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Poster Session III

1. Pharmacological Characterization of MEM 3454, a Novel Nicotinic Alpha7 Receptor Partial Agonist: Therapeutic Potential for the Cognitive Deficits Associated with Alzheimer's Disease and Schizophrenia

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Sponsor: James E. Barrett

Background: Alpha7 nicotinic acetylcholine receptors (nAchRs) play a vital role in cognition and alpha7 nAchR agonists represent a novel drug class with therapeutic potential to restore cognitive abnormalities associated with Alzheimer's disease, schizophrenia and other CNS disorders. MEM 3454 is a novel alpha7 nAchR partial agonist with 5HT3 receptor antagonist activity. Here we describe the preclinical pharmacological and behavioral effects of MEM 3454 as well as the Cognitive Drug Research (CDR) battery test results obtained from healthy volunteers during the Phase1 clinical trial.
Methods: MEM 3454 was characterized using preclinical pharmacological and behavioral assays. In the Phase1 clinical trial, MEM 3454 was evaluated using the Cognitive Drug Research (CDR) battery test in a double-blind placebo-controlled study in healthy volunteers.
Results: In a proprietary human recombinant mutant alpha7 nAchR cell line, MEM 3454 activated alpha7 nAchRs and produced concentration-dependent increases in calcium flux signals that were right-shifted by the alpha7 nAchR antagonist methyllycaconitine (MLA). In a monkey wild-type alpha7 nAchRs cell line, MEM 3454 elicited an EC50 of 0.4 μM and a maximum response of 67% compared to that of acetylcholine, demonstrating a partial agonist profile. MEM 3454 displayed high affinity at rat alpha7 nAchRs (Ki= 6 nM; [^{3}H]MLA-labeled sites) and human 5-HT3 receptors (Ki= 2 nM; [^{3}H]BRL43694-labeled sites). MEM 3454 showed minimal affinities/efficacies at other nAchRs ($\alpha4\beta2$, $\alpha3\beta$, and $\alpha1\beta1\delta\gamma$) and maintained selectivity in broad receptor and enzyme profiling. MEM 3454 (0.01-10 mg/kg, ip, sc or po) was assessed in several preclinical behavioral models representing multiple cognitive (e.g., attentional, episodic, spatial reference and working memories) and sensory gating domains. MEM 3454 enhanced object recognition memory at a 48hr delay internal, an effect antagonized by MLA and pharmacological tolerance did not occur after 10 days of repeated administration. MEM 3454 completely reversed the water-maze spatial memory performance deficits in aged cognitively-impaired rats and reversed the DMTS performance deficits in aged rhesus monkeys. MEM 3454 produced significant improvements in sustained visual attention (i.e., percent correct hit accuracy performance) via the signal detection task and completely reversed the PCP-induced attentional set-shifting extradimensional discrimination performance deficit. MEM 3454 also significantly reversed the apomorphine-induced prepulse startle inhibition (PPI) deficit. In Phase1 clinical testing in healthy subjects, Cognitive Drug Research (CDR) battery test performance was significantly improved particularly in domains associated with secondary memory. Furthermore, pharmacokinetic parameters from these studies reveal linear, dose-dependent increases in exposures in single and repeated dose studies.
Discussion: The preclinical data presented here, along with preliminary findings in healthy human subjects, suggests that MEM 3454 represents a new and promising therapeutic candidate for the treatment of cognitive symptoms associated with Alzheimer's disease, schizophrenia and other CNS disorders.

2. Long-Term Safety and Efficacy of Memantine Treatment in Moderate to Severe Alzheimer's Disease: Results from a Three-Year Trial

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Background: The purpose of this study was to evaluate the long-term safety and efficacy of memantine in moderate to severe Alzheimer's disease (AD) patients, and to investigate the tolerability of a shorter titration period and once-daily dosing.
Methods: This 134-week extension study enrolled moderate to severe AD patients from two 24-week, double-blind, placebo-controlled lead-in clinical studies (memantine monotherapy study MEM-MD-01; memantine/donepezil study MEM-MD-02). The extension consisted of a 4-week double-blind titration period (Phase A) followed by open-label maintenance periods B (24 weeks), C (52 weeks), and D (54 weeks). Total exposure to memantine was 158 weeks in patients previously randomized to memantine and 134 weeks for patients previously randomized to placebo. In Phase A, patients previously treated with memantine were either maintained on current memantine dosing (10 mg b.i.d.) or switched to 20 mg q.d. dosing; patients previously treated with placebo were randomized to one of four treatment groups to investigate two titration schemes (22-day vs. 8-day) and two dosing schemes (10 mg b.i.d. vs. 20 mg q.d.). In Phases B, C, and D, all patients were administered 10 mg b.i.d. dosing for a total of 130 weeks. Long-term efficacy in the open-label phase was assessed using the Severe Impairment Battery (SIB) and compared to a projected placebo decline, based on historical data from the ADCS SIB validation analysis (Schmitt, 2002). Adverse events (AEs) and vital signs were monitored at each visit; laboratory measures and clinical outcomes were evaluated at endpoint.
Results: Compared to the projected rate of decline for untreated patients, long-term memantine treatment was associated with a significantly slower rate of decline on the SIB one, two, and three years after the baseline assessment. In the titration phase A, there were no marked differences associated with b.i.d. versus q.d. dosing. Throughout the trial, AEs were similar in type and frequency, predominantly mild to moderate in severity, and judged unrelated to memantine. Overall, the most frequent AEs were agitation, fall, inflicted injury, and urinary tract infection.
Discussion: Consistent with other published extension data, these analyses support the long-term efficacy and safety of memantine in the treatment of moderate to severe AD.

3. In Vivo Distribution of Amyloid Plaque Deposition in Mild Cognitive Impairment

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Background: Positron emission tomography (PET) imaging has shown clear distinction of AD and control subjects based upon the cortical retention of the amyloid-binding radiotracer, PIB. Mild cognitive impairment (MCI) is a probabilistic transition state to AD and PIB PET imaging is being used to better understand the state of pathological changes in vivo in MCI to aid in diagnosis, finding effective treatments, and strategizing disease prevention. The present work reports on the status of University of Pittsburgh PIB PET imaging in MCI to determine the presence, quantity and distribution of PIB binding/retention in MCI compared to normal subjects and AD patients.
Methods: MCI subjects were classified as either MCI-amnestic or MCI-multiple cognitive domain (MCI-MCD). Thirteen MCI subjects (70±9 yrs; MMSE range: 23-29) were studied using PIB PET imaging (~15 mCi, 90 min). Comparative PIB PET data were acquired

for 18 control (76±7 yrs; MMSE range: 26-30), and 12 AD (69±9 yrs; MMSE range: 18-28) subjects. All subjects were recruited and evaluated by the University of Pittsburgh ADRC. Magnetic resonance imaging was performed for region definition (including posterior cingulate/precuneus (PRC) and parietal (PAR) cortex) and partial volume correction. The PIB data were analyzed using the Logan graphical method with cerebellar (CER, reference region) data as input. Amyloid deposition was assessed via regional distribution volume (DV) ratio (DVR) measures of PIB retention (mean±1SD).
Results: PIB retention in controls was low and generally uniform with cortical DVR values that ranged from 1.07–1.32, while AD DVR values were about 2-fold greater in PRC (2.4±0.3) and PAR (2.0±0.2). The DVR values of the 13 MCI subjects spanned the entire range of control and AD values, with MCI-amnestic and MCI-MCD both in the control-like and AD-like ranges. Non-specific PIB retention in white matter and cerebellum was similar for all groups.
Discussion: The in vivo PIB retention measures of amyloid deposition in MCI was low like controls, elevated to AD levels, or intermediate, depending on the region. The results suggest that 1) PIB retention can immediately identify cases that will progress to AD by identification of PIB binding equivalent to AD; this is especially helpful with MCI-MCD, which is still under intense study; 2) absence of PIB retention in MCI subjects may indicate that they will not progress to AD, or that some cases will develop detectable levels later in the course. Longitudinal follow-up of these cases is ongoing. This work was supported by NIA, MH070729, Dana Foundation, Alzheimer's Association, GE Health Care.

