psychopathological states, alterations in CRF-BP function may contribute to dysregulation of the CRF system. Indeed, a recent study suggests that variants of the CRF-BP gene may contribute to the genetic vulnerability of depression. Therefore, we examined amygdala CRF-BP gene expression in post mortem brains from patients who suffer from unipolar depression, bipolar disorder, schizophrenia, and age-, sex- and post mortem delay-matched controls. This is the first report of the anatomical distribution of human CRF-BP mRNA in the amygdala and medial temporal lobe region. Preliminary statistical analysis revealed significantly lower CRF-BP mRNA levels in the bipolar and schizophrenic groups compared to the control group. These data raise the possibility of dysregulation of amygdala CRF-BP in psychopathology.

63. Mifepristone (Ru486) in the Treatment Of Psychotic Depression: Re-Evaluation of Published Data

Robert T Rubin* and Bernard J Carroll

Center for Neurosciences Research, Allegheny General Hospital, Pittsburgh, PA, USA

Increased hypothalamo-pituitary-adrenal cortical (HPA) axis activity occurs in 30-50% of patients with major depression and perhaps more often in those with psychotic features, defined in DSM-IV

as major depression with the presence of delusions or hallucinations. Standard treatment of psychotic depression is with a combination of antidepressant and antipsychotic drugs, or by ECT. Under the hypothesis that increased HPA axis activity may underlie some of the symptoms of psychotic depression, reduction of the effects of the glucocorticoid, cortisol, have been attempted by suppression of cortisol synthesis and by glucocorticoid receptor blockade. Mifepristone (RU486), a progesterone receptor inhibitor and a glucocorticoid receptor inhibitor at higher doses, is the latest endocrine treatment to be investigated. It is in clinical trials sponsored by Corcept Therapeutics, which holds the license for its use in psychotic depression. There have been two published studies to date, both reported as positive (1,2). In the first study (N = 5), two placebo cells were eliminated post hoc because they were considered a drug carryover effect. Even though the outcome data were paired (subjects were their own controls), an independent-samples analysis apparently was performed, yielding a p value < 0.07. In contrast, our paired-data analysis yielded a clearly nonsignificant difference ($p < 0.30$). In the second study (N = 30), mifepristone was considered to be effective, even though no statistical analysis of the outcome data was presented. In this study, as well, our analysis yielded a clearly nonsignificant difference ($p = 0.25$). Furthermore, most subjects did not show increased HPA axis activity, and many failed to show the expected HPA axis response to mifepristone. Even in the few patients who manifested both these key features (N = 5), we were unable to demonstrate a trend toward efficacy ($p > 0.50$). Finally, in large, double-blind trials (N > 200), only a small number of patients became asymptomatic, with no significant difference between drug and placebo (3). Thus, all the published data on mifepristone to date indicate it is not significantly better than placebo for treating the primary symptoms of psychotic depression. Our re-examination of these data supports the principle that appropriate and thorough statistical analysis of outcomes is needed in all published drug studies to accurately develop a therapeutic profile of a drug, starting with its earliest clinical use. Additionally, for a drug based on an endocrine principle, internal validation, by endocrine measures, of the sample and treatment is important. (1) Belanoff JK et al: J Clin Psychopharmacol 21:516, 2001. (2) Belanoff JK et al: Biol Psychiatry 52:386, 2002. (3) Corcept Therapeutics: Initial Public Offering Prospectus 14 April 2004. Supported by NIH grant MH28380-26 to RTR.

64. *IN VITRO* Hypothalamic-Pituitary-Adrenal Axis Responses to Cholinergic Drugs and Hormones in a Novel Perfusion System

Melissa A Moidel, Kimberly J Jenko, Tracy E Billings, R. K Czambel, Robert T Rubin* and Michael E Rhodes

Center for Neurosciences Research, Allegheny General Hospital, Pittsburgh, PA, USA

The hypothalamic-pituitary-adrenal (HPA) axis is a three-gland endocrine system and an important mediator of the stress response. In rats, we previously found a sexual diergism (functional sex difference) in the response of this axis to cholinergic stimulation by graded doses of physostigmine (PHYSO); males had greater hormone responses than did females. Pretreatment with mecamylamine, a nicotinic receptor blocker, augmented hormone responses to PHYSO in females but not in males. In contrast, pretreatment with scopolamine, a muscarinic receptor blocker, augmented hormone responses in both sexes, but to a significantly greater extent in males. We therefore developed an *in vitro* model of the HPA axis to study, in greater detail, pharmacological and hormonal challenges to male and female tissue components, without influence from external variables such as stress, CNS activity, and other hormones. Hypothalami, pituitaries, and adrenal glands were harvested from male and female rats. One-half hypothalamus, one-half pituitary, and one adrenal gland were placed individually into three flasks connected by tubing and perfused with modified Bradbury buffer. Sampling ports between flasks were used to collect buffer for measurement of 1) corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), 2) adrenocorticotropic hormone (ACTH), and 3) corticosterone (CORT) release from the hypothalamus, pituitary, and adrenal flasks, respectively. Hormones were measured by highly specific immunoassays. The system produced steady hormone baselines over 2-3 hours. CRH and CRH AVP administered into the pituitary flask increased ACTH and CORT production from their respective flasks, within 5 min for ACTH and 10-15 min for CORT. Acetylcholine and nicotine administration into the hypothalamus flask increased ACTH production in the pituitary flask by increasing CRH and AVP release, respectively, from the hypothalamus flask. Dexamethasone administration into the hypothalamus flask decreased ACTH and CORT release from the pituitary and adrenal flasks, respectively, but had little effect on CRH release from the hypothalamus flask. This *in vitro* system can serve as a model to study physiological and pharmacological activation of the HPA axis. Further validation of the model will include dose-response studies of hormonal feedback with various concentrations of CORT at the hypothalamic and pituitary levels, and comparison of our findings in vitro with the effects of drugs administered to rats *in vivo*. Supported by a Howard Hughes Medical Institute Grant for Off-Campus Research to MAM and NIH grant MH28380-24 to RTR.

65. Long-term Antidepressant Effects of Vagus Nerve Stimulation (VNS) in Treatment-Resistant Depression

Harold A Sackeim*, A. J Rush, Lauren B Marangell, Mark S George and Stephen Brannan

Psychiatry and Radiology, Columbia University, New York, NY, USA

Two central challenges in the therapeutics of treatment-resistant depression (TRD) are achieving short-term response and maintenance of benefit. Nearly 30,000 patients with seizure disorders have been treated with VNS. Prospective, longitudinal, uncontrolled investigations indicate that the number of patients who have clinically meaningful improvement in seizure control is substantially greater 1 year than 3 months after starting VNS, with little loss of benefit when the observation period is extended to two years. The possibility that VNS is associated with high likelihood of maintaining clinical gains was a key reason for its study in TRD. In D01, 59 TRD patients participated in an open pilot study. In D02, 205 evaluable patients were randomized to VNS or sham conditions, with short-term outcome assessed 12 weeks after implantation. Sham-treated patients were offered active VNS. Patients in both studies were monitored for a period of at least 2 years following the start of VNS. Response was defined as an improvement in HRSD (24-item) scores of at least 50% relative to preVNS baseline. For patients who met the response criterion at the end of the acute treatment phase (3 months), maintenance of benefit was examined at the 1- and 2-year time points. For patients who first met the response criterion at the 1-year assessment, maintenance of benefit was examined at the 2-year time point. Maintenance of benefit was defined a priori as a HRSD improvement relative to preVNS baseline of at least 40%. In D01, 18 of 59 (30.5%) patients met the response criterion at the acute (3 month) time point, and 44.1% and 42.4% did so at the 12- and 24-month time points, respectively (LOCF analysis). In D02, the comparable rates were 14.6%, 28.3% and 29.3%. Among the 18 responders at the acute time point in D01, 72.2% maintained the benefit at the 12 month assessment and 55.6% maintained the benefit at the 24 month assessment. Eight of the 11 (72.7%) patients who were responders at one year, but not at the earlier 3 month time point, maintained the benefit at the 24-month assessment. Among the 30 responders at the acute time point in D02, 63.3% maintained the benefit at the 12 month assessment and 76.7% maintained the benefit at the 24 month assessment. Similarly, 23 of the 38 (60.5%) responders at one year, but not at the earlier 3 month time point, maintained the benefit at the 24-month assessment. The response rates in the VNS trials increased in the period from 3 to 12 months

post-implantation, and was stable at the 24 month time point. Most critically, a high percentage of responders retained benefit at the two long-term time points. This maintenance of improvement also persisted for at least a year in patients who did not respond at the acute time point but did so at the 12 month time point. Since the data were collected under open, naturalistic conditions factors other than VNS, such as alterations in medication regimens, might have been responsible for the pattern of increased and sustained benefit. Abstractly, these outcomes could reflect placebo effects. However, these alternatives are not compatible with the fact that patients in both studies often had highly chronic episodes, and that all of these patients evidenced a high level of treatment resistance. In this light, it is likely that VNS exerted an unusual pattern of therapeutic effects in TRD, with a substantial number of patients showing signficant and, most surprisingly, sustained benefit.

66. Riluzole Augmentation in the Treatment of Major Depessive Disorder

Steven Kendell, Lisa Fenton, Vladimir Coric, Arthur Simen, John H Krystal and Gerard Sanacora*

Psychiatry, Yale University, New Haven, CT, USA

Increasing evidence suggests the glutamatergic system contributes to the pathophysiology and treatment of mood disorders. Several studies have demonstrated that drugs that act on the glutamatergic system, either as NMDA antagonist, AMPA potentiators, or glutamate release inhibitors possess antidepressant properties. In this open label pilot study we sought to determine if augmentation therapy with riluzole (Rilutek ®), a drug with antiglutamatergic properties that has USFDA approval for the treatment of ALS, improves depressive symptoms. Methods: Nine subjects with treatment refractory major depressive disorder were enrolled in the study after providing written informed consent. Riluzole 50mg bid was added to the subjects′ current medication regimen. Subjects provided weekly ratings using the Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), and the Clinical Global Impression Scale (CGI). Subjects were evaluated at the end of week 6 to determine if riluzole should be continued for an additional 6-week period. Data was analyzed by paired t-test. Results: 8 of the 9 subjects completed the initial 6-week study. The addition of riluzole was associated with a statistically significant decrease in HDRS and HARS scores at the level of $p \leq 0.02$ beginning at week three, and continuing through week six of the study in the 8 subjects who completed the 6 week course. The HDRS and HARS scores remained decreased $p \leq 0.05$ in the 6 subjects who continued riluzole for the entire 12-week study. Furthermore, 3 of the 8 subjects met criteria for remission with HDRS scores ≤ 8 at end of the 6-week period. These 3 subjects all maintained a greater than 50% improvement in HDRS through 12 weeks of treatment, with endpoint CGI scores of 2 or less. One of the subjects terminated the study in week 3 due to worsening of symptoms. A second subject′s standing medication regimen was changed at week 2 due to visual hallucinations, however she continued to receive riluzole and remained in the study without any additonal perceptual disturbances. The dose of riluzole was decreased to 50mg QD in one subject due to a complaint of sedation during the initial 6-week study period. The most commonly reported adverse event was moderate sedation. One subject had a noted transient increase in transaminase levels that did not reach 5 times the upper limit of normal, criterion for study termination. Conclusions: The results of this pilot study are consistent with those of Zarate *et al.* 2004, who recently reported improvement of depressive symptoms following open label treatment with riluzole monotherapy. Several mechanisms of action have been proposed to account for riluzole′s antiglutamatergic effects, including decreased glutamate release and facilitated uptake of glutamate from the synapse. Additional randomized placebo controlled studies are required to further investigate riluzole′s efficacy and safety in the treatment of depression.

67. Adverse Rearing Alters Hypothalamic-Pituitary-Adrenal Axis Function and Startle Response in Developing Non-Human Primates: Effects of Sex and Serotonin-Transporter Genotype

Mar M Sanchez*, Casie K Lyon, Pamela L Noble, Kai M McCormack, James L Crawford, Matthew Boudreau, J D Higley, Charles B Nemeroff, Paul M Plotsky, Michael Davis, Timothy K Newman and James T Winslow

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA

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Abundant evidence indicates that early life adversity represents a risk factor for the subsequent development of anxiety and mood disorders. Most studies of the impact of early adversity on non-human primate development have focused on the effects of prolonged maternal and social deprivation early in life. However, these intense experiences result in severe behavioral deficits very difficult to palliate. Instead, our study tries to model more subtle developmental alterations that result in increased vulnerability for anxiety and mood disorders, without those severe behavioral deficits. For this, we investigated short- and long-term consequences of repeated maternal separation during sensitive periods of social and emotional development (3-6 months of age) in rhesus monkeys (M. mulatta). We examined immediate effects of the separation protocol on hypothalamic-pituitary adrenal (HPA) axis function (diurnal cortisol rhythm and reactivity) of infants and mothers, as well as on the mother-infant relationship. We also studied long-term effects on emotionality and HPA axis function. Our repeated maternal separation protocol produced significant alterations in mother-infant contact, as well as a sex-dependent increased cortisol reactivity to the separations. In addition, it resulted in long-term alterations in HPA axis activity and emotionality, including a flattened secretory rhythm of cortisol and elevated acoustic startle reactivity several months after the end of the separation protocol, in comparison to half-sibling controls. Interestingly, the cortisol reactivity to the separations predicted alterations in cortisol diurnal rhythm (flattening) and emotionality (increased acoustic startle response) at later ages. We are currently analyzing the effect of variation in the serotonin-transporter (5-HTT) promoter region polymorphism on both HPA axis function and startle response amplitude. Although we have detected 5-HTT genotype x rearing interactions on infant cortisol reactivity to maternal separation and cortisol diurnal rhythm, the effects are different in males and females. In summary, maternal separations affected HPA axis function and emotionality of developing rhesus monkeys, comparable to changes associated with mood/anxiety disorders. Some of the effects were dependent on sex and 5-HTT genotype. Our results are consistent with the hypothesis that early adverse experiences, including alterations in access to maternal care, may alter normal physiological and emotional development, posing a risk factor for the development of anxiety/mood disorders during childhood and adolescence. But they also demonstrate that sex and genetic factors also play an important role modulating this vulnerability. Supported by: MH58922 and MH42088 (CBN), MH01005 (MMS, PMP), MH57704 (JTW), MH 47840 (MD), NSF Agreement IBN-9876754 & RR-00165.

68. Developing Outcome Measures for Therapeutic Trials for Dementia in Aging Individuals with Down Syndrome

Mary Sano*, Arthur Dalton, Paul Aisen and Howard Andrews

Psychiatry, Mount Sinai School of Medicine & Bronx VAMC, Bronx, NY, USA

Background: Most individuals with Down Syndrome (DS) develop the clinical symptoms and neuropathological features of Alzheimer Disease (AD) at a relatively early age. Randomized treatment trials for this population are necessary to guide management,

and may have implications for the prevention or treatment of sporadic AD in the general One obstacle to conducting trials with DS participants in the paucity of data on outcome measures to assess treatment efficacy. To our knowledge this is the first report of a multi-national cohort of individuals with DS enrolled in a clinical trial. Specific Aims: This report describes clinical features of the study cohort, describes newly developed or adapted outcome measures, and evaluates the performance of these measures in cross-sectional analyses of both demented and non-demented elderly (age 50 and over) individuals with DS enrolled in the trial. **Methods and Procedures:** The primary outcome measure is the Brief Praxis Test (BPT), a non-verbal, 20-item version of a longer praxis scale for adults with DS. Use of the shortened version minimizes fatigue and increases likelihood of completion over a three-year period. In addition a series of secondary outcome measures were adapted including a verbal memory test (i.e. list learning), a visual memory test (delayed non-match to sample,) a 10 item orientation test, an expressive vocabulary test, an informant-rated assessment of behavior and function, and an adaptation of the Clinical Global Impression of Change. **Results:** The mean age of enrolled subjects was 54.7; approximately 70% were not demented and 30% had a diagnosis of probable AD. The level of intellectual disability (based on highest lifetime functioning) was mild (IQ: 50-69) for 24% of the cohort, moderate (IQ:35-49) for 51% of the cohort and severe or profound for the rest. The majority (83%) live in a residential facility. The primary outcome measure had excellent test-retest reliability (r = .805). It also appeared to be sensitive to a diagnosis of dementia, with significantly lower BPT scores in subjects with dementia at the time of enrollment (dementia: 58.9 + 15.49 vs. no dementia: 65.2 + 12.14. $F(1, 103) = 4.95$, $p < .03$). Verbal learning and memory was highly associated with the presence of dementia ((mean score: dementia = 8.6 vs. no dementia= 19.7; F=18.453; P<0.0001) as was delayed recall (F=1.494; P=0.007). Visual memory and orientation proved too difficult for some members of the cohort. Vocabulary was sensitive to both premorbid intellectual disability and the presence of dementia. Few subjects had either ceiling or floor effects on the behavior and function test suggesting that it will permit assessment of change in either direction. The Clinical Global Impression of Change ratings were not correlated with age, gender or MR level, but were associated with dementia status. **Conclusion:** It appears that appropriate primary and secondary measures to assess cognitive therapies in DS have been identified, providing the first step to assessing disease altering drugs.

69. Escitalopram Treatment of Social Anxiety Disorder with Comorbid Major Depression

Franklin R Schneier*, Carlos Blanco, Raphael Campeas, Roberto Lewis-Fernandez, Arturo Sanchez-Lacay and Michael R Liebowitz

Anxiety Disorders Clinic, New York State Psychiatric Institute, New York, NY, USA; Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA

Sponsor: Donald Klein

Background: Treatment of patients with concurrent social anxiety disorder and major depression has been little studied although social anxiety disorder and depression frequently co-occur. Each disorder individually has been shown to respond to escitalopram treatment. Objectives of this study were to characterize a sample of patients with social anxiety disorder and comorbid major depressive disorder, and to assess response to treatment with escitalopram. **Method:** Patients with primary DSM-IV generalized subtype of social anxiety disorder (GSAD) and comorbid major depressive disorder (MDD) (N=20) were assessed for symptoms of each disorder, including atypical depressive features, and functional impairment. Patients were treated with a flexible 10-20mg/day dose of open label escitalopram for 12 weeks, with post-study naturalistic follow-up for an additional 12 weeks. **Results:** Response rates for the intention-to-treat sample at week 12 were 6/20 (30%) for social anxiety disorder and 14/20 (70%) for depression. Among completers of at least 6 weeks, response rates were 6/16 (37.5%) for social anxiety disorder and 13/16 (81%) for depression. All continuous measures of social anxiety, depression, and functional impairment improved significantly with treatment, but depression symptoms responded more rapidly and more completely than social anxiety symptoms. Mean dose of escitalopram at week 12 (or study endpoint for patients who terminated prematurely) was 15.0 mg/d. Seven patients (35%) fulfilled DSM-IV criteria for atypical features of depression, and 14 (70%) fulfilled the criterion for interpersonal rejection sensitivity. Among the 10 patients observed for up to 12 weeks of naturalistic follow-up, the one MDD nonresponder became a responder, and 3 of the 6 GSAD nonresponders became responders, increasing overall intent-to-treat response rates to 75% for MDD and 45% for GSAD. **Conclusion:** Escitalopram treatment appears efficacious for depression, and modestly efficacious for social anxiety disorder in patients with primary social anxiety disorder and comorbid major depression, and it should be further studied in controlled trials. Improvement in social anxiety disorder symptoms lagged behind improvement in depression, and greater than 12 weeks of treatment may be required to assess full social anxiety response in patients with comorbid depression.

70. Comparison of cFos Induction by the Anxiogenic mGlu2/3 Receptor Antagonist LY341495 and Anxiolytic mGlu2/3 Receptor Agonist LY354740

Darryle D Schoepp*, Anni-Maija Linden and Marcelle Bergeron

Neuroscience Discovery Research, Eli Lilly and Company, Indianapolis, IN, USA

LY341495 is a potent and selective antagonist for group II (mGlu2 and mGlu3) metabotropic glutamate (mGlu) receptors, which has been used to antagonize the in vivo actions of the anxiolytic mGlu2/3 receptor agonist LY354740. Here we further investigated the activity of LY341495 administration per se in the mouse elevated plus maze (EPM) test and its ability to produce regionally selective brain activations using cFos expression as a marker. LY341495 (3-6 mg/kg, i.p.) was anxiogenic in the EPM test under low stress conditions, significantly decreasing the time spent in open arms without altering total maze ambulations. When administered in a low-stress (home-cage) environment, LY341495 (3 mg/kg) significantly increased c-Fos expression in almost all brain regions analyzed (34 out of 38 regions). Robust c-Fos induction was observed in all cortical regions, hippocampal CA1 and CA3 subregions, amygdala and several other subcortical nuclei. However, LY341495 did not increase c-Fos expression in the paraventricular nucleus of the hypothalamus (PVN) which is usually activated by stress/fear and several anxiogenic compounds. The anxiolytic mGlu2/3 receptor agonist LY354740 has been shown to selectively induce c-Fos in the central nucleus of the amygdala (CeA) (Linden et al., 2003). Therefore, we compared c-Fos induction patterns in the subdivisions of the CeA after LY341495 or LY354740 administrations. Compared to LY341495, LY354740 produced significantly stronger c-Fos induction in the capsular division of the CeA, while no difference was observed in the lateral or medial CeA. These studies show that endogenous mGlu2/3 receptor tone is important in modulation of emotionally relevate behaviors such as anxiety. Furthermore, glutamatergic tone at mGlu2/3 receptors is important in the maintenance of the excitatory/inhibitory balance in many regions of the brain. Strategies to modulate mGlu2/3 receptors for therapeutic applications may be dependent on the degree of endogenous receptor tone under different physiological and pathological conditions.

71. Cognitive Behaviour Therapy plus Treatment as Usual Compared to Treatment as Usual Alone for Severe and Recurrent Bipolar Disorders: A Randomised Controlled Treatment Trial

Jan Scott*, Eugene Paykel, Morriss Richard, Bentall Richard, Peter Kinderman and Tony Johnson

Psychological Treatments Research, Institute of Psychiatry, London, United Kingdom

Sponsor: Eugene Paykel

Background: There is promising evidence that the combination of pharmacotherapy and a brief evidence-based manualized therapy such as cognitive behaviour therapy, family focused therapy and group psycho-education may significantly reduce recurrence rates in individuals with bipolar disorders in comparison to a control intervention. We undertook a pragmatic clinical trial to establish whether cognitive behaviour therapy added to usual treatment is more effective than usual treatment alone in reducing recurrence rates and symptom levels in a clinically representative sample of individuals with recurrent bipolar disorders. **Methodology:** Two hundred and fifty three subjects who gave written informed consent to participate in a multi-centre, pragmatic, randomized parallel group controlled treatment trial the study were allocated to usual treatment by their clinical team or usual treatment plus 22 sessions of individual cognitive behaviour therapy. Patients were assessed immediately prior to randomization and then in face-to-face interviews every eight weeks for 72 weeks (18 months). Time to recurrence of an episode of mood disorder and longitudinal weekly severity ratings of symptoms were determined through an intention to treat analysis undertaken by independent experts employing an analysis strategy designed prior to data access. **Results:** Although attrition rates were low and were not significantly different between groups, there were 131 (52%) recurrences during follow-up, 67 (53%) in the cognitive behaviour therapy plus usual treatment group and 64 (51%) in the usual treatment group. We did find a post-hoc interaction between treatment group and past clinical history in that individuals who had fewer than 12 previous mood episodes who received adjunctive cognitive therapy did significantly better than those receiving usual treatment alone, but this pattern was reversed in those with 12 or more previous episodes. **Conclusions:** It appears that psychological therapies for bipolar disorders may benefit those with a less severe or less complex presentations who are currently euthymic but at high risk of future mood episodes. However, these subjects formed a minority of the participants recruited from the general adult mental health services in the UK.

72. Peripheral Blood Mononuclear Cells Gene Expression Profiles Identify Emergent Posttraumatic Stress Disorder Among Trauma Survivors

Ronnen H Segman*, Noa Shefi, Tanya Goltser-Dubner, Friedman Nir, Naftali Kaminski and Arieh Y Shalev

Psychiatry, Hadassah University Hospital, Jerusalem, Israel

Sponsor: Arieh Shalev

Background: Trauma survivors show marked differences in posttraumatic stress disorder (PTSD) symptoms severity and persistence. Early symptoms subside in most, but persist as acute and chronic PTSD in a significant minority. The underlying molecular mechanisms or outcome predictors determining these differences are not known. Furthermore, molecular markers for identifying any mental disorder are currently lacking. We hypothesized that gene expression signatures in peripheral blood mononuclear cells (PBMCs) will correlate with PTSD outcome when evaluated shortly after a traumatic event and classify PTSD when evaluated four months later. **Methods:** Trauma survivors presenting to an emergency room (ER), (mean time between incident and arrival = 45±130 minutes), were followed for four months, and blood samples were obtained at the ER and four months later. Subjects meeting all DSM-IV criteria for PTSD, and those meeting no PTSD diagnostic criterion at four months after the event were included. Oligonucleotide microarrays containing probes for ~12,600 transcripts were used to analyze gene expression signatures in RNA from PBMCs. **Results:** Gene expression signatures distinguished subjects with persistent PTSD, and correlated with long term core PTSD symptom clusters of re-experiencing avoidance and increased arousal. Gene expression signatures from cells harvested hours or four months after trauma exposure distinguished survivors who met DSM-IV diagnostic criteria for PTSD at one and four months, from those who met no PTSD criterion. Expression signatures at both time points correlated with the severity of each of the three PTSD symptom clusters assessed four months following exposure among all survivors. Results demonstrate a general reduction in PBMCs expression of transcription activators among psychologically affected trauma survivors. Among differentially expressed gene sets in PBMCs, there was a significantly increased proportion of genes known to be co-expressed in amygdalar and hippocampal regions and in the hypothalamus pituitary and adrenal. Several differentiating genes were previously described as having a role in stress response. **Conclusions:** Expression profiles of PBMCs, including those obtained within hours of a traumatic event, are informative of an evolving neuropsychiatric disorder, and its main underlying symptoms clusters. Information gathered through peripheral expression signatures may provide clues to the pathogenesis of PTSD, and identify survivors a risk. Results should encourage research into the diagnostic value of gene expression signatures in PBMCs as well as illuminating the mechanistic factors that determine these changes.

73. Clinical Predictors of Fluoxetine Treatment Response in Obsessive-Compulsive Disorder

Eric A Storch, Nathan A Shapira*, Herbert E Ward, Tanya K Murphy, Gary R Geffken, Holly Valerio and Wayne K Goodman

Psychiatry, University of Florida College of Medicine, Gainesville, FL, USA

Sponsor: Wayne Goodman

The efficacy of fluoxetine in OCD treatment is well established. However, up to 40% of patients with an adequate fluoxetine trial do not experience clinically significant improvement underscoring the importance of identifying factors that may partially account for treatment response and in turn, guide adjunctive treatment recommendations. To date, relatively little is known about clinical and sociodemographic characteristics that may predict response to fluoxetine. Among seretonergic medications, early onset, male gender, higher frequency of compulsions, and tic severity have been related to non-response. Less consensus is present for other variables. For example, poor response has been related to shorter and longer illness durations; both positive and negative response has been linked to high OCD and depression severity scores. One explanation that may in part explain inconsistent findings is the use of statistical techniques, namely stepwise logistic regression. Stepwise analytic procedures increases the probability of finding models that represent spurious relationships and capitalize on chance. Indeed, stepwise models often fail to replicate when applied to new sets of comparable data, a finding that characterizes this particular literature. We examine the association between response rate and demographic (e.g., gender and age) and clinical characteristics (e.g., age of onset, illness duration, pharmacological treatment history, and baseline scores on the Y-BOCS, HAM-D, and YGTSS) in one of the largest clinical predictor investigations of fluoxetine. Further, we incorporate an analytic plan that addresses the limitations inherent to stepwise procedures. Our sample consisted of 60 adults with OCD who completed an open label fluoxetine trial. To be consistent with other predictive investigations, a 35% reduction in Y-BOCS total score was defined as treatment response. Independent t-tests detected differences between responders and non-responders in terms of illness duration, baseline age, and baseline OCD severity as measured by the Y-BOCS. Longer illness duration, older age, and greater symptom severity were associated with

non-response. No differences existed between responders and non-responders in gender, age of onset, pharmacological treatment history, tic severity, and depression severity. Multiple logistic regression showed that baseline OCD severity, illness duration, and age at admission predicted response. Implications of these findings on clinical practice in adults with OCD will be discussed, highlighting recommendations for adjunctive treatment approaches in 'at risk' patients. This work was supported by NIMH MH-45802 with medication provided by Eli Lilly & Company.

74. Effects of Exposure to Lithium On Morphology of Dendrites in Hippocampus and Parietal Cortex

Sung Shim*, Rebecca Russell and Ronald Mervis

Psychiatry, Case Western Reserve University, Cleveland, OH, USA

Sponsor: Pedro Delgado

Lithium produces diverse effects on cellular function by influencing a wide array of biological mechanisms including neurotransmitter systems, gene expression, synaptic transmission and intracellular signal transduction cascades. Lithium treatment has been shown to ameliorate the atrophy of the prefrontal cortex in patients with bipolar disorder. Lithium treatment also increases the overall gray matter volume of cerebral cortex in humans. Lithium treatment has also been shown to have effects on synaptic transmission and synaptic strength as measured by an input/output function, long-term potentiation and paired-pulse inhibition. This has led to the hypothesis that treatment with lithium may promote synaptic transmission with an increase in synaptic connections as shown in dendritic elongation, branching and an increase in dendritic spine count. These effects then may explain the increases in cortical matter and synaptic transmission observed with lithium treatment. To test this hypothesis rats were given two weeks of lithium treatment (1mEq/kg/day IP) then sacrificed and their brains stained with a modified Golgi stain. Areas of the hippocampus that had shown changes in synaptic transmission (the area CA1 and the dentate gyrus) were examined for increases in dendritic length and branching and dendritic spine counts. Areas of the parietal cortex were also examined to see if changes in the same parameters here might account for the increases in cortical mass resulting from lithium treatment of patients with bipolar disorder. Our examination of these parameters in the hippocampus and the parietal cortex did not support the hypothesis. Factors including dendritic length and branching and dendritic spine counts studied did not differ between the lithium-treated and control animals. There were however a few instances of specific parameters such as the number of N type spines being significantly different. In this instance there were fewer N type spines on the area CA1 pyramidal cells of the lithium-treated animals. The number of spines in the terminal dendrites of neurons in the parietal cortex was also significantly less in lithium-treated animals. This study suggests that 1) cellular mechanisms other than changes in morphology of dendrites may be involved in lithium-induced changes in synaptic transmission and 2) lithium affects dendritic morphology in healthy brains differentially from unhealthy ones as was seen in rats exposed to persisting restraint stress.

75. An fMRI Study of Amygdala and Medial Prefrontal Cortex Responses to Overtly Presented Fearful Faces in Posttraumatic Stress Disorder

Lisa M Shin*, Christopher I Wright, Paul A Cannistraro, Michelle M Wedig, Katherine A McMullin, Brian Martis, Michael Macklin, Natasha Lasko, Sarah R Cavanagh, Terri S Krangel, Scott P Orr, Roger K Pitman, Paul J Whalen and Scott L Rauch

Psychology, Tufts University, Medford, MA, USA; Psychiatry, Massachusetts General Hospital, Charlestown, MA, USA

Sponsor: Past Travel Awardee, Memorial, 2003

Previous functional neuroimaging studies have demonstrated exaggerated amygdala responses and diminished medial prefrontal cortex responses during the symptomatic state in PTSD. The goals of this research were (1) to determine whether these abnormalities also occur in response to overtly presented, trauma-unrelated, affective stimuli; (2) to examine the functional relationship between amygdala and medial prefrontal cortex, as well as their relationship to PTSD symptom severity, in response to these stimuli; and (3) to determine whether responsivity of these regions habituates normally across repeated stimulus presentations in PTSD. In a volunteer sample of 13 men with PTSD (PTSD group) and 13 trauma-exposed men without PTSD (Control group), we used fMRI to study blood oxygenation level dependent (BOLD) signal during the presentation of emotional facial expressions. The PTSD group exhibited exaggerated amygdala responses and diminished medial prefrontal cortex responses to Fearful vs. Happy facial expressions. In addition, only in the PTSD group were BOLD signal changes in the amygdala negatively correlated with signal changes in medial prefrontal cortex. Furthermore, in the PTSD group, symptom severity was negatively related to BOLD signal changes in medial prefrontal cortex. Finally, relative to the Control group, the PTSD group tended to exhibit diminished habituation of Fearful vs. Happy responses in the right amygdala across functional runs, although this effect did not exceed our a priori statistical threshold. The results provide evidence for exaggerated amygdala responsivity, diminished medial prefrontal cortex responsivity, and a reciprocal relationship between these two regions during passive viewing of overtly presented, trauma-unrelated, affective stimuli in PTSD.