4. A Randomized, Single-Dose, Opioid Challenge Study of Extended-Release Naltrexone in Opioid-Using Adults
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Sponsor: Charles O'Brien

Background: To evaluate the efficacy and safety of extended-release naltrexone (XR-NTX) in the blockade of an opioid agonist (hydromorphone) in opioid-using adults.
Methods: A phase II, multicenter, double-blind, pilot study randomized opioid-using adults to a single gluteal IM injection of XR-NTX 75, 150, or 300 mg. Hydromorphone challenges (0, 3, 4.5, 6mg IM in ascending order at 1-hr intervals, to assess the level of mu-opioid blockade) were scheduled at pretreatment and on days 7, 14, 21, 28, 42, and 56, with an placebo challenge sequence randomly substituted on one of these days. Plasma naltrexone and 6-beta-naltrexol levels were obtained at each hydromorphone/placebo challenge session. Opioid blockade was based upon (1) the objective measure of pupil size, and (2) the subject-rated Visual Analog Scale (VAS) measure, "Do you feel any drug effect?"
Results: Twenty seven XR-NTX injections were administered. There were 21 completers, including 8 of 9 in the 75 mg group, 6 of 8 in the 150 mg group, and 7 of 10 in the 300 mg group. Pupil measurements were more sensitive to opioid response than the VAS measure. Subjective responses indicated that XR-NTX blockade of hydromorphone 3 mg was complete for up to 42 days at 75 mg, and for to up to 56 days at 300 mg. Pupil diameter indicated that XR-NTX blockade of hydromorphone 3 mg was complete for 28 days following the 150 and 300 mg doses. XR-NTX showed a dose-related response in blockade of higher doses of hydromorphone at 28 days. Pharmacokinetic analysis found that XR-NTX yielded dose-related plasma naltrexone and 6β-naltrexol concentrations. Blockade of hydromorphone, although variable, was correlated with plasma naltrexone and 6-beta-naltrexol concentrations in both extent and duration. Opioid blockade was evident at concentrations above 1 ng/mL of plasma naltrexone. Throughout, there were no serious or severe adverse events; the type and incidence of other adverse events were similar for all dose groups.
Discussion: This study demonstrates that XR-NTX, at doses of 75, 150, or 300 mg, is well-tolerated in non-physically-dependent opioid users and provides opioid blockade over a substantial sustained duration — at least 28 days after a single 300mg IM injection of XR-NTX. This finding has important implications for understanding the success of XR-NTX in reducing alcohol drinking behavior rewarded via endogenous opioids and suggests that XR-NTX would also be successful in blocking relapse in exogenous opiate (heroin) addiction.

5. Alteration of Nicotine Self-Administration Behaviour by Opioid Receptor Modulating Compounds in Rats
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Sponsor: Past Travel Awardee, Memorial, 2001

Background: Recent clinical trials have demonstrated attenuation of cigarette smoking behaviour by cyclazocine, a mixed μ-opioid and κ-opioid receptor partial agonist. Several preclinical studies have also reported alteration of nicotinic responses by opioid receptor stimulation.
Methods: The aim of the present study was to investigate modification of nicotine-taking behaviour by μ-, δ- and κ-opioid receptor agonists and antagonists in male hooded Lister rats. Graded doses (0.3, 1.0 & 3.0 mg/kg SC) of each compound were tested consecutively for 3 days on behaviour maintained by intravenous nicotine infusion (0.03 mg/kg/inf).
Results: The selective The selective κ-opioid receptor agonist U50,488, attenuated nicotine self-administration in doses of 1 mg/kg ($P<0.05$) and 3 mg/kg ($P<0.01$) compared to vehicle. Moreover, there was a small increase in nicotine intake following treatment with 0.3 mg/kg U50,488 ($P<0.05$). In similar tests, naloxone produced a dramatic reduction in nicotine self-administration across all doses tested ($P<0.001$) compared to vehicle treatment. However, tests with naltrindole, a specific δ-opioid receptor antagonist had no effect on nicotine self-administration in all doses.
Discussion: The findings from this investigation highlight the potential roles of μ- and κ-opioid receptor subtypes in modulating nicotine self-administration behaviour. Such knowledge may be exploited to develop more effective smoking cessation aids. (Research supported by Newcastle University)

6. Neurotensin Analogs: Possible Novel Therapy for Addiction
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Sponsor: Elliott Richelson

Background: NT69L is a neurotensin analog that can be administered peripherally. It blocks amphetamine- and cocaine-induced hyperactivity in rats. It also blocks nicotine-induced locomotor activity and has shown sustained efficacy in a rat model of nicotine-induced sensitization. The present study tested the effects of NT69L on nicotine and cocaine self-infusion in rats using the operant behavioral paradigm.
Methods: Male Sprague-Dawley rats (200-220g) were trained to press the lever for nicotine or cocaine self-administration (0.03 mg/kg and 1 mg/kg per infusion I.V. for nicotine and cocaine, respectively). Trained rats were injected with NT69L (1 mg/kg) 30 min before the testing session. Nicotine and cocaine self-infusion was recorded as responses/min and compared to saline pretreated rats. Additionally, the number of infusions per session across multiple sessions was used as a measure of responding for nicotine and cocaine infusions. All animal procedures were approved by the Mayo Clinic Institutional Ani-

mal Care and Use Committee. Dopamine levels, tyrosine hydroxylase, and dopamine receptors mRNA levels were determined.
Results: NT69L significantly suppressed both nicotine and cocaine self-administration. The modulatory effect of NT69L on the dopaminergic system is discussed relative to changes occurring due to drug infusion.
Discussion: Neurotensin and its receptors co-localize with the dopaminergic system which is implicated in addiction. The neurotensin analog, NT69L, may suppress psychostimulant abuse by modulating the dopaminergic system as well as other neurotransmitter systems involved in drug dependence. Neurotensin receptors may be considered as novel therapeutic targets for nicotine and cocaine addiction.

7. Bupropion Reinstates Cocaine Seeking Behavior in Rats
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Sponsor: Everett Ellinwood

Background: Bupropion (Wellbutrin) is an antidepressant with dopamine (DA) and norepinephrine (NE) transporter blocking properties. Bupropion (BUP) has been found to have some clinical use in attenuating obesity and nicotine abuse. It is currently being tested in cocaine dependence in humans. Antidepressants have been routinely used in the treatment of stimulant withdrawal anhedonia. Thus antidepressants, and in particular bupropion, may be useful in both the treatment of addiction and in the treatment of withdrawal symptoms. Preclinical work in non-human primates however, suggests that BUP is readily self-administered. Thus judicious use of BUP may be merited. Here we test 3 common antidepressants with different profiles at the DAT, NET and SERT, in a cocaine seeking reinstatement paradigm. We hypothesize that BUP, with its high affinity for the DAT, may have a greater propensity to induce reinstatement than antidepressants with more selective affinity for the NET and SERT.
Methods: We trained adult male rats to nose-poke for cocaine (1 mg/kg/infusion) on an FR5 schedule of reinforcement. After 10 days of training, rats routinely nose-poke ~250 times for a maximum of 50 infusions (50 mg/kg/day maximum to avoid overdose). Rats were then withdrawn for a week to allow for consolidation of putative neurochemical changes. On day 8 of withdrawal rats were put back in their nose-poke boxes but no cocaine was infused. On the following 5 days rats received saline, desipramine (DMI), clomipramine (CLO), BUP and cocaine (COC), all at 10 mg/kg s.c. just prior to being reintroduced to the nose-poke boxes. Other rats received only saline control injections, or saline for the first 3 days and then BUP to determine whether the DMI or CLO injections had any effect on the subsequent response to BUP or COC.
Results: The 2 days of extinction decreased baseline responding by about 65%. DMI and CLO had no effect on responding. BUP and COC both reinstated nose-poke behavior above baseline values (to approximately 300 (BUP) and 400 (COC) nose-pokes), whether or not they were preceded by DMI and CLO.
Discussion: These data suggest that DMI and CLO may be used safely in the treatment of cocaine withdrawal symptoms, but BUP may be contraindicated due to its ability to cause reinstatement, a model for relapse. However it is likely that the BUP dosing regimen and route of administration are critical to these effects and need to be further examined.