76. Exploring the Association of Anxiety Comorbidity with Suicidality in Bipolar Disorder

Naomi M Simon*, Diana Fischmann, Michael W Otto, Michael J Ostacher, Christina M Demopulos, Andrew A Nierenberg and Mark H Pollack

Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Sponsor: Mark Pollack

Background: Anxiety comorbidity appears to be a significant marker of history of suicide attempts for patients with bipolar disorder. However, there is a paucity of data elucidating this association. This may in part explain why anxiety comorbidity has not been highlighted as critical for the identification of high-risk patients nor for integration into suicide prevention strategies for patients with bipolar disorder. This inattention has persisted despite early suggestions that anxiety symptoms may be a modifiable risk factor for suicide in individuals with bipolar disorder (Fawcett et al, 1990). **Methods:** As the baseline phase of a follow-up study adjunct to STEP-BD, we examined the association of diagnosed anxiety comorbidity and self-rated measures of anxiety symptoms with detailed measures of suicidality and a reported history of prior suicide attempts in individuals with bipolar disorder. **Results:** The sample was comprised of 120 individuals (59% women, mean age 44+/-13 years) with a primary diagnosis of bipolar disorder (62% bipolar I, mean duration illness 26.7+/-12.7 years). Most patients (70%) were not in an active bipolar episode at assessment (i.e. they were in "recovery or recovering"). A substance use diagnosis was present for 11% currently and 42% lifetime. At least one anxiety disorder was present currently in 30%, and lifetime in 59% of the sample, with 37% meeting DSM-IV criteria for more than one lifetime anxiety disorder (excluding specific phobias). While only 5% met current criteria for panic disorder, fully 34% (n=40) of patients reported full or partial symptom panic attacks in the past week. Lifetime suicide attempts were reported for 30% of the sample, with more than one attempt for 16% (n=19), and a mean of 12.0+/-11.8 years since the most recent attempt. On the Beck Scale for Suicidal Ideation (BSI), 20% of patients (n=24/120) were positive on the screening questions for current active or passive suicidality; for this group, the mean BSI score was 14+/-6.6, compared to a mean BSI of 3.7+/-6.2 in the full sample. Significant ($p<0.05$) univariate predictors of past suicide attempts included: a lifetime anxiety disorder, lifetime social anxiety disorder, multiple anxiety disorders (with in-

creasing risk for additional disorders), as well as an early age of onset for the first mood episode. After controlling for age of onset of mood disorder, social anxiety disorder and multiple anxiety disorders each remained significant predictors. Univariate predictors of current suicidality based on the BSI screening questions included: current anxiety disorder, panic attack and level of distress associated with panic attacks in the past week, as well as history of prior suicide attempts and current mood episode not in recovery. Panic attack presence and severity, and social anxiety each remained significant predictors of suicidality after controlling for current mood episode. **Conclusions:** Baseline assessments in the first phase of this prospective study support that anxiety disorders, and specifically lifetime social anxiety disorder and multiple anxiety comorbidity are highly associated with a history of suicide attempts even after control for age of first mood episode, while current panic attacks, current social anxiety disorder and multiple anxiety disorders strongly predict current suicidal ideation, even after controlling for current mood state. Additional dissection of the detailed association of anxiety symptoms and disorders with suicidality is needed to allow the development of interventions to reduce suicide risk.

77. Aripiprazole Augmentation of SSRIs and SNRIs for the Treatment of Partial and Non-Responding Patients with Major Depressive Disorder

Charles B Nemeroff, Jeffrey S Simon*, Andy Forbes, William H Carson and Robert McQuade

Psychiatry, Northbrooke Research Ctr, Brown Deer, WI, USA

Sponsor: Charles Nemeroff

Objective: To determine the efficacy and tolerability of aripiprazole, a dopamine D2 and 5-HT1A receptor partial agonist, when used in conjunction with SSRIs and SNRIs for the treatment of partial and non-responders with unipolar depression. **Methods:** Fifteen patients diagnosed with major depressive disorder (MDD) who had either an incomplete response or no response to standard antidepressant monotherapy (SSRIs and SNRIs) were treated with aripiprazole for 8 weeks in an open label study. HAM-D (17 item) and CGI scales were performed to assess progress. **Results:** Patients entered the study with an average duration of antidepressant monotherapy on an SSRI or SNRI of 43 weeks. The average baseline HAM-D (17 item) score was 18.5 (CGI-S 4.33). After administration of aripiprazole, 40% of patients achieved remission (HAMD <7) by week 1. At 2 weeks, 60% of patients had achieved remission. An intent to treat (ITT) analysis revealed a completion rate of 60%, with 88% of completers achieving remission. The observation of akathisia in patients who discontinued early in the study prompted a change in the starting aripiprazole dose from 10 mg to 2.5 mg. This dosing change resulted in a 50% reduction in the incidence of discontinuation due to akathisia. The mean duration of therapy was approximately 6 weeks. No differences were noted in the aripiprazole response as a function of which SSRI or SNRI with which it was combined. **Conclusion:** Aripiprazole was highly effective in improving response in partial or and non-responders when administered in combination with standard antidepressant therapy. A double blind, placebo-controlled study is clearly warranted based upon the present observations.

78. Hypocretins and Anxiety: Preliminary findings in Startle Potentiated Startle

Ravi Kumar Singareddy*, Thomas W Uhde and Randall Commissaris

Psychiatry; Anxiety, Stress, & Trauma Research Division, Penn State College of Medicine, Hershey, PA, USA

Sponsor: Thomas Uhde

Available literature suggests the possible role of noradrenergic, serotonergic, gamma-aminobutyric acid (GABA) ergic, and corticotropin-releasing hormone (CRH) in the neurobiology of anxiety. Hypocretins/Orexins (Hypocretin-A and Hypocretin-B) are recently discovered neuropeptides, synthesized exclusively by a small proportion of neurons in the lateral and posterior hypothalamus and have excitatory efferents to noradrenergic neurons in locus ceruleus, serotonergic neurons in dorsal raphae, and GABAergic neurons in pars reticulata and increase CRH secretion. It is possible that these novel neuropeptides might be involved in the neurobiology of anxiety, fear, arousal, stress, or startle mechanisms. We examined the effects of intracebroventricular (ICV) administration of Hypocretin-A and Hypocretin-B on behavior in the Startle Potentiated Startle (SPS) paradigm, a repeated measures, non-shock animal model for studying the classically-conditioned enhancement of acoustic startle in the rat. SPS testing sessions consist of 20 presentations of the acoustic startle stimulus (115 dB noise burst, 40 msec duration), half (10 presentations) in the dark and half (10) immediately following the brief (3500 msec) presentation of a 15 watt light. Although the light does not affect startle amplitude initially, repeated pairing of the light with the noise burst results in an increase in the magnitude of the startle response when compared to the noise burst alone. After the first test day, the magnitude of this SPS effect is stable across repeated test days for several months. Thus, the SPS paradigm provides a measure of both baseline acoustic startle (Noise Alone) as well as a measure of the conditioned enhancement of startle (SPS effect: Light + Noise startle amplitude minus Noise Alone startle amplitude). Male Sprague Dawley rats (200-215 g) were tested using the SPS paradigm for three days (M-W-F). Following training, rats were anesthetized and 26 gauge stainless cannulae were permanently implanted into the lateral ventricle for intraventricular (ICV) infusions. Following a one-week recovery period, the M-W-F SPS testing was resumed. The effects of ICV administration of 1 and 3 nM Hypocretin-A and 3 and 10 nM Hypocretin-B were compared to vehicle in subsequent SPS test sessions. The drug challenge test sessions were 70 min in duration, consisting of a 10-min pre-infusion baseline, followed by a 10-min period for ICV treatment infusion, followed by a 50-min period of post-infusion SPS behavioral testing. Data were transformed to square root values prior to analysis to reduce variability, followed by factorial ANOVA, followed by post hoc comparisons with Student Neuman Kuels (SNK) comparisons; $p < 0.05$ was used as the criteria for statistical significance. Infusion with vehicle did not affect Noise Alone Startle amplitude compared to pre-infusion baseline. ICV infusion with both Hypocretin-A (1 and 3 nMoles) and Hypocretin-B (10 nMoles) produced a significant reduction in Noise Alone Startle amplitude compared to pre-infusion baseline. The effect of Hypocretin-B was brief (first 10 min post-infusion), whereas the effects of Hypocretin-A persisted across much of the 50-min post-infusion period. However, neither, Hypocretin-A nor Hypocretin B significantly altered the magnitude of the SPS response. Possible explanations for the unexpected decrease in Noise Alone Startle with the hypocretins will be discussed within the context of future research directions.

79. Smaller Cingulate Gray Matter Volumes in Unipolar Depression

Jair Soares*, Simerjit Kaur, Sheila Caetano, Paolo Brambilla, Roberto Sassi, Mark Nicoletti, John P Hatch, Matcheri S Keshavan, Alan G Mallinger, David J Kupfer and Ellen Frank

Psychiatry, University of Texas Health Science Center, San Antonio, TX, USA

Objective: The anterior cingulate cortex is a key structure in brain networks involved in mood regulation. Abnormalities in this brain region are implicated in the pathophysiology of depression. In anatomical magnetic resonance imaging (MRI) studies, smaller bilateral anterior cingulate gray matter volumes were found in currently depressed patients compared with healthy controls, but no differences have been demonstrated in unipolar patients in remission. This MRI study compared cingulate cortex volumes in untreated unipolar

patients, currently depressed and in remission, and age and sex-matched healthy controls. **Method:** Thirty-one unmedicated DSM-IV unipolar patients (24 females, 7 males, mean age±S.D. = 39.2±11.9 years) and 31 healthy controls (24 females, 7 males, mean age±S.D.= 36.7±10.7 years) were studied in a 1.5 T GE Signa magnet. Cingulate gray matter volumes were compared using analysis of covariance with intracranial volume as the covariate. **Results:** The unipolar patients had significantly smaller anterior and posterior cingulate volumes bilaterally compared to healthy controls. The mean ± sd volumes for the unipolar patients versus the healthy controls were, respectively: left anterior, 2.41±0.48 cm3 vs. 3.02±0.52 cm3 ($F=23.29$, df=1,59, $p<0.001$); left posterior, 2.27±0.44 cm3 vs. 2.57±0.47 cm3 ($F=9.68$, df=1,59, $p=0.003$); right anterior, 2.52±0.43 cm3 vs. 2.85±0.53 cm3 ($F=7.83$, df=1,59, $p=0.007$); right posterior, 2.12±0.39 cm3 vs. 2.53±0.57 cm3 ($F=10.91$, df=1,59, $p=0.002$). Currently depressed patients had significantly smaller anterior and posterior cingulate volumes bilaterally compared to healthy controls. The mean±sd volumes for the currently depressed patients were: left anterior, 2.35±0.48 cm3 ($p<0.001$); left posterior, 2.12±0.34 cm3 ($p=0.002$); right anterior, 2.46±0.33 cm3 ($p=0.014$); right posterior, 2.10±0.36 cm3 ($p=0.006$). Remitted patients had significantly smaller left anterior cingulate volumes compared with healthy controls. The mean±sd volumes for the remitted patients were: left anterior, 2.56±0.47 cm3 ($p= 0.04$); left posterior, 2.44±0.56 cm3 ($p=0.78$); right anterior, 2.66±0.59 cm3 ($p=0.52$); right posterior, 2.19±0.48 cm3 ($p=0.20$). **Conclusions:** Gray matter abnormalities in the cingulate cortex are implicated in the pathophysiology of unipolar depression. Smaller cingulate volumes in currently depressed but not in remitted patients supports the hypothesis that cingulate cortex abnormalities are state-dependent. However, left anterior cingulate abnormalities may persist after remission and be trait-markers of the illness. This work was partly supported by NIMH grants MH 01736, MH 30915, NARSAD, and Dr. Sassi and Dr. Caetano were supported by a scholarship from the CAPES Foundation (Brazil).

80. Evidence for Multiple Deficits in Intracellular Signal Transduction Pathways and Myelination-related Abnormalities in the Temporal Cortex of Patients with Bipolar Disorder

Boris P Sokolov*, Lixin Jiang and Christopher Aston

Molecular Neuropsychiatry, NIDA, Baltimore, MD, USA

Sponsor: Benjamin Weiss

Bipolar disorder (BD) is a severe and common psychiatric disorder. In order to identify candidate mechanisms for BD, expression levels of approximately 12,000 RNA transcripts were examined in postmortem temporal cortex (Brodmann area 21, BA21) from 11 patients with BD and 14 matched normal controls using Affymetrix HgU95A GeneChip oligonucleotide arrays. Changes in gene expression in BD were compared with changes found in BA21 from patients with schizophrenia (SZ) and major depressive disorder (MDD). Using the same thresholds for significant changes, the number of changes revealed in BD was greater than in MDD and SZ. The vast majority of changes revealed in BD were not present in MDD or BD. Overall there were more similarities between BD and MDD than between BD and SZ. Common for BD, MDD and SZ were down-regulation of several myelination-related genes. In patients with BD there was decreased expression of multiple genes involved in synaptogenesis/axonal growth and genes encoding for synaptic proteins, while only few of these genes were changed in MDD and SZ. Several receptor genes, including (GABAR1, NMDAR2 and serotonin 5-HT2AR receptor) were down regulated in BD but not in MDD and SZ. The most abundant and consistent changes in BD were down regulation of a large number of genes involved in intracellular signal transduction, particularly related to the phosphatidylinositol (PI) system and MAP cascades, that include both protein kinases and protein phosphatases. Only a few of these changes were found in MDD and even less in SZ. These findings indicate that molecular pathology in the temporal cortex of patients with BD may be associated with significant deficits in signal transduction pathways and neurodevelopmental synaptic abnormalities. In addition, the data support the idea that BD, MDD and SZ may share common abnormalities in regulation of some myelination-related genes.

81. Short-Term Treatment of Depressed and Anxious Primary Care Patients with Multiple, Unexplained Somatic Symptoms: A Pilot Study

Kurt Kroenke, Isma Benattia, Jeff Musgnung, Jay Graepel and Stephen Stahl*

Neuroscience Education Institute, Carlsbad, CA, USA

Background/Objectives: Multisomatoform disorder (MSD) is associated with impairment of health-related quality of life, and a higher number of sick days and greater rate of health care utilization than what is found in the general population. After controlling for the comorbidity of other psychiatric illnesses, it also appears to increase the difficulty of caring for patients with mood and anxiety disorders in the primary care setting. This pilot study explored the efficacy and safety of venlafaxine extended release (XR) in the treatment of anxious and/or depressed patients with MSD. **Methods:** This 12-week, multicenter, randomized, double-blind study evaluated adult outpatients from primary care or general practice settings who met criteria for MSD (≥3 current somatoform symptoms reported on the 15-item Patient Health Questionnaire [PHQ-15] and a ≥2 years of somatoform symptoms) and who met DSM-IV criteria for major depressive disorder, generalized anxiety disorder, or social anxiety disorder. Of 117 patients randomly assigned to treatment with flexible-dose venlafaxine XR or placebo, 112 were included in the intent-to-treat population (venlafaxine XR=55; placebo=57). The primary efficacy variable was the baseline-to-endpoint change in PHQ-15 score. Secondary variables included baseline-to-endpoint changes in the 17-item Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, McGill Quality of Life Questionnaire Physical Symptoms Scale (MQOL-PS), and Medical Outcomes Study Short-Form 36-Item Questionnaire (SF-36). Last-observation-carried-forward results are reported. **Results:** Differences between the venlafaxine XR and placebo groups in PHQ-15 total scores were not statistically significant at week 12, the study endpoint ($P=0.09$). The venlafaxine XR group showed significantly ($P<0.05$) greater improvement than the placebo group on the PHQ-15 composite pain subscale and on various secondary variables: the CGI-I, MQOL-PS, and SF-36 mental health domain. Venlafaxine XR was generally well tolerated. **Conclusion:** The results of this pilot study suggest that venlafaxine XR may be effective in relieving some types of somatic symptoms, particularly painful physical symptoms, in patients with depression and/or anxiety disorders. Further research is needed in this area of clinical interest.

82. Safety and Tolerability of Quetiapine in Bipolar Mania

Stephen Strakowski* and Martin Brecher

Bipolar and Psychotic Disorders Research Program, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Objective: Patients with bipolar disorder often require long-term treatment; hence safety and tolerability are important considerations of therapy for these individuals. Quetiapine has recently been shown to be effective in the treatment of bipolar mania.(1,2) This analysis aims to evaluate its safety and tolerability in these placebo-controlled studies. **Methods:** Clinical laboratory evaluations, adverse events, the Simpson Angus Scale (SAS), and the Barnes Akathisia Rating Scale (BARS) were monitored in patients with bipolar I disorder (manic episode, DSM-IV) randomized to double-

blind, placebo-controlled treatment with quetiapine (up to 800 mg/day) monotherapy (2 studies; 12 weeks) or in combination with lithium (0.7-1.0 mEq/L) or divalproex (50-100 mcg/mL) (2 studies; 3 or 6 weeks). The effect of quetiapine monotherapy on serum prolactin levels was also assessed. **Results:** There were no clinically significant changes in laboratory tests, vital signs, weight, or ECG. Most adverse events were mild to moderate. Common adverse events (&#8805 10% and at least twice the rate of placebo) with quetiapine treatment both as monotherapy and combination treatment were somnolence and dry mouth. Treatment-related discontinuations due to adverse events with quetiapine were no different from placebo. The incidence of extrapyramidal symptoms (including akathisia) in quetiapine-treated patients was also no different from placebo (quetiapine monotherapy 12.9% vs placebo 13.1%, and 21.4% vs 19.2% for combination therapy). In addition, the mean change from baseline to end of treatment in SAS and BARS scores was not statistically significantly different between groups. The mean change in weight (last observation carried forward) at the end of treatment was moderate: quetiapine monotherapy versus placebo +1.8 kg vs -0.15 kg and +1.97 kg vs +0.27 kg with combination therapy. Importantly, no patients withdrew from treatment due to weight gain. Across the dose range of quetiapine, the effect of monotherapy on serum prolactin levels was no different from placebo. **Conclusions:** The results of both monotherapy and combination therapy studies indicate that quetiapine is a well-tolerated treatment for mania associated with bipolar disorder. References: 1.Jones M, Huizar K. Quetiapine monotherapy for acute mania associated with bipolar disorder (STAMP 1 and STAMP 2). Bipolar Disord. 2003;5:57 (Abstract P95); 2. Mullen J, Paulsson B. Quetiapine in combination with mood stabilizer for the treatment of acute mania associated with bipolar disorder. Bipolar Disord. 2003;5:70 (Abstract P140).

83. The Arachidonic Acid Cascade in Affective Disorders

M. Elizabeth Sublette*, Stanley I Rapoport, James Demar, Mark J Russ, Francesca Bosetti, Ken Ma and Jane Bell

Department of Psychiatry, Zucker Hillside Hospital, North Shore Long Island Jewish Health System, Glen Oaks, NY, USA; Department of Neuroscience/Psychiatry, Columbia University New York State Psychiatric Institute, NY, NY, USA

Sponsor: Stanley Rapoport

Arachidonic acid (AA) and prostaglandins (PG) are important second messengers in the central nervous system that participate in signal transduction, inflammation and other vital processes. AA is released from brain phospholipids by activation of phospholipase A2 (PLA2), through neuroreceptor ligand-mediated occupancy of specific G-protein coupled receptors, or through calcium entry via NMDA receptors induced by glutamate. AA can then be recycled back into membrane phospholipids or can be converted to PG and other eicosanoids by cyclooxygenases, lipoxygenases or P450 enzymes. This cycle of release, turnover, and metabolism represents the "arachidonic acid cascade". A significant body of diverse clinical and preclinical research suggests that the arachidonic acid cascade may be important in affective states. For instance, recent animal research has discovered that lithium and valproic acid are both associated with a decrease in AA turnover within brain phospholipids and a decrease in PG production (Rintala et al., 1999; Chang et al., 2001). Other evidence suggests that a "functional hyperactivity" of n-6 compared with n-3 fatty acid metabolism may be implicated in the pathophysiology of abnormal mood states (Rapoport and Bosetti, 2002). Herein we present results of preliminary investigations of the arachidonic acid cascade in bipolar disorder and schizoaffective disorder, bipolar type. Fatty acid levels, including arachidonic acid, were measured in human subjects experiencing an acute manic episode, pre- and post-treatment, and compared with healthy controls. Analyses were done in a blinded fashion. We discuss our results in context of pre-existing literature.

84. Neurogranin: A Critical Molecule at the Nexus of 3 Major Signaling Pathways and Mood Modulation

Steven T Szabo*, Haim Einat, Wenxin Chen, Cynthia Falke, Jing Du and Husseini K Manji

Mood and Anxiety Disorders Program - Laboratory of Molecular Pathophysiology, National Institutes of Mental Health, Bethesda, MD, USA

Sponsor: Travel Awardee, BMS, 2004

Background: Neurogranin (also know as RC3 - Rich in Cortex Transcript 3) is a brain-specific postsynaptic protein involved in synaptic plasticity, responses to stress and fear, and found in high density in forebrain regions implicated in mood disorders. Originally identified as a calmodulin (CaM) binding protein kinase C (PKC) substrate under specific regional and temporal control by thyroid hormones, neurogranin is now known to also be a critical regulator of type II Ca2+/CaM-kinase (CaMKII) and protein kinase A (PKA) signaling. These intracellular pathways, as well as thyroid hormone function, are thought to be important in the regulation of mood. We have therefore carried-out a series of rodent behavioral and cellular studies to more definitively investigate the potential involvement of neurogranin in affective-like behavior. **Methods:** Baseline behavioural and biochemical studies were undertaken in neurogranin knock-out mice. A separate group of animals was treated twice daily with i.p. injections of the antidepressant imipramine for 10-days. The frontal cortex and hippocampus from these animals were rapidly dissected and prepared for biochemical assays. **Results:** Neurogranin knock-out mice exhibited a reduction in immobility in the forced-swim test to a degree similar as that of wild-type mice undergoing a sustained antidepressant treatment. These results are in-line with neurogranin knock-out mice having antidepressant-like behaviours. Thus, we decided to investigate biochemical changes accompanied with this behavioural change and observed an increase in total CaMKII activity in the frontal cortex and hippocampus of neurogranin knock-out mice. On the other hand, autonomous CaMKII activity was decreased in neurogranin knock-out mice in forebrain regions as determined by CaMKII enzyme assay. These findings were also confirmed by western blot analysis showing attenuated levels of phosphorylated αCaMKII (Thr 286). Moreover, PKA activity in these mice were attenuated and in agreement with decreased GluR1 phosphorylation at a PKA recognition site (Ser 845) in the frontal cortex. Of profound interest was that phosphorylated levels of neurogranin in forebrain regions of wild-type mice were robustly increased following a sustained imipramine treatment, suggestive of a role of neurogranin in antidepressant action. Interestingly, sustained administration of the antidepressant imipramine to wild-type mice increased kinase activity and levels of all of the abovementioned CaMKII and PKA parameters in the forebrain. A sustained imipramine treatment was incapable of further impacting altered CaMKII activity and αCaMKII (Thr 286) levels in neurogranin knock-out mice, consistent with neurogranin acting as a potent regulator of CaMKII activity. In keeping with this, phosphorylated levels of myristoylated alanine-rich C-kinase substrate (MARCKS) at a non-specific CaMKII site mirrors changes observed in total CaMKII activity in the frontal cortex of neurogranin knock-out and wild-type mice undergoing a sustained antidepressant treatment. **Conclusions:** Neurogranin appears not only crucial in regulating basal CaMKII and PKA signaling, but also to the effect of chronic imipramine treatment on these intracellular pathways. Further investigation of the role of a CaM-neurogranin interaction, Ca2+ regulation, and synaptic plasticity in the pathophysiology and treatment of mood disorders is warranted. **Acknowledgements:** This work was supported by the NIMH Intramural Program, NARSAD, and Stanley Medical Research Institute. We would like to thank Freesia Huang, Ph.D., and K.P. Huang, Ph.D., for providing us with neurogranin knock-out mice.

85. Regulation of Mood in Rats by Kappa Opioid Receptor Ligands

Mark S Todtenkopf*, Jennifer A DiNieri, Cecile Beguin, Philip S Portoghese, David Y Lee, Bruce M Cohen and William A Carlezon, Jr.

Psychiatry, Harvard Medical School / McLean Hospital, Belmont, MA, USA

Sponsor: Francine Benes

There is substantial evidence that the transcription factor CREB (cAMP response element binding protein) plays important roles in the regulation of mood states. For example, elevations in CREB function within the nucleus accumbens (NAc) of rats reduces cocaine reward in place conditioning and increases immobility in the forced swim test (FST). These behavioral effects may reflect depressive-like mood states such as anhedonia, dysphoria, and despair. These depressive-like states appear related, in turn, to the ability of CREB to regulate expression of dynorphin, an endogenous kappa opioid receptor ligand. We have previously shown that the selective kappa receptor agonist U-69593 increases immobility in the FST, a depressive-like effect. The present experiments were designed to further examine the behavioral effects of kappa-selective ligands in rats. We utilized intracranial self-stimulation (ICSS), an assay that is highly sensitive to the function of brain reward systems and thus may offer a unique approach with which to study the neurobiology of depressive disorders. In the ICSS assay, rats self-administer rewarding electrical stimulation through electrodes implanted within the limbic system. Several conditions that cause depressive-like behaviors in humans attenuate ICSS behavior, as reflected by elevations in the minimum amounts of stimulation required to sustain responding (thresholds). For example, antipsychotic drugs, drug withdrawal, and stress each can elevate ICSS thresholds, indicating hypofunction of brain reward systems and depressive-like symptoms such as anhedonia and dysphoria. In our initial studies, we examined ICSS thresholds in rats after treatment with U-69593. We found that systemic administration of U-69593 dose-dependently elevated ICSS thresholds, a depressive-like effect. We then confirmed that this behavioral effect is caused by stimulation of kappa receptors using two separate approaches. First, we conducted similar studies with salvinorin-A, a high affinity kappa receptor agonist derived from the *salvia divinorum* plant. After extracting, isolating, and purifying salvinorin-A from the plant leaves, we found that systemic administration of salvinorin-A elevated ICSS thresholds, indicating depressive-like effects that were qualitatively similar to those caused by U-69593. Next, we examined if administration of a selective kappa receptor antagonist would block the kappa agonist-induced behavioral effects. For these studies, we used ANTI (5'-acetamidinoethyl-naltrindole), a highly lipophilic and bioavailable kappa receptor antagonist. Pretreatment with ANTI dose-dependently blocked the elevations in ICSS thresholds caused by both U-69593 and salvinorin-A, an antidepressant-like effect. Importantly, ANTI alone did not affect ICSS thresholds at any of the doses tested. This new work indicates that both U-69593 and salvinorin-A act at kappa receptors to produce depressive-like signs in rats, and that these same signs can be blocked by pretreatment with a kappa receptor antagonist. Additionally, these new data are broadly consistent with previous work indicating that kappa antagonists (including ANTI) have antidepressant-like effects in other behavioral assays (e.g., the FST). Thus there is accumulating evidence to suggest that, at least in rats, stimulation of kappa receptors triggers depressive-like signs in a variety of behavioral models. As such, agents that act at kappa receptors may offer new approaches to the study and treatment of depressive disorders.

86. Depression Remission With Venlafaxine XR or Selective Serotonin Reuptake Inhibitors in a Primary Care Setting Using Treatment Algorithms and Length of Treatment Guidelines

Madhukar H Trivedi*, Isma Benattia, Jeff Musgnung, Jay Graepel and Alan Gelenberg

University of Texas Southwestern Medical Center, Dallas, TX, USA

Sponsor: Paula Clayton

Background/Objective: Treatment algorithms and clinical practice guidelines allow primary care physicians to make evidence-based treatment decisions. However, relatively few large-scale, controlled clinical studies have directly compared the effects of the newer antidepressant treatments on therapeutic outcomes in primary care or psychiatric care settings. The purpose of this study was to compare remission rates of patients with major depressive disorder (MDD) treated with venlafaxine extended release (XR) or selective serotonin reuptake inhibitors (SSRIs) using treatment algorithms and length of treatment guidelines. **Methods:** In this open-label, rater-blinded, multicenter study, outpatients with MDD and a 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) total score ≥20 were randomly assigned to treatment with flexible doses of venlafaxine XR (75-225 mg/day; n=688) or an SSRI selected by the investigator (n=697 [fluoxetine (20-80 mg/day; n=114), paroxetine (20-50 mg/day; n=131), citalopram (20-40 mg/day; n=159), or sertraline (50-200 mg/day; n=193)]) for ≤180 days. Treatment was started at the lowest effective dose, with dose increases permitted at days 30 and 60 depending on treatment response and dosing guidelines. Remission was defined as a $HAM\text{-}D_{17}$ total score <8. **Results:** Mean maximum prescribed doses were venlafaxine XR 157 mg/day, fluoxetine 55 mg/day, paroxetine 41 mg/day, citalopram 35 mg/day, and sertraline 135 mg/day. Remission rates (intent-to-treat population; last observation carried forward) were significantly greater in the venlafaxine XR group versus the SSRI group at days 30 (13% vs 9%), 60 (23% vs 18%), 90 (29% vs 24%), and 135 (33% vs 27%) (all $P<0.05$). Day 180 remission rates were 35.5% and 32% for venlafaxine XR and SSRIs, respectively (P=NS). Individual SSRI remission rates at day 180 were fluoxetine 36%, paroxetine 28%, citalopram 31%, and sertraline 33%. **Summary and Conclusion:** Venlafaxine XR is an effective treatment for MDD and may bring patients to remission earlier in treatment than studied SSRIs when treatment algorithms and length of treatment guidelines are used.

87. Automated Monitoring and Feedback of Clinician Adherence to Pharmacotherapy in STARD

Madhukar H Trivedi*, A. J Rush, Stephen Wisniewski, Bradley Gaynes and Andrew Nierenberg

Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Sponsor: A. John Rush

Background/Objectives: Unlike most standard randomized controlled trials for the treatment of depression, which have rigid pre-defined dose and duration requirements, STARD utilizes a treatment protocol that is adaptable to clinical situations and factors in multiple clinical issues in determining the most optimal recommendations for that particular patient. A natural tension exists between the desire for maximal participant retention and the most diligent implementation of protocol treatments and the desire for maximal generalizability of findings. In addressing this tension, STAR*D aims to ensure that the treatments are properly implemented and maximal patient retention occur since the main objective is to compare the effectiveness of different treatments that are reasonably well implemented. **Methods:** Three specific objectives of adherence monitoring were identified: (1) checking adherence on an ongoing basis to identify straying from protocol and provide an opportunity for rapid corrective action; (2) providing

documentation that clinicians adhered to the manualized treatments that can be cited in study publications; and (3) demonstrating that the clinician feedback and prompt system does provide a means of improving adherence to a manualized but to a large extent a clinically relevant treatment algorithm implementation procedure. **Results:** Symptom severity and side effect burden were reported for pre-defined critical decision points for weeks 4, 6, 9 and 12 during the acute phase treatment with all the medications in the sequential algorithm for the STARD protocol. An electronic alert system provided continuous feedback with specific flags for each deviation from the algorithm. Reports generated results for adequacy of dose and duration of the antidepressant for the particular critical decision points. Non-adherence to the algorithm was monitored by the clinical site, the regional center director(s) and the National Coordinating Center through the use of web based reports. **Conclusion:** It is clearly feasible to implement a flexible and yet rational system of monitoring and feedback loop to physicians during antidepressant treatment. The system is also able to ensure the delivery of optimal antidepressant treatment in terms of dose, duration and management of side effects while still allowing much needed flexibility in complex difficult to treat patients with medical and psychiatric co-morbidities in busy primary and specialty practices.

88. Temperament and Cortisol Response to the DEX/CRH Test in Healthy Adults

Audrey R Tyrka*, Linda L Carpenter, Andrea A Mello, Marcello F Mello, Gerard G Gagne and Lawrence H Price

Psychiatry, Butler Hospital/Brown University, Providence, RI, USA

Sponsor: Travel Awardee, BMS, 2004

Personality traits such as neuroticism have been closely linked to the development of major depression. Neuroticism has been shown to be a prospective predictor of the development of depression and to share genetic risk factors with depression. Temperamental features such as neuroticism that confer sensitivity to negative stimuli or stressors are of particular interest because early-life stress and adult stressors have been clearly linked to the development of major depression. Numerous lines of research have documented the importance of hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in the pathophysiology of major depression. Given the central role of the HPA axis in coordinating the stress response, HPA dysfunction may provide a link between stressful life events, stress-reactive temperaments, and the development of major depression. A recent report found that cortisol hyper-reactivity was highly correlated with levels of neuroticism and depressive temperament in a sample of healthy adults. The present pilot study tested the hypothesis that domains of temperament related to stress-reactivity would be significantly associated with HPA axis hyper-reactivity in 25 healthy non-depressed adults. Participants completed diagnostic interviews, questionnaires assessing personality domains and depressive symptomatology, and the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test, a standardized neuroendocrine challenge protocol which combines oral dexamethasone pretreatment with intravenous CRH infusion. After controlling for age and depressive symptomatology, the trait of harm avoidance, which is closely linked to neuroticism, and low levels of novelty seeking were predictive of high cortisol responses to the DEX/CRH test. The results of this pilot study are consistent with a recent report that temperamental sensitivity to negative stimuli is associated with HPA axis hyper-reactivity. Further investigations are needed to replicate this finding and determine whether HPA axis dysfunction, which has previously been shown to be linked to major depression and to early-life stress in animal models and human studies, might account for some of the association previously found between personality factors and major depression.

89. Sleep Deprivation and Excitatory Amino Acids

Thomas Uhde*, Matthew Galloway, Jidong Fang, Todd Mitchell, Edward Bixler, Bernadette Cortese, Ravi Singareddy, Alexandros Vgontzas, Matthew McEchron and Gregory Moore

Department of Psychiatry, Penn State College of Medicine, Hershey, PA, USA; Neuroscience Research Institute, Penn State College of Medicine, Hershey, PA, USA

Several lines of evidence suggest that sleep deprivation produces anxiety in humans. Total sleep deprivation also has distinctly different effects in patients with mood versus anxiety disorders. For example, unlike patients with major depression, 24-h of total sleep deprivation worsens symptoms of generalized anxiety and induces panic attacks, particularly nocturnal or sleep panic attacks, in panic disorder. Sleep deprivation also impairs short-term and long-term memory tasks in humans. Despite these observations, the interactive effects of stress or anxiety and sleep deprivation on brain biochemistry and neuroanatomical structures (e.g. hippocampus) remain poorly understood. In a first-phase feasibility study, we employed high-resolution magic angle spinning proton magnetic resonance spectroscopy at 11.7T to determine the effects of sleep deprivation (6 hrs of novel stimuli) on the neurochemical profile of 16 metabolites in brain tissue of sleep-deprived male rats (n=8) compared to controls (n=8) with normal sleep/wake cycles. Immediately following sleep deprivation, rats were sacrificed, brains immediately removed, coronal slices obtained and 2.1 mm punches from the prefrontal cortex and hippocampus rapidly frozen. HR-MAS 1H-MRS analysis of the intact tissue was performed with standard techniques using a Brucker Avance 500 spectrometer and a custom LCModel basis set for a spectral fit of each neurochemical and data quantitation. Compared to the rats with normal sleep/wake cycles, sleep deprived rats demonstrated signficantly greater ($p<0.05$) levels of glutamate and aspartate in the medial prefrontal cortex. In contrast to the medial prefrontal cortex, sleep deprivation was associated with lower levels of glutamate in the hippocampus. Behavioral observations suggested that sleep deprivation was associated with increased reactivity to environmental cues. These preliminary data indicate that sleep deprivation affects excitatory neurotransmitters in the hippocampus and prefrontal cortex, two brain regions implicated in the neurobiology of human anxiety disorders. Ongoing studies in our laboratory, investigating the longitudinal effects of sleep deprivation on selective brain substrates and brain biochemistry in different animal models of stress or anxiety will discussed within the context of current theories of panic disorder and post traumatic stress disorder.

90. Tiagabine in Patients with Generalized Anxiety Disorder: A Randomized, Double-blind, Placebo-controlled Study

Michael Van Ameringen, Mark H Pollack and Karl Rickels*

Mood & Anxiety Disorders Section, University of Pittsburgh, Philadelphia, PA, USA

Introduction: Generalized anxiety disorder (GAD) is a disabling condition, with a lifetime prevalence of 5% in the general population. The pathophysiology of GAD involves several neurotransmitter systems, including γ-aminobutyric acid (GABA). Tiagabine is a selective GABA reuptake inhibitor (SGRI) that increases synaptic GABA availability via inhibition of the GAT-1 GABA transporter. In a randomized, controlled, open-label study in patients with GAD, tiagabine significantly reduced symptoms of GAD and improved overall clinical condition. The objective of this study was to evaluate the efficacy and tolerability of tiagabine in adult patients with GAD. **Methods:** Patients meeting DSM-IV criteria for GAD were enrolled into this 8-

week, double-blind, randomized, placebo-controlled, parallel-group, flexible-dosage study. Tiagabine was initiated at a fixed dose of 4 mg/d for 1 week. During weeks 2-6, the dose was individually titrated, according to efficacy and tolerability, in increments up to 4 mg/week up to a maximum dosage of 16 mg/d. Dose was to be maintained during weeks 7 and 8. Following week 8, study drug was tapered in decrements of 2 mg every other day. Tiagabine was administered in two daily doses, one with breakfast and one at 2100 with a snack. Efficacy assessments included the Hamilton Rating Scale for Anxiety (HAM-A), Clinical Global Impression (CGI), and Sheehan Disability Scale (SDS). Safety and tolerability were monitored using the Montgomery and Åsberg Depression Rating Scale (MADRS), Massachusetts General Hospital Sexual Functioning Questionnaire (MGSQ), and Physician Withdrawal Checklist (PWC). Adverse events were reported, and patients' weight was recorded at baseline and week 8. **Results:** A total of 272 patients were randomized. Of these, 266 (tiagabine, n=134; placebo, n=132) received at least one dose of study drug and were included in the safety analysis. A total of 260 patients (tiagabine, n=130; placebo, n=130) completed at least one post-baseline assessment and were included in the efficacy analysis. Mean dose of tiagabine over the double-blind treatment period was 10.5 mg/d. Tiagabine reduced the symptoms of GAD, with an early onset of effect, shown by a significant mean change from baseline in HAM-A total score at weeks 1 and 8 compared with placebo ($P<0.05$). Based on the mixed models repeated measures analysis, tiagabine significantly reduced the mean HAM-A total score (change from baseline) over the entire treatment period compared with placebo ($P<0.01$). Tiagabine improved overall clinical condition, with 57% of patients receiving tiagabine being rated 'very much improved' or 'much improved' according to CGI-I scale score at week 8, compared with 43% receiving placebo. Tiagabine also improved patients' functional status, as shown by a significant mean change from baseline in SDS total and work domain scores at week 8 compared with placebo ($P<0.05$). Tiagabine was generally well tolerated, did not adversely affect patients' sexual functioning or depressive status, and was not associated with weight gain or discontinuation effects. **Conclusions:** In this randomized, placebo-controlled study, tiagabine reduced the symptoms of GAD, with an early onset of action. Patients receiving tiagabine showed an improvement in overall clinical condition and functional status. Tiagabine was generally well tolerated and not associated with weight gain, sexual dysfunction, or worsening of depressive symptoms. Results suggest tiagabine may be a useful treatment option in adult patients with GAD. References: 1. Rosenthal M. J Clin Psychiatry. 2003;64:1245-1249. Support: This study was sponsored by Cephalon, Inc., West Chester, PA.

91. Mitochondrial Related Gene Expression In Affective Disorders In Postmortem Brain: An Epiphenomenon?

Marquis P Vawter*, Mary E Atz, Fan Meng, Hiroaki Tomita, Benjamin M Bolstad, Jun Z Li, Ling Shao, Terry E Speed, Prabhakara Choudary, Charles Neal, John Stead, Shelly Flagel, Simon Evans, Kevin Overman, David M Walsh, Richard Myers, Stanley J Watson, Edward G Jones, Huda Akil and William E Bunney

Psychiatry and Human Behavior, University of California, Irvine, CA, USA

Sponsor: William Bunney

Reports of mitochondrial related gene expression in bipolar disorder [(1)] and schizophrenia [(2)] have increased interest as to whether the observed mitochondrial gene expression differences are relevant to agonal and diagnostic group differences. The broad effects of pH and agonal factors on microarray analysis of gene expression were also reported in pathways related to stress and oxidative phosphorylation [(3,4)]. We have analyzed molecular profiles in multiple brain regions from bipolar disorder type I (BPD), recurrent major depression (MDD), and control groups for mitochondrial related gene expression by microarray, Q-PCR, and in situ hybridization. Comparison of microarray results between control subjects stratified by either pH or agonal factors resulted in gene expression differences related to mitochondrial pathways such as oxidative phosphorylation. The direction of gene expression differences is such that lower pH in controls resulted in an apparent down-regulation of gene expression in a large number of genes related to mitochondrial function in cortical and cerebellar cortices. After eliminating low pH cases with agonal factors from all three groups, the BPD and MDD groups were compared to control subjects. The 'mitochondrial effect' is reduced in amplitude in affective disorder comparisons to controls. Mitochondrial encoded transcripts and the copy number of mtDNA were specifically measured by Q-PCR after elimination of low pH cases with agonal factors from all three groups. Alterations in mitochondrial transcript levels and copy number by Q-PCR were found in mood disorders compared to controls. In situ hybridization for a selected mitochondrial-related transcript indicated a significant effect for agonal factor, and after elimination of cases with low pH and agonal factors, the transcript was increased in bipolar disorder which confirmed the Q-PCR and microarray results. Taken together, the data suggest dysregulation at the mitochondrial level in affective disorders independent of agonal factors and pH and offers evidence in support of the mitochondrial dysregulation hypothesis of bipolar disorder [(5)] and extension to major depression. Whether the mitochondrial dysregulation occurs as a result of upstream signals or genetic predisposition is unknown and will require further research. **References:** 1. Konradi, C., et al., Molecular evidence for mitochondrial dysfunction in bipolar disorder. Arch Gen Psychiatry, 2004. 61(3): p. 300-8.; 2. Prabakaran, S., et al., Mitochondrial dysfunction in schizophrenia: evidence for compromised brain metabolism and oxidative stress. Mol Psychiatry, 2004. 9(7): p. 643; 3. Li, J.Z., et al., Systematic changes in gene expression in postmortem human brains associated with tissue pH and terminal medical conditions. Hum Mol Genet, 2004. 13(6): p. 609-16; 4. Tomita, H., et al., Effect of agonal and postmortem factors on gene expression profile: quality control in microarray analyses of postmortem human brain. Biol Psychiatry, 2004. 55(4): p. 346-52; 5. Kato, T. and N. Kato, Mitochondrial dysfunction in bipolar disorder. Bipolar Disord, 2000. 2(3 Pt 1): p. 180-90.

92. Teaching Psychiatrists To Prescribe 'The Right Drug For The Right Patient'

Oldrich Vinar*

Czech Psychiatric Society, Prague, Czech Republic

A psychiatrist can choose from approximately 20 antipsychotc drugs and from 20 antidperessants when treating schizophrenia or depressive disorders respectively. Evidence based medicine helps only little in his choice because of the scarcity of randomized double-blind comparisons which found differences in the response related to symptoms or to other clinical parameters. Nevertheless, experience obtained with psychiatrists during a postgraduate course showed a surprisingly good consensus. **Method**: Annually, Psychopharmacological Section of the Czech Psychiatric Society organizes courses for practising psychiatrists. During the 2003 course the participants were randomly divided in 6 groups of 7-8 persons. Each group had to write brief fictious case reports about patients treated successfully with one of the following psychotropic drugs: alprazolam, buspiron, citalopram, clomipramin, clozapine, mirtazapine, moclobemide, tianeptine, ziprasidon and zuclopentixol. The symptoms and other chracteristics of patients had to fit in the best way to the the effects of the drug as believed by the group. In other words, the psychiatrists had to find target symptoms which were more or less specific for the drug. Each group received a sealed envelope with the names of drugs which were not known to the doctors of other groups. The vignettes had to describe the premorbid history,

symptoms and the course of the treatment. The reasons for the choice of the drug had not to be given. The author who organized the course, visited each group during their work, reviewing the text and sometimes censoring it if it was too explicite (e.g.if the dosage or other specific characteristics of the drug action were mentioned which would make an unequivocal judgement about the identity of the drug possible, irrespective of the course of the disorder described by the vignette). All members of each group had to agree with the final text. Then, the vignettes were read in the main conferecence room where all participants of the course gathered. Questions from the floor related to the patients' history were allowed. Then, the participants (except the authors of the vgbnettes) were asked to guess what drug was used. **Results**: When adding up the individual "votes" (guesses) of the participants, the guesses of the majority of the participants were always correct. The guesses about buspiron, clozapine and zuclopentixol were even unanimous. **Discussion**: This experience is far from bringing evidence that Czech psychiatrists know how to choose the right drug for the right patient. There is no external criterion showing that their opinions is correct. The process - and recent experience - of coming to a consesus in the group of 7-8 psychiatrists might have contributed to the atmosphere which helped achieve consensus among all participants. A certain indoctrination by the more assertive members in the group ("opinion leaders") might have been as important as the knowledge about the drug effects. On the other hand, the method seems to be feasible when teaching clinical psychopharmacology to psychiatrists. The interest in the task and cooperative activity (or even creativity when inventing the events in the patients' life) was surprising.

93. Hydrocortisone Impairs Hippocampal-Dependent Trace Eyeblink Conditioning In Posttraumatic Stress Disorder

Meena Vythilingam*, Megan Lawley, Carlos Collin, Omer Bonne, Kayleen Hadd, Dennis S Charney and Christian Grillon

Mood and Anxiety Disorders Program, National Institute of Mental Health, Bethesda, MD, USA

Sponsor: Daniel Pine

Background: Studies evaluating hippocampal mediated neuropsychological function in post-traumatic stress disorder (PTSD) are mixed. Trace eye blink conditioning is an explicit memory task that is dependent on the stress sensitive hippocampal neurons and the cerebellum and could help resolve the discrepancy in the PTSD literature. Since trace eyeblink conditioning can be pharmacologically manipulated and is sensitive to glucocorticoids, it can also shed light on the status of the glucocorticoid receptors in PTSD. This study assessed baseline and hydrocortisone mediated changes in hippocampal and cerebellar function in patients with PTSD and healthy controls using trace eyeblink conditioning. **Method:** Twelve patients with PTSD and 12 age- and sex-matched healthy controls participated in a trace eyeblink test (1000-ms trace) 6 hours following intravenous administration of 35 mg of hydrocortisone. **Results:** Spontaneous blink rates were similar between PTSD patients and healthy controls. There was no significant difference in the mean conditioned response between PTSD subjects and healthy controls under placebo conditions. Following hydrocortisone administration, only the PTSD patients demonstrated a significant reduction in conditioned response in contrast to healthy subjects who did not demonstrate any change. **Conclusions:** Hydrocortisone administration impairs associative learning in patients with PTSD but not in healthy controls, suggesting a differential sensitivity to glucocorticoids in PTSD. However, baseline hippocampal and cerebellar function as evaluated by trace eye blink conditioning was normal in PTSD.

94. Anxiety Symptoms Are Associated with Poorer Word Generation and Inhibitory Control in Older Psychiatric Outpatients

Julie L Wetherell*, Elizabeth W Twamley, Enid Rockwell, Patricia H Judd, Daniel Sewell, Thomas L Patterson and Dilip V Jeste

Dept. of Psychiatry, UCSD, La Jolla, CA, USA; VA San Diego Healthcare System, San Diego, CA, USA

Sponsor: Travel Awardee, BMS, 2004

In younger adults, anxiety is associated with threat-related biases in attention, interpretation, and in some studies, memory. Because of age-related cognitive declines in frontal lobe functions, the effects of anxiety on cognitive performance may be more pronounced in older adults than in younger adults. Previous investigations examining the relationship between anxiety and cognitive performance in older adults have yielded inconsistent results. Most studies have been limited by the use of community rather than clinical samples and inadequate assessment of executive functioning, which may be particularly vulnerable to the effects of anxiety. In the present study, a convenience sample of 35 psychiatric outpatients (63% women, mean age 64.3 years, *SD* = 17.4, range 28-96), most of whom were diagnosed with depressive or anxiety disorders, completed a self-report measure of anxiety symptoms (BSI-18 Anxiety subscale) and a neuropsychological battery comprised of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Controlled Oral Word Association Test (FAS), neutral and anxiety word Stroop test, and the Card Sort test from the Delis-Kaplan Executive Function System (DKEFS). 25.7% of the sample scored above the cutoff for clinically significant anxiety on the BSI-18. Gender and education were not significantly related to performance on any test with the exception of DKEFS Confirmed Correct Sorts Scaled, which was positively correlated with education ($r = .361$, $p = .04$). Regression models were computed for each test using age, anxiety, and the age by anxiety interaction as predictors. The interaction between anxiety and age was significantly related to poorer performance on the FAS ($\beta = -1.327$, $p = .047$), and the anxiety word Stroop ($\beta = 1.443$, $p = .02$), but not to performance on the DKEFS Card Sort or any RBANS scale. These results suggest that in older adults, anxiety may interfere with performance on verbal executive function tasks involving word generation and inhibitory control, two domains associated with frontal lobe functioning. Other cognitive domains did not appear to be as sensitive to the effects of anxiety, including an executive function task with a visual component (DKEFS Card Sort), visuospatial tasks (RBANS Visual Spatial index), and simpler language, memory, and attentional tasks that do not seem to tax the frontal lobes as heavily (RBANS Language, Attention, and Immediate and Delayed Memory indices). These findings are consistent with with previous research suggesting that the primary mechanism for the effect of anxiety on cognitive performance in older adults may be the verbal process of worry interfering with verbally-based tasks of executive functioning.

95. T cell Proliferation and Anti-basal Ganglia Antibody Characterization in Response to Streptococcal Virulence Factor Immunization

Kyle A Williams*, Suk W Kim and Patrick M Schlievert

Microbiology, University of Minnesota Medical School, Minneapolis, MN, USA; Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA

Sponsor: Horace Loh

Sydenham's chorea (SC) is a rare but serious sequela of group A β-hemolytic Streptococcus pyogenes (GABHS) infection, and is recognized as a major manifestation of Acute Rheumatic Fever (ARF). Multiple studies have isolated autoreactive anti-basal ganglia antibodies from peripheral blood in patients with SC, and these antibodies have been shown to cross react with streptococcal M proteins, a

major GABHS virulence factor. Additional virulence factors, bacterial superantigens (SAGs), are a class of immunostimulatory exotoxins produced by GABHS. SAGs undermine immune function by binding both the class II major histocompatibility complex (MHC II) molecules on antigen-presenting cells (APC) and specific Variable-β (Vβ) regions on the T cell receptor (TCR). We hypothesize that highly rheumatogenic strains of GABHS encode both autoimmune-inducing M protein epitopes and SAGs capable of expanding T cells that bind these cross-reactive epitopes, leading to possible antibody dysregulation. In the current study, we assessed CD4 T cell response to the M18 GABHS serotype M protein and the superantigens SpeC, SpeL, and SpeM cloned from a GABHS strain which produces high rates of Sydenham's Chorea. Cloned, recombinant M18 protein was generated and injected subcutaneously (50μg adjuvant) into PL/J mice (n=5). Experimental groups received M18 subcutaneously and 10ηg of either SpeC, SpeL, or SpeM i.p. (n=5). Groups were sacrificed at 2, 6, and 8 weeks. Splenocytes were harvested, pooled, and used in a T cell proliferation assay. Overlapping M18 peptide fragments were used in T cell proliferation and ELISA assays to determine the specific region of the M protein that is dominantly recognized by CD4 T cells, and the affect of superantigens upon a CD4 T cell antigen recognition. Our data indicate a highly significant ($p<.001$) downregulation of T cell reactivity to the variable region of the M protein. Autoreactive anti-basal ganglia antibody generation was assessed using Western blots. Homogenized mouse striatum (15μg/lane) was run on SDS-PAGE gels and transferred to a PVDF membrane. Membranes were incubated in pooled serum (1:100 dilution) from each experimental group and assessed for antistriatal antibodies. Serum from mice immunized with both M18 protein and SpeC demonstrated reactivity to an approximately 40 kDa murine striatal antigen. The preliminary data support our hypothesis that superantigens significantly affect the CD4 T cell antigen response, leading to an aberrant immune response to M protein. The data also support our hypothesis that specific streptococcal virulence factors, namely the M protein and streptococcal superantigens, may be sufficient to induce auto-reactive antibodies that react to basal ganglia proteins. This may have implications in the pathogenesis of Sydenham's Chorea, and other post-streptococcal neuropsychiatric disorders.

96. Clinical Relevance of Depressive Symptom Improvement in Bipolar Depressed Patients Treated with Olanzapine-Fluoxetine Combination

D Williamson, E Brown, R Perlis, J Ahl and Gary Tollefson*

Eli Lilly and Company, Indianapolis, IN, USA

Background: The clinical relevance of results from a bipolar I depression study may be determined by examining the relationship between improvement in depressive symptoms on a standard rating scale and clinical impression of overall depression severity. **Methods:** This was post hoc analysis of a double blind, 8-week bipolar I depression study. Patients were randomized (4:4:1)to receive placebo (PLA, n=355), olanzapine (OLZ, n=351), olanzapine-fluoxetine combination (OFC, n=82). Principal components analysis was used to extract factors using baseline MADRS scores. **Results:** A unit change in MADRS factor scores for "sadness", "negative thoughts", "concentration", and "neurovegetative symptoms" corresponded to a 0.70, 0.67, 0.76 and 0.57 change in CGI, respectively (all $p<.001$). OFC had superior therapeutic effect (TE) over PLA ($p<.001$) and OLZ ($p<.01$) for mean change from baseline to endpoint (LOCF) on all factor scores. TE for OFC versus PLA was significant at week 1 and thereafter ($p<.05$); significant differences were detected early in treatment between OFC and OLZ for "sadness" and "negative thoughts". OFC significantly reduced CGI compared to PLA ($p<.001$) or OLZ ($p=.001$); most of this difference was attributable to effects on MADRS factor score improvement. **Conclusions:** Changes in MADRS factors and CGI were closely related, suggesting a high degree of clinical relevance. References: Mulder RT, Joyce PR, Frampton C. Relationships among measures of treatment outcome in depressed patients. J Affect Disord 2003;76:127-135; Muller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord 2003;77:255-260.

97. Effect of Sertraline on a Peripheral Glucocorticoid-Mediated Response in PTSD

Rachel Yehuda*, Ren-Kui Yang, Julia A Golier, Linda M Bierer, Lisa Tischler and Robert A Grossman

Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA; Mental Health Patient Care Center, Bronx VA Medical Center, Bronx, NY, USA

Introduction: We have previously demonstrated that lower concentrations of dexamethasone (DEX) are required to inhibit lysozyme activity in mononuclear leukocytes (MNL) from subjects with posttraumatic stress disorder (PTSD) than comparison subjects, reflecting a greater responsiveness of the glucocorticoid receptor (GR) to corticosteroids in this peripheral cellular population in PTSD. In the current study, we examined the effects of *in vitro* sertraline administration on DEX- inhibited lysozyme activity in MNL from 7 subjects with PTSD and 7 comparison subjects. **Method**: 60 ml of blood was withdrawn by venipuncture at 8:00 a.m. from subjects free of all psychotropic medications for a minumum of four weeks at the time of study. MNL were isolated and divided into two portions: the first contained live cells incubated with varying concentrations of DEX; the second contained cells that were co-incubated with sertraline. ANCOVA compared the $IC_{50\text{-}DEX}$ for lysozyme inhibition under conditions of DEX-only and sertraline+DEX. **Results**: Sertraline substantially altered the lysozyme $IC_{50\text{-}DEX}$ in the direction of decreasing the sensitivity of the receptor in subjects with PTSD while having no effect in cells from comparison subjects ($IC_{50\text{-}DEX}$ for PTSD: 4.96±2.37 (DEX-only) and 8.93±4.34 (sertraline+DEX); controls: 6.14±1.0 and 6.08±2.76, respectively; Group x Condition: $F=6.19$; $df=1,12$; $p=.03$). **Conclusions**: Insofar as increased responsiveness to glucocorticoids has been linked with PTSD, the action of sertraline on the $IC_{50\text{-}DEX}$ for lysozyme inhibition suggests that sertraline may alleviate PTSD symptoms, at least in part, by helping to correct a biologic alteration associated with PTSD pathophysiology. The actions of sertraline on DEX-inhibition of lysozyme activity in PTSD may involve direct effects on the GR, however, the extent to which the effects of sertraline in PTSD are comparable to those occurring in persons with major depressive disorder remains to be determined.

98. Comparing Diagnostic Efficiency of Multiple Screeners for Pediatric Bipolar Disorder

Eric Youngstrom*, Oren I Meyers, Christine Demeter, Jennifer K Youngstrom, Laura Morello, Norah C Feeny, Joseph R Calabrese and Robert L Findling

Psychology and Psychiatry, Case Western Reserve University, Cleveland, OH, USA

Sponsor: Past Travel Awardee, BMS, 2003

Objective: To compare three promising parent-report measures, the Parent Mood Disorder Questionnaire (P-MDQ), the ten-item short form of the P-GBI (PGBI-SF10), and the adolescent self-report MDQ (A-MDQ) in a demographically diverse outpatient sample. Bipolar disorder is being diagnosed and treated in children and adolescents at a rapidly increasing rate, despite the lack of validated instruments to help screen for the condition or differentiate it from more common disorders. The study extend prior investigations of the PGBI-SF10, P-MDQ, and A-MDQ by comparing them simultane-

ously in a new, independent sample, and it also examines the generalizability of these instruments to a low income and demographically diverse sample (85% qualifying for Medicaid). **Methods:** Participants were 145 outpatients (including 103 males and 69 African-Americans) presenting to either an academic medical center (n = 95) or a CMHC (n = 50). Diagnoses were determined by a semi-structured (KSADS) interview conducted by a highly trained rater and involving the parent and then the youth sequentially. Final diagnosis was based on a consensus conference involving at least one doctoral level clinician and the KSADS rater, but recusing the screening questionnaires. **Results:** Fifty-three youths (37%) met criteria for a bipolar spectrum disorder. The rest of the sample included 32 cases with a primary diagnosis of unipolar depression; 49 had a primary diagnosis of ADHD or a disruptive behavior disorder, 5 had no KSADS diagnosis on axis I, 3 met for adjustment disorder, 1 for schizoaffective, 1 for social phobia, and 1 for cannabis dependence. The most frequent comorbid diagnosis was ADHD, present in 63% of cases overall (and 67% of the bipolar cases). All three measures showed good reliability, comparable to what had been previously reported in their respective validation samples. The PGBI-SF10 had alpha = .90; the P-MDQ had alpha = .85, and the A-MDQ had alpha = .81. There were no significant differences in the reliability of the measures in the CMHC versus academic outpatient samples. The two parent-reported measures correlated highly, $r = .68$, $p < .0005$. The A-MDQ failed to correlate significantly with either parent measure, $r = .03$ with the PGBI-SF10 and $r = .17$ with the P-MDQ. The PGBI-SF10 had an Area Under Receiver Operating Curve (AUROC) of .72, $p < .0005$. The P-MDQ had an AUROC of .67, $p = .001$. The A-MDQ had an AUROC of .59, n.s. There were no significant site differences in the performance of the three measures. Only the PGBI-SF10 made a significant contribution to logistic regression models examining all combinations of the three instruments. **Discussion:** Results replicate previous findings that the Parent versions of the MDQ and PGBI Short Form significantly discriminate bipolar from nonbipolar cases in youths ages 5 to 18 years; and they appear robust in a demographically diverse CMHC setting. The A-MDQ is less efficient, not performing better than chance in these data. Findings suggest that the PGBI-SF10 and the P-MDQ both could be used as screening devices to identify bipolar disorder in youths. The PGBI-SF10 showed a statistical advantage as a screener in logistic regression analyses. The parent instruments could be combined in a multiple gating strategy (although the P-MDQ did not significantly improve prediction after controlling for PGBI-SF10 in logistic regressions), or one could be used as a screen and the other could be used as a symptom measure for quantifying outcomes in the same sample.

99. Neurocognitive Function after Treatment with Lithium or Olanzapine: A Double Blind Study

Deborah A Yurgelun-Todd*, Staci A Gruber, Richard Risser, Susan Briggs and Mauricio Tohen

Cognitive Neuroimaging Laboratory, Brain Imaging Center, McLean Hospital, Belmont, MA, USA; Department of Psychiatry, Harvard Medical School, Boston, MA, USA

Background. Neurocognitive function has gained increasing recognition as an important factor in the course of bipolar disorder. A number of studies have proposed that cognitive performance may play a role in the onset of the illness while additional studies have highlighted the importance of neurocognitive ability in treatment outcome. The current international investigation examined neurocognitive performance and clinical outcome prospectively in 328 bipolar patients entered in a double blind, 52 week, multi site study of olanzapine versus lithium who completed neurocognitive testing and ratings of clinical symptoms. **Methods**. Patients were stratified by both treatment and relapse status in order to identify the changes in cognitive processing ability associated with drug type in non-relapsing bipolar patients. Mean changes from baseline to endpoint (LOCF) were assessed with an analysis of variance containing terms for therapy and country. **Results**. While relapse-free treatment subgroups did not differ significantly on YMRS or HAM-D change scores, they did demonstrate a number of significant changes on cognitive performance. On the Rey Auditory Verbal Learning Test (RAVLT), the lithium treated group showed a significantly greater improvement in recall of the first word list ($p=.026$) and a trend for improved total recall ($p=.09$) compared to those treated with olanzapine. In contrast, the olanzapine treated group showed a significantly greater improvement on the WMS-R Digit Forward subtest ($p=.014$), with a trend toward improvement on the overall WMS-R Digit Span Test($p=.09$)compared to lithium treatment. Significantly greater improvement was also seen for the lithium treated patients relative to the olanzapine treated patients on the number of categories completed on the Wisconsin Card Sorting Test (WCST)($p=.042$) and on the Immediate Recall of the Rey Complex Figure Test (ROCF) $p=.035$). **Conclusion**. Improved organizational capacity and immediate recall was seen in lithium treated patients whereas improved attentional capacity was seen in the olanzapine treated patients. These findings suggest that both olanzapine and lithium treatment result in improved cognitive function in non-relapsing bipolar patients and that these improvements are observed in different cognitive domains.