8. Gamma-Hydroxybutyric Acid Alters Spatial Learning and Memory in an Age-Specific and Gender-Specific Manner
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Sponsor: Herbert Barry

Background: Gamma-hydroxybutyric acid (GHB) belongs to the class of substances referred to as "club drugs". It is abused for its euphoric, sedative and anabolic effects, and in almost all cases of GHB abuse, users report of amnesia. GHB use and abuse is most prevalent among adolescents and young adults. Adolescence is a unique developmental stage in terms of behavior and pharmacological sensitivity, and is a critical period for vulnerability in the onset of substance abuse. Recent studies have shown that adolescent animals differ from adults in their sensitivity to several drugs of abuse including alcohol and nicotine. Effects of GHB on learning and memory in animals remain unknown.
Methods: In this study the effects of GHB exposure on spatial learning and memory was tested using the Morris water maze. Adolescent and adult male and female rats were treated with a single daily injection of GHB for five days. Control rats received equivalent volumes of vehicle. Rats were tested in the reference memory task of the Morris water maze.
Results: GHB-treated adolescent rats took significantly longer to find the platform than control rats. Swim speed in GHB-treated rats was not different from that in vehicle-treated rats. Also, performance in the visual task did not differ between drug-treated and control rats. In the probe trial, GHB-treated rats spent less time in the quadrant where the platform was present prior to its removal than control rats. Adult male and female rats treated with GHB did not show similar differences in the water maze performance.
Discussion: Together, these data indicate that GHB exposure in rats negatively impacts spatial learning and memory, and adolescent rats appear to be uniquely sensitive to the cognitive-impairing effects of GHB.

9. Aripiprazole in the Treatment of Alcohol Dependence: Results from a Multisite Study
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Background: Aripiprazole is a novel medication with both dopaminergic and serotonergic stabilizing properties and fewer adverse effects than typical antipsychotics. Its unique pharmacology has led investigators to consider it for the study of substance abuse in general and alcohol dependence in particular. Abused substances, including alcohol, are known to elevate dopamine in the nucleus accumbens and potentially to leave the addicted individual in a dopamine deficiency state once the substance has been withdrawn. During treatment, a medication such as aripiprazole could theoretically remediate alcohol-induced effects on the brain dopamine system leading to decreased reinforcement and craving, and thereby reduce the risk of relapse to alcohol use. On this basis, we conducted a double- blind, placebo-controlled, randomized, multisite clinical trial of aripiprazole for alcohol dependence.
Methods: A total of 295 medically stable, alcohol dependent-outpatients participated in this 16-site study. Subjects had no other substance abuse, and averaged >5 drinks/day on at least 70% of the days in the 90 days prior to screening. Subjects were randomly assigned to treatment with either aripiprazole at a target dose of 30 mg/day or placebo for 12 weeks with concomitant cognitive behavioral therapy. The sample was 69% male, with drinking on 93% of days in the 60-day screening period, with an average of 9 drinks per drinking day. OCDS score averaged 26, ADS score averaged 13, and DrInc score averaged 46. Twenty percent of subjects were on stable doses of antidepressants (mainly SSRI's) at randomization. The average dose of aripiprazole was 23 mg. The a priori defined primary end point was percent days abstinence.
Results: Fifty-nine percent of aripiprazole subjects and 73% of placebo patients completed the study. There was a clear differential increase in dropout by aripiprazole subjects over placebo subjects after about day 28, as doses reached the 20-30 mg range. Using a conservative approach of classifying all dropouts as having returned to

baseline drinking levels, there was no significant difference in percent days abstinent (PDA) between placebo (63%) and aripiprazole-treated (59%) subjects. There also was no significant difference in the number of subjects who relapsed to heavy drinking (23% vs. 23%), or in the % heavy drinking days (20% vs. 21%). However, compared with placebo subjects, aripiprazole-treated subjects reported significantly (p=0.001) fewer drinks per drinking day, had a significantly (p=0.004) lower end-of-study ADS score, a greater reduction in %CDT (p=0.02), and endorsed more positive aripiprazole effects on reduction of craving and drinking.
Discussion: Although aripiprazole was no better than placebo on the main outcome measure of percent days abstinent, this may have resulted from an increased frequency of adverse events (i.e., insomnia and anxiety) at higher dose levels, leading subjects to relapse to drinking and/or drop out of treatment. This interpretation is supported by the fact that, on a number of secondary measures, aripiprazole outperformed placebo. Given these findings, it would be useful to evaluate the effects of aripiprazole at a dose lower than 30 mg and possibly combined with other efficacious relapse reducing medications.

10. The Effect of Acute Cocaine on the Brain Response to the Anticipation of Monetary Losses and Gains
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Background: Models of reward processing suggest that midbrain dopaminergic function is involved in the attribution of incentive salience to rewarding stimuli. Both human and animal studies indicate ventral striatal and mesial forebrain involvement in incentive-driven behavior. Acute administration of cocaine has been shown to alter brain function in these regions and there are data to suggest a dysregulation of reward processing in cocaine users. Thus, brain areas associated with reward processing are likely the same as exhibit functional changes following cocaine administration. Our aim was to determine the effects of acute cocaine administration on the neurobiological substrates underlying incentive driven behavior in reward processing in cocaine-dependent individuals. Specifically, the modulatory effect of cocaine on brain regional activity associated with the anticipation of monetary losses and gain.
Methods: Six cocaine-dependent adults underwent functional magnetic resonance imaging while performing an adaptation of the Monetary Incentive Delay task, where participants aim to maximize their winnings by responding to a target stimulus that appears for a limited time period. Prior to the target participants were shown two primes. The first indicated the trial type: win, loss or neutral. The second indicated the potential magnitude of losses or gains. On win trials participants always won at least $1, but won a greater amount (indicated by the second prime) if they were fast enough to respond to the target. On loss trials participants always lost at least $0.75, but lost a greater amount if they responded too slowly to the target. On neutral trials the participants total winnings did not change. Each participant completed the task twice, in two separate scanning sessions – one following acute IV cocaine (30mg/70kg, administered over 3 minutes), and the other following IV saline. To equate performance on the task between participants and between sessions, the presentation time of the target was adjusted based on prior performance.
Results: A significant interaction between experimental session (i.e. cocaine vs. saline) and prime (loss and gain) for the second prime stimulus was found. Post-hoc analysis revealed a significant decrease in activation in a striatal cluster comprising the caudate, putamen, and nucleus accumbens in the right hemisphere (cluster volume = 237) in the cocaine condition, compared to the saline condition. This decrease in BOLD activation was consistent across different magnitudes of potential loss (i.e. -$1.50 vs. -$6 vs. -$9). No difference was seen between conditions in BOLD response when the second prime indicated a win.
Discussion: These preliminary data suggest that at a stage in reward processing when cocaine-dependent adults are anticipating a specific outcome (i.e. either win or loss) and can prepare to maximize the outcome of a trial (i.e. maximize wins or minimize losses), acute cocaine has no effect on the salience of win stimuli or the motivation to maximize wins. Conversely, in response to stimuli indicating an upcoming loss that can be avoided, acute cocaine administration leads to a decrease in activity, in midbrain dopaminergic brain regions that may be necessary for the attribution of salience to loss predicting stimuli and the motivation to minimize losses. This decrease was noted in the right hemisphere, in which activation is more commonly seen for negative, vs. positive, affective stimuli. These data suggest that cocaine-dependent adults, while under the influence of cocaine acutely, may be less able to appropriately attend to stimuli that would normally be considered to be negative, possibly even aversive, and may be less able to adjust their behavior to avoid or minimize the outcomes of such stimuli.