100. Are Oligodendrocytes Under-appreciated Targets for Long-term Mood Stabilization?

Lei Zhang*, James Barrett and Husseini Manji

Psychiatry, USUHS, Bethesda, MD, USA; NIMH, NIH, Bethesda, MD, USA

Sponsor: James Barrett

Within the last 3 years, there has been tremendous progress in our understanding of the critical roles of glial cells in regulating neuronal function, as well as their involvement in severe mood disorders. The possibility of glial dysfunction in severe mood disorders has only recently received serious consideration due to the converging neuroimaging, postmortem morphometric and microarray studies, which have clearly revealed glial abnormalities in severe mood disorders. Notably, recent genomic studies (differential display, microarray and RT-PCR) of postmortem brain tissue have revealed the surprising findings that the expression of myelination-related genes are markedly down-regulated in severe mood disorders. These unexpected observations raise the possibility that these disorders may be associated with disruption of white matter tracts regulating critical neuronal circuitry. Complementary diffusion tensor imaging (used to measure the fractional anisotropy of the white matter) has revealed regional microstructural changes in the white matter. It is now know that oligodenrocyte proliferation, differentiation, growth and survival are regulated by signaling cascades known to be targets for mood stabilizers; this raises the possibility that their therapeutic actions may also involve oligodendrocytes. To investigate this more definitively, we have undertaken a series of in vitro and in vivo studies examining lithium's effects on oligodendrocytes. Chronic lithium treatment significantly increased the total number of oligodendrocytes in a dose-dependent manner, with a maximal effect was observed with 1.0 mM lithium. To determine whether lithium affects BrdU incorporation, oligodendrocytes were treated with BrdU for 6 h in the absence or presence of lithium (1.0 mM). BrdU incorporation was determined by immunocytochemistry. BrdU-labeled cells were markedly increased by lithium treatment. To further determine the cell phenotype of these BrdU-labeled cells, O4 expression was examined by immunocytochemistry. BrdU-positive cells were also O4 positive. Quantitatively, the percentage of BrdU-positive oligodendrocyte, as well as that of BrdU+O4+ cells were significantly increased by the lithium treatment. Our data demonstrate — for the first time - that chronic lithium exerts a major effect on oligodendrocytes. These observations raise the possibility that lithium may serve to correct

abnormalities in white matter tracts, thereby restoring the functioning of critical circuits mediating affective, cognitive and motoric symptoms.

101. Memantine in Major Depression: A Double-Blind, Placebo-Controlled Study

Carlos A Zarate*, Jaskaran B Singh, Jorge A Quiroz, Kirk K Denicoff, Georgette De Jesus, David Luckenbaugh, Husseini K Manji and Dennis S Charney

Mood and Anxiety Disorders Program, NIMH, Bethesda, MD, USA

Sponsor: Mauricio Tohen

Objective: There is growing consensus that for many depressed patients, new agents, which, like traditional agents, increase intrasynaptic monoamine levels, may be of limited benefit. Since considerable research implicates a potential role of the N-methyl-D-Aspartate receptor (NMDA) receptor complex in mediating the deleterious effects of stress and in the actions of antidepressants, we undertook the present study as a proof of the concept that NMDA antagonists may have efficacy in the treatment of major depression. **Method:** In a double-blind, placebo-controlled study, 30 patients between ages 18 and 80 years old with major depression and a Montgomery-Asberg Depression rating scale (MADRS) ≥22 for two consecutive weeks were randomly assigned to receive memantine (5-20 mg/day) (N = 14) or placebo (N = 16) for 8 weeks. Primary efficacy was assessed by the MADRS. **Results:** Baseline demographic and clinical parameters were comparable between the two groups; mean age was 46.5 ± 10.5 years, 50% were females, and 16.7% had a current comorbid anxiety disorder diagnosis. 73.3% were not taking an antidepressant at study entry and 20% had previously failed an adequate antidepressant trial. Completions rates were for memantine 78.6% and placebo 81.3%. The mean dose for memantine was 19.3 mg/day. The ANOVA for total MADRS scores did not show a significant treatment effect (memantine: from 30.6 ± 3.9 to 27.9 ± 9.7, placebo: from 31.7 ± 5.4 to 26.1 ± 10.6; p=.358). Response rates (>50% decrease in MADRS from baseline) did not differ between groups and were 14.3% in the memantine group and 12.5% in the placebo group. Memantine was well tolerated. **Conclusions:** The NMDA antagonist memantine failed to show a significant antidepressant effect at dose of 5-20 mg/day in subjects with major depression; additional studies utilizing higher doses of memantine are underway.

102. Genomic Studies Identify a Novel Plasticity Regulating Glucorticoid Receptor (Gr) Chaperone Protein as a Target for Mood Stabilization: from Microarray to Functional Studies

Rulun Zhou*, Neil A Gray, Peixiong Yuan, Jing Du, Lei Zhang, Xiaoxia Li, Jingshan Chen, Guang Chen, Patricia J Damschroder-Williams and Husseini Manji

NIMH, NIH, Bethesda, MD, USA; Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Sponsor: Husseini Manji

The mood stabilizers lithium and valproate are both effective in the treatment of bipolar disorder; however, their therapeutic mechanisms remain unclear. Because of the delayed onset of clinical efficacy (days to weeks), it has been proposed that adaptive changes in gene expression, rather than their initial pharmacological actions, may be directly responsible. To investigate the strategic regulation of signaling pathways and gene expression in critical neuronal circuits likely involved in the long term treatment of bipolar disorder, we used microarray methodologies to identify novel targets of therapeutic relevance with validating criteria including the following: (1) dose and time frame consistent with clinical therapeutic effects; (2) observed with structurally highly dissimilar but clinically efficacious agents; (3) specific to brain regions implicated in the disorder (4) specific for mood stabilizers (5) validated at a protein level. Using these stringent criteria, our recent microarray studies have revealed a novel target for the long-term actions of the mood stabilizers lithium and valproate. Chronic administration of both agents at therapeutic doses increased the expression of BAG-1 (bcl-2 associated athanogene) in rat hippocampus. Furthermore, these findings were validated in the hippocampus at the protein level, the effects were seen in a time frame consistent with therapeutic effects, and were specific for mood stabilizers. Bag -1 is an important chaperone of bcl-2, and enhances bcl-2's anti-apoptotic functions; furthermore, through interaction with raf, Bag-1 is able to activate ERK MAP kinases. Consistent with this, we found that lithium and valproate activate ERK MAP kinases and exert anti-apoptotic effects. Bag-1 also inhibits GR activation, which may counteract the deleterious effects of hypercortisolemia seen in BD. Anti-GR antibody immunostaining plus double staining with DAPI showed either lithium or VPA, at therapeutically relevant levels, inhibited dexamethasone induced glucocorticoid receptor (GR) nuclear translocation. In addition, glucocorticoid response element (GRE) transfection assay showed lithium, at therapeutically relevant levels, inhibited GR activity in SH-SY5Y cells. Evaluated through siRNA silencing of BAG-1, the inhibition of mood stabilizers to GR nuclear translocation and to GR activity is mediated, at least in part, by BAG-1. The effect that BAG-1 inhibits glucocorticoid activation suggests mood stabilizers may counteract the deleterious effects of hypercortisolemia seen in BD by up-regulating BAG-1. Together, the data suggests that BAG-1 may represent a novel, highly therapeutically relevant target in the long-term treatment of bipolar disorder. Complementary human studies have shown that chronic lithium significantly increases gray matter content in a regionally selective manner, suggesting a reversal of illness-related atrophy and an increase in the volume of the neuropil. Interestingly, the gray matter changes are seen in a regionally-specific manner, and are only observed in treatment-responders. The growing body of preclinical/clinical data suggests that for many refractory patients, optimal treatment may only be attained by providing both trophic and neurochemical support; the trophic support would be envisioned as enhancing and maintaining normal synaptic connectivity, thereby allowing the chemical signal to reinstate the optimal functioning of critical circuits necessary for normal affective functioning.

103. Genome-Wide Linkage Survey for Genetic Loci That Affect the Risk of Suicide Attempts in Families With Recurrent, Early-Onset, Major Depression

George Zubenko*, Brion S Maher, Hugh B Hughes, Wendy Zubenko, J. S Stiffler and Mary L Marazita

Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Suicide is a prevalent outcome of psychiatric disorders and a major public health problem. Efforts to elucidate the genetic, physiologic, and environmental factors that contribute to suicide attempts provide a rational approach to preventing this tragic outcome. Evidence from epidemiologic, family, twin, and adoption studies has suggested the existence of an independent predisposition that contributes to the emergence of suicidal behavior through an interaction with a coexisting psychiatric disorder, most often a mood disorder. We previously described the results of a genome-wide linkage survey for genetic loci that influenced the development of unipolar mood disorders in 81 families identified by individuals with Recurrent, Early-Onset, Major Depressive Disorder (RE-MDD)(Zubenko et al., 2003). In the current study, we extended this linkage analysis by including the history of a suicide attempt as a covariate to identify chromosomal regions that harbor genes that influence the risk of this behavior in the context of mood disorders. This approach identified six linkage peaks with maximum multipoint DLOD scores that reached genome-wide adjusted levels of significance (2p, 5q, 6q, 8p, 11q, and Xq). Four of these (2p, 6q, 8p, and Xq) exceeded the criterion for

"highly-significant linkage" (genome-wide adjusted $p < 0.001$) recommended by Lander and Kruglyak (1995). The strongest evidence for linkage was observed in analyses employing affected relative pairs (ARPs) with the most severe and disabling Mood Disorders: Depression Spectrum Disorder and RE-MDD. The highest DLOD score that emerged from this linkage analysis, 5.08, occurred for ARPs with Depression Spectrum Disorder at D8S1145 (37.0 cM, 8.2 Mbps, $p < 0.0001$) at cytogenetic location 8p22-p21. Significant linkage results on Xq arose from analyses of ARPs with RE-MDD at DXS1047 (143 cM, 127.8 Mbps, DLOD = 3.87, $p < 0.0001$), a finding that may contribute to the higher rate of suicide attempts among women than men. These findings provide evidence for suicide risk loci that are independent of susceptibility loci for Mood Disorders, and suggest that the capacity for suicide risk loci to affect the development of suicidal behavior depends on the psychiatric disorder or subtype with which they interact.

104. An Open Label Pilot Study Of The Effects Of Galantamine On Depressive Symptoms In Inpatients With Chronic Schizophrenia

Matthew W Nelson*, Rhonda L Benham, Richard B Rosse and Stephen I Deutsch

Maryland Psychiatric Research Center, University of Maryland, Baltimore, Baltimore, MD, USA; Mental Health Service Line, VISN 5 VA, Washington, DC, USA

Sponsor: Robert Conley

Depressive symptomatology is common in schizophrenia and is associated with poor outcomes and risk of suicide. Galantamine is an acetylcholinesterase inhibitor with allosteric potentiating properties at nicotinic acetycholine receptors (nAChR) in the brain. Acetylcholinesterase inhibitors have been shown to improve depressive symptoms in patients with Alzheimer's disease. Furthermore, galantamine's action at nAChR has a potential role in the treatment of both schizophrenia and depression. In this ongoing trial, inpatients with stable, chronic schizophrenia are given galantamine in addition to their existing psychiatric medication regimen in a prospective, open-label design. Subjects are titrated to a dose of 24mg/day over three weeks and maintained at that dose for eight weeks. The primary outcome measure is the Montgomery-Asberg Depression Rating Scale (MADRS). Other measurements include the Brief Psychiatric Rating Scale depression cluster, the Neuropsychiatric Inventory depression and depression plus anxiety item scores, and the Clinical Global Impression scale. Paired student t-tests will be used to analyze changes between baseline and endpoint. Eleven subjects have enrolled in the study and seven subjects have received study medication to date. The average decrease in the total MADRS score from baseline is 8.5±6.6 ($p = 0.02$). Galantamine has been well tolerated and no subjects have withdrawn from the study due to side effects. No worsening of extrapyramidal symptoms or movement disorders has been observed. Data from additional subjects will be included and presented at the meeting. This preliminary data suggests promise for the adjuvant use of galantamine in treating depressive symptoms associated with schizophrenia.

105. Atypical Antipsychotic Treatment Effects On Adiposity And Tissue Specific Insulin Sensitivity In Humans

Karen Flavin, Daniel Haupt, Julie A Schweiger, Bruce Patterson, Samuel Klein and John W Newcomer*

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Increased adiposity can disturb glucose and lipid metabolism via disturbances in insulin sensitivity, and schizophrenia patients experience an increased prevalence of diabetes mellitus and the metabolic syndrome in comparison to the general population. Increased adiposity, plasma glucose, and lipids are risk factors for cardiovascular disease (CV), and schizophrenia patients experience higher rates of CV. Adiposity can be directly measured using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging. Such adiposity measures can be analyzed in relation to whole-body glucose and lipid kinetics measured with stable isotope tracer methodology during hyperinsulinemic-euglycemic clamp conditions. These sensitive methods can be used to measure tissue-specific changes in insulin sensitivity that might occur independent or dependent on fat mass. In this ongoing study, schizophrenia patients undergo prospective randomized assignment to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, with no other medication changes allowed. Preliminary analysis indicates significant time X treatment condition effects for body mass index ($F[2,6]=3.5$, $p=.02$) and DEXA total fat ($F[2,6]=4.3$, $p=.007$), with changes exemplified by increases in mean DEXA total fat in the olanzapine treatment arm and decreases in the ziprasidone treated arm. Covarying baseline DEXA total fat mass (to control for baseline differences in fat), significant time X treatment group interactions for glycerol rate of appearance (Ra) ($F[1,3]=194$, $p=0.005$) are observed, suggesting treatment group-related differences in the regulation of hepatic glucose production. Exemplifying changes in relation to changing fat mass, ziprasidone treated subjects experienced predicted changes in glucose Ra ($p=.03$), rate of disappearance (Rd) ($p=.04$) and glycerol Ra ($p=.01$). These results suggest beneficial treatment-related changes in insulin sensitivity in liver, skeletal muscle, and adipose tissue, respectively, in a subject group experiencing decreases in adiposity. These sensitive measures can be used to evaluate medication-induced changes in glucose and lipid metabolism, relevant to the risk of diabetes and cardiovascular disease. Direct measures of adiposity can be used to quantify treatment-induced changes in fat mass, and corresponding risk for diabetes and cardiovascular disease. Support Contributed By: National Institute of Mental Health, R01 63985; National Institute of Health, USPHS #M01RR00036): General Clinical Research Center Washington University, Clinical Nutrition Research Unit Center Grant P30 DK56341 and P60-DK20579.

106. Differential Effects of Atypical Antipsychotics on Indices of Metabolic Syndrome

John W Newcomer*, Jonathan Meyer, Antony Loebel and Guy M Cohen

Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Objective: To determine the rates of dyslipidemia and metabolic syndrome associated with the use of atypical antipsychotics in schizophrenic subjects in the ziprasidone clinical trial database. **Methods:** As of April 30, 2003, the ziprasidone clinical trial database comprised 8243 subjects with schizophrenia or schizoaffective disorder who were given ziprasidone (N=5622) or comparators (N=2621) in 37 trials involving other atypical antipsychotics. Trials included 15 short-term (≤12 week) studies, 19 long-term (>12 week) studies, and 3 studies where laboratory parameters were collected in a fasting state (2 short term, 1 long term). Per current NCEP guidelines, abnormal lipid values were defined as TChol ≥240 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, and triglycerides ≥200 mg/dL; metabolic syndrome was defined as ≥3 of the following: blood pressure (any position) ≥130/85 mm Hg; HDL-C <40 mg/dL (males) or <50 mg/dL (females); triglycerides ≥150 mg/dL; glucose (random or fasting) ≥110 mg/dL; and, as a surrogate for waist circumference, body mass index (BMI) >30. (Waist circumferences were not obtained in any trial.) HDL-C measurements were not obtained consistently in any trial, except in those employing fasting measurements. **Results:** Results are summarized for the short-term and long-term study groupings and individually for the 3 fasting studies. At last visit in the fasting studies, ziprasidone-treated subjects had a prevalence of serum lipid abnormalities comparable to that of placebo and consistently

lower than that of comparators. Olanzapine, by contrast, was associated with a nearly 2-fold higher prevalence of lipid abnormalities than ziprasidone. In studies with random laboratory measures, differences were not as marked or consistent. When metabolic syndrome was defined using a BMI threshold >30, the rate in ziprasidone vs olanzapine subjects was 3.3% vs 8.8%, respectively, in the short-term studies, and 4.8% vs 12.4% in the long-term studies. In fasting trials with ziprasidone and olanzapine treatment groups, rates of metabolic syndrome at endpoint in subjects with BMI >30 were 15.2% vs 23.6%, respectively (short-term trial), 25.7% vs 46.4% (short-term trial), and 22.6% vs 19.7% (long-term trial). In studies including risperidone, the rate of metabolic syndrome was higher than that of ziprasidone but less than that of olanzapine. Endpoint prevalence of dyslipidemia and metabolic syndrome in all studies is reported descriptively without adjusting for metabolic syndrome status at study baseline. **Conclusions:** In this comprehensive review of comparative atypical antipsychotic trials in the ziprasidone schizophrenia database, a differential effect on the rates of dyslipidemia and metabolic syndrome was observed. The observed differences at endpoint between groups indicated rates of metabolic abnormalities of ziprasidone < risperidone < olanzapine. This is consistent with findings from a recent ADA/APA consensus statement (Diabetes Care 2004; 27:596-601).

107. Effects Of Antipsychotics On Regions Of The Cerebral Cortex In Patients With Schizophrenia

Peg C Nopoulos*, Marcus Pressler, Laurie McCormick, Alison Kopelman, Lawrence Decker and Nancy C Andreasen

Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Background: One of the hottest topics in structural brain imaging in schizophrenia has been the finding of changes to the structure of brain due to antipsychotic medications. The notion that antipsychotic medications could actually change the structure of the brain began to surface several years ago with reports of the basal ganglia increasing in size after treatment with typical neuroleptics and decreasing in size after exposure to atypical neuroleptics. More recently, other groups have reported that when evaluating large regions of the cortex (cerebral lobes), the findings are reversed with atypical neuroleptics increasing volume of the cortex over time ("neuroprotective") while typical neuroleptics decrease volume over time ("toxic effects"). Our group has been systematically studying the effects of antipsychotic medications on the structure of small regions of the cortex such as the insula and the anterior cingulate gyrus. **Methods:** Two non-overlapping data sets of patients with schizophrenia: the first data set is cross sectional design and compares the morphology of the brain regions in chronic subjects (n=30) to matched healthy controls, and evaluates the relationship between volume and exposure to medication. The second data set is longitudinal in design and evaluates within-subject change in morphology between intake into study protocol (neuroleptic naïve) and two-year follow-up (n=31). All subjects are part of a naturalistic study, thus medication is not standardized. Instead, medication history is obtained, documented in detail, and quantified using a dose-years formula, which calculates drug exposure, weighted for dose and time, used. The insula and anterior cingulate measures are obtained via manual tracing guided by a well-validated cortical parcellation scheme. Morphology of the brain regions is then correlated with drug exposure. **Results:** Both data sets show that the volume of the insula and the anterior cingulate is directly related to medication exposure. Like the findings in the basal ganglia, these regions of the cortex enlarge with exposure to typical antipsychotics and decrease with exposure to atypical antipsychotics. In the longitudinal sample, the volume increase due to typical antipsychotics was directly related to clinical improvement. No relationship between clinical improvement and volume change was seen in regard to atypical exposure. **Conclusion:** The structure of small regions of the cortex, the insula and the anterior cingulated gyrus is directly affected by exposure to medications and with typical neuroleptics, this change is related to clinical outcome. These findings are in contrast to reports of larger regions of the cortex that show changes in the opposite direction with regard to class of medication exposed to.

108. Neurocognitive Function in Individuals "At-Risk" for Psychosis

Diana Perkins*, Hongbin Gu, Robert B Zipursky, Bruce K Christensen, Vicki Dixon and Richard S Keefe

Psychiatry, University of North Carolina at Chapel HIll, Chapel Hill, NC, USA

Sponsor: Richard Keefe

Introduction: Clinically defined prodromal diagnostic criteria identify "at-risk" individuals with a 35-40% likelihood of developing a psychotic disorder within a year. At present it is unclear when the characteristic neurocognitive deficits of schizophrenia develop, and whether the presence of cognitive deficits may enhance psychosis risk prediction. **Methods:** A comprehensive neurocognitive battery and clinical assessments were administered at baseline, 6-month, and 12-month follow-up to 37 subjects meeting Criteria of Prodromal States (COPS) criteria for "at-risk", and two comparison groups: 59 first episode and 48 healthy subjects. Analyses used a neurocognitive composite score derived from weights of the first principle component analysis of CPT, CVLT, visual working memory, verbal working memory, Finger Oscillation and WAIS-R test scores of the healthy normal sample. **Results:** At baseline there was significant difference in neurocognitive performance between groups ($F(2,138)=37.10$, $p<.0001$). "At-risk" subjects performed more poorly than healthy subjects ($F(1, 138)=22.40$, $P<.0001$), but better than first episode subjects ($F(1, 138)=7.65$, $P<.01$). Different cognitive test domains show significantly different levels of deficit. These differences between groups in overall cognitive function were not consistent for the individual tests ($F(10, 690)=5.60$, $p<=.0001$). Baseline neurocognitive function did not predict time to development of psychosis over one year ($Chi2(1)=1.99$, $p=.16$). More detailed results will be presented including findings based on individual neurocognitive test scores and the longitudinal course of neurocognitive function in the three groups and in "high-risk" subjects that did and did not develop psychosis. **Conclusion:** Neurocognitive function may be impaired in individuals clinically at risk for a psychotic disorder.

109. Reduction in Estrogen Receptor Alpha mRNA Levels in the Anterior Hippocampus of Patients with Schizophrenia

William R Perlman*, Maree J Webster, Joel E Kleinman and Cynthia S Weickert

Clinical Brain Disorders Branch, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

Sponsor: Joel Kleinman

Convergent data from multiple approaches suggest that altered synaptic circuitry within the hippocampal formation in the medial temporal lobe may be central to the pathophysiology of schizophrenia. Estrogens, acting predominantly through estrogen receptor alpha (ERα), exert powerful influences on hippocampal synaptic spine densities, and ERα mRNA is expressed in the human hippocampal sub-fields. We hypothesized that levels of ERα mRNA may be reduced in the hippocampal formation of patients with schizophrenia. Using quantitative film autoradiography following in situ hybridization with a previously characterized 495 base pair cDNA spanning

human ERα exons 1 and 2 we measured the levels of ERα mRNA on adjacent sections in 4 groups (N=15 each of schizophrenia, major depression, bipolar disorder and unaffected controls) provided by the Stanley Consortium. Two slides per case were analyzed taking one density measurement per slide, per hippocampal sub-field (dentate gyrus, CA4, CA3, CA1) and averaging the measurements from the two slides to provide one density score per hippocampal sub-field per case. A 3-way ANOVA with diagnosis and gender as between group measures and hippocampal sub-field as a within group repeated measure was used to detect main effects of diagnosis ($F=2.83, p<0.05$) and hippocampal subfield ($F=164.68, p<0.001$) on ERα mRNA levels, but no main effect of gender ($F=0.33, p=0.57$). By using a post-hoc least squares difference test, we determined that patients with schizophrenia exhibited reductions in ERα mRNA expression in the dentate gyrus (18%), in CA4 (13%), in CA3 (9%), and in CA1 (14%) as compared to normal controls, with no significant reductions detected in bipolar or depressed patients. ERα mRNA expression levels in the hippocampal sub-fields differed significantly with highest expression detected in the dentate gyrus, followed by CA3, and lowest expression levels were detected in CA4 and CA1 which did not significantly differ from each other. Our results suggest that estrogen-related signaling may be compromised in the anterior hippocampal sub-fields of patients with schizophrenia with possible implications for neurogenic or synaptogenic processes.

110. Functional Biomedical Informatics Research Network: Multi-Center fMRI Methods

Steven Potkin*, G G Brown, G. H Glover, G. McCarthy, K. O Lim, R Gollub, B. Rosen, A. Toga, R. Kikinis, A. Dale, J. Lauriello, D. O'Leary, J. Lieberman, A. Belger, D. Greve, L. Friedman, T. Cannon, J. Fallon, D. B Keator, J. S Grethe and J. A Turner

University of California, Irvine, Irvine, CA, USA

Department of Psychiatry and Human Development, University of California, Irvine, CA Background. Many clinical fMRI studies, for example of schizophrenia, involve sample sizes which are small and restricted to specific populations. The combination of data across institutions allows for rapid data collection, access to unique populations, and assessment of validity and generalizability of findings. Researchers must be ready to account for differences in technique, equipment and population focus to overcome the challenges of accessing and sharing large imaging and clinical datasets. Previous multi-site imaging studies have not assessed intersite variability and reliability of the imaging data prior to data combination; or have avoided data combination in favor of meta-analysis methods. Methods. The Function BIRN is a multi-site project funded by NCRR/NIH (www.nbirn.net) for the following goals: 1) Standardized calibration of equipment and imaging activation paradigms using geometric and human phantoms; 2) Developing a multi-site, standardized protocol for fMRI data collection on populations of persons with schizophrenia, including value-added, site-specific data; 3) Use of a federated clinical, genetics and imaging database to leverage multi-site data, leading to a deeper understanding of the functional neuroanatomy of schizophrenia than would be possible within a single site study or through meta-analysis. The eleven sites involved in the project are dedicated to collecting calibration fMRI data, developing experimental paradigms and analysis methods, populating a virtual data grid, and designing a searchable federated database of MRI and clinical data from multiple sites. Results. Using a set of mechanical phantoms to measure spatial distortions and temporal drift across sites, the FBIRN has collected a unique dataset of machine characteristics in fMRI data, which have served to assess initial inter-site differences. Using a set of traveling human subjects repeatedly scanned at each site, the FBIRN has determined that inter-site variability in the BOLD signals can exceed inter-subject variability, thus limiting the usefulness of combining raw imaging data across sites. Initial assessments indicate that intersite variability can be decreased through use of a variety of calibration methods. Conclusions. The unified efforts of researchers across universities have resulted in novel approaches to human subject data sharing, experimental design, fMRI data standardization, and clinical and imaging database design. Issues related to multi-site differences and integration of fMRI images will be demonstrated. The inter-site calibration and correction, and standardization of protocols, allows multi-center data to be combined more robustly to identify differences between patient groups and treatments, thus increasing the value of multi-site imaging trials. Support Contributed By: NCRR (NIH), 5 MOI RR 000827, www.nbirn.net.

111. Locomotor Hyperactivity in mGluR5 Knockout Mice is Potentiated by the Serotonergic Hallucinogen DOM and Attenuated by the 5-HT2A Antagonist, M100,907

Susan B Powell*, Virginia D Lehmann-Masten, Mahalah R Buell and Mark A Geyer

Psychiatry, University of California, San Diego, La Jolla, CA, USA

Metabotropic glutamate receptors (mGluR) have received much attention recently for their potential role in neuropsychiatric disorders including schizophrenia, drug abuse, and depression. Based on the observations that serotonergic hallucinogens increase glutamate release and that mGluRs modulate serotonin release, there has been increased interest in interactions between serotonin (5-HT)2A receptors and mGluRs. For example, mGlu2/3 agonists antagonize and mGlu2/3 antagonists potentiate DOI-induced head shakes in rats (Gewirtz and Marek, 2000). Also, studies from our laboratory have shown that the 5-HT2A agonist DOI and the mGluR5 antagonist MPEP potentiate the effects of PCP on locomotor activity in rats (Krebs-Thomson et al., 1998; Henry et al., 2002). Hence, we hypothesized that mGluR5 receptors contribute to the behavioral effects of serotonergic hallucinogens and that 5-HT2A receptors contribute to the behavioral phenotype of mGluR5 KO mice. Specifically, we tested the effects of the serotonergic hallucinogen and 5-HT2A agonist, 2,5-dimethoxy-4-methylamphetamine (DOM), and the 5-HT2A antagonist, M100,907, on locomotor activity in mGluR5 WT and KO mice. Thirty male and female mGluR5 WT and KO mice on a C57 background were tested for 60 min in a novel mouse behavior pattern monitor (BPM), a photobeam system enabling measures of locomotor activity, locomotor patterns, and investigatory behaviors in the dark. Both male and female mGluR5 KO mice showed locomotor hyperactivity and diminished locomotor habituation compared to their WT counterparts. After the initial characterization, mGluR5 WT and KO mice received vehicle or DOM (0.5 mg/kg, IP) in a crossover design with one week between tests. Mice were then treated with M100,907 (1.0 mg/kg, SC) in a similar crossover design. DOM potentiated the locomotor hyperactivity in mGluR5 KO mice, while increasing locomotor activity only slightly in WT mice. Conversely, M100,907 attenuated the locomotor hyperactivity in mGluR5 KO mice, while having minimal effects on locomotor activity in WT mice. Contrary to previously published data, these studies suggest that mGluR5 KO mice display a locomotor hyperactivity phenotype. This discrepancy may be explained by our ability to test the mice in the dark and during the dark phase of their diurnal cycle. The effects of the 5-HT2A agonist and antagonist in mGluR5 KO mice suggest that mGluR5 modulate the effects of 5-HT2A ligands on locomotor activity. These data may indicate that glutamate release associated with serotonergic hallucinogens could be diminished in mGluR5 KO mice or that mGluR5 KO mice may have altered serotonergic function. These studies were carried out in accordance with the Guide for Care and Use of Laboratory Animals. Supported by DA02925 (MG).

112. *COMT* Val/Met Polymorphisms and Cerebral Morphometry in First Episode Schizophrenia

Konasale M Prasad*, Michael E Talkowski, Kodavali Chowdari, Meghana Keshavan, Vishwajit L Nimgaonkar and Matcheri S Keshavan

Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; Human Genetics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Sponsor: Travel Awardee, PMRTP, 2004

Background: *COMT* (catechol-O-methyl transferase) has been proposed as a candidate gene for schizophrenia. The *COMT* gene which codes for the dopamine catabolizing enzyme is deleted in Velocardiofacial syndrome, a condition known to be associated with significantly increased incidence of schizophrenia. *COMT* polymorphisms have been linked to abnormal dorsolateral prefrontal cortex (DLPFC) function and working memory deficits in healthy and schizophrenia subjects. Postmortem studies have reported that Val/Val individuals had enhanced mesencephalic tyrosine hydroxylase levels suggesting that increased catabolism by the Val/Val variant of *COMT* may be associated with increased synthesis. The impact of such variations on the cortical and subcortical gray matter density in human beings has not been evaluated. We evaluated the gray matter concentration using voxel-based morphometry in previously unmedicated first episode schizophrenia patients and healthy subjects genotyped for *COMT* polymorphisms. We were particularly interested in gray matter changes in DLPFC and mesencephalic regions. **Methods:** We sequenced 63 age-matched Caucasian subjects (schizophrenia and schizoaffective disorder=33 and healthy subjects=30) for Val/Met polymorphism on *COMT* gene using single-base extension reaction (SNAPSHOT) assay. We obtained structural MRI scans on all these subjects using a standard protocol. We performed voxel-based morphometry to compare subjects across the genotypes and examine the allele dose effect on gray matter concentration within each group controlling for age and gender. **Results:** Patients homozygous for Val/Val showed decreased gray matter concentration in the DLPFC compared to Met/Met individuals and the former showed increased mesencephalic gray matter concentration in the substantia nigra pars compacta (SNPC) and ventral tegmental area (VTA). Similarly, patients showed a progressive increase in gray matter concentration in the DLPFC as Met allele was added and with the addition of Val allele gray matter concentration increase was observed in the SNPC and VTA. This effect was not observed in control subjects. **Discussion:** The results suggest an association of decreased gray matter concentration in the prefrontal regions in patients homozygous for Val/Val. This finding supports previous reports of less efficient prefrontal perfusion and working memory performance in these individuals. Increased gray matter concentration in the mesencephalic dopaminergic nuclei of patients homozygous for the Val/Val variant may suggest overactive dopaminergic neurons, perhaps compensating for deficits in prefrontal DA neurotransmission. A postmortem report of increased tyrosine hydroxylase in Val/Val individuals supports our finding. Observation of these changes in patients but not healthy subjects may suggest an interaction of the *COMT* polymorphisms with other illness-related variables including other risk genes. Further morphometric analyses based on *COMT* haplotypes is pressently going on and the findings will be presented.

113. Celecoxib Add-on Therapy Does Not Have Beneficial Antipsychotic Effects Over Risperidone Alone in Schizophrenia

Fred Rappard* and Norbert Mueller

Pfizer Global Research and Development, Ann Arbor, MI, USA

Sponsor: David Garver

Increases in circulating proinflammatory cytokine levels have been linked to schizophrenia pathogenesis in a patient subgroup. A previous trial suggested that short-term add-on treatment with the COX-2 specific inhibitor, celecoxib, to risperidone in schizophrenic patients resulted in a greater beneficial effect on psychopathology than risperidone alone.[i] We sought to confirm these findings in a larger and longer 11-wk trial. Patients aged 18-50 y with a diagnosis of schizophrenia according to DSM-IV TR criteria hospitalized for acute disease exacerbation were included. Each patient had a total Positive And Negative Syndrome Scale (PANSS) score of ≥60 at screening and a history of schizophrenia of ≤10 y from onset of prodromal symptoms. After screening, all patients underwent a 1-wk antipsychotic switchover period (unless already on risperidone) followed by risperidone only treatment for 1 wk prior to randomization. Patients were randomized to receive open-label risperidone + double-blind celecoxib 200mg bid, or risperidone + double-blind placebo for 11 wks. The dose of risperidone was flexible, started at 2mg/d, and ranged between 2-6mg/d. Assessments were carried out at Wks 1, 2, 4, 6, 8, and 11, and included the PANSS score and the Comprehensive ExtraPyramidal Symptom Scale (CEPPS). Primary study endpoint was change from baseline in total PANSS score at Wk 11 (using the last observation carried forward method). A total of 270 patients were randomized to treatment (138 celecoxib, 132 placebo). Mean age was 30 y and the majority of patients were diagnosed with paranoid or undifferentiated schizophrenia (>85% in each group). The mean daily dose of risperidone was not significantly different between treatment groups for the duration of the study (4.7mg/d). At baseline, the total PANSS score was 78.6 and 81.3 in the celecoxib and placebo groups, respectively. Patients in both treatment groups showed a clinically significant improvement in psychopathology during the study as reflected by a mean reduction (± SEM) in total PANSS score from baseline to the 11-wk assessment (-27.9±2.5 and -30.1±2.5 in the celecoxib and placebo groups, respectively). Reductions were evident in all subscales of the PANSS from baseline to 11 wks: -8.3±0.6 and -8.4±0.7, -5.8±0.8 and -6.8±0.8, and -13.7±1.2 and -14.8±1.2 in the celecoxib and placebo groups for the positive, negative, and general psychopathology subscales, respectively. However, there were no significant differences in the level of improvement between patients receiving risperidone + celecoxib or risperidone alone in total PANSS ($P=0.32$) and its 3 subscales ($P\geq0.20$). With respect to extrapyramidal side effects, no significant differences were observed between celecoxib and placebo arms in change from baseline to the 11-wk assessment in total CEPSS scores for Parkinsonism, dystonia, dyskinesia or akathisia ($P\geq0.30$ for all). A total of 68.4% of patients in the celecoxib and 73.3% in the placebo group experienced treatment-emergent adverse events. The most common of these were gastrointestinal, nervous system, and psychiatric disorders; there were no major differences in incidence between treatment groups. Despite previous positive findings after short-term therapy,[i] the results of this 11-wk study demonstrate that addition of celecoxib to risperidone for longer-term treatment of schizophrenia does not improve disease psychopathology beyond that observed with risperidone alone. Consequences for further research on the chronic inflammation hypothesis of schizophrenia will be discussed.

[i] Mueller N et al. Beneficial Antipsychotic Effects of Celecoxib Add-On Therapy Compared to Risperidone Alone in Schizophrenia. Am J Psychiatry. 2002;159:1029-34.

114. The orexin-1 Receptor Antagonist SB-334867 Blocks the Effects of Antipsychotics on the Number of Spontaneously Active A9 and A10 dopamine neurons

Kurt Rasmussen*, Yili Yang, Mei-Ann Hsu and kalpana Merchant

Eli Lilly & Co, Indianapolis, IN, USA

Sponsor: Barry Jacobs

Acute administration of antipsychotics increases the activity of dopamine neurons in the ventral tegmental area (A10) and substantia nigra pars compacta (A9). Since there is a dense projection of orexin neurons from the lateral hypothalamus to A10 dopaminergic neurons (Fadel and Deutch, Neuroscience, 2002) and antipsychotics have been shown to increase the expression of c-fos in

orexin containing cells in the hypothalamus (Fadel et al., J Neurosci, 2002), we hypothesized that stimulation of orexin receptors plays a role in the activation of A9 and A10 cells by antipsychotics. We examined the number of spontaneously active A10 and A9 cells in chloral hydrate anesthetized male Sprague-Dawley rats. The electrode was passed through 9 tracks in A9 or A10; each track was separated by 0.2 mm. The first 3 tracks were control tracks prior to drug treatment. One hour following haloperidol (1 mg/kg, sc) or olanzapine (10 mg/kg, sc) administration, 3 additional tracks were recorded. SB-334867 (2 mg/kg, iv) was then given and 3 additional tracks were recorded. This dose of SB-334867 has been used previously in our laboratory to block the excitatory effects of orexin-A administration (icv) on locus coeruleus neurons in anesthetized rats. As has been shown previously, haloperidol administration significantly increased the number of spontaneously active A9 and A10 cells and olanzapine administration significantly increased the number of spontaneously active A10 (but not A9) cells. Administration of SB-334867 reversed this increase and returned the number of spontaneously active dopamine cells to baseline levels for both haloperidol and olanzapine. Administration of SB-334867 alone did not alter the number of spontaneously active A9 or A10 cells. These results indicate that activation of orexin-1 receptors plays an important role in the effects of antipsychotic drugs on dopamine neuronal activity and may play an important role in the clinical effects of antipsychotic drugs.

115. Familiality of Intellectual,Language and Behavioral Impairments in Schizophrenia: Evidence for Early Origin

Avi Reichenberg*, David A Greenberg, Mark Weiser,
Jeremy M Silverman, Asaf Caspi, Schmeidler James, Haim Y Knobler, Philip D Harvey and Michael Davidson

Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Sponsor: Michael Davidson

Background: There are numerous reports on cognitive deficits in first degree relatives of schizophrenia patients, reflecting the broader goal of searching for endophenotypic traits that may index genetic liability to schizophrenia. Findings indicate that relatives are impaired on a variety of cognitive functions, but especially on measures that involve working memory, executive functions and attention. The majority of studies thus far focused on measures collected after the disease has already manifested, which brings in possible bias for the measured trait in both the proband and the unaffected sibling. **Methods:** We conducted a historical population-based cohort study. The cohort included all sibling pairs born in Israel over four consecutive years, mandatory assessed by the Draft Board at age 17, and followed up for psychiatric hospitalization with schizophrenia by means of a national psychiatric hospitalization case registry until age 30 to 34, when risk of schizophrenia considerably drops. Data were available on tests assessing abstract verbal and non-verbal reasoning, attention/speed of processing, scholastic knowledge, reading comprehension, vocabulary and spelling, as well as on several behavioral variables. **Results:** Future patients from discordant pairs performed worse than never-hospitalized sibling pairs on all measures. The never-hospitalized (unaffected) siblings from discordant pairs performed intermediate between probands and never-hospitalized sibling pairs. Relative risk for siblings was especially elevated on measures of reasoning and reading comprehension. Relative risk for siblings was also elevated for some of the behavioral measures. **Conclusions:** In an epidemiological cohort, siblings of patients with schizophrenia were impaired on several cognitive and behavioral domains. Cognitive domains impaired support the hypothesis that working memory and executive processes may be more closely related to the genetic liability to schizophrenia.

116. Quetiapine Pretreatment Inhibits Abnormal Behavior Following Neonatal Hippocampal Lesion

Neil Richtand*, Benjamin Taylor, Rebecca Ahlbrand, Jeffrey A Welge, Jeffrey Burr, Lique M Coolen, Laurel Pritchard,
Michelle M Ostrander, James P Herman and Robert K McNamara

Psychiatry Service, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH, USA; Department of Psychiatry, University of Cincinnati, Cincinnati, OH, USA

Sponsor: Lei Yu

Objective: Longstanding behavioral abnormalities emerge after puberty in neonatal hippocampal lesioned rats, providing a developmental model of abnormal rat behavior. Treatments inhibiting behavioral alterations in the neonatal hippocampal lesion model may have predictive validity in identifying preventive treatments for schizophrenia. This study evaluated the efficacy of quetiapine in preventing behavioral abnormalities following neonatal lesion, and evaluated a wider dose range than feasible in human studies. **Methods:** Seven-day-old male Sprague-Dawley rats were randomized to lesioned or sham-lesioned status. On postnatal days 35 to 56, rats received saline or quetiapine injection (3, 6, 12, or 18 mg/kg IP). Quetiapine dosages were comparable to human dosages of 200, 400, 800, or 1200 mg/d. On day 57, behavioral measures were assessed by evaluating locomotor activity under 3 conditions: novelty, amphetamine injection (1.5 mg/kg), and nocturnal response. Data were analyzed by three-way ANOVA with LESION STATUS and DRUG DOSE as main factors and LOCOMOTOR TIME INTERVAL as a repeated measure. Significant effects or interactions from the ANOVAs were further analyzed using Fisher's Least Significant Difference (LSD) test. Statistical significance was defined as $P<0.05$. **Results:** Analysis of behavioral response to novelty demonstrated significant main effects of LESION STATUS and LOCOMOTOR TIME INTERVAL. Significant LESION STATUS x LOCOMOTOR TIME INTERVAL and LESION STATUS x DRUG DOSE x LOCOMOTOR TIME INTERVAL interactions were also observed. In agreement with earlier studies, locomotor response was significantly increased in lesioned rats in the saline group. Analysis of behavioral response to amphetamine revealed significant main effect of LOCOMOTOR TIME INTERVAL. Significant LESION STATUS x LOCOMOTOR TIME INTERVAL, DRUG DOSE x LOCOMOTOR TIME INTERVAL, and LESION STATUS x DRUG DOSE x LOCOMOTOR TIME INTERVAL interactions were observed. Post-hoc analyses demonstrated that locomotor response to amphetamine was increased in lesioned rats in the vehicle and 6 mg/kg treatment groups, but not in the 3 mg/kg, 12 mg/kg, or 18 mg/kg treatment groups. Analysis of behavioral response to nocturnal locomotion revealed significant main effect of LOCOMOTOR TIME INTERVAL. Significant DRUG DOSE x LOCOMOTOR TIME INTERVAL interactions were also observed. **Conclusions:** These data are consistent with a protective effect of higher quetiapine dosages (comparable to 800 mg/day or greater in humans) in preventing selected behavioral abnormalities following neonatal hippocampal lesion, and provide theoretical support for studies to determine the efficacy of quetiapine for prevention of first-episode psychosis. A limitation of our findings is that we are unable to distinguish between prevention, vs suppression or postponement, of the emergence of abnormal behaviors following neonatal hippocampal lesion. Additional studies using later time points will be needed in order to address this important issue. Finally, these data suggest that studies with the hippocampal lesion model may also provide insight into pathophysiological mechanisms underlying the development of schizophrenia and other psychotic disorders. Acknowledgements: This work was supported by the Department of Veterans Affairs Medical Research Service and AstraZeneca (NMR), and by Scottish Rite Schizophrenia Fellowship Award (LMP).

117. Olanzapine and Clozapine Inhibit Carbachol-Enhanced Insulin Secretion from Perifused Rat Islets via Muscarinic Receptor Blockade

David E Johnson, Hanae Yamazaki, Karen M Ward, Anne W Schmidt, Wesley S Lebel, E M Gibbs, Judtith L Treadway, Walter Zawalich, B K Koe and Hans Rollema*

CNS, CVMD and General Pharmacology, Pfizer Global Research and Development, Groton, CT, USA

Sponsor: Katherine Halmi

Background. Treatment with olanzapine and clozapine has been associated with an increased risk for hyperglycemia, ketoacidosis and diabetes, in some cases independent of weight gain.[1] Since a) cholinergic activation of insulin release is mediated by M3 receptors, and b) olanzapine and clozapine are potent muscarinic receptor antagonists, we hypothesized that hyperglycemic events may be in part a consequence of their ability to directly alter cholinergic-stimulated insulin secretion. **Methods**. We measured the effects of 5 antipsychotics on insulin secretion by perifusing isolated rat islets with 7 mM glucose and stimulating insulin release with either the nonspecific cholinergic receptor agonist carbachol (10 μmM) or glucose (8 mM), in the presence and absence of test compounds. In addition, we determined their binding affinities in the INS-1 cell line and their functional antagonist activities at hm3 receptors in CHO cells and at rM3 receptors in isolated rat urinary bladder tissue. **Results**. Olanzapine, clozapine or atropine at 10-100 nM significantly reduced insulin secretion stimulated by 7 mM glucose plus 10 μM carbachol, but risperidone, haloperidol or ziprasidone had no effect on cholinergic-induced insulin secretion. None of the compounds tested affected the islet responses to 8 mM glucose alone. In vitro binding and functional studies confirmed that olanzapine and clozapine, unlike risperidone, ziprasidone and haloperidol, are high affinity muscarinic M3 receptor antagonists, with Ki and Kb values of 25-80 nM. **Discussion**. Considering the importance of acetylcholine in the regulation of insulin secretion, selective impairment of cholinergic-potentiated insulin secretion in pancreatic islets by olanzapine and clozapine at near therapeutic concentrations provides a plausible mechanism that may contribute to the hyperglycemic liability of olanzapine and clozapine. Our finding that neither compound modifies glucose-stimulated insulin release is consistent with clinical observations that in healthy subjects olanzapine does not affect insulin secretion under hyperglycemic clamp conditions.[2] These results suggest that treatment with antimuscarinic antipsychotics may interfere with islet compensation via drug-induced loss of β-cell function and precipitate hyperglycemia, diabetes or acute ketoacidosis reported in olanzapine- or clozapine-treated patients.[3-5] Olanzapine and clozapine are functionally potent muscarinic M3 antagonists and most likely inhibit carbachol-enhanced insulin secretion by blocking M3 receptors, which mediate cholinergic activation of insulin release. M3 receptor antagonism is however not the sole responsible mechanism, since several marketed drugs that target muscarinic receptors do not produce hyperglycemia or diabetes. Given the complexity of glucose regulation and the binding profiles of atypical antipsychotics, it is evident that in addition to muscarinic receptor blockade other factors are involved in impairing glucose regulation. **References**. [1]Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care* 27: 596-601. [2]Sowell et al (2002) Hyperglycemic clamp assessment of insulin secretory response in normal subjects treated with olanzapine, risperidone, or placebo. *J Clin Endocrinol Metab* 87: 2918-2923. [3]Koller et al (2002) Olanzapine-associated diabetes mellitus. *Pharmacotherapy* 22: 841-852. [4]Koller et al (2001) Clozapine-associated diabetes. *Am J Med* 111: 716-723. [5]Avella et al (2004) Fatal olanzapine-induced hyperglycemic ketoacidosis. *Am J Forensic Medicine Pathology* 25: 172-175.

118. The Schizophrenia Treatment Acceptance Response Trial: Evaluation of a Novel Psychosocial Approach to Supporting Patient Acceptance of a Long-acting, Injectable Antipsychotic

Ronald Urioste, Robert A Lasser, Georges M Gharabawi and Nina R Schooler*

Zucker Hillside Hospital, Glen Oaks, NY, USA

Background: The effectiveness of any therapy depends upon the patient's success in accepting, adhering to, and maintaining prescribed treatment. Unless the patient remains sufficiently motivated to initiate and continue treatment, the therapeutic outcome will be suboptimal. There is mounting evidence of a strong relationship between treatment acceptance, ongoing adherence, and resultant treatment outcome in psychiatric illness. Positive responses to both pharmacologic and psychosocial treatment are bolstered by the enhancement of treatment acceptance. **Objective:** This study evaluated the effectiveness of a novel approach to supporting treatment that is based on the principles of motivational enhancement therapy (MET). This approach, called GAIN, is a structured clinical discussion tool developed to address patient ambivalence to treatment. The approach comprises 4 sequential steps that promote the setting of long-term goals (G = goal setting), the development of a treatment action plan (A = action), the initiation of treatment (I = initiation), and the continual nurturing of goal-oriented behaviors (N = nurturing motivation). **Method**: This study (known as the Schizophrenia Treatment Acceptance Response Trial, or START) measured the effectiveness of GAIN compared with approach as usual (AAU) in supporting treatment acceptance and adherence to long-acting risperidone in patients with schizophrenia. The study incorporated a 6-week "approach" phase and a 12-week "treatment" phase in community mental health centers in the United States. Centers were randomly assigned to either GAIN or AAU. As a primary measure of effectiveness, the percentage of patients accepting long-acting risperidone therapy at sites randomized to the use of GAIN was compared with the percentage of patients accepting such therapy at sites using the AAU method. As a secondary measure of effectiveness, the number of patients who adhered to treatment (as measured by discontinuation rates) over the 12-week treatment phase was compared between both treatment conditions. In addition, healthcare provider satisfaction with GAIN or AAU was measured through the use of self-report questionnaires. **Results**: A total of 650 patients were entered into the study (386 GAIN, 264 AAU) across 268 sites. Preliminary analysis of the data indicates high treatment acceptance across groups. Patients treated at the sites randomized to GAIN displayed lower discontinuation rates compared with the AAU group. Preliminary data indicate high levels of healthcare provider satisfaction with the ease of implementation and effectiveness of GAIN. Final data analyses will be available for presentation in December 2004. **Conclusions**: Preliminary results suggest that GAIN can be implemented with relative ease by schizophrenia treatment teams in clinical settings. Final data analyses will test the hypothesis that GAIN provides a more effective method of engaging clinicians and their patients into a collaborative relationship to support acceptance and adherence to treatment with a long-acting, injectable antipsychotic. Furthermore, the innovative study design of combining both pharmacologic and psychosocial interventions to enhance treatment adherence may encourage others to implement future studies of this type. This study is funded by Janssen Medical Affairs, L.L.C.

119. Altered Brain Activation In Dorsolateral Prefrontal And Parietal Cortex In Adolescents And Young Adults At Genetic Risk For Schizophrenia: A Functional Magnetic Resonance Imaging Study Of Working Memory

Larry J Seidman*, Heidi W Thermenos, Russell A Poldrack, Nicole K Peace, Jennifer K Koch, Stephen V Faraone and Ming T Tsuang

Department of Psychiatry, Harvard Medical School, Boston, MA, USA; Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA

Sponsor: Ming Tsuang

BACKGROUND: First-degree adult relatives of persons with schizophrenia carry elevated genetic risk for the illness, demonstrate working memory impairments, and manifest differences in prefrontal cortical function during working memory. However, there is far less research evaluating these parameters in adolescent and young adult high risk subjects. We used functional magnetic resonance imaging (MRI) to test whether young (age 13-26), non-psychotic relatives of persons with schizophrenia also show altered prefrontal and parietal lobe activation during working memory. **METHODS:** A case-control design was used to compare blood oxygen level dependent signal in controls and young relatives of persons with schizophrenia performing a 2-back visual working memory task and a control, simple vigilance task during fMRI. Participants were recruited from control and patient families from the community and a number of hospitals in metropolitan Boston, MA. Participants were 21 non-psychotic, un-medicated relatives of persons with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type and 27 unmedicated controls. Blood oxygen level dependent signal changes was measured using two whole-brain gradient echo EPI pulse sequences (21 contiguous, 5 mm axial slices), acquired on a Siemens 1.5T full-body MR scanner while subjects performed the cognitive tasks. Data were analyzed using Statistical Parametric Mapping-99. Differences in working memory-related signal (relative to control task-related signal) were compared between the two groups. **RESULTS:** The groups did not differ on demographic, neuropsychological or working memory performance variables. Compared to controls, high-risk subjects had significantly higher Psychoticism scores and showed greater task-elicited activation in the right DLPFC (BA 46) and right superior parietal lobule (BA 7). Although Psychoticism and Paranoid Ideation, both measured by the Hopkins SCL-90-R were significantly related to parietal lobe activity, they did not account for group differences. **CONCLUSION:** Data replicate findings in adult relatives of schizophrenics, and add to the growing literature identifying neurobiological vulnerabilities to schizophrenia. Future studies of this population may be useful in studying the relationship of these abnormalities in predicting later onset of schizophrenia.

120. Efficacy And Safety Of Ziprasidone In First Episode Psychosis

Tonmoy Sharma*, Veena Kumari, Anil Kumar and Ravi Mehrotra

Clinical Neuroscience Research Centre, Dartford, Kent, United Kingdom

Sponsor: Gerard Hogarty

There is very little data on the efficacy and safety of Ziprasidone in patients with a first episode of psychosis who meet the criteria for schizophrenia or a related psychotic disorder. This study evaluated the effectiveness in acute first episode psychotic patients who were largely neuroleptic-naïve. Ten patients with first-episode psychosis participated in this 6-week study. Domains measured included psychopathology, neurocognitive functioning, and changes in blood flow using functional Magnetic Resonance Imaging. This report presents data from clinical measures of treatment response, and safety data from the 6-week study evaluating the clinical efficacy. Patients were assessed weekly using clinical scales to assess efficacy and safety.in this open label dose finding study. Ziprasidone was associated with substantial baseline-to-endpoint reductions in symptom severity, as measured by the Positive and Negative Syndrome Scale total score and positive subscale, and by the Clinical Global Impression severity rating. Neuroleptic-naïve first episode psychotic patients tolerated doses of Ziprasidone up to 80mg daily without any treatment-emergent parkinsonism or akathisia. There were no treatment emergent cardiac abnormalities seen in this patient group. As expected on the basis of previous studies in chronic patients, Ziprasidone was effective in the acute reduction of psychopathological symptoms in this group of patients with first-episode psychosis. Doses above 80mg daily might be tolerated less well by neuroleptic-naïve first episode psychotic patients.

121. Convergence and Divergence in the Neurochemical Regulation of Prepulse Inhibition and N40 Gating in Rats

Jody M Shoemaker*, Pamela P Auerbach, Mark A Geyer, Gregory A Light, Richard Sharp, Weiye Xu, Karen E Stevens and Neal R Swerdlow

Dept. Psychiatry, UCSD, La Jolla, CA, USA

Sponsor: Neal Swerdlow

Introduction: Prepulse inhibition of startle (PPI) is an operational cross-species measure of sensorimotor gating. N40 event-related potential suppression (N40 gating) is an operational measure of sensory gating thought to be the rat homolog of human P50 gating. Both PPI and P50 gating are deficient in schizophrenia patients and their unaffected first degree relatives, and both PPI and N40 gating are used to study the mechanisms of these familial gating deficits in schizophrenia. Emerging evidence suggests differences in the neurobiology of deficits detected by these gating measures. In the present study, we simultaneously recorded PPI and N40 gating in rats, to assess convergence and divergence in the dopaminergic, serotonergic and glutamatergic regulation of these measures. **Methods:** PPI and N40 gating were assessed in male Sprague Dawley rats in a test session that included stimuli to elicit startle (40 ms 120 dB(A) pulses (P)), PPI (pulses preceded 100 ms by 20 ms prepulses 5, 10 and 15 dB over a 65-dB(A) background (pp+P)) and N40 gating (1 ms "click pairs" (S1, S2) 20 dB over background, separated by 500 ms). Rats were tested without drug, and after acute treatment with apomorphine (APO), phencyclidine (PCP), DOI or vehicle. Parallel studies in separate rats examined full dose response properties of these drugs on motor responses to identical stimuli. **Results:** Robust PPI, N40 potentials and N40 gating could be detected during simultaneous measures. APO, PCP and DOI disrupted both PPI and N40 gating. Inspection of the data revealed that drug-induced deficits in PPI reflected a reduction in the effectiveness of the prepulse, that led to relatively increased startle levels on pp+P trials. Drug-induced deficits in N40 gating reflected a suppression of the N40 response to S1. In parallel measures, the expected dose dependent PPI-disruptive effects of APO, PCP and DOI were detected. N40 clicks elicited motor signals (mean < 1 unit) that were less than 0.5% of those elicited by startle stimuli (typically 300-500 units), but which nonetheless exceeded those detected when no stimulus was delivered (typically about 0.5 units). N40 click pairs elicited "paired-pulse inhibition", with S2/S1 ratios of about 0.4 in vehicle-treated rats. This paired-pulse inhibition was also disrupted by APO, PCP and DOI, in a dose-dependent manner. **Conclusions:** PPI and N40 gating can be studied simultaneously in rats and are both disrupted by APO, PCP and DOI. The disruption of PPI reflects reduced inhibition of the startle response, while the disruption of N40 gating reflects response suppression to S1. Despite similarities in drug sensitivity, these results suggest that very distinct neurobiological mechanisms underlie drug-induced deficits in PPI and N40 gating. Supported by MH01436 and MH42228.

122. Surgically Implantable Long-term Delivery Systems for Atypical Antipsychotic Medications

Steven J Siegel*, Jody M Shoemaker, Neal R Swerdlow, William Beckerman, Yuling Liang, Jan Tokarczyk, Stphen J Kanes, Ted Abel and Christina R Maxwell

Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Background: Although a great deal of research has focused on new pharmaceutical compounds to improve treatment for schizophrenia, nonadherence with prescribed medication remains one of the highest determinants of relapse and rehospitalization. To address this need, we previously developed a long-term delivery system using the typical antipsychotic agent haloperidol. However, feedback from patients, their families and physicians indicates that such a delivery system would be more acceptable if it contained a newer antipsychotic medication. Therefore, we have developed biodegradable surgically implantable formulations of three atypical antipsychotic medications including clozapine, risperidone and quetiapine to examine the ability to deliver other medications through this modality. **Methods:** All testing was done in accordance with NIH guidelines and protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Pennsylvania and University of California at San Diego. Each drug was combined with poly-lactide-co-glycolide (PLGA) using solvent casting and compression molding. Implants were placed either in phosphate buffered saline for in vitro kinetic analyses or placed subcutaneously in rats or mice for in vivo behavioral testing with prepulse inhibition of startle (PPI) or auditory evoked potentials (ERP). **Results:** In vitro release data are presented for each of these formulations. All agents can be successfully released using poly-lactide-co-glycolide polymers. Behavioral testing in rat indicates that 9-14 days post-implantation, clozapine implants (1 mg/day; 2.5 mg/kg/day) marginally opposed the ability of apomorphine to disrupt PPI in rats ($p = 0.06$). Haloperidol implants (1 mg/kg/day) reversed amphetamine (10 mg/kg acute) induced PPI deficits in mice between 7 - 28 days ($p=0.0099$). Quetiapine implants have been designed to deliver either 2.2 or 4.4 mg/day (5.5 or 11 mg/kg/day in rat) for 2 months and are also being tested in this paradigm. Both quetiapine and risperidone implants will also be tested in mice using both PPI and ERPs as measures of bioactivity. Data for all three atypical agents will be presented in the context of previous studies demonstrating the use of haloperidol implants in rats and mice. **Discussion:** Surgically implantable systems represent a novel method to help patients remain well for periods of time never before possible with oral or injectable formulations. Additionally, PLGA implants can be used as a powerful experimental tool to provide laboratory research animals with a small, easily tolerated method for chronic drug exposure. The use of implants in various animal models will also allow for more widespread use and evaluation of biodegradable delivery systems within the psychiatric and medical scientific communities before progressing to human trials. Acknowledgment: Stanley Medical Research Institute (SJS), NIMH Award P50 MH 6404501 (SJS, SJK, TA), and NIMH Award MH42228 (NS, JS) funded this research.

123. Metabolic Changes During 5 Months Treatment with Olanzapine or Risperidone: Preliminary Results From Randomized Trial

Robert C Smith*, Jean-Pierre Lindenmayer, Adriana Buga, Melissa Matute, Sumathi Vaidhyanathaswamy and Jessy Warner-Cohen

Psychiatry, NYU Medical School, Hewlett, NY, USA; Psychiatry, Manhattan Psychiatric Center, Wards Island, NY, NY, USA

Atypical antipsychotics have been reported to be associated with glucose and lipid abnormalities and increased risk of diabetes. In a previous large cross-sectional study we reported no differences in most metabolic measures in comparisons of conventional antipsychotics, clozapine, olanzapine, and risperidone, except for increased triglycerides in the clozapine and olanzapine treated groups, and higher 1 hr glucose in glucose tolerance test(GTT) for risperidone. We are now conducting a study of patients randomly assigned to treatment with olanzapine (OL) or risperidone (RIS) for five months, who are tested ,at baseline and several pints during treatments, for fasting glucose and lipid metabolic levels, 75 gm 2 hr glucose tolerance test, and metabolic evaluation after a fatty meal. Preliminary results form the first 19 patients show a trend for the increase in fasting glucose levels and c-peptide levels to be higher for OL than for RIS treated patients (with some of these differences statistically significant), but no significant differences for changes in cholesterol, triglyceride or leptin levels comparing the OL vs RIS treatment groups. 2 OL and 1 RIS patients had at least 1 fasting glucose level >126 mg/dL during study drug treatment. There were no significant differences in 1 hr or 2 hr mean glucose levels during GTT's between OL vs. RIS treatment groups, and no differences in insulin levels during GTT when these were covaried with differences in baseline insulin before beginning study drug treatment. The frequency of 2 hr GTT glucose > 200 mg/dL were as follows: at baseline zero OL and zero RIS, after 1-month treatment zero OL and 1 RIS, after 2- month treatment 1 OL and 2 RIS; after 5 months (reduced sample size) 2 OL and 1 RIS patient. Both olanzapine and risperidone produced an increase in weight but there were no significant differences in weight gain in patients treated with olanzapine vs. risperidone, although the mean increase in weight was slightly higher for olanzapine. Mean prolactin levels increased on risperidone and decreased on olanzapine, and the difference was statistically significant. Additional metabolic parameters are being analyzed and will be presented. These results suggest that a small percent of patients treated with both OL and RIS develop potentially clinically significant abnormalities in glucose metabolism during treatment with these medications over several months, but only RIS patients showed prolactin elevation. Previously reported significant differences in triglyceride response to OL vs. RIS were not confirmed in this preliminary sample. Supported by an Independent Investigator Grant from Eli Lilly to Robert C. Smith MD - PI.

124. Clozapine Treatment of Childhood Onset Schizophrenia: Evaluation of Efficacy, Adverse Effects, and Long-Term Outcome

Alexandra L Sporn*

child psychiatry, NIMH, Bethesda, MD, USA

Sponsor: Irvin Feinberg

Background: Clozapine is a unique atypical neuroleptic with superior efficacy in treatment-resistant populations, including children and adolescents with schizophrenia. Clinical response may be related to plasma concentration of clozapine and its major metabolite N-desmethylclozapine (NDMC). In this study we evaluate clozapine and NDMC levels as well as other measures as predictors of short- and long-term response to clozapine. **Methods:** 54 children and adolescents participated in double-blind or open clozapine trials. Clinical measures at baseline, week 6 on clozapine, and at 2-6 year follow-up were studied in relation to epidemiological data, age of onset, IQ, clozapine dose, as well as levels of prolactin, clozapine, NDMC, and NDMC/clozapine ratio. **Results:** At week 6 of clozapine treatment 39% patients were considered to be responders Stepwise regression analysis with percent improvement on Brief Psychiatric Rating Scale at 6-week of clozapine trial as an outcome measure showed that NDMC/clozapine ratio, but not any other measure was significantly associated with greater clinical improvement on clozapine ($p=0.003$). Rate of adverse effects in children and adolescents(especially akathesia and neutropenia) exceeded reported rates for adults, but was not associated with neither clozapine dose nor clozapine or NDMC levels or NDMC/clozapine ratio. Better long-term outcome (as measured by Clinical Global Assessment Scale at follow-up) was associated with lesser severity of symptoms at medication-free baseline, greater percent improvement during the first 6 weeks of clozapine treatment,

and higher NDMC/clozapine ratio at week 6 of treatment (r=0.57, p=0.001). **Conclusion:** Clozapine has unique efficacy for children and adolescents with schizophrenia. NDMC/clozapine ratio can be used as a valuable predictor of outcome as well as a lead to new psychopharmacological avenues.