11. Reduced Functional Connectivity in Cocaine Users Revealed by Resting-State Functional MRI
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Background: Functional connectivity in the brain can be investigated using synchronized low-frequency fluctuations in the resting-state using functional magnetic resonance imaging (fMRI). This technique has been used recently both in healthy individuals and in various disease states including the assessment of Alzheimer's disease, schizophrenia, epilepsy and depression. In this study, we used resting-state fMRI to test the hypothesis that system specific functional connectivity is altered in cocaine addicts comparing to healthy controls.
Methods: Resting-state fMRI data were acquired from 12 cocaine dependent individuals and 12 healthy controls on a 3.0 T Siemens Allegra scanner. The user group and control group were matched for years of education and age. All participants gave informed written consent prior to scan and were instructed to close their eyes and not to think of anything in particular during the scan. Thirty-nine slices were prescribed to cover the whole brain and 180 image volumes were acquired with a TR of 2 s, TE of 27 ms and spatial resolution of 3.43×3.43×4 mm3. Data were processed and analyzed using AFNI. Before being transformed to Talairach space, all resting data were slice-timing corrected, volume registered and linearly detrended. They were then spatial Gaussian smoothed with FWHM of 6 mm and temporal low-pass filtered with cutoff frequency of 0.1 Hz. Five spherical ROIs with a 3 mm were selected in left amygdala, hippocampus, anterior cingulate cortex (ACC), medial dorsal (MD) thalamus, and precentral gyrus/primary motor cortex. Time courses from voxels within these 5 ROIs were averaged to generate five templates. Correlation coefficients (CCs) of each voxel in the brain were calculated between the voxel time course and the templates, which were then converted to z-scores. Assuming low frequency fluctuation (LFF) signals from white matter is less interesting and significant, an average time course was extracted from voxels in white matter, to which the image data were orthogonalized in calculating CC. Two-sample t-tests were performed on z-score maps to assess significant differences between the two groups for each of the five ROIs.
Results: Preliminary results showed a general reduction in functional connectivity in cocaine addicts compared with match control subjects. Specifically, when the seed point was in the amygdala, significant reductions in functional connectivity was found in a large area of the medial prefrontal cortices (MPFC), anterior and posterior cingulate cortices (ACC & PCC), bilateral hippocampus, and contralateral amygdala in the cocaine group. Similar brain areas in MPFC and PCC showed decreased connectivity when the seed point was in hippocampus, although connectivity was also decreased in the inferior-orbitofrontal cortices (OFC). When the seed was in the ACC, func-

tional connectivity was significantly reduced in the dorsal lateral prefrontal cortices (DLPFC), nucleus accumbens (NAc), insula, middle cingulate, and a small area of ACC. Connectivity was decreased only in the striatum when the seed was placed in MD thalamus. No significant differences were seen in the primary motor cortex when the seed was in precentral gyrus.
Discussion: Cocaine dependence has been previously revealed to lead to reduced orbitofrontal metabolism, impaired cognitive functions and reductions in presumptive gray matter size as revealed by VBM. Using LFF analysis, we have been able to demonstrate consistent, system dependent decreases in functional connectivity that appear to help explain these deficits and point to a powerful new tool to study cocaine-induced neurotoxicity. It will be of interest to now determine if and when these putative connectivity alterations are reversible during treatment and abstinence.

12. Basolateral Amygdala Involvement in Consolidation and Reconsolidation Processes Relevant to Drug Context-Induced Reinstatement of Cocaine Seeking

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Sponsor: Past Travel Awardee, Young Investigator Memorial, 2005

Background: Exposure to a cocaine-associated environmental context can elicit craving and relapse in cocaine users. Additionally, drug context re-exposure can precipitate the retrieval of context-cocaine associations followed by their reconsolidation into long-term memory or extinction learning followed by the consolidation of context-no cocaine associations. We hypothesized that the former process dominates following short context re-exposure, whereas the latter dominates following longer context re-exposure. Furthermore, we postulated that de novo protein synthesis in the basolateral amygdala (BLA) plays a critical role in each of these processes.
Methods: To test these hypotheses, rats were trained to press a lever for unsignaled cocaine infusions (0.25 mg/kg) in a distinct environmental context. Self-administration training was followed by extinction sessions in a distinctly different environmental context. Once the rats reached the extinction criterion (25 or less responses per session on two consecutive days), they were re-exposed to the cocaine-associated context for 5, 15, or 120 min, in the absence of cocaine reinforcement. The protein synthesis inhibitor, anisomycin (ANI; 62.5 μg/0.5 μl), or vehicle was microinfused bilaterally into the BLA immediately after context re-exposure. The effects of these manipulations on reinstatement of extinguished cocaine-seeking behavior (nonreinforced lever presses) were assessed in the cocaine-associated context.
Results: Exposure to the cocaine-associated context reinstated extinguished cocaine-seeking behavior in saline pretreated rats. The effects of intra-BLA ANI treatment on cocaine-seeking behavior differed depending on the length of context re-exposure. ANI administered after 5 min of re-exposure to the cocaine-associated context failed to alter subsequent context-induced cocaine-seeking behavior. This finding suggests that 5 min of context re-exposure is insufficient to reactivate the cue-context memory or it triggers processes that are not dependent on de novo protein synthesis in the BLA. ANI administered after 15 min of context re-exposure attenuated subsequent context-induced cocaine-seeking behavior. This finding suggests that 15 min of context re-exposure predominantly facilitates retrieval and reconsolidation of the context-cocaine memory, and this process is dependent on de novo protein synthesis in the BLA. Furthermore, ANI administered after 120 min of context re-exposure impaired the extinction of cocaine-seeking behavior. Thus, 120 min of context re-exposure predominantly facilitates the consolidation of extinction learning, and this process is also dependent on the BLA.
Discussion: Manipulations that facilitate extinction memory (re)consolidation or impair context-cocaine memory reconsolidation are of considerable interest from a drug-abuse treatment perspective. The viability of this treatment approach will depend on whether different molecular mechanisms mediate these processes, allowing for their manipulation independently for therapeutic purposes.