125. Neural Synchrony Indexes Disordered Perception and Cognition in Schizophrenia

Kevin M Spencer*, Paul G Nestor, Ruth Perlmutter, Margaret A Niznikiewicz, Meredith C Klump, Melissa Frumin, Martha E Shenton and Robert W McCarley

Psychiatry, VA Boston/Harvard Medical School, Brockton, MA, USA

Sponsor: Robert McCarley

Contemporary views of schizophrenia suggest that the disorder results from abnormalities in neural circuitry, but empirical evidence in the millisecond range of neural activity has been difficult to obtain. We have proposed that neural synchrony in the gamma-band (30-100 Hz) of the scalp-recorded electroencephalogram (EEG) may be sensitive to such neural circuit abnormalities in schizophrenia. Previously, we have demonstrated that perceived visual Gestalt stimuli are associated with abnormal patterns of EEG phase-locking in schizophrenia patients. Phase locking measures the inter-trial variability of EEG phase (computed via the Morlet wavelet transform), ranging from 0 (random distribution of phases) to 1 (same phase on each trial). The abnormal phase-locking patterns observed in schizophrenia patients may reflect impairments in neural assemblies, which have been proposed to use gamma band oscillations as a mechanism for synchronization. Here we report the novel finding that, in both healthy controls and chronic schizophrenia patients (N=20 each), visual Gestalt stimuli elicit a high-frequency EEG oscillation that is phase-locked to reaction time, and hence may reflect processes leading to conscious perception of the stimuli. However, the frequency of this oscillation is lower in schizophrenics (22-24 Hz) than in healthy individuals (~40 Hz). These data suggest that, while synchronization must occur for perception of the Gestalt, it occurs at a lower frequency in schizophrenics due to a reduced capability of their neural networks to support high-frequency synchronization. Furthermore, the degree of phase-locking of this oscillation is correlated with perceptual and cognitive positive symptoms in the schizophrenia patients: visual hallucinations, thought disorder, and disorganization. These data provide support for linking dysfunctional neural circuitry, non-invasive measures of neural synchrony, and the core symptoms of schizophrenia.

126. Use and Cost of Polypharmacy in Schizophrenia: Data from a Randomized, Double-blind Study of Risperidone and Quetiapine

Stephen Stahl*, Marcia Rupnow, Andrew Greenspan, Colette Kosik-Gonzalez, Young Zhu and Georges Gharabawi

Neuroscience Education Institute, Carlsbad, CA, USA

Background/Objectives: In order to achieve optimal response in subjects with schizophrenia, additional psychotropics are frequently employed. This is the first prospective study to examine the use of concomitant antipsychotics and other psychotropic medications, symptom improvement in polypharmacy users, and the economic implications of polypharmacy in patients randomized to risperidone or quetiapine. **Methods:** This was a randomized, double-blind, placebo-controlled clinical trial in subjects with an acute exacerbation of schizophrenia or schizoaffective disorder. The trial consisted of two phases: a 14-day acute treatment phase, in which patients were randomized to risperidone, quetiapine, or placebo monotherapy, followed by a 28-day additive therapy phase (also blinded) to mimic a naturalistic setting, in which clinicians were allowed to add antipsychotics and/or other psychotropic medications (including antidepressants, anxiolytics, mood stabilizers and sedative/hypnotics) as per clinical judgment. Dose of risperidone or quetiapine was fixed in the additive therapy phase. Rate of and time to polypharmacy were examined using Cochran-Mantel-Haenszel, Kaplan-Meier, and Cox regression methods. PANSS scores were analyzed using ANCOVA models. Cost of polypharmacy was analyzed by non-parametric Wilcoxon two-sample tests. **Results:** Mean (±SD) doses at monotherapy endpoint were 4.7±0.9 mg/day of risperidone and 579.5±128.9 mg/day of quetiapine. Among 133 patients randomized to risperidone, 44 (33%) received antipsychotic polypharmacy and 53 (40%) received one or more psychotropics (including antipsychotics). In comparison, in the quetiapine group 65/122 (53%) and 69/122 (57%) received antipsychotic or psychotropic polypharmacy, respectively (P<.005 vs risperidone in both). In the placebo group, the rate of additive antipsychotics was 57%, and of additive psychotropics was 62%. The relative risk of antipsychotic polypharmacy for quetiapine vs risperidone was 1.90 (95% CI 1.29-2.80), and for psychotropic polypharmacy was 1.68 (95% CI 1.16-2.42). Mean (±SE) reductions in total PANSS scores at day 14 (monotherapy phase) endpoint were -30.2±1.4 for risperidone, -23.2±1.5 for quetiapine (P<.001 vs risperidone; NS vs placebo), and -22.4±2.2 for placebo (P=.001 vs risperidone). Reductions in PANSS total scores at day 42 (additive psychotropics phase) endpoint were -36.6±1.4 with risperidone, -34.6±1.5 with quetiapine (NS vs risperidone or placebo), and -30.6±2.1 with placebo (P=.008 vs risperidone). The mean cost of psychotropic polypharmacy per randomized patient (for the duration of additive psychotropics phase) was $62.34 in the risperidone group and $105.05 in the quetiapine group (P=0.013). When translated into cost per 1000 patient-months of treatment, the cost of polypharmacy amounted to $63,322 for patients treated with risperidone and $108,428 for those on quetiapine. When the cost of primary medication was added, the total drug cost per 1,000 patient-months of treatment amounted to $360,364 in the risperidone group, compared to $528,300 in the quetiapine group. **Conclusions:** Polypharmacy to treat schizophrenia is a common practice, yet limited data exist on the clinical and economic implications. This is the first study to provide polypharmacy data in risperidone and quetiapine, in a randomized, double-blind design. Our study confirmed the earlier observations from naturalistic/retrospective studies of higher rates of polypharmacy with quetiapine compared with risperidone. The substantial cost associated with polypharmacy should be a consideration in making decisions as to the choice of antipsychotic medication. Supported by Janssen Medical Affairs, L.L.C.

127. Deficit Syndrome Symptoms and Duration of Illness in Schizophrenia

Arielle D Stanford*, Scott Yale, Ray R Goetz, Cheryl Corcoran and Dolores Malaspina

Medical Genetics, NYSPI, NY, NY, USA; Psychiatry, Columbia University, NY, NY, USA

Sponsor: Robert Spitzer

Schizophrenia is a heterogeneous illness whose subtypes remain ill defined. The deficit syndrome is a stable diagnosis that may define a subgroup of schizophrenia patients with its characteristic premorbid, symptomatic and outcome features. While the DS is present at illness onset, it is unclear if the presence and severity of the DS change with time. We examined 263 schizophrenia patients as to DSS diagnosis and six item severity by duration of illness using the Schedule for the Deficit Syndrome. We found that the proportion of patients with the DS did not change with illness duration. However, individual DS symptoms did vary with duration of illness ($F=3.03, df=18/702, p<0.001$). In particular, diminished sense of purpose significantly worsened with duration (p=0.001) and diminished social drive tended to worsen as well (p=.058). These data suggest that the prevalence of the deficit syndrome in schizophrenia remains

stable while specific deficit symptoms increase over the course of the illness. An increase in symptom severity with illness duration could also make the DS easier to detect and therefore may have artificially increased prevalence rates in some studies. A worsening of deficit syndrome symptoms could underlie the inability of these patients to reengage in occupations, socially etc., after illness onset. Longitudinal examination of these symptoms may reveal associations between symptom worsening and decline in function.

128. Risperidone Nonadherence and Return of Positive Symptoms in the Early Course of Schizophrenia

Kenneth L Subotnik*, Keith H Nuechterlein, Ventura Joseph, Michael J Gitlin, Manickam Aravagiri, Marder R Stephen, Siegel V Benjamin and Thornton A Leslie

Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, USA

Sponsor: Michael Green

Despite the development of second generation antipsychotic medications that have fewer bothersome side-effects than conventional antipsychotics, nonadherence to antipsychotic medication treatment remains a major clinical problem, particularly during the initial course of schizophrenia. The impact of risperidone nonadherence on the return of positive symptoms was examined among recent-onset schizophrenia patients participating in a UCLA longitudinal study, Developmental Processes in Schizophrenic Disorders (PI: Keith Nuechterlein, Ph.D.). Forty-nine patients received risperidone, psychoeducation, group skills training, and individual case management. The main focus of this longitudinal study is to predict and to improve return to work or school for patients recently diagnosed with schizophrenia. The degree of antipsychotic medication nonadherence was assessed weekly for up to 18 months following initial stabilization on risperidone, using all available sources of information, including pill counts, monthly risperidone blood plasma assays, patient self-reports, and clinician reports. Three different operational definitions of risperidone nonadherence were used: 1) missed 50% or more of prescribed medication for at least four consecutive weeks during the 18-month follow-through period, or left treatment (29% of participants), 2) missed 50% or more of prescribed medication for at least two consecutive weeks during the 18-month follow-through period, or left treatment (47% of participants), or 3) missed 25% or more of prescribed medication for at least two consecutive weeks during the 18-month follow-through period, or left treatment (76% of participants). Thirty-one percent (31%) of patients had an exacerbation of positive symptoms during the follow-up period. Survival analysis was used to determine whether medication nonadherence was a risk factor for psychotic exacerbation. All three definitions of antipsychotic medication nonadherence predicted a return of psychotic symptoms, with missing 50% or more of medication, regardless of the duration (Definitions #1 and #2) resulting in the strongest prediction of positive symptom exacerbation (Definition #1: X^2 (df = 1, N = 49) = 10.3, p = .001, risk ratio = 16.3, and Definition #2: X^2 (df = 1, N = 49) = 10.8, p = .001, risk ratio = 14.0). Missing only 25% of medication (Definition #3) significantly, but less strongly, predicted return of psychotic symptoms (X^2 (df = 1, N = 49) = 7.7, p = .006, risk ratio = 9.0). Our findings show that nonadherence with second generation antipsychotic medications, especially nonadherence as high as 50% or greater, continues to have substantial clinical significance. Further, our findings are consistent with the suggestion that the current clinical practice of using the lowest effective dosage of antipsychotic medication to minimize side effects makes it more difficult to maintain effective blood levels during even brief periods of even minor degrees of nonadherence. Future work with this sample will attempt to determine what factors predict nonadherence, and to examine the relationships between nonadherence and functional outcome.

129. Galantamine but not Donepezil Activates Mesocorticolimbic Dopamine Neurons via Nicotinic Acetylcholine Receptors

Torgny H Svensson*, Vladimir Ivanov, Charlotte Wiker and Bjorn Schilstrom

Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

Galantamine is currently used in the treatment of Alzheimer's disease. Recent clinical studies suggest that galantamine may also be useful as adjunct therapy in schizophrenia, improving cognitive and negative symptoms. Galantamine possesses two mechanisms of action which both serve to enhance cholinergic neurotransmission in the brain. At low doses it binds to nicotinic acetylcholine receptors (nAChRs) and at higher doses it also acts as an inhibitor of acetylcholine esterase (AChE). Given that several lines of evidence suggest a role for α7 nAChRs in the etiology or pathophysiology of schizophrenia, and that the selective AChE-inhibitor donepezil has, to date, not proven effective in the pharmacological management of this disease, the beneficial effect of galantamine may be mediated, largely, through potentiation of nAChRs. Cognitive deficits in schizophrenia, such as impairments in working memory, are thought to be at least partly linked to an impaired dopaminergic neurotransmission in the prefrontal cortex. Nicotine, which is known to enhance working memory, activates mesocorticolimbic dopamine neurons by stimulating nAChRs in their cell body region. Thus, we hypothesized that the beneficial effects of galantamine on cognition in schizophrenia might be due to potentiation of such somatodendritic nAChRs. To test this hypothesis, the effects of galantamine (0.01 to 1.0 mg/kg s.c.) on dopamine cell firing were tested in anaesthetized rats. Galantamine increased both firing rate and burst firing of dopaminergic cells in the ventral tegmental area. The effect was observed already at a low dose, unlikely to result in significant AChE-inhibition. Moreover, the effect of galantamine was not mimicked by the selective AChE-inhibitor donepezil (1.0 mg/kg s.c.) and it was blocked by the nAChR antagonist mecamylamine (1.0 mg/kg s.c.) but not the muscarinic receptor antagonist scopolamine (0.1 mg/kg s.c.). Consequently, our results indicate that galantamine enhances dopaminergic activity through potentiation of nAChRs and supports the notion that allosteric potentiation of nAChRs may improve cognitive function in schizophrenia. Supported by The Swedish Research Council, The Karolinska Institutet, Stockholm, and Janssen-Cilag AB, Sweden

130. Location And Volumes Of The Auditory Core, Lateral Belt, And Parabelt Cortices In The Human Superior Temporal Gyrus

Robert A Sweet*, Karl-Anton Dorph-Petersen, Hans Jorgen G Gundersen and David A Lewis

Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Sponsor: David Lewis

Subjects with schizophrenia demonstrate deficits in auditory sensory processing, with associated loss of gray matter volume of the auditory cortex of the superior temporal gyrus (STG). Recent postmortem studies have begun to delineate alterations in the underlying auditory corticocortical circuits. In non-human primates, auditory sensory information is processed in the STG in the hierarchically related auditory core (primary), lateral belt (secondary), and parabelt (tertiary) cortices. Interpretation of the abnormalities detected in subjects with schizophrenia would clearly be enhanced by identifying the human analogues of core, lateral belt, and parabelt. The auditory core has been mapped in humans, where it corresponds to BA41. Criteria for the lateral belt and parabelt have not been previously described in humans, nor have they been mapped on the human STG. To map the auditory

lateral belt and parabelt in humans, and to confirm prior observations of the localization of the auditory core, we undertook to delineate these regions in human auditory cortex of the STG, developing and applying combined cytoarchitectonic and chemoarchitectonic criteria established in macaque. We further applied an unbiased stereologic approach to processing and sampling the human tissue in order to estimate the volumes of these regions in 8 right handed male normal control subjects. The lateral belt and parabelt appeared in humans as subdivisions of BA42, distinguishable by cytoarchitectonic features, immunoreactivity for parvalbumin, and staining for acetylcholinesterase. The lateral belt was localized predominantly in Heschl's sulcus, at times appearing on Heschl's gyrus and/or the planum temporale. The parabelt was predominantly localized to the planum temporale, but also extended onto the lateral STG at the rostral end of Heschl's gyrus. A subdivision of the parabelt into internal and external components was identified. Detailed description of the cytoarchitectonic and chemoarchitectonic features used to identify these regions will be presented, as will detailed maps and unbiased estimates of the regional volumes for the normal control subjects. Supported in part by: MH66231, MH71533, and MH45156

131. Developing a Novel Measure for Assessing Gating Deficits in Schizophrenia via Cross Modality Matching

Neal R Swerdlow*, Derek Nagy, Ashley N Sutherland and Jo A Talledo

Psychiatry, UCSD, La Jolla, CA, USA

Introduction: Deficits in the automatic and attentionally-driven inhibition of irrelevant sensory, cognitive and motor information are thought to contribute to the symptoms of a number of different neuropsychiatric disorders. These deficits and their neurobiological and genetic underpinnings are studied using laboratory-based operational surrogate measures of sensory (e.g. "P50 suppression") and sensorimotor gating (e.g. prepulse inhibition of startle, "PPI"). We recently initiated studies utilizing a simple measure of perceptual gating based on prepulse inhibition of perceived stimulus intensity (PPIPSI) assessed via cross-modality matching (CMM). In these studies, PPIPSI was found to be deficient in schizophrenia patients. The present studies were designed to address critical methodological questions regarding the use of PPIPSI to study gating deficits in patient populations. **Methods:** Schizophrenia patients and normal controls (NC) participated in studies of cross-modality matching and PPIPSI. Patients and NC completed CMM intensity functions, using 90-110 dB white noise pulses over a 70 dB(A) background. NC completed a new computerized CMM task utilizing 105 dB pulses alone or preceded by prepulses 15-35 dB over background. In separate studies, PPI was assessed in the NC subjects with and without concomitant CMM. **Results:** CMM functions in patients and controls demonstrated orderly intensity dependence. Both PPIPSI and PPI exhibited maximal values with prepulses 15-20 dB over background, with more intense prepulses eliciting progressively less inhibition. Within-subject comparisons revealed that PPI was not impacted by the simultaneous completion of this CMM task, and between-subject comparisons revealed that prior PPI testing did not impact subsequent measures of PPIPSI. **Conclusions:** PPIPSI is a simple, direct and parametrically sensitive measure of sensory gating, using a CMM task that is performed effectively by schizophrenia patients. Computerized measures of PPIPSI do not alter simultaneous measures of automatic gating (PPI), nor does previous startle experience appear to interfere with PPIPSI, suggesting that this measure can be added easily to existing psychophysiological batteries in patient populations. Supported by MH01436 & MH69589.

132. Abnormal Prefrontal White Matter in First-Episode Schizophrenia

Philip R Szeszko*, Steven Chen, Delbert Robinson, Claudia Rupp, Kelvin O Lim, Manzar Ashtari, Barbara Napolitano, Anil K Malhotra, John Kane and Robert M Bilder

Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA; Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA

Sponsor: John Kane

Objective: To investigate whether patients experiencing a first-episode of schizophrenia have grey and white matter prefrontal structural abnormalities in topographically defined brain regions compared to healthy volunteers. **Method:** Volumes of the superior frontal gyrus (SFG), anterior cingulate gyrus (ACG) and orbital frontal lobe (OFL) were computed manually from contiguous 1.5mm coronal magnetic resonance (MR) images in 63 (39M/24F) patients experiencing a first-episode of schizophrenia and in 60 (32M/28F) healthy comparison subjects and segmented into grey and white matter. Boundaries for the frontal lobe subregions were based on the cerebral sulci and a set of coronal planes keyed to sulcal landmarks. **Results:** Patients had less SFG and ACG white, but not grey matter volume in these regions compared to healthy volunteers. Similar findings were obtained when analyses were restricted to the subgroup (N=34) of antipsychotic drug naive patients. **Conclusions:** Our findings suggest that white, but not grey matter volumetric alterations in the SFG and ACG are evident at the onset of a first-episode of schizophrenia.

133. Sarcosine (N-methylglycine) or D-serine Add-on Treatment for Acute Exacerbation of Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

Guochuan E Tsai*, Hsien-Yuan Lane, Yue-Cune Chang, Yi-Ching Liu and Chih-Chiang Chiu

Psychiatry, Harbor/UCLA Medical Center, Torrance, CA, USA

Treatment response to acute schizophrenia affects the prognosis and long-term outcome. Hypofunction of the N-methyl-D-aspartate (NMDA) glutamate receptor has been implicated in the pathophysiology of schizophrenia. Treatment with agents that enhance NMDA receptor function through the glycine modulatory site (D-serine, glycine, D-cycloserine) and glycine transporter-1 (sarcosine) improves the symptoms of stable chronic schizophrenic patients receiving concurrent antipsychotic medications. But it is unclear whether NMDA-glycine site agonists or GlyT-1 inhibitors have better efficacy. In addition, whether NMDA-receptor enhancing agents have beneficial effects for acute exacerbation of schizophrenia remains to be determined. Sixty-five schizophrenic inpatients with acute exacerbation were enrolled in a 6-week, randomized, double-blind trial comparing sarcosine (2 grams/day), D-serine (2 grams/day), and placebo. All subjects also received concomitant optimal risperidone therapy. Primary outcome measures included the Positive and Negative Syndrome Scale (PANSS) and the Scale for the Assessment of Negative Symptoms (SANS). The secondary outcome measures were the subscales of PANSS and SANS. Measures of clinical efficacy and side effects were determined at baseline, and at weeks 1, 2, 4, and 6. Patients, who received sarcosine plus risperidone, showed significantly more improvements in their both primary outcome measures of PANSS and SANS than the other two treatment groups. For secondary outcome measures, PANSS-general, cognitive and depressive symptoms, SANS-alogia and blunt affect improved significantly more in the sarcosine-cotreated patients than patients receiving risperidone monotherapy. Sarcosine adjunctive therapy also surpassed D-serine in terms of PANSS-general, positive, negative, and depressive symptoms. Co-treatment with D-serine and risperidone did not differ significantly from risperidone monotherapy in all efficacy domains. Three treatments were all well tolerated and comparable in their side-effect profiles. Combined with our recent studies, this first

acute-treatment study on NMDA receptor-enhancing agents suggests that sarcosine, is superior to D-serine, can benefit not only chronically stable patients, but also acutely ill persons with schizophrenia. The efficacy of sarcosine further supports the hypothesis of NMDA receptor hypofunction in schizophrenia. Glycine transporter-1 is a novel target for the pharmacotherapy to enhance NMDA receptor function.

134. Altered Brain Activation in the Parahippocampus, Cingulate Gyrus and Nucleus Accumbens in Adolescents and Young Adults at Genetic Risk For Schizophrenia: A Functional Magnetic Resonance Imaging Study Of Verbal Encoding

Larry J Seidman, Heidi W Thermenos, Russell A Poldrack, Nicole K Peace, Lisa Gabel, Stephen V Faraone and Ming T Tsuang*

Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA, USA; Institute of Behavioral Genomics, University of California, San Diego, La Jolla, CA, USA

Sponsor: Ming Tsuang

INTRODUCTION: First-degree relatives of persons with schizophrenia exhibit structural abnormalities in the medial temporal lobe, and also show stable deficits on verbal encoding and memory tasks. We used functional magnetic resonance imaging (fMRI) to test whether young (age 13-25), non-psychotic relatives of persons with schizophrenia show altered brain function in the medial temporal lobe memory system during verbal encoding. **METHODS:** Participants were twenty-one young high risk ("YHR") relatives of persons with DSM-IV diagnosis of schizophrenia or schizoaffective disorder (depressed type), and 27 healthy control subjects, who were comparable ($P > .05$) on age, sex, parental education, ethnicity, and handedness. Subjects performed a word-pair encoding task during fMRI, in which alternating task blocks contained either all novel noun pairs or the same noun pair repeated throughout the block. In response to word-pairs, subjects were instructed to silently generate a sentence using both words, and were explicitly instructed to remember the stimuli for a later word recognition test. During performance of the tasks, blood oxygen level dependent (BOLD) signal was measured using two whole-brain gradient echo EPI pulse sequences (21 contiguous, 5 mm axial slices), acquired on a Siemens 1.5T full-body MR scanner. BOLD signal during novel word-pair encoding (relative to signal during repeated word-pair encoding) was compared in the two groups using Statistical Parametric Mapping (SPM-99) software. **RESULTS:** The groups differed on the several scales of the Miller Selfridge Memory test and on the SCL-90-R Psychoticism scale. Groups did not differ on any other demographic and neuropsychological variables, or on performance of a post-encoding word recognition task. Compared to controls, YHR exhibited greater activation in the left anterior parahippocampal gyrus, the left posterior cingulate (BA 31/23) and the left nucleus accumbens ($p < 0.05$, corrected for multiple comparisons) during novel word-pair encoding. Increased activation in the left nucleus accumbens was associated with reduced later recognition of words seen during the word-pair encoding task, as well as poorer performance on sub-scales of the Miller Selfridge Memory test. However, between group-differences in the nucleus accumbens remained significant when the effect of memory task performance was controlled. Compared to YHR performing below the group median on the memory tests, YHR with above-median performance showed a trend toward more activation in a region of the left inferior frontal gyrus. Activation in this region was strongly associated with activation in the nucleus accumbens in both YHR and controls. Increased left nucleus accumbens activation was also associated with higher SCL-90 Psychoticism scores in controls. **CONCLUSION:** These data add to the growing literature identifying abnormalities in the limbic system as part of the neurobiological vulnerability to schizophrenia. Future studies of this population may prospectively identify abnormalities in brain function that predict later onset of schizophrenia.

135. Course of Weight & Metabolic Benefits 1 Year After Switching to Ziprasidone

Peter Weiden*, David G Daniel, Antony Loebel, Stephen Murray, Ruoyong Yang, Harold Lebovitz and Nina Schooler

Department of Psychiatry- Box 1203, SUNY HSC at Brooklyn, Brooklyn, NY, USA

Sponsor: Nina Schooler

Objective: To determine the time course of weight and lipid reductions over 58 weeks in outpatients switched to ziprasidone from other antipsychotics. **Methods:** Three open-label, flexible-dose, 1-year extension studies enrolled stable completers of 6-week trials of outpatients switched from conventionals (n=71), olanzapine (n=71), or risperidone (n=43) to ziprasidone. Follow-up to 1 year of ziprasidone monotherapy (median duration 34.6 weeks) permitted longitudinal assessment of improvement in weight and metabolic side effects. A mixed-model regression analysis was used to estimate LS mean change over time (58 weeks total). LOCF analysis (intent-to-treat population) over the 58-week period was also performed. **Results:** Mixed-model analysis showed that patients switched to ziprasidone from risperidone or olanzapine demonstrated progressive, sustained weight loss and body mass index (BMI) reduction over the study period. For the preswitch olanzapine group, estimated LS mean weight loss was -3.4 (±0.6 SE) lb at 6 weeks ($P<0.0001$) and -21.6 (±3.6) lb at 58 weeks ($P<0.0001$). For the preswitch risperidone group, estimated weight loss was -2.1 (±0.8) lb at 6 weeks ($P<0.05$) and -15.2 (±4.5) lb at 58 weeks ($P<0.005$). Statistically significant improvements in triglycerides and total cholesterol occurred rapidly during the initial 6 weeks of ziprasidone monotherapy, and were sustained through endpoint of the extension studies. For the preswitch olanzapine group, estimated LS mean triglyceride reductions were -78.0 (±11.7) mg/dL ($P<0.0001$) at 6 weeks and -54.5 (±15.5) mg/dL ($P<0.0005$) at 58 weeks. For the preswitch risperidone group, the respective improvements were -39.2 (±14.6) mg/dL ($P<0.05$) and -36.7 (±18.9) mg/dL. **Conclusions:** Patients switched from olanzapine and risperidone to ziprasidone demonstrated progressive and sustained weight loss and BMI reduction for up to 58 weeks. Improvements in lipid parameters were substantial, occurred rapidly, and were sustained during long-term ziprasidone monotherapy. Ziprasidone monotherapy was also associated with long-term improvements in the clinical status of patients (Simpson GM et al. APA Annual Meeting, New York, 2004).

136. Urbanicity and Schizophrenia: A population-based Longitudinal Study

Mark Weiser, Abraham Reichenberg, Daniella Nahon, Gad Lubin, Efrat Kravitz, Haim Y Knobler and Michael Davidson*

Department of Psychiatry, Sheba medical center, Tel Hashomer, Israel

Objective: The association between urban dwelling and increased prevalence of psychotic disorders is a consistently replicated finding. While its biological significance remains obscure, increased tolerability for aberrant behavioral in rural areas, and hence under-diagnosis, as well as social isolation in cities have been suggested as plausible hypotheses. To test these hypotheses we used the results of the national screening for psychopathology carried out by the Israeli draft board on all male adolescents in the population, both from urban and rural areas, and data from the national psychiatric hospitalization registry. If under-diagnosis in individuals living in rural areas was the reason for the association, one would expect the association to appear in the psychiatric registry but not in the draft board screening. **Method:** Subjects were a population-based cohort of 378,347 Israeli born male adolescents, assessed by the Israeli draft board at age 16-17. Data on population

density (in persons/km2), based on address, was obtained from the Israeli Central Bureau of Statistics. In the first analysis, we examined the effect of population density on the risk of being diagnosed with a psychotic disorder in the national screening performed in the draft board. We then used the Israeli Psychiatric Hospitalization Case Registry, which records all psychiatric hospitalizations in the country, to ascertain hospitalization for psychosis over 1-17 years. We assessed the effect of population density on the risk of later hospitalization for psychosis. An additional Cox regression analysis assessed the effect of urbanicity on hospitalization for psychosis, including social functioning as a covariate. **Results:** Increased population density was associated with a diagnosis of psychotic disorder in the draft board (OR=3.991, 95% CI: 3.395-4.691). Increased population density was also associated with increased risk for later hospitalization for psychotic disorder (HR=1.164, 95% CI: 1.055-1.284). When examining risk for hospitalization for psychosis while controlling for social functioning, the effect of urbanicity remained significantly increased (adjusted HR=1.142, 95%CI: 1.029-1.268). **Conclusions:** The associations between urbanicity, measured as population density, and increased risk for psychotic disorders is not accounted by higher threshold for aberrant behavior in rural areas, and probably not by social isolation in cities. Thus, other social or biological causes must be investigated.

137. Impaired Reading or Mathematical Abilities in Adolescents with Average or Above General Intellectual Abilities are Associated with Psychopathology

Mark Weiser*, Abraham Reichenberg, Jonathan Rabinowitz, Daniella Nahon, Gad Lubin, Haim Y Knobler and Michael Davidson

Department of Psychiatry, Sheba medical center, Tel hashomer, Israel; Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Sponsor: James Leckman

Objective: In order to investigate the co-occurrence of learning disorders and psychopathology, we assessed the prevalence of psychiatric disorders in individuals with impaired reading comprehension or arithmetic abilities, but average or above-average general intellectual abilities. **Method:** Subjects (N=200,000) were part of a population-based cohort of military recruits, with general cognitive abilities in the 50th-100th percentile, as reflected by Ravens Progressive Matrices-Revised scores. We operationally defined subjects with impaired reading comprehension (IRC) or impaired arithmetic ability (IAA) as those who scored between the 1st-23th lowest percentile on the respective tests, when these tests had been administered to the entire cohort). The comparison group was comprised of adolescents scoring in the 24th percentile and above on these tests. Ratings of behavior and psychiatric disorders were obtained from the Draft Board assessments, and subsequent hospitalizations for schizophrenia and psychotic disorders were recorded using the Israeli National Psychiatric Registry, which records all psychiatric hospitalizations in the country. **Results:** Subjects with IRC and IAA had poorer scores on the behavioral assessment (all $p<0.001$), and higher prevalences of psychopathology: IRC (adjusted HR=1.51, 95% CI: 1.39-1.64); IAA (adjusted HR=1.38, 95% CI: 1.27-1.49). Adolescents with IRC were at increased risk for later hospitalization for schizophrenia (adjusted HR=2.08, 95%CI: 1.44-2.99). **Conclusions:** Male adolescents with average and above-average general intellectual abilities, coupled with IRC or IAA are at increased risk for psychopathology. Impairments in putative intellectual functions and abnormal behaviors may share a common neuro-biological substrate. Clinicians assessing adolescents with LDs should be aware of their increased propensity to suffer from psychopathology.

138. Deficit in Prepulse Inhibition and Enhanced Sensitivity to Amphetamine in Mice Lacking the Trace Amine-1 Receptor

Toni D Wolinsky*, Chad J Swanson, Huailing Zhong, Kelli E Smith, Theresa A Branchek and Christophe P Gerald

Neuroscience, Synaptic Pharmaceutical Corp., a Lundbeck Company, Paramus, NJ, USA

Sponsor: Theresa Branchek

Trace amines are implicated in a number of neuropsychiatric disorders including depression, schizophrenia and ADHD. Although trace amines have long been known to modulate neurotransmission indirectly through the release of catecholamines, the recent identification of the Trace Amine 1 receptor (TA1), along with a family of related GPCRs, offers a mechanism by which trace amines can influence synaptic activity directly. TA1 is present in the mouse, rat, and human CNS, and all three species homologs bind and are activated by trace amines such as b-PEA and tyramine. Amphetamine is also a full agonist at TA1. However, in the absence of selective ligands for TA1 that do not also possess catecholamine-releasing properties, it has not been possible to study its physiological role in the CNS. To that end, a line of mice lacking the TA1 receptor was generated in an effort to begin to characterize the contribution of TA1 to the regulation of behavior. Compared to wildtype (WT) littermates, TA1 knock-out (KO) mice were found to have a reproducible deficit in prepulse inhibition (ppi), with no difference in baseline startle response. These animals also displayed a dose-dependent increase in sensitivity to the psychomotor stimulating effects of amphetamine. Simultaneous monitoring of locomotor behavior and neurochemistry using in vivo microdialysis revealed that the enhanced behavioral sensitivity of KOs to a single dose of amphetamine was accompanied by significantly larger increases in the release of both dopamine and norepinephrine in the dorsal striatum, relative to WTs. These data suggest that agonist activity at TA1 serves to dampen the stimulatory effects of amphetamine; this inhibitory component is absent in TA1 KO animals. Thus, TA1 appears to play a modulatory role in the expression of behaviors traditionally associated with catecholamines, including sensorimotor gating and sensitivity to psychostimulants. Future behavioral and pharmacological studies with selective agonist and antagonist compounds may reveal additional roles for TA1, as well as a potentially novel mechanism for the treatment of neuropsychiatric disorders.