13. Testing the I-RISA (Impaired Response Inhibition and Salience Attribution) Model in Cocaine Addiction Using a Newly Developed Drug Stroop Task for fMRI

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Background: An attentional bias to the salience of drug-related stimuli in drug addicted individuals represents automatic cognitive and emotional processing that possibly contributes to the loss of control evidenced by the compulsive nature of drug self-administration. However, the underlying neuronal mechanisms of these Impairments in Response Inhibition and Salience Attribution (I-RISA) (Goldstein and Volkow, 2002) remain elusive. Functional MRI (fMRI) studies in non addicted psychiatric populations use the emotional Stroop task to probe the neurobiology underlying the attentional bias to salient symptom-related words (e.g., combat words in PTSD patients) as compared to neutrally valenced words. These studies point to a central role for the rostro-ventral anterior cingulate cortex (ACC) and medial orbitofrontal cortex (mOFC) in emotional processing. A dysregulated function of the ACC and mOFC has been previously suggested to mediate the core I-RISA characteristics in drug addiction. However, to date, an emotional Stroop fMRI task using drug words has not been implemented in drug addicted individuals as compared to healthy controls.
Methods: We developed and tested a drug Stroop fMRI task in 16 cocaine addicted individuals and 18 matched (on sex, race, age, and education) healthy controls. This task presented 40 drug-related words and 40 matched neutral words and required the subjects to press a button corresponding to the word color in both salience conditions. Thus, this task explicitly combined salience processing with inhibitory control mechanisms to directly probe the role of the ACC and mOFC in modulating attentional bias to drug cues in drug addicted individuals.
Results: Surprisingly, the study groups did not differ in valence ratings of the drug or neutral words; the drug words were rated negatively while the neutral words were not, across all subjects (word main effect, $F=20.4$, $df=1,34$, $p<.0001$). Nevertheless, objective task performance indicated differential processing of the drug words in the addicted subjects. Thus, there were trends for a word by diagnosis interaction on all behavioral measures ($Fs>1.8$, $df=1,34$, $p<.09$; these effects did not reach significance because word reading was separated from button pressing when measured inside the scanner) such that the addicted subjects had a tendency towards faster reaction times and lower accuracy for the drug as compared to the neutral words, possibly indicative of higher impulsivity in a drug context. Moreover, SPM2 whole brain analyses indicated a word by diagnosis interaction in the ACC/mOFC ($F=5.9$, $df=1,32$, $p<.05$) and in the dorsal striatum (caudate and putamen) ($F=4.1$, $df=1,32$, $p<.05$), such that hypoactivations in the cocaine but not control subjects were noted for the drug and not for neutral words. Moreover, only in the cocaine addicted subjects, the higher the ACC/mOFC hypoactivation to the drug vs. neutral words, the more the errors committed specifically in the drug vs. neutral condition ($r=-.73$, $p=.001$) and the higher the frequency of recent cocaine use ($r=-.53$, $p<.05$).
Discussion: These data suggest that the ACC/mOFC and dorsal striatum modulate processing of salient drug-related cues in cocaine addicted individuals. Responses to this new task may model the on-line experience of addicted individuals when facing salient drug cues. During these experiences, unregulated emotional and behavioral reactions may be automatic, paramount and not successfully controlled (e.g., suppressed). Overall, this task provides behavioral and neural

markers of the I-RISA model in drug addiction, suggesting that a disproportionate and automatic (and not necessarily conscious) salience which is attributed to drug cues may lead to dyscontrol in a drug context in susceptible individuals.

14. Effects of Topiramate on Alcohol Cue Reactivity and the Subjective Effects of Drinking

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Sponsor: Past Travel Awardee, Young Investigator Memorial, 2005

Background: Topiramate (TOP) was recently reported to be efficacious in reducing drinking rates and craving among men and women with alcohol dependence in a randomized controlled 12-week trial (Johnson et al., 2003). An important observation in this study was that significant differences on self-reported drinking measures started at the 200 mg/day dose in week 6, but doses continued to increase up to week 8. As a result, the effects of time and dose on drinking were confounded. To date, no dose response study of TOP with alcohol dependent individuals has been done. It is of considerable clinical importance to determine at what dose TOP has the most favorable benefit-to-side effect ratio. In addition, it has been recognized that improvements in pharmacotherapy may occur through identification of the biobehavioral mechanisms by which interventions exert their beneficial effects. Both trials of TOP conducted to date (Johnson et al., 2003; Rubio et al., 2004) suggest that an attenuation in craving may mediate its effects on drinking. However, no laboratory studies have assessed urge to drink while on TOP. Other mechanisms by which TOP could be beneficial for persons with alcohol dependence is through an attenuation of euphoric and stimulatory effects, and a potentiation of dysphoric effects of alcohol ingestion. These also have not yet been examined.
Methods: In the present study, heavy drinking male and female alcohol dependent individuals who were not seeking treatment were randomized to one of 3 conditions in a 3-group (TOP 200 mg/day; TOP 300 mg/day; placebo) double-blind study. Participants reached the target dose after a 32-day titration period and were stabilized for 1 week. All then participated in a laboratory assessment to evaluate the possible dose-dependent effects of TOP on craving and the subjective effects of alcohol ingestion. Participants underwent a cue reactivity protocol that involved exposure to their preferred alcoholic beverage. All then completed an alcohol-challenge procedure wherein they consumed a dose of alcohol that was adjusted by gender, height, and weight, such that the targeted blood alcohol level (BAL) was 0.06. All were given 20 minutes to consume the beverage followed by a 20-minute absorption period. Next, BAL was assessed and measures of the subjective effects of alcohol were completed. All remained in the laboratory until their BAL was < .04. Because identifying individuals most likely to benefit from TOP may improve treatment and cost-effectiveness, we examined potential psychosocial and genetic moderators of TOP's effects.
Results: 57 participants completed the protocol. All groups were highly compliant (MEMScaps®; placebo 98%, 200 mg 96%, & 300 mg 97%) and compliance to the medication regimen was verified by testing blood samples on two occasions for each participant. No serious or non-serious adverse events were reported. TOP reduced drinking during the trial compared to placebo. Effects of TOP on craving will be presented.
Discussion: The results to be presented will provide an efficient and comprehensive analysis of putative biobehavioral mechanisms of TOP's effects on drinking and afford a better understanding of whether large-scale randomized clinical trials with long-term follow ups are warranted.

15. Psilocybin Occasions Experiences Having Sustained Personal Meaning and Spiritual Significance

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Background: Psilocybin, which is the principal psychoactive component of a genus of mushrooms (Psilocybe), is a naturally-occurring tryptamine alkaloid with actions mediated primarily at serotonin 5-HT2A/C receptor sites. Psilocybin, in the form of these mushrooms, has been used for centuries for religious purposes. The psychological effects of psilocybin include changes in perceptual, cognitive, affective, volitional, and somatesthetic functions, including visual and auditory sensory changes, difficulty thinking, mood fluctuations, and dissociative phenomena. Despite long-term religious use and recreational abuse, few studies have rigorously evaluated the acute and persisting effects of psilocybin when administered under comfortable, supportive conditions.
Methods: Recently we reported the results of a double-blind study which evaluated the psychological effects of a high dose of psilocybin (30 mg/70 kg) relative to a comparison compound (methylphenidate, 40 mg/70 kg) when administered to 36 hallucinogen-naïve adults (Psychopharmacology, 187(3):268-83, 2006). This poster will provide a preliminary summary of the 14-month follow-up data from that study. During sessions, volunteers were encouraged to close their eyes and direct their attention inward. Volunteers completed questionnaires assessing drug effects and mystical experience immediately, 2 months, and 14 months after sessions.
Results: Acutely, psilocybin produced a wide range of subjective and perceptual effects, varying among sessions and from time to time within sessions. About one third of the volunteers (11 of 36) reported "strong" or "extreme" fear sometime during their psilocybin session, including six subjects who had mild, transient ideas of reference or paranoia. Sixty-one percent of the volunteers met pre-established criteria, as measured on standardized scales, for a full mystical experience. At 2 months after sessions volunteers attributed to the psilocybin experience positive changes in attitudes and behavior that were consistent with changes rated by community observers. At 14 months after the session, 67% of volunteers rated the experience as among the five most spiritually significant experiences of their lifetimes, and 89% rated that the experience produced positive behavioral changes, with almost half of these indicating that the degree of change was strong or extreme. Sixty-four percent of volunteers rated that the experience had increased their current sense of personal well-being or life satisfaction "moderately" or "very much." and no volunteer indicated that it produced a decrease.
Discussion: The study shows that with careful volunteer screening and preparation and when sessions are conducted in a comfortable, well-supervised setting, a high dose of 30 mg/70 kg psilocybin can be administered safely. Because of concern about recreational abuse of these compounds, in communicating about these findings it is important that the risks hallucinogen-induced panic reaction and the possible precipitation of enduring psychiatric conditions also be emphasized. The ability to prospectively produce mystical-type experiences having sustained personal meaning and spiritual significance should permit rigorous scientific investigations about their causes and consequences, providing insights into underlying pharmacological and brain mechanisms, nonmedical use and abuse of psilocybin and similar compounds, as well as the short-term and persisting effects of such experiences.