139. Decreased Dopamine-Related Transcription Factors Nurr1 And NGFI-B In The Prefrontal Cortex In Schizophrenia And Bipolar Disorders

Guoqiang Xing*, Lei Zhang, Shani Russell and Robert Post

Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD, USA

Sponsor: Robert Post

Dopaminergic and mesoprefrontal cortex abnormalities are among the most consistent neuropathological findings in schizophrenia. The molecular mechanisms have not been specified. The orphan nucleus hormone receptors NGFI-B and Nurr1 are closely related transcriptional factors involved in neural cell differentiation and maturation, midbrain dopaminergic neurogenesis and apoptosis. NGFI-B knockout mice do not show behavioral response to dopamine receptor agonists, whereas Nurr1 knockout animal show disruption in midbrain dopaminergic neuron development. To date, brain expression of Nurr1 and NGFI-B has not been studied in schizophrenia and bipolar disorders. We determined the laminar (I-VI) expression of Nurr1 and NGFI-B mRNA by in situ hybridization in the postmortem prefrontal cortex Brodmann areas 9 (BA 9) and 46 (BA 46) of patients with schizophrenia, major depression and bipolar disorders and non-psychiatric control subjects (n=15, each group), as well

as the protein levels of NGFI-B and Nurr1 in BA 9 by western blotting. We found that NGFI-B mRNA ($P<0.05$) and protein ($P<0.01$) were significantly lower in patients with schizophrenia (BA 9) and NGFI-B mRNA lower in bipolar disorder (BA 9 and BA 46) than in the controls. In the deep cortical layers of BA 46, Nurr1 mRNA was significantly ($P<0.05$) lower in patients with bipolar disorder and schizophrenia than in the controls. Nurr1 mRNA in BA 46 was significantly correlated with prefrontal gray matter GFAP mRNA expression. Cortical Nurr1 protein in BA 9 was significantly lower in major depression ($P<0.05$) and at a trend level in schizophrenia ($P=0.056$) than in the controls. Nurr1 and NGFI-B mRNA in the deep cortical layers of the prefrontal cortex were significantly correlated with brain pH. No significant correlation between Nurr1 or NGFI-B mRNA, and age, duration of illness, and dose of neuroleptics were found. These results suggest that reduction in prefrontal Nurr1 and NGFI-B expression could contribute to the abnormal dopaminergic innervation and cortical function of patients with schizophrenia and bipolar disorder.

140. Efficacy and Safety of Intramuscular Aripiprazole Treatment for Acute Agitation in Patients with Psychosis

Frank Yocca*, David Daniel, Elyse Stock, Dan Oren, Ronald Marcus, William Carson, George Manos and Taro Iwamoto

Bristol-Myers Squibb, Wallingford, CT, USA

Objectives: To evaluate the efficacy and safety of intramuscular (IM) aripiprazole for the treatment of acute agitation in patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. **Methods:** In this 24-hour, double-blind, multicenter study, 357 patients presenting with acute agitation were randomized to one of four aripiprazole IM doses (1 mg, 5 mg, 10 mg, or 15 mg), haloperidol IM (7.5 mg dose), or placebo. The key outcome measure was the PANSS-Excited Components score (PEC), which was evaluated every 15 minutes for the first 2 hours after dosing. **Results:** Patients treated with aripiprazole 10 mg IM experienced a rapid reduction in PEC compared with placebo (at 30 min: –3.2 vs –1.76, $p=0.051$; at 45 min: –4.39 vs –2.22, $p<0.01$; at 60 min: –5.48 vs –2.41, $p<0.001$). The improved efficacy observed with aripiprazole 10 mg IM over placebo was maintained for the duration of the study. Aripiprazole 5 mg IM and aripiprazole 15 mg IM first showed significant reductions in PEC over placebo at 60 minutes, and haloperidol 7.5 mg IM first showed a significant reduction in PEC at 105 minutes. Aripiprazole IM also resulted in significant improvement in agitation, without excessive sedation, as measured by the Agitation-Calmness Evaluation Scale. Aripiprazole IM was associated with minimal pain at the injection site (3.0% vs. placebo, 3.3%), and two patients discontinued aripiprazole IM due to adverse events. **Conclusions:** The results of this study suggest that aripiprazole 10 mg IM is an effective treatment for the rapid reduction of acute agitation in this patient population, without resulting in excessive sedation or pain at the injection site.

141. A Randomized, Double-blind Study of Quetiapine and Risperidone in the Treatment of Schizophrenia

Kate Zhong*, Philip Harvey, Martin Brecher and Dennis Sweitzer

Clinical Research, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

Sponsor: Andrew Winokur

Objectives: To compare the efficacy and tolerability of quetiapine and risperidone in the treatment of schizophrenia, and to assess the effects of both agents on cognitive and social functioning in patients with schizophrenia. **Methods:** This was a double-blind, randomized, multicenter, flexible-dose study. Eligible patients who met Diagnostic and Statistical Manual of Mental Disorders, 4th ed criteria for schizophrenia with a minimum Positive and Negative Syndrome Scale (PANSS) score of 60 were randomized to receive either quetiapine (200—800 mg/d) or risperidone (2—8 mg/d) for 8 weeks. The primary efficacy measure was change from baseline on PANSS total scores. Secondary efficacy outcomes included response rate (defined as proportion of patients with either ≥40% reduction in PANSS scores or rated ≤3 on Clinical Global Impression—Change scale [CGI-C] scores) and change from baseline on cognitive and social functioning assessment scores. The incidence of treatment-emergent adverse events and change from baseline on weight, glucose, and prolactin were assessed as part of the tolerability evaluation. **Results:** A total of 673 patients were randomized, 338 to quetiapine and 335 to risperidone. The baseline characteristics of patients were comparable between the 2 groups; the mean daily doses were 525 mg and 5.2 mg for quetiapine and risperidone, respectively. There was no statistically significant difference between treatment groups on change from baseline to endpoint in PANSS total scores. Similar proportions of patients in each group showed ≥40% reduction in PANSS total and subscales; the percentage of patients rated "much" or "very much" improved on CGI-C was comparable. Cognitive improvement was observed in both treatment groups. Whereas both quetiapine and risperidone significantly improved episodic memory, verbal fluency, and social skills performance, only risperidone significantly improved vigilance. Improvements in executive functioning and total learning correlated with social skills performance for both quetiapine- and risperidone-treated patients. The completion rate was similar for quetiapine (46%) and risperidone (50%); withdrawal due to adverse events was 6% and 8% for quetiapine and risperidone, respectively. Changes in glucose and weight were similar between groups. Extrapyramidal symptom (EPS)-related adverse events were significantly higher in the risperidone group (22%) compared with the quetiapine group (12.7%). Plasma prolactin levels increased markedly by the end of study in risperidone-treated patients, whereas they decreased in quetiapine-treated patients. **Conclusions:** This study suggested that quetiapine and risperidone were equally efficacious in treating patients with schizophrenia; both agents improved the cognitive and social functioning of those patients. Although both agents had minimum effects on weight and glucose, patients treated with risperidone had a significantly higher incidence of EPS-related adverse events and significantly higher elevation of prolactin plasma levels compared with those treated with quetiapine.

142. Effects of Early Postnatal Loss of Dopamine in the Medial Prefrontal Cortex on Amphetamine-evoked Locomotor Behavior in the Rat

janet M Finlay* and Patricia J Boyce

Psychology, Western Washington Uuniversity, Bellingham, WA, USA

Sponsor: Robert Greene

Neurodevelopmental abnormalities in the mesocortical dopamine (DA) projection are thought to contribute to the emergence of symptoms in schizophrenic subjects in late adolescence/early adulthood. Furthermore, Use of recreational drugs such as amphetamine, at this time, may evoke or exacerbate the positive symptoms of the illness. In the present study, we examined the effects of early partial loss of mesoprefrontal DA sustained on postnatal day 12-14 (PN12-14) on d-amphetamine-evoked (1.5 mg/kg, ip)motor activity in prepubertal (PN30-35) and adult (PN60-65) rats. Lesioned rats tested prior to puberty exhibited a reduction in amphetamine-evoked horizontal motor behavior to 81±14% of control values during the first 15 min following the drug injection (n=5-6/group). Tissue DA concentrations in the prefrontal cortex were reduced to 62±5% of control values. In contrast, lesioned rats tested as adults exhibited enhanced amphetamine-evoked motor activity to 112±7% of control (n=5-6/group). Tissue DA concentrations in the prefrontal cortex of adult-tested lesioned rats were 58±6% of control. The present data suggest that neurodevelopmental abnormalities in the mesopre-

frontal DA system results in a modest attenuation and sensitization in the motor stimulant effects of amphetamine in the prepubertal and adulthood organism, respectively. The present work is supported by PHS grant MH61616.

143. Selective Effects of Simultaneous Monoamine Depletion on Mood, Emotional Responsiveness and Cognitive Function

Pradeep Nathan*, Jay Maree Hughes, Cathy Matrenza, Andrew Kemp, David Liley, Keith Wesnes and Ben Harrison

Brain Sciences Institute, Swinburne University, Melbourne, VIC, Australia

Sponsor: Past Travel Awardee, Memorial, 2002

Monoamines play a significant role in the regulation of emotion and cognitive function. While the selective effects of serotonin and catecholamine depletion on emotional regulation and cognitive function have been described, the effects of simultaneous monoamine depletion on subjective measures of mood, emotional responsiveness and cognition are yet to be examined. This is of particular interest given that multiple neurotransmitter abnormalities have been implicated in many psychiatric disorders. Twenty female participants completed a randomized, double blind, placebo-controlled study, under a balanced control condition (B), and a combined monoamine depletion condition (CMD; via tryptophan, tyrosine and phenylalanine depletion). Mood ratings, measures of emotional responsiveness and cognitive testing were conducted at baseline and five hours post-depletion. Following CMD, participants rated themselves as feeling sadder, more antagonistic and mentally slower on ratings of mood. There were no significant mood changes found on measures of emotional responsiveness. The CMD condition relative to the B condition also resulted in deficits in digit vigilance, a measure of sustained attention. There were no effects on measures of learning and memory or psychomotor function. These findings suggest that simultaneous depletion of all monoamines may have selective effects on mood and cognitive function. The findings provide evidence that the simultaneous monoamine depletion technique may be a useful experimental method to probe central monoamine function in humans.

144. MAOA Gene Promoter Polymorphism Influences Aggression And Impulsivity In Male Rhesus Macaques (*Macaca mulatta*)

Timothy K Newman*, Christina S Barr, Paul L Babb, Maribeth Champoux, Steven J Suomi, Klaus-Peter Lesch and J D Higley

Laboratory of Clinical Studies and Neurogenetics, NIAAA/NIH, Rockville, MD, USA

Sponsor: Redford Williams

A polymorphism in the promoter region of the monoamine oxidase A gene (MAOA) alters transcriptional efficiency, resulting in alleles imparting high or low enzymatic activity. In human subjects, decreased MAOA activity tends to increase aggressive and impulsive behavior, as well as susceptibility to antisocial personality disorder and conduct disorder in males, especially in the context of early childhood stress. We test two hypotheses: 1) That an orthologous polymorphism in the rhesus macaque MAOA gene (rhMAOA-LPR) influences aggressive behavior and impulsivity in male rhesus, and 2) whether stressful infant experience modulates the effect of genotype. Forty-five unrelated male subjects were raised either by their mothers or were nursery reared in peer-only groups (a model for early life stress). In separate experiments, aggressive behavior was assessed using dyadic food competition and observation of normal social group behavior. Impulsivity was assessed using an intruder challenge paradigm in which latency to respond to a stranger was measured. rhMAOA-LPR genotypes were grouped into two categories according to whether they increased or decreased gene transcription determined through in vitro luciferase expression assays. Aggressive behavior during food competition and in normal social group settings was influenced by an interaction between rhMAOA-LPR genotype and rearing condition ($p = .03$), but without main effects of either variable. That is, mother reared subjects with the low activity allele had higher aggression scores. Latency to respond to a stranger was decreased in males with the low MAOA activity allele ($p = .028$), with no main or interactive effects of rearing. Although we observed a clear effect of inferred MAOA activity on impulsive behavior, the effect on aggression was evident only when subjects were divided by rearing condition. Moreover, normally reared males, not those maternally deprived, exhibited more aggression. Impulsive/aggressive behavior in humans, particularly when excessive, is considered antisocial, and low MAOA activity is thus a potential risk factor. We suggest that in rhesus males, reduced MAOA activity induced via the promoter polymorphism may be selectively advantageous, in that moderate aggression and impulsive behavior is essential for successful male reproductive strategies.

145. The Novel 5-HT_{1A} Receptor Antagonist SRA-333 Demonstrates Procognitive Properties in Nonhuman Primates

Menelas N Pangalos*, Deborah L Smith, Sharon Rosenzweig-Lipson, Stacey Sukoff, Lee A Dawson, Karen Marquis, Deborah Jones, Michael Piesla, Terrance Andree, Josie A Harder, Matthew D Womack, Jerry J Buccafusco, Alvin V Terry, Bart Hoebel, Pedro Rada, Michael Kelly, Magid Abou-Gharbia, James E Barrett, Wayne Childers and Lee E Schechter

Neuroscience Discovery, Wyeth Research, Princeton, NJ, USA

Sponsor: Mark Rasenick

A compelling rationale has been proposed for treating Alzheimer's disease (AD) based on data suggesting that 5-HT_{1A} receptor antagonists heterosynaptically modulate neurotransmitters involved in learning & memory and are capable of reversing cognitive deficits in multiple animal models. SRA-333, a novel selective 5-HT_{1A} receptor antagonist, was profiled in multiple *in vitro* and *in vivo* pharmacological assays as a drug to treat cognitive dysfunction. *In vitro* binding and intrinsic activity determinations demonstrated that SRA-333 is a potent and selective 5-HT_{1A} receptor antagonist. SRA-333 binds with high affinity to recombinant human 5-HT_{1A} receptors (Ki = 1.6 nM and 4.5 nM vs agonist and antagonist radioligands, respectively) and with greater than 60-fold selectivity compared with more than 60 other binding sites. In an *in vitro* functional assay, SRA-333 profiles as a potent receptor antagonist, blocking the cyclic adenosine 3',5'-monophosphate (cAMP) response of the prototypical 5-HT_{1A} agonist, 8-hydroxy-dipropylaminotetralin (8-OH-DPAT) with an IC_{50} value of 25 nM and an I_{max} of 100%. Using *in vivo* microdialysis in rats, SRA-333 (0.3 mg/kg, sc) antagonized the decrease in hippocampal extracellular 5-HT induced by a challenge dose (0.3 mg/kg, sc) of 8-OH-DPAT and had no effects alone at doses 10-fold higher, indicating that the compound has no measurable presynaptic 5-HT_{1A} receptor agonist/partial agonist activity. These results were corroborated using parallel *in vivo* electrophysiological methods. Chronic administration of SRA-333 did not lead to receptor tolerance or desensitization of the 5-HT_{1A} receptor in a behavioral model indicative of 5-HT_{1A} receptor function. In drug discrimination studies, SRA-333 (0.01-1 mg/kg, im) did not substitute for 8-OH-DPAT and produced a dose-related blockade of the 5-HT_{1A} agonist discriminative stimulus cue. Together, these data confirm SRA-333 as an antagonist of 5-HT_{1A} receptors. Further neurochemical assessment indicated that SRA-333 significantly potentiated potassium chloride-stimulated release of glutamate and acetylcholine in the dentate gyrus of the hippocampus without affecting basal levels of neurotransmitter. In cognitive testing in aged rhesus monkeys, SRA-333 produced a significant improvement in performance measures of

a delayed match-to-sample task with an optimal dose calculated as 1 mg/kg (po). Learning deficits induced by the glutamatergic antagonist dizocilpine [MK-801] (assessed by perceptually complex and visual spatial discrimination) and by specific cholinergic lesions of the hippocampus (assessed by visual spatial discrimination) were reversed by SRA-333 (2 mg/kg; im) in marmosets. The heterosynaptic nature of the effects of SRA-333 imbues this compound with a novel dual-mechanism mode of action directed at the neurochemical pathology underlying the cognitive loss observed in AD and potentially other disorders involving cognitive dysfunction. SRA-333 has successfully completed Phase 1 studies and is continuing clinical investigation in Phase 2 as an agent to reverse cognitive loss in AD.

146. Identification of Memory-related Genes in Human Populations

Andreas Papassotiropoulos* and Dominique J De Quervain

Div. of Psychiatry Research, University of Zurich, Zurich, Switzerland

Sponsor: James L. McGaugh

Human memory is a genetically complex trait. Heritability estimates of roughly 50% suggest that genetic variations such as single nucleotide polymorphisms (SNPs) have an important impact on this cognitive ability. The polygenic nature of this trait is a challenge to research groups working on the identification of memory-related genes: First, the number of SNPs influencing human memory is estimated to be high. Second, the effect size of each individual SNP is expected to be moderate with multiple levels of gene-gene and gene-environment interactions. Third, genetic analyses in outbred populations are subjected to genetic heterogeneity as potential source of bias, i.e. allelic differences may be due to non-random differences in ancestry rather than true differences in trait characteristics. Here we present our strategy for the reliable identification of memory-related genes, which is based upon two methodological principles: **a.**) We take into account the multigenic nature of this trait and **b.**) We statistically control for background genetic heterogeneity. To identify trait-associated SNPs and to extract the fundamental pattern of gene interactions we use data reduction methods such as the set-association method and hierarchical cluster analysis along with logistic regression models. To control for genetic heterogeneity we genotype each subject for at least 50 non-functional SNPs distributed over all autosomes and use the Structured Association method. By capitalizing upon the recent advances in high-throughput genotyping and computerized algorithms able to deal with large amounts of data we identify genes robustly associated with human memory performance.

147. Ziprasidone in Bipolar Mania: Efficacy Across Patient Subgroups

Steven Potkin*, Paul Keck, Earl Giller, Kathleen Ice, Lewis Warrington and Anthony Loebel

University of California, Irvine, Irvine, CA, USA

BACKGROUND: To evaluate the efficacy and tolerability of ziprasidone in acute bipolar mania, focusing on clinically relevant subgroups. **METHODS:** This was a pooled analysis of two randomized, double-blind 21-day trials comparing flexible-dose ziprasidone (40 to 80 mg BID) to placebo in adults with mania associated with bipolar I disorder. Changes in Mania Rating Scale (MRS) score and CGI-S were calculated for combined study populations and in subgroups of patients with manic episodes or mixed episodes, and with or without psychotic symptoms. **RESULTS:** At last visit (LOCF), mean change in MRS in patients receiving ziprasidone (n=268) was -11.72 (baseline 26.82) vs -6.69 (baseline 26.53) in patients receiving placebo (n=131) ($P<0.001$). Change in CGI-S for ziprasidone was -1.19 (baseline 4.71) vs -0.66 (baseline 4.76) for placebo ($P<0.001$). Significant improvement vs placebo was observed from Day 2 for MRS and Day 4 for CGI-S. MRS and CGI-S changes were comparably robust whether patient's manic episode was classified as acute or mixed, or was complicated by psychotic symptoms or not. Overall, ziprasidone subjects had a response rate of 48% and a remission rate of 40% (both $P<0.01$ vs placebo). **CONCLUSIONS:** Ziprasidone rapidly improves symptoms and global illness severity in bipolar mania. It is comparably efficacious in mixed and manic episodes and in the presence or absence of psychotic symptoms, and is well tolerated.

148. Potential Diagnostic Value of Polypeptide-patterns in Cerebrospinal Fluid: A Capillary Electrophoresis - Mass Spectroscopy (CE-MS) Study

Thomas J Raedler*, Stefan Wittke, Harald Mischak, Eva Weissinger and Klaus Wiedemann

Psychiatry, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Sponsor: Gwenn Smith

Introduction: The current analysis of CSF-proteins is limited to total protein content and a few selected polypeptides. However, many more proteins are secreted into the liquor that may carry disease-specific information for neuropsychiatric disorders. We attempted to apply a novel analytical technique (capillary electrophoresis on-line coupled to an electrospray ionisation time of flight mass spectrometer [CE-ESI-TOF-MS]) to the analysis of CSF. **Methods:** CSF-samples were obtained from four healthy controls with no known psychiatric or neurological disorders. The CSF-samples were analysed with CE-ESI-TOF-MS as outlined in the poster. In addition, the CSF from eight patients with Alzheimer disease and seven patients with schizophrenia was analysed under similar conditions. **Results:** Over 300 different polypeptides were analysed in the CSF from healthy controls with a detection-threshold in the fmol-range. These proteins formed a specific protein-pattern in the healthy controls. Patients with neuropsychiatric disorders showed different protein-patterns. **Discussion:** Our results suggest that CE-ESI-TOF-MS provides a useful tool for the analysis of CSF-proteins. Further studies are needed to establish specific protein-patterns in healthy controls and neuropsychiatric disorders.

149. Syndrome of Chronic Fatigue in Patients Receiving Interferon-alpha for Chronic Hepatitis C

Charles L Raison*, Andrey S Borisov, Sherry D Broadwell, Lucile Capuron, Bobbi J Woolwine, Charles B Nemeroff and Andrew H Miller

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Sponsor: Andrew Miller

Objectives: A high percentage of patients with chronic fatigue syndrome (CFS) report the onset of symptoms following viral infection. Moreover, viral agents (e.g. Epstein Barr Virus) have been implicated in the pathophysiology of CFS. In addition, immunologic abnormalities including activation of innate and acquired immune responses in CFS patients have been reported. Interferon (IFN)-alpha is a cytokine released early in viral infection that contributes to antiviral immunity in part through activation of innate/inflammatory immune responses. Relevant to CFS, IFN-alpha is notorious for causing a variety of behavioral symptoms including fatigue. Of note, alterations in IFN-alpha mediated responses have been observed in CFS patients as manifested by increased activity in the 2-5A synthetase/ribonuclease L pathway. To further examine the relevance of the immune system in general and IFN-alpha (and its downstream mediators) in particular in the pathophysiology of CFS, we examined the prevalence of CSF symptoms in patients receiving IFN-alpha plus

ribavirin for chronic hepatitis C virus (HCV) infection. **Method:** We conducted a 24-week prospective cohort study of 162 patients receiving pegylated IFN-alpha-2b (1.5 mcg/kg a week) and ribavirin (800-1400 mg a day) for HCV infection. Study participants were evaluated at baseline (prior to initiation of IFN-alpha) and following 4, 8, 12 and 24 weeks of IFN-alpha/ribavirin therapy. Fatigue and other CFS symptoms were derived from the Zung Self Rating Depression Scale (SDS), a 20-item self-report instrument widely used to evaluate depressive symptoms in the medically ill and from the Health Problems Checklist (HPC), a 236-item self-report questionnaire that assesses the presence or absence of a variety of emotional and physical symptoms. **Results:** At baseline, 22% of the sample reported moderate to severe fatigue and 3% endorsed symptoms sufficient to meet criteria for CFS (excluding the time requirement). During IFN-alpha therapy, 70% of the sample reported moderate to marked fatigue and 30% endorsed symptoms sufficient to meet CFS criteria (for fatigue chi square = 73.83, df = 1, $p<0.0001$; for CFS syndrome chi square = 41.70, df = 1, $p<0.0001$). **Conclusion:** These data from IFN-alpha-treated patients provide further support for the role of viruses and/or antiviral immune responses in the pathophysiology of fatiguing illnesses including CFS.

150. Relapse Prevention of Disruptive Behavioral Disorders in Children and Adolescents: a Long-Term Trial of Risperidone Versus Placebo

Magali Reyes*, Robert Findling, Jan Buitelaar, Ilse Augustyns and Marielle Eerdekens

Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, USA

Sponsor: Robert Findling

Objectives: Placebo-controlled trials have demonstrated that risperidone has acute efficacy in the treatment of Disruptive Behavior Disorders (DBDs), [1,2,3] but the majority of these trials were short term or in children with below-average intelligence. This study is the first to explore the long-term efficacy of risperidone in preventing recurrence of symptoms in children and adolescents, including those with average intelligence, suffering from DBDs. **Methods:** This international, randomized, double-blind, placebo-controlled relapse prevention study included patients (5-17 years) with DBDs and a wide range of intellect (IQ range = 54-144). Patients who were suffering from any other serious medical or psychiatric condition (with the exception of Attention-deficit hyperactivity disorder, ADHD) were excluded. Patients who responded within 6 weeks to open-label treatment with risperidone, and maintained that response at the end of 6 weeks were randomized to 6 months of either risperidone or placebo (double-blind). The dose was optimized over the first 5 days of the open-label treatment, with a target dose of 0.25-0.75 mg/day for patients <50kg and 0.5-1.5 mg/day for patients ≥50kg. The primary efficacy parameter in the DB treatment was time to relapse, defined as deterioration at two consecutive weekly visits as measured by an increase ≥2 points on the CGI-S or an increase of ≥7 points on the the Nisonger Child Behavior Rating Form Conduct subscale. Secondary parameters included scores on the Clinical Global Impression of Improvement (CGI-I) and the Conduct-problem subscale of N-CBRF. Safety was assessed by reported adverse events, and clinical measures. **Results:** 527 patients (average IQ 92.1 ± 18.06; mean age 11.1 ± 2.95) entered the study with average N-CBRF scores of 35 (± 6.74). At 12 weeks, 335 patients entered the 6-month relapse-prevention phase. At 6 months, the Kaplan-Meier relapse estimates were 47.1% (placebo) versus 29.7% (risperidone) ($P<0.001$). Mean change from baseline on the N-CBRF during the initial 12-week period was -24.8 (±8.0). Mean changes from the start of the double-blind phase at endpoint of the trial were 8.8 (±11.23) and 5.0 (±9.45) for placebo and risperidone, respectively ($P<0.001$). Risperidone was generally well tolerated. The most common adverse events were upper respiratory tract infection (7.6% vs. 5.5% in risperidone and placebo groups, respectively), rhinitis (5.8% vs. 5.5%), pharyngitis (5.8% vs. 2.5%), and headache (4.7% vs. 6.7%). Extrapyramidal symptoms were rare and no patient developed tardive dyskinesia. **Conclusions:** These data provide evidence that risperidone can maintain its beneficial effect and prevent relapse in the long-term treatment of DBDs. These data also extend prior results to patients with average IQ. References: 1. Aman MG, De Smedt G, Derivan A, Lyons B, Findling RL. Am J Psychiatry 2002;159(8):1337-1346; 2. Findling RL, McNamara NK, Branicky LA, et al. J Am Acad Child Adolesc Psychiatry 2000;39(4):509-516; 3. Snyder R, Turgay A, Aman M, Binder C, Fisman S, Carroll A, Risperidone Conduct Study Group. J Am Acad Child Adolesc Psychiatry 2002;41:1026-36. This study was supported by Johnson & Johnson Pharmaceutical Research and Development.

151. Somatic Side Effects of ECT in a Hispanic Population

Maria L Reyes*, Lelis L Nazario, Roberto Norniella, Jorge Santiago, Michael Velez and Diana Diaz

Department of Psychiatry, University of Puerto Rico, San Juan, Puerto Rico

Sponsor: ACNP Secretariat

While substantial literature exists on the cognitive side effects of electroconvulsive therapy (ECT), little is known about the somatic side effects of this therapeutic modality. We reviewed 129 medical records of patients who received ECT in the Acute Inpatient Psychiatric Ward at the Hospital of the University of Puerto Rico. In this retrospective study, we identified the types and incidences of somatic side effects reported in a Hispanic population. Associations between somatic side effects and psychiatric diagnosis, demographic factors, length of seiuzure, electrode placement, and number of treatments were also evaluated. Headache was the most common side effect reported followed by nausea, agitation and vomiting. Both, total motor duration of seizure and length of seizure measured by EEG, were positively correlated with somatic side effects. Patients with longer duration of psychiatric illness and lower education were more likely to present postictal agitation. The major finding of this study was that younger patients were at a higher risk of reporting headache and vomiting.

152. 25 years of Drug Surveillance of Psychiatry - The AMSP system, A Multinational Approach

Eckart Ruether*, Stefan Bender, Detlev Degner and Renate Grohmann

Psychiatry and Psychotherapy, University of Goettingen, Goettingen, Niedersachsen, Germany

Sponsor: Angelos Halaris

In Germany a task force named AMUP (Arzneimittelueberwachung in der Psychiatrie) was launched in 1978, in which two Psychiatric University Hospitals (Munich and Berlin) took part. They started a safety program that ensures the continuous assessment of severe adverse drug reactions (ADR) in psychiatric inpatients under natural conditions of routine clinical treatment. Based on the knowledge gained by the AMUP study and the experience accumulated in such an investigation, a new drug surveillance program, the AMSP (Arzneimittelsicherheit in der Psychiatrie) was put into operation in 1993. Currently 35 hospitals in German-speaking countries participate in the study (1). This report describes the methods of the AMSP, gives detailed definitions of ADRs assessed to be severe , and discusses the incidence of severe ADRs of antidepressants (AD) and neuroleptics from 1993 to 2000. Here we describe 53 042 of totally 122 562 patients treated with antidepressants (2). The overall incidence of severe ADRs was 1.4% of exposed patients. ADRs rates were higher for TCAs

(imputed in 1.0% of patients overall, respectively in 0.6% of patients when only ADs were imputed) and lower for MAO inhibitors and SSRIs (0.7% for both, respectively 0.3% and 0.4%). In particular, TCAs were associated with known risks, such as toxic delirium, grand mal seizures, and hepatic, urologic, allergic or cardiovascular reactions. In SSRIs-treated patients (non-delirious) psychic and neurological ADRs were most prominent, followed by gastrointestinal, dermatological, and endocrinological/electrolyte reactions. Agitation, hyponatremia, increased liver enzymes, nausea, and serotonin syndrome were leading unwanted symptoms. Venlafaxine was associated with adverse CNS and somatic symptoms such as severe agitation, diarrhea, increased liver enzymes, hypertension and hyponatremia. Mirtazapine was mostly connected with increased liver enzymes, cutaneous edema, and collapse. In this time period also 86 439 patients treated with at least one neuroleptic agent were monitored (3). In 1.1% of the patients severe ADRs occurred. In contrast to the results from controlled trials, atypical neuroleptics caused more severe ADRs than typical neuroleptics. These results were mainly caused by the high number of severe ADRs in patients treated with clozapine and concerned delirium and non-EPS neurological, gastrointestinal, hepatic, dermatological, hematological, and edocrinological ADRs. Atypical neuroleptics were found to be superior in EPS and urological ADRs. Excluding the data on clozapine, we found typical and atypical neuroleptics to be similar in the occurrence of severe ADRs, although the profile differs between the two groups as well between the single substances. Our findings provide valuable information on the type and frequency of ADRs in psychiatric practice. Thus enabling differential indication of antidepressants and neuroleptics based not only on the efficacy and tolerability data of controlled trials, but also on their differential ADR profile especially in combination therapy occurring in the real-life setting of routine clinical setting.

153. Effects of the BDNF Val66met Polymorphism on Verbal Episodic Memory: Hits, False Alarms, Delay, and depth of Encoding

Christie R Russo*, Terry E Goldberg, Jennifer E Iudicello, Brita E Elvevaag, Richard Straub, Michael F Egan and Daniel R Weinberger

Genes, Cognition and Psychosis Program; Clinical Brain Disorders Branch, National Institutes of Health, Bethesda, MD, USA

Sponsor: ACNP Secretariat

Recently a polymorphism in the BDNF gene has been associated with hippocampal structure and function. Previous work has indicated that the BDNF Met allele, linked to inefficient intraneuronal trafficking, is associated with decreased hippocampal NAA levels, decreased hippocampal BOLD activation during learning, and attenuated verbal memory for stories. In the current study, we sought to determine more specifically the role of BDNF during verbal episodic memory processing: One, does BDNF have a differential role in deep encoding or shallow encoding of words? Two, does the BDNF val/met polymorphism effect become greater as memory after a delay becomes longer? And three, is the BDNF polymorphism associated with "hits" during recognition and/or false alarms? Twenty-four Val/Val and twenty-four Met carriers were presented with encoding tasks involving non-emotional, neutral words (deep: living, non-living, and shallow: letter "A" in word, "A" not in word) followed by recognition tasks at the following time intervals: immediate, 0.5 hours, and 24 hours. Under both deep and shallow encoding conditions the BDNF polymorphism effect was consistent; Val/Val subjects performed at a significantly greater level than the Met carriers for "hits." This BDNF effect was independent of time. Therefore, the effects did not become greater with longer delays, but remained of similar magnitude. No BDNF genotype effect was observed for false alarms. These findings suggest that the BDNF polymorphism is associated with verbal episodic memory at the behavioral level and are generally consistent with molecular findings that indicate that BDNF is involved in initiating LTP and thus plays a role in early-phase long-term memory.