16. Cognitive Performance and Relapse to Methamphetamine-Seeking in Rats

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Background: The role of various risk factors in relapse with methamphetamine dependence remains to be determined. Methampheta-

mine poses unique challenges, in that it's highly addictive nature is compounded by drug-induced cognitive deficits. Here we show the utility of an animal model for conditioned cue and drug induced relapse by using a reinstatement model of methamphetamine-seeking behavior in rats. In addition, cognitive performance was assessed in order to determine the deficits that arise from chronic methamphetamine exposure and the relationship of these changes in cognitive performance to methamphetamine-seeking behavior.
Methods: Male rats were trained to lever press during 1, 2, or 6 hr daily sessions for intravenous methamphetamine (0.06 mg/kg/infusion) paired with the presentation of a compound stimulus cue (light + tone). Responding was then allowed to extinguish in the absence of either methamphetamine or the drug-paired cue. Reinstatement of methamphetamine-seeking behavior (i.e. responding on the previously methamphetamine-paired lever) was then tested either in the presence of the compound stimulus or after a methamphetamine priming injection (1.0 mg/kg, IP). Before and after chronic methamphetamine self-administration, animals were assessed using a novel object recognition test, a behavioral task in rats that is analogous to cognitive assessments previously used in methamphetamine dependent human subjects.
Results: Animals showed robust methamphetamine self-administration over time, followed by a decrease in responding across extinction sessions, and significant increases in reinstated responding for methamphetamine-paired cues, or after a methamphetamine injection. Animals showed a pattern of more persistent lever pressing across extinction trials compared to responding seen after other drugs (e.g. cocaine). Furthermore, longer methamphetamine access regimens increased responding during reinstatement testing. Changes in novel object recognition and the relationship of cognitive performance to reinstatement behavior will be presented and discussed.
Discussion: Methamphetamine-trained animals showed high drug intake, resistance to extinction, and robust reinstatement of methamphetamine-seeking behavior. We will discuss the utility of this model for understanding the relationship of various risk factors, including cognitive deficits, with drug-taking and drug-seeking behavior. The use of this model for assessment of novel pharmacotherapies aimed at relapse prevention and cognitive dysfunction in methamphetamine dependence will also be discussed. These studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health. This research was supported by NIH grants RO1 DA10462 and P50 DA15369.

17. Affective Circuitry in Unaffected Adolescent/Young Adult Offspring from Multiplex Alcohol Dependence Families: Structural and Functional MRI Studies

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Background: Yearly longitudinal follow-up of offspring from multiplex families using imaging and ERP has pointed to developmental differences in cognitive functioning including P300 amplitude differences in these high-risk offspring. Previously we reported morphometric differences in amygdala volume in the right hemisphere in these high-risk offspring and slower pruning of cerebellar grey through adolescence. These morphometric differences appear to be minimally influenced by exogenous factors, as the majority of the offspring had not yet developed alcohol or drug dependence. These results suggested the importance of further study of components of cognitive and affective circuits that may place these offspring at higher risk for developing substance use disorders.
Methods: Anatomic brain MRI scans are being obtained at regular intervals as part of a longitudinal study. In a morphometric analysis of first time scans, orbitofrontal volumes were obtained in the right and left hemisphere for high and low risk participants. Data for a total of 107 children, adolescents and young adults (50 female and 57 male) were analyzed. A functional imaging study was completed for sixteen high and low risk adolescent/young adults (mean age 22 years). Groups were matched for age and gender and fMRI completed using an emotion recognition test (the Reading the Mind in the Eyes test of Baron-Cohen).
Results: For the structural imaging analysis, a right/left ratio for total OFC in each hemisphere was calculated (right-left/right +left) for each participant. OFC volumes were larger in the right hemisphere for both groups. Risk group comparisons were performed adjusting for ICV, age, BMI and hand preference. This analysis revealed significantly smaller Right/Left ratios in the high-risk group ($F = 8.95$, $p = 0.003$). For the functional imaging study, SPM5 fMRI analyses were performed. Contrast maps (Emotion >Fixation) were submitted to random effects analyses (HR, LR, and HR vs. LR; threshold, $p < .005$). Intra-group analyses indicated that whereas LR showed robust and bilateral activation of the OFC, such activation was absent in HR subjects. Inter-group analyses indicated reduced activation in the inferior frontal and orbital-frontal regions.
Discussion: The significantly reduced Right/Left OFC ratio in these HR offspring suggests involvement of the affective fronto-limbic system that includes the OFC, cingulum, and amygdala. Dysregulation of this circuit has been associated with pediatric bipolar disorder, impulsive disorders and cocaine dependence. Our preliminary findings indicating reduced activation of the OFC in HR offspring seen in our fMRI analyses are consistent with our structural findings, and are in accord with observations that D2 receptors and dopamine release are associated with reduced activation of the OFC (Volkow et al 2004). Functional polymorphisms in D2 receptor gene (C957T) appear to be associated with alcohol (Hill et al., unpublished) and heroin (Xu et al 2004) dependence. These findings suggest that offspring from multiplex families may be at genetic risk for alterations in affective circuitry that may increase their susceptibility for substance use disorders.

18. Effects of Naltrexone on Ethanol Self-Administration in Rhesus Macaques Exposed to Early-Life Stress

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Sponsor: Charles W. Bradberry

Background: Preclinical and clinical studies have shown that opiate receptors may play an important role in alcohol reinforcement, as demonstrated by the effectiveness of the opiate receptor antagonist naltrexone in reducing alcohol consumption. Rodent studies have revealed that maternal separation can induce long-lasting changes in brain levels of the endogenous opioids, and in nonhuman primates, early-life stress, modeled using a mother-absent, peer-rearing condition, produces increases in alcohol consumption during late adolescence and adulthood. However, whether naltrexone's efficacy in reducing ethanol consumption differs according to exposure to early-life stress is yet to be tested.
Methods: The present study aimed to assess naltrexone's efficacy in reducing oral ethanol self-administration in female rhesus macaques that were reared with their mothers (mother-reared: MR; n=6) or without adults in peer only groups (peer-reared: PR; n=6) during the first 6 months of life. At approximately 8 months of age, all monkeys were housed together as a single same-age cohort until adolescence (~4.5 years of age). Using a five-station computer-automated liquid dispensing apparatus, all monkeys, each equipped with a neck-collar identification chip, were trained in daily 1-hr sessions 4-5 days per week to self-administer an aspartame-sweetened vehicle solution.