154. Real-Time Digital Data Capture (DDC): A Clinical Trial Tool for Enhancing Data Quality and Promoting Clinical Rating Reliability

Ester Salman* and Michael R Liebowitz

ChiMatrix, LLC, New York, NY, USA; The Medical Research Network, LLC, New York, NY, USA

Sponsor: Michael R. Liebowitz

Background: Missing data and inconsistencies across ratings are two of the major problems that interfere with the efficiency and rigor of clinical trials. The problem is especially acute for psychiatric studies where individual symptom items or groups of items across different scales assess similar constructs, but congruence of these various measures is never examined during the course of a study. The objective of this validation study is to evaluate the features of a DDC system specifically designed to minimize the aforementioned problems. **Methods:** The ChiMatrix system employs Palm OS and web based technology to capture clinical research data in real time. Data are collected digitally by the raters and physicians while the subject is present and data queries are generated as the data are being collected, allowing raters to review inconsistencies before they are introduced into the database. For the present validation study, the clinical data were derived from an ongoing clinical trial in Social Anxiety Disorder. The study tests a rapidly acting anxiolytic compound by having subjects participate in both a performance and social interaction challenge in a single blind placebo phase, as well as in a double blind phase. Data were collected in the standard manner, and then were forwarded to both ChiMatrix and the study sponsor. Data were then entered into the DDC system by mock raters to test the automated consistency, clinical rating, and data completeness checks. Errors identified by the system were logged automatically in the audit trail with a time and date stamp and are described herein. **Results:** Data from the first 24 of the planned 90 patient sample were entered into the ChiMatrix DDC system. The system successfully identified a total of 391 errors. Of these errors: 203 were missing data points; 59 represented protocol required procedures that were not done; 10 were protocol violations; 39 represented vague or unclear data points; 26 were rule violations of predefined rating scale conventions between the Liebowitz Social Anxiety Scale (LSAS) and the Clinical Global Assessment of illness severity and improvement (CGI) within and/or across visits; and 54 were rule violations of predefined rating scale conventions, specifically, inconsistencies between the Subjective Units of Discomfort Scale (SUDS), the main efficacy assessment for the study, and the CGI illness severity and CGI improvement scales within and across visits. **Conclusion:** Results to date suggest that if the DDC system was utilized as designed from the inception of the clinical trial, these errors may have been eliminated. Many of the errors represent irretrievable data points in the study. Also, the inconsistencies between ratings, which affect the main efficacy assessments, could impact the outcome of the study and the fair evaluation of the study compound. In this validation study these inconsistencies were brought to the foreground before the data were actually reviewed and analyzed. Such problems plague many clinical trials, especially as time progresses and raters drift away from the original training and rating conventions provided to them, raters for a given patient change, or new raters join the study. Both the site and the sponsor can view patient data the same day the visit occurs, the ultimate goal of this system being the production of clean, high quality data that are available for analysis soon after the last visit of the last patient is completed. This is possible because the usual extensive data cleaning phase has been eliminated.

155. WAY-466: *In Vitro* and *In Vivo* Pharmacological Characterization of a Novel and Selective 5-HT$_6$ Receptor Agonist

Lee E Schechter*, Deborah L Smith, GuoMing Zhang, Ping Li, Qian Lin, Irwin Lucki, Sharon Rosenzweig-Lipson, Albert Robichaud, Ron Bernotas and Chad E Beyer

Neuroscience Discovery, Wyeth Research, Princeton, NJ, USA

Sponsor: Irwin Lucki

Since the initial cloning of the 5-HT$_6$ receptor, there has been considerable effort focused on the development of selective 5-HT$_6$ receptor antagonists. Several lines of evidence indicate that such compounds may in fact be potential therapeutic agents for the treatment of cognitive dysfunction. However, further elucidation of the biological role of the 5-HT$_6$ receptor has been hampered to an extent by the lack of suitable and selective 5-HT$_6$ receptor agonists which would allow the consequences of receptor stimulation to be studied. Herein, we report a novel selective 5-HT$_6$ receptor agonist, WAY-466, whose pharmacological properties have been characterized *in vitro* and *in vivo*. WAY-466 displays high affinity binding (5 nM) at the human 5-HT$_6$ receptor and greater than 60-fold selectivity over other GPCRs and ion channel sites. A determination of the intrinsic activity of WAY-466 at the human 5-HT$_6$ receptor using a cAMP accumulation assay reveals the compound is a full agonist (EC50 = 7 nM; Emax = 100%) relative to the efficacy of serotonin. In depth studies investigated the neurochemical effects of WAY-466 in the rat using *in vivo* microdialysis. In the frontal cortex, WAY-466 (3, 10 & 30 mg/kg; sc) increased extracellular levels of GABA, but had no effect on levels of glutamate. Similar results were found in the dorsal hippocampus. The ability of the compound to increase extracellular GABA levels in both brain regions was blocked by the 5-HT$_6$ receptor antagonist, SB-271046. Chronic administration (14 day) of WAY-466 (10 mg/kg, s.c.) produced a significant elevation in cortical GABA levels (845%), an effect that was greater than that induced by acute treatment (360%). Other cortical neurotransmitters including glutamate, NE, DA and 5-HT were not altered by chronic WAY-466 administration. Using a hippocampal slice preparation, WAY-466 produced a concentration-dependent decrease in stimulated glutamate levels. Behavioral activity of WAY-466 is currently being assessed in multiple animal models of psychiatric diseases. Taken together, WAY-466 is the first selective 5-HT$_6$ receptor agonist with potent *in vitro* and *in vivo* properties. The data support the previous evidence that 5-HT$_6$ receptors are co-localized on GABAergic neurons and suggest that these receptors may tonically regulate glutamatergic neurotransmission through the modulation of GABAergic input. In contrast to previously reported *in vitro* assay conditions, it appears that the 5-HT$_6$ receptor is not rapidly desensitized *in vivo*. Furthermore, the increase in extracellular GABA levels was greater following 14 days of chronic dosing compared to the effects noted after acute drug administration. The results indicate that the 5-HT$_6$ receptor can regulate GABAergic function in limbic brain regions and suggests that selective 5-HT$_6$ receptor agonists may be useful in treating a variety of psychiatric disorders especially where abnormal GABAergic function is a contributing factor.

156. Use of Rivastigmine in Patients with Traumatic Brain Injury with Cognitive Deficits: A Pilot Study

Jonathan M Silver*, Adrian Rabinowitz, Barbara Koumaras, Michael Chen, Steven G Potkin, David B Arciniegas, Patricio F Reyes, Deborah Warden, Philip D Harvey, John Rotrosen and Dario Mirski

Department of Psychiatry, New York University, New York, NY, USA; University of Colorado, Denver, CO, USA

Sponsor: John Rotrosen

Introduction: Traumatic brain injury (TBI) is common with an incidence estimated at 1,500,000 persons per year in the United States. Closed brain injury, (non-penetrating TBI) is a significant medical problem. A substantial number of individuals with a non-penetrating TBI have persistent cognitive deficits or other neuropsychiatric disorders. There are currently no approved treatments for the cognitive and behavioral changes resulting from TBI. Based upon findings in Alzheimer's disease (AD) patients, available preclinical data, and evidence for involvement of the cholinergic system affected in TBI, this study tests the hypothesis that enhancement of central cholinergic activity using rivastigmine improves cognitive, memory, attention and behavioral deficits secondary to TBI. **Methods:** This was a 12-week prospective, randomized, double-blind, placebo-controlled multi-center pilot study assessing the safety and efficacy of rivastigmine 3-6 mg/day in patients with non-penetrating TBI with persistent cognitive deficits. Eligible patients had injury at least one year prior to baseline. The primary objective was to compare the effects of rivastigmine 3 to 6 mg/day versus placebo following 12 weeks of treatment on measures of attention or memory as assessed with the Hopkins Verbal Learning Test (HVLT) trials 1-3 total score, or the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Rapid Visual Information Processing) RVIP A'. Another objective was to assess the safety and tolerability of rivastigmine 3 to 6 mg/day compared to placebo over 12 weeks. The results reported here describe the characteristics of the study population. Results for the primary efficacy and safety parameters of this study will be available and reported in the poster presentation following this abstract. **Results:** One-hundred fifty-seven patients are included in the demographics analysis, 106 males and 51 females. The mean age was 37 years (range 18 to 55). Patients satisfied the ICD-9-CM 854.0 criteria for TBI. Eighty-nine percent of patients were Caucasian. Patients had a mean education of 14 years. Eighty-six percent of the patients had a known loss of consciousness (LOC) associated with the TBI. Of those patients reporting a known duration of LOC, the mean time was approximately 23 days. Of all patients studied, 76 patients (48%) had a Glasgow Coma Scale (GCS) score, collected within 24 hours of the injury, with the mean GCS score being 6.5. Eighty-five percent of patients reported a loss of memory, and 92% experienced an alteration in their mental state. **Conclusion:** These demographic results present a sample of non penetrating traumatic brain injury patients with persistent cognitive or attention deficits for at least 12 months following their injury. The subject population appears to be representative of individuals with moderate to severe TBI: a predominance of men (2:1 ratio), and many subjects had LOC and GCS in the severe range. Prior to this study, there have been no double-blind placebo controlled trials completed, designed for neuropsychiatric problems following TBI with more than 2 sites and 20 patients. This study demonstrates the feasibility of conducting rigorous clinical trials in this significant, underserved population.

157. Effects of Histamine H3 Receptor Ligands on Motor Activity and Histamine Release in the Rat Prefrontal Cortex

Kenneth W Perry, Jason Katner, Scott D Gleason, Jeffrey W Witkin, David L Nelson, Kalpana M Merchant, Frank P Bymaster and Kjell A Svensson*

Neuroscience Research, Eli Lilly & Company, Indianapolis, IN, USA

Sponsor: Arvid Carlsson

Histamine is regarded as a neurotransmitter or neuromodulator in the central nervous system(CNS). The cell bodies of histaminergic neurons are located in the tuberomamillary nucleus within the posterior hypothalamus with fibers widely distributed throughout the brain. Increasing evidence suggests that central histamine is involved in the regulation of various physiological functions including arousal, circadian rhythms, feeding and drinking behavior. To date four histamine receptor subtypes have been cloned and characterized, of these the H3 receptor has received increased attention as a potential target for drug discovery including cognitive deficiencies (Witkin and Nelson, 2004). The histamine H3 receptor is primarily located in the

CNS where it functions as a presynaptic autoreceptor regulating the synthesis and release of histamine as well as other neurotransmitters. In this study we evaluated the effects of the H3 selective antagonists ciproxifan and thioperamide and the selective H3 agonist R- alpha-methylhistamine (RAMH) on histamine release, motor activity and water consumption in the rat. The microdialysis experiments were performed in freely moving rats with dialysis probes placed in the medial prefrontal cortex. Dialysate levels of histamine were measured by means of HPLC with fluorometric detection after derivatization of histamine with ortho-phtaldialdehyde. In some of the experiments, the animals horizontal and vertical motor activity was measured concomitantly with dialysis sampling using the EMPIS system from BAS (West Lafayette, IN). While dialysate histamine levels of vehicle treated animals slowly declined during the course of the experiment, ciproxifan (0.3-10 mg/kg, PO) and thioperamide (1-30 mg/kg, IP) increased histamine release for up to 4 hours after dosing with a 3-hour average response of approximately 100% above vehicle control levels. When compared to vehicle treated animals, horizontal and vertical activity was increased by ciproxifan and the weak behavioral arousal coincided with increased release of histamine. The H3 agonist RAMH (3 and 10 mg/kg, SC) strongly suppressed dialysate histamine levels with a 3 hour average decrease of approximately 70% below basal histamine levels. In addition, motor activity was clearly reduced in these animals. Both thioperamide and ciproxifan blocked RAMH (10 mg/kg, IP)-induced increase in water consumption in rats in a dose dependent manner (ED50s of 7.1 and 0.43 mg/kg, PO respectively), confirming their activity as H3 receptor antagonists in vivo. Our data support previous findings that the H3 receptor has an important autoregulatory function for histamine release in the CNS. The motor activation, corresponding with EEG arousal (literature) suggests that there is a direct link between extracellular histamine levels in the prefrontal cortex and arousal, an important component of cognition. All animal testing was carried out according to USDAs Animal Welfare Act Regulations and the NIH Guide for the Care and Use of Laboratory Animal in a facility accredited by The American Association for the Accreditation of Laboratory Animal Care (AAALAC). Eli Lilly and Company sponsored this study

158. Modafinil as Augmentation of SSRI Monotherapy in Major Depressive Disorder: A 12-week, Open-label Extension Study

Michael E Thase*, Maurizio Fava, Charles DeBattista and Joseph Fannelli

University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA, USA

Objective: An 8-week, multicenter, double-blind, placebo-controlled study found that modafinil is a well-tolerated and potentially effective augmenting agent in patients with major depressive disorder (MDD) who were SSRI-partial responders and had persistent excessive sleepiness and fatigue. This 12-week, open-label (OL) extension of the 8-week double-blind study evaluated the long-term use of modafinil augmentation in this patient population. **Method:** Patients who had completed the 8-week double-blind period and were eligible for participation in this 12-week OL extension received modafinil in addition to fixed-dose SSRI monotherapy. Modafinil dosing was flexible to allow for individualized treatment. Patients received modafinil 100–400 mg/day in addition to fixed-dose SSRI monotherapy. Assessments included the Clinical Global Impression of Improvement (CGI-I), Epworth Sleepiness Scale (ESS), and Brief Fatigue Inventory (BFI). **Results:** At final visit, modafinil augmentation of SSRIs improved overall clinical condition in 70% of patients (n=171 [of 245] with a CGI-I response of "very much improved" or "much improved"). Modafinil augmentation also significantly improved wakefulness (ESS: mean change from baseline= -4.6; 95% CI, -5.2 to -4.0) and significantly reduced the worst level of fatigue in the last 24 hours (BFI: mean change from baseline= -2.0; 95% CI, -2.4 to -1.65) at final visit. The most commonly reported adverse event was headache (18%, n=44). Of 254 patients enrolled in OL treatment, 250 received modafinil and 194 completed the study. **Conclusion:** Modafinil augmentation of SSRI therapy in MDD patients was well tolerated and had sustained effects in overall clinical condition, wakefulness, and fatigue. Funding Source: Cephalon, Inc., West Chester, PA.

159. Meta-Analysis and Funnel Plot Analysis of Studies Comparing Venlafaxine and Selective Serotonin Reuptake Inhibitors: The Evidence Revisited

Michael E Thase*, Saeed Ahmed, Richard Entsuah, Diane M Sloan and Charles B Nemeroff

University of Pittsburgh Medical Center, University of Pittsburgh, Pittsburgh, PA, USA

Background: Prior research suggested that treatment with venlafaxine may be more effective than selective serotonin reuptake inhibitors (SSRIs) in treatment of depressed patients. However, previous meta-analyses generally have not included the results of studies with sponsors other than the manufacturer of venlafaxine. This review of all available studies regardless of sponsor, including 2 large (N >1000 patients per study) recently completed randomized controlled trials (RCTs) was conducted to further evaluate the differential effects of these treatments. **Methods:** A previous meta-analysis included individual patient data from 33 double blind RCTs of venlafaxine/venlafaxine XR and SSRIs in treatment of depression identified via a worldwide search of all clinical trials sponsored by Wyeth Pharmaceuticals. For the purposes of this analysis, we have extended the original data set via inclusion of 11 additional studies comparing venlafaxine/venlafaxine XR to SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline): 2 large recently completed Wyeth-sponsored RCTs; 2 small Wyeth-sponsored studies previously excluded because treatment was open-label; and 7 independently sponsored RCTs. To compare results across studies, we used a standardized measure of efficacy, the odds ratio (OR) for remission with venlafaxine vs SSRIs. Because most studies were ≤8 weeks, this time point was chosen as the primary endpoint wherever possible. For studies in which individual patient data were available, remission was defined as a 17- item Hamilton Rating for Depression ($HAM\text{-}D_{17}$) score ≤7 (intent-to-treat population; last observation carried forward method). For studies in which individual patient data were not available, summary data from the published articles/abstracts were used to compute an OR for remission using the most stringent definition provided. Odds ratios and 95% confidence intervals were computed using Mantel-Haenszel methods for each individual study and the overall data set. A pooled OR for the 2 large recently completed RCTs was computed separately as a means of assessing the representativeness of the original meta-analysis of smaller studies. Funnel plot analysis was used to detect selection bias. **Results:** The OR for remission in the original meta-analysis of 33 RCTs was 1.30 (95% CI 1.17-1.44; P<0.0001) compared with 1.31 (95% CI 1.08-1.59; P=0.007) for the 2 large, recently completed RCTs. The updated meta-analysis, with the inclusion of the original 33 studies and all additional studies, yielded similar results, with an OR of 1.25 (95% CI 1.15-1.36; P<0.0001). Visual inspection of the funnel plot analysis did not reveal evidence of selection bias. Results of statistical tests measuring funnel plot asymmetry will be presented. **Conclusion:** Taken as a whole, these findings confirm and extend prior data suggesting that venlafaxine therapy is more effective than SSRIs as a class. The results of 2 large recently completed RCTs were consistent with the findings of a previous meta-analysis of 33 smaller studies. The inclusion of all available studies, regardless of sponsor, did not result in a substantial change in overall outcome. No evidence of selection bias was detected via funnel plot analysis. Of note, it remains unclear if the observed advantage for venlafaxine extends beyond 8 weeks of therapy and if it is consistent across all individual SSRIs.

160. Cranial Irradiation Results in Dose-dependent Changes in Gene Expression in the Rodent Hippocampus

Pragathi Achanta, Kenira J Thompson*, Srikanth Kota, Martin Fuss and Joe L Martinez

Biology, University of Texas at San Antonio, San Antonio, TX, USA; Cajal Neuroscience Institute, University of Texas at San Antonio, San Antonio, TX, USA

Sponsor: Joe L. Martinez, Jr

Therapeutic cranial irradiation results in debilitating cognitive impairments that are attributed to a diminished capability to learn and memorize new tasks and information, as well as to a dramatic reduction in full-scale IQ. Because of the involvement of the hippocampus in learning and memory mechanisms, it is important to identify irradiation-induced alterations in gene expression in this structure following whole-brain radiation treatment. Male Fischer 344 rats (3 mo, Charles River Laboratories) were given cranial irradiation at single doses of 0.3Gy, 3Gy, 10Gy, and 30Gy. Twenty-four hours following cranial irradiation, rats were euthanized, and hippocampi were harvested prior to total RNA isolation and cRNA synthesis. Fragmented cRNA was hybridized to an Affymetrix rat U34 Neuro array. Glial fibrillary acidic protein alpha (GFAP), c-fos, synapsin 2a, heat shock protein (Hsp-27), potassium channel-like protein (KATP-2), interleukin-1 receptor protein, c-erb-A tyroid hormone receptor, beta-adrenergic receptor kinase 2 (beta-ARK2) are some of the genes that were altered significantly across the various doses of irradiation. Real-time RT-PCR was used to verify mRNA expression for candidate genes such as GFAP, EST AI176456, and HSP-27. Our results indicate that substantial gene expression changes occur in the hippocampus following varying doses of cranial irradiation. These findings will help to clarify the cellular and molecular impact of cranial irradiation on the brain. Support Contributed By: DA 04195 (JLM), Ewing Halsell and Kleberg Foundations (JLM), and 1 T32 MH65728-2 (KJT).

161. Effects of Oxycodone/paracetamol and Bromfenac on Actual Driving Performance

Edmund R Volkerts*, Dieuwke S Veldhuijzen, Berend Olivier, Herman M Van Praag and Joris C Verster

Psychopharmacology, University of Utrecht, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands

Sponsor: Herman van Praag

Objective: It has been suggested that when compared to opioid analgesics, driving a car is relatively safe when treated with Non-Steroid Anti-Inflammatory Drugs (NSAIDs). Hence, the objective of this study was to determine the effects of an NSAID (bromfenac 25 mg and 50 mg) and an opioid (oxycodone/paracetamol 5/325 mg and 10/650 mg), and placebo on driving ability. In addition, memory functioning, psychomotor performance, pupil size and mood were determined. **Methods:** Eighteen healthy volunteers participated in a randomized, double-blind, placebo-controlled crossover study. One hour after administration, subjects performed a standardized driving test during normal traffic. Thereafter, subjective driving quality, mental effort and mental activation during driving were assessed. A laboratory test battery was performed 2.5 h after treatment administration. Pupil measurements and mood assessments were determined on several occasions during each test day. **Results:** Both analgesics did not significantly affect performance on any test. However, significantly more effort was needed to perform the driving test when treated with oxycodone/paracetamol 10/650 mg ($p<0.0001$), and subjects reported significantly increased sedation ($p<0.01$) and reduced alertness ($p<0.0001$).After oxycodone/paracetamol 5/325 mg alertness was also significantly reduced ($p<0.04$), but mental effort needed to perform the driving test and reported sedation were not significantly different from placebo. Pupil size was significantly decreased after both doses of oxycodone/paracetamol ($p<0.0001$). In contrast, subjective assessments and pupil measurements after both doses of bromfenac matched that of placebo. **Conclusions:** No significant impairment on any behavioral test was found for both bromfenac and oxycodone/paracetamol. The data suggest that behavioral impairment after oxycodone/paracetamol may be compensated by significantly increased effort during test performance.

162. Predictors of Success in Smoking Cessation Studies: An Analysis of Socioeconomic, Behavioral and Demographic Variables

Charles S Wilcox*, Judy L Morrissey, Arnelle I Hardy, Jon F Heiser, Barbara B Katz, Donna M Adkins, My-Linh Tong and Daniel E Grosz

Pharmacology Research Institute, Newport Beach, CA, USA

Sponsor: Ernest Noble

European data reported in the 1980's and this year as well have consistently indicated a positive correlation between socioeconomic status and successful smoking cessation efforts. In parallel, over the same period of time, the prevalence of cigarette smoking in the United States [particularly in California] has declined. We previously reported on baseline and demographic characteristics that were associated with an increased probability of completing a smoking cessation trial. Here we are reporting on our analysis of socioeconomic status, smoking behavior and demographic variables as potential predictors of successful smoking cessation efforts, vis-à-vis a clinical trial. We statistically analyzed more than 200 patients recently enrolled in and completing three of our double-blind, placebo-controlled, smoking cessation clinical trials. We evaluated several purportedly predictive variables, including Gender, Years of Education, Marital Status and Age. We also investigated the potential predictive utility of key smoking behavior variables such as the Number of Years one has Smoked, the Number of Cigarettes Per Day one smokes and the Number of Prior Quit Attempts reported at the time of entry into a clinical trial. In contrast with the European data on smoking cessation [as well as our data on retention/completion rates], our statistical analyses indicated that neither socioeconomic status nor marital status was associated with differential smoking cessation results. In harmony with the European data, our analysis did indicate that Gender was a key variable, with men being more likely to stop smoking ($p<.005$). Moreover, with regard to Smoking Behavior, the Age (that one) Started Smoking was statistically significant ($p<.001$) and the presence of Other Smokers in the Household was highly significant($p<.0001$). Additional key variables associated with successful cessation efforts included the Number of Cigarettes Per Day that one smokes, as well as the Number of Prior Quit Attempts, reported at entry into a clinical study. These data provide both contrasting and confirmatory results when compared with reports from Europe. Furthermore, our results provide one with additional insights into pertinent patient characteristics [e.g. variables] relevant to patient recruitment, retention, completion and, most importantly, successful smoking cessation efforts.

163. Molecular Mechanisms Controlling Epinephrine During Stress

Dona Lee Wong*, T.C. Tai, Robert Claycomb and Richard Kvetnansky

Psychiatry/Laboratory of Molecular and Developmental Neurobiology, Harvard Medical School/McLean Hospital, Belmont, MA, USA

Stress stimulates the release of epinephrine and corticosteroids from the adrenal gland, as part of the fight or flight response, thereby permitting the organism to meet the challenge of the stress. When rats are subjected to single or repeated immobilization (IMMO) stress, adrenal corticosterone is elevated. IMMO for 30 or 120 min induces corticosterone ~12.0-fold above basal levels. With repeated

stress, corticosterone continues to be elevated when sampled immediately after IMMO but is not significantly different from basal when sampling is delayed. In contrast, adrenal medullary epinephrine remains unchanged. However, sufficient synthesis of this neurohormone occurs to replenish medullary pools and sustain elevated circulating levels for the heightened alertness required by the fight or flight response. In part, stress controls epinephrine expression by inducing PNMT gene transcription. PNMT mRNA increases after single or repeated IMMO, with a 6.9-fold rise 3 hr after one 120 min IMMO and 5.5-fold rise 3 hr after 7 daily 120 min IMMOs. Glucocorticoid activation of glucocorticoid receptors (GRs) likely contributes to PNMT mRNA changes. In addition, induction of the PNMT gene transcriptional activator, Egr-1, a member of the immediate early gene family, also occurs with a 25.9-fold rise in its mRNA immediately after 30 min of IMMO or a 19.3-fold induction immediately after 7 days of 30 min IMMO. A corresponding increase in Egr-1 protein occurs, with a similar change in the ability to form Egr-1 protein-DNA binding complex. While expression of three other PNMT transcriptional regulatory proteins were unaltered, Sp1, the glucocorticoid receptor and AP-2, gel mobility shift assays showed that stress leads to phosphorylation of existing Sp1 protein, facilitating Sp1interaction with its DNA consensus element and potentially permitting more PNMT gene transcription. Finally, enzyme activity measurements and chemiluminescent western analysis demonstrated a rise in functional PNMT enzyme, although changes in the latter did not strictly reflect differences in gene expression.

164. V1a Vasopressin Receptor Expression in the Septum is Necessary and Sufficient for Social Recognition in Mice: A Knockout and Gene Replacement Study

Larry J Young*, Shang-Bao Hu and Isadora F Bielsky

Psychiatry, Emory University, Atlanta, GA, USA

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Considerable evidence suggests that the neuropeptide arginine vasopressin (AVP) is critically involved in the regulation of many social and non-social behaviors, including emotionality. We have previously reported that male mice with a null mutation in the V1a Receptor (V1aR) exhibit markedly reduced anxiety-like behavior and a profound impairment in social recognition. Using a viral vector mediated gene transfer approach V1aR were re-expressed in the lateral septum of V1aR knockout mice (V1aRKO). This septal re-expression of V1aR resulted in a complete rescue of social recognition using the habituation/dishabituation paradigm ($p < 0.001$). V1aR re-expression did not affect anxiety-related behavior in the V1aRKO. The same viral vector was used to over-express the V1aR in the lateral septum of wildtype (WT) mice. This septal over-expression of V1aR resulted in a potentiation of social recognition behavior by significantly increasing the duration of social memory, using the social discrimination paradigm ($p < 0.001$). The V1aR over-expression also resulted in a mild increase in anxiety-related behavior in the WT (one-tailed, $p < 0.05$). These findings suggest that viral vector gene transfer in combination with knockout technology is an effective and innovative tool for investigating the behavioral effects of localized gene expression in the brain; and specifically that V1aR expression in the lateral septum is necessary and sufficient for normal social recognition in mice.

165. Stimulants Selectively Reverse Vigilance Decrement in a 5-choice Serial Reaction Time Task with Unpredictable Cue Patterns

Kehong Zhang*, Taylor Moran-Gates, Minlin Liu, Frank I Tarazi and Ross J Baldessarini

Psychiatry, McLean Hospital/Harvard Medical School, Belmont, MA, USA

Sponsor: Past Travel Awardee BMS, 2002

Sustained attention is commonly assessed in rodents with a 5-choice serial reaction time task (5-CSRTT), which is comparable to continuous performance task in humans. A fundamental problem of this behavioral paradigm was a lack of vigilance decrement, or deterioration of performance over time. Higgins and colleagues recently reported a modification with extended sessions consisting of >200 trials as opposed to 100 trials/session in the standard paradigm. With extended sessions, performance of rats decreases progressively as more trials have been completed. In the present study, we examined behavioral effects of d,l-methylphenidate (0.6 and 2 mg/kg) and d-amphetamine (0.3 and 1 mg/kg) in young Lister hooded rats performing a 5-CSRTT. Testing sessions consisted of 240 trials of different stimulus duration/SD and temporal pattern (fixed or variable intertrial interval/ITI). When SD was 0.5 sec, and ITI was 5.0 sec, subjects maintained a relatively stable level of performance (correct response percentage) throughout the 240-trial sessions. When SD was decreased to 0.25 sec (with a fixed ITI at 5.0 sec), performance decreased significantly as more trials were completed. Neither methylphenidate nor amphetamine produced any noticeable effect on correct response percentage under these conditions. Disrupting the temporal pattern of cue signals with a variable ITI (randomly chosen from 1.5 to 8.5 sec, with an average of 5.0 sec) also led to vigilance decrement. Vigilance decrement induced as such was completely reversed by pretreatment with either methylphenidate or amphetamine. Parameters indicative of motivation and impulsivity were not affected. These findings demonstrated that vigilance decrement in the 5-CSRTT can be induced by either decreased stimulus strength or unpredictable stimulus pattern. However, stimulants reverse only vigilance decrement induced by unpredictable pattern of the stimulus. Supported in part by 1RO3 MH068507-1 (KZ), the Bruce J. Anderson Foundation and the McLean Hospital Private Donors Neuropharmacology Research Fund (RJB).

166. A Video Method for the Clinical Study and Trial of Antidepressants

martin M Katz*, John P Houston, Steven Brannan, Janet L Tekell, Nancy Berman, Charles L Bowden and Alan Frazer

Psychiatry, univ of Texas HSC at San Antonio, Bethesda, MD, USA

Measuring efficacy and behavioral actions of a new antidepressant (AD) is greatly enhanced by having a video record of the assessment interviews. It permits, e.g., detached observation of symptom changes during treatment by multiple observers; increased focus on expressive and social behavior; juxtaposing baseline and outcome during the same viewing session, thereby reducing the role of memory in the rater's observations. This study describes a revision of the Video Interview Behavioral Evaluation Method (VIBES) shortened to make it more applicable to clinical trials. It tests the effectiveness of the VIBES, when compared with conventional methods, in measuring efficacy, onset and early behavioral actions of established ADs and placebo. The time for the standardized video interview was reduced from the original 25' to 10 to 15'. The shortened VIBES expressive, symptom and social behavior scales are completed during the interview so that the entire process of observing and rating a session is about 12 to 18'. Intraclass correlations showed the VIBES and Social Behavior constructs to be reliably rated at baseline, during and at the end of treatment. A principal components analysis derived four "severity" dimensions: Withdrawn Social Behavior- Motor Retardation, Anxiety-Agitation, Hostility, Depressive- Cognitive Symptoms. The method was applied in an investigation of the early behavioral actions of a selective noradrenergic reuptake inhibitor [desipramine (DMI)], an SSRI [paroxetine (Par)] and placebo, through use of multiple behavioral assessment methods. The main aims for this substudy were to determine whether the VIBES could measure superior efficacy of DMI vs. placebo (found with behavioral methods, including HAM-D, in the study proper) and detect onset of changes within the first two weeks of treatment in DMI and Par responders. Results showed DMI acted more rapidly and was more efficacious than placebo on the VIBES "depressive symptoms" severity dimension at

two weeks and outcome. It also showed DMI acted earlier on and with greater improvement than placebo on mood and cognitive functioning at 10 days and at two weeks on "bodily tension". In tracing behavioral changes that precede full response to DMI, the initial change, in accord with earlier study, was on "motor retardation" by day 10, reduction in "bodily tension" by day 13. For Par, overall severity and specifically, "indecisiveness" and "confusion" were reduced significantly more in responders than in non-responders by day 7 persisting throughout the treatment course, reflecting early improvement in cognitive clarity and reduced anxiety. Although the smaller sample in the Video Study reduced its power, the VIBES was able to determine efficacy of established ADs and to provide information on early and different specific behavioral changes effected by the two drugs. It, therefore, has the potential to uncover behavioral mechanisms underlying efficacy and to identify new applications for the drug in the treatment of other mental disorders.