This was followed by similar training on an 8.4% aspartame-sweetened ethanol solution, until all animals consumed in two or more sessions at least 0.7 g/kg/hr of ethanol, an amount sufficient to produce a pharmacological effect. Monkeys were then allowed to self-administer ethanol or vehicle in 23-h sessions on 3 consecutive days per week for up to 26 weeks to establish a history of volitional ethanol consumption. The effects of naltrexone on ethanol self-administration in MR and PR monkeys were then examined. All monkeys were first exposed to intramuscular injections of saline (0.1 ml/kg) 30 mins prior to the start of a 23-h self-administration session, during which access to both ethanol and vehicle was provided (Week 0: baseline, 3 consecutive days). In Weeks 1 and 2 of treatment testing, baseline procedures were repeated with the exception that half the subjects were randomly selected (with rearing conditions counterbalanced) to receive saline while the other half received naltrexone (1.0 mg/kg) in a within-subjects cross-over drug treatment design. Immediately following the final session of Weeks 0-2, blood sampling from the animals were performed to assess blood ethanol concentrations (BECs).
Results: Consistent with previous findings, PR monkeys consumed more ethanol over time and under saline-treated conditions, as compared with MR monkeys. When injected with naltrexone, PR, but not MR, monkeys, showed a reduction in ethanol consumption. Vehicle consumption was comparable between and within rearing groups across saline- and naltrexone-treated conditions. BEC levels correlated positively with ethanol intake levels, providing physiological evidence of actual ethanol consumption and further validating the reliability of the measures obtained using the alcohol dispensing apparatus employed in the present study.
Discussion: These early data may indicate that differences in alcohol consumption among monkeys exposed to early-life stress result from long-term changes in the endogenous opioid system and may further suggest that naltrexone may be particularly efficacious in the treatment of alcohol dependence among individuals with a history of adversity. All research was carried out in accordance with the NIAAA Institutional Animal Care and Use Committee and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

19. Quantitative Proteomic Profiling of Cocaine's Effects in the Primate Brain

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Sponsor: Bankole Johnson

Background: Previous studies from our lab have demonstrated significant dysregulation of ionotropic glutamate receptors in limbic brain regions of human cocaine overdose victims and rhesus monkeys following chronic cocaine self-administration histories (Hemby et al 2005; Tang et al 2003). To explore further the intricate neuroadaptive machinery involved in cocaine addiction, broad scale proteomics approaches were undertaken to assess coordinate changes of multiple proteins in the nucleus accumbens of both COD and monkeys self-administering cocaine.
Methods: Cytosolic-enriched proteins from the NAc were separated by two dimensional-differential gel electrophoresis (2D-DIGE), followed by quantitative DeCyder™ image analysis and identification of target proteins by MALDI-ToF/ToF mass spectrometry. Comparisons were made between cocaine overdose victims and controls and between rhesus monkeys self-administering cocaine and controls. In addition, the phospho-proteome of the NAc in rhesus monkeys following cocaine self-administration was also examined Pro-Q® Diamond gel stain and MALDI ToF/ToF analysis.
Results: Comparison of COD and controls revealed fifteen proteins to be differentially regulated including β tubulin, liprin α3, neuronal enolase, parvalbumin, ATP synthase β chain and periredoxin 2. Comparatively, ten significantly altered proteins were identified in the NAc of monkeys self-administering cocaine including syntaxin binding protein 3, β SNAP, isocitrate dehydrogenase α subunit, ATP synthase H+ transporting mitochondrial F1 complex β subunit, dihydropyrimidinase-like 2,14-3-3 Z/δ; brain creatine kinase and neural enolase.
Discussion: In summary, these studies sugest invovlement of proteins regulating cytoskeleton, membrane, protein folding/binding, transporter activity, metabolism, neuroprotection and anti-oxidant functions. The first expression and functional proteomic fingerprint of cocaine-induced alterations in the primate brain may yield new insights into the neuropathological consequences of long-term cocaine use and abuse. (Supported by National Institutes of Health grants DA013772, DA00517, DA016589, RR00165).

20. A Simple Invertebrate Model of Dopamine-Related Neurotoxicity: Possible Relevance to Parkinson's Disease

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Sponsor: Lewis R. Baxter, Jr.

Background: Platyhelminths ("flat worms", planaria) have the simplest nervous systems with bilateral symmetry and cephalic enlargement. All major neurotransmitter groups are present. Heads of free-living species possess optical, chemical and vibratory sensors, mediating tropisms/anti- to light, food, chemical, electrical and vibration gradients. Learning is documented. Pharmacological-behavioral similarities to vertebrates are established for many serotonin (5-HT), dopamine (DA), ACh, GABA, glutamate, and endorphin drugs. All cellular reproduction is via migratory toti-potential stem cells, allowing regeneration, including brain. Similar animals were ancestral to more complex cephalids: nematodes to annelids ... to complex invertebrates and prochordates. Most "higher" brain functions developed in planarians. *Dugesia* sp. planaria are used extensively in toxicology. Here development of bradykinesia and its drug-treatment, along with DA depletion and CNS degeneration are shown in a model of Parkinson's disease, exposure to rotenone (mitochondrial complex I inhibitor) in the aquatic *D. tigrina.*
Methods: Animals were exposed to vehicle/rotenone for dose-response vs. days. We established a measure of motivated locomotor speed: time to travel 5 cm. from bright to dim in a standard light gradient. Response to a noxious stimulus (pin prick) was also done. Loss of heads—and subsequent regeneration—as well as deaths were noted over time. Effects of anti-Parkinsonian drugs were examined. Levels of DA, 5-HT and norepinephrine (NE) were via HPLC.
Results: Rotenone (0, 10, 30, 100, 300, 1000 nM) gave a dramatic dose-response, with significant slowing over days at 100 and 300 nM; all died at 1000 nM. At 300 nM slowing was significant by day 1 and progressed to >300% of vehicle by day 2. However, all living animals, regardless of dose, responded briskly to pin prick. Head loss in 300 nM rotenone began day 2 (40%; day 3= 75%), but no deaths until day 4 (21%). Rotenone reduced DA levels to 6% of controls ($p<0.05$), NE to 30% ($p<0.05$), 5-HT to 80% (ns). Removed from rotenone, animals recovered pre-drug speed by day 2. By days 4-5, rotenone headless animals had light response restored (eye's present), similar to non-exposed head-amputated animals. Rotenone-slowed animals had increases in speed to acute L-DOPA (μM) (mean 61 sec/5 cm $\pm$ 26 SD before drug, to 40$\pm$17 after) vs. non-treated animals (51$\pm$16 to 52$\pm$12), $p<0.05$. Non-rotenone-exposed animals had no L-DOPA speed change (24$\pm$2 prior, 25$\pm$5 after). Bromocriptine (50 nM) improved speed in rotenone treated animals (20$\pm$7%), vs. no drug (0$\pm$8%), $P<0.05$. Planaria co-treated with 100 nM deprenyl (anti-MAO-B) in 300 nM rotenone had less slowing than without (34$\pm$4 s. vs. 49$\pm$15 s.), $p<0.05$. Spiperone (DA blocker, 0, 1, 10, 100, 1000 nM)

gave bradykinesia at 100nM; 1000 nM gave marked dystonia. Antimuscrinic benztropine (1 nM) reversed dystonia, but not bradykinesia.
Discussion: At present this model seems to have good face, construct and predictive validity as a simple model of the bradykinesia characteristic of Parkinson's disease. We are developing other "neurological" tests for planaria by which to examine other symptoms. Although rotenone has been used to date because of it's relative safety for human experimenters, we will also employ 6-OH-dopamine and MPTP as well in similar work. Besides use as a possible screen for anti-Parkinsonian drugs, this model may well provide a good platform to study the basic effects of DA-system related neurotoxicity. We are presently using it for amphetamine toxicity as well. The planarian has the simplest nervous system of all, allowing cell-by-cell examination, as well as regenerative stem cells to target in work examining regeneration.

21. Skin Conductance Responses to Electric Shock Extinction During Cannabis Discontinuation: A Conditioning Study

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Sponsor: Past Travel Awardee, ADAA, 2005

Background: Anxiety sensitivity (or fear of anxiety) has been found to be associated with ongoing cannabis use. Thus, the anxiolytic effects of cannabis may be part of a reward system that potentiates ongoing use. One method of exploring whether anxiety sensitivity is affected off of cannabis is to document autonomic reactivity during a fear-conditioning paradigm. We utilized a fear-conditioning paradigm to measure changes in skin conductance in cannabis dependent users 72 hours after cannabis discontinuation compared to controls. Hypotheses: Relative to controls (NC), and 72 hours after cannabis discontinuation: (1) cannabis dependent smokers (CAN) would demonstrate an increase in skin conductance response (SCR) during the conditioning phase, and (2) CAN would demonstrate a longer time to extinguish this response after conditioning.
Methods: Fourteen NC subjects and eight CAN smokers who met criteria for cannabis dependence were included in this study. After IRB approval, all subjects participated in a fear-conditioning experiment using a cutaneous electrical shock as the unconditioned stimulus. SCR was measured during three phases: an initial habituation phase during which subjects viewed blue (future CS+) and white (future CS-) circles on a computer screen; an acquisition phase during which blue circles only were paired with an aversive electrical stimulus, and an extinction phase during which neither blue nor white circles were accompanied by an aversive stimulus. All reported SCR measurements are the maximum SCR values during exposure to the blue circles from which the mean SCR of the preceding 5 seconds was subtracted in order to account for the effects of anxiety during anticipation of the stimulus. The main effect of group was investigated using a repeated-measures ANOVA to examine SCR changes during the CS+ exposure.
Results: Relative to controls: (1) CAN smokers demonstrated increased SCR during the habituation and acquisition phases, but these changes did not reach statistical significance; (2) During the extinction phase CAN smokers demonstrated significant differences in SCR during CS+ exposure ($F = 10.3$, $p = .015$, repeated measures ANOVA). CAN smokers produced significantly higher SCR on the first six trials prior to normalizing during the last four trials. The HAM-A score was higher for the CAN group (3 ± 0.86) compared to NC (1.4 ± 0.56), and this was the only observed clinical difference between groups ($F = 2.35$, $p = 0.1$, ANOVA).
Discussion: Cannabis discontinuation in cannabis-dependent individuals appears to be associated with the failure to extinguish conditioned fear responses compared to non-psychiatrically ill control subjects. Furthermore, this alteration in ability to extinguish conditioned responses to fear is associated with a higher anxiety level. This suggests that cannabis discontinuation is associated with an anxious disposition and the recurrent threat of conditioned fear. It is possible that the need for more cannabis occurs in the context of the need to diminish subtle autonomic responses such as increased skin conductance associated with cannabis discontinuation.

22. Repeated Amphetamine Exposure Alters the Electrophysiological Properties and Fear-Related Behaviors Mediated by the Basolateral Amygdala-Prefrontal Cortical Pathway

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Background: The basolateral amygdala (BLA) and the prefrontal cortex (PFC) form a neural circuit that regulates certain emotional and cognitive functions. Recent research indicates that chronic abuse of stimulants like amphetamine (AMPH) is associated with impairments in emotional and decision-making processes mediated by BLA-PFC circuits. The present study was conducted to explore changes in emotional processes mediated by BLA-PFC circuitry and to investigate the neuroadaptive cellular mechanisms that may mediate associated changes in behavior. Specifically, we assessed the effects of repeated administration of AMPH on 1) the expression and extinction of a conditioned fear response and 2) inhibitory and excitatory responses of PFC neurons evoked by BLA stimulation.
Methods: Long Evans rats were trained to lever press for food on a variable interval 60 s schedule, after which they received injections of saline or d-AMPH (1mg/kg) every 48 hrs for 10 days. Following ~2 week washout period, rats received a fear conditioning session, consisting of 5 or 10 tone-footshock pairings while lever pressing for food. On the following day, half of the animals in each group received acute injections of d-AMPH (1mg/kg); the other half received saline. They then received their first extinction session (20 tones, no footshock). The next day, rats received a second, drug-free extinction session identical to the first. Both conditioned freezing and lever pressing were recorded. Two to four weeks after behavioral testing, rats were anaesthetized with urethane. Single-pulse electrical stimulation (800 uA) was delivered to the BLA, while making 4-6 vertical passes of an extracellular single-unit recording electrode through the dorsal/ventral extent of the PFC, recording activity from neurons that responded in some manner to BLA stimulation.
Results: Behavior: Predictably, acute AMPH reduced freezing and lever pressing during the first extinction session. Sensitized rats not receiving acute AMPH took slightly longer to extinguish the freezing response compared to controls. Furthermore, in control rats, acute AMPH prior to the first extinction session impaired consolidation of extinction learning, as these animals displayed more freezing and reduced lever pressing during the second extinction session; an effect that was not observed in sensitized rats receiving acute AMPH the day before. Electrophysiology: BLA stimulation evoked two distinct classes of responses in separate populations of PFC neurons; i) a monosynaptic excitatory response and ii) inhibition of spontaneous firing. In control rats, ~75% of BLA-responsive PFC neurons were inhibited by BLA stimulation and ~25% displayed an excitatory response. In contrast, rats that received repeated AMPH showed the opposite profile; 66% of responsive neurons were excited by BLA stimulation, and the remaining 33% were inhibited. In sensitized rats, BLA-responsive neurons also displayed higher firing rate (~5 Hz) compared to control animals (~2.5 Hz). In addition, acute injections of AMPH (1 mg/kg) increased the average spontaneous firing rate of BLA-responsive neurons in control rats; an effect that was not observed in sensitized rats.

Discussion: Collectively, these data indicate that repeated AMPH exposure 1) may influence extinction learning, 2) increases the excitability of the BLA-PFC pathway, with the BLA exerting a greater excitatory influence over populations of PFC neurons and 3) attenuates the actions of acute AMPH on PFC neural firing, which may be indicative of a disruption in dopaminergic transmission. Furthermore they suggest that the changes in the electrophysiological properties of this circuit may be an underlying cause for alterations in emotional processes induced by repeated AMPH exposure.

23. Dopaminergic Modulation of Effort and Risk-Based Decision Making

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Background: There has been a growing interest in the neurobiological basis underlying different types of decision making. For example, the preference to choose a larger reward that comes with a greater effort is mediated by a distributed neural network which includes the basolateral amygdala, the anterior cingulate, and the mesolimbic dopamine system. Similarly, lesions of the ventral striatum (a main target of dopaminergic enervation) alter risk-based decision making, where rats choose between certain, smaller rewards and larger rewards that are delivered in a probabilistic manner. However, the specific role that the dopamine system plays in mediating these types of decision making has yet to be explored fully. The present study assessed the effects of systemic administration of the dopaminergic antagonist flupenthixol and the indirect agonist d-amphetamine, using effort and risk-discounting decision making procedures conducted in an operant chamber.
Methods: For the effort-discounting task, over 4 discrete blocks of 10 trials, rats were trained to either press one lever that always delivered a low reward (LR: 2 pellets) after a single press or another lever to obtain a high reward (HR: 4 pellets) after an ascending fixed ratio (FR) of presses (2, 5, 10, or 20). In a subsequent experiment, rats were trained on a modified effort-discounting procedure, where the delay to reinforcement on each lever was equalized (0.5-7s). Rats were then trained on a risk discounting procedure. Over 4 discrete blocks of 10 trials, rats were given the choice between emitting a single response on the LR lever that delivered 1 pellet with 100% probability, or a single response on the HR lever that delivered 4 pellets with a decreasing probability (100%, 50%, 25% or 12.5%).
Results: Effort-Based Decision Making: Administration of the dopamine antagonist flupenthixol (0.125, 0.25 or 0.5 mg/kg, i.p.) dose dependently reduced the preference for the HR lever during both the effort discounting task and effort discounting with equivalent delays. These effects were more pronounced when rats had to expend more effort (FR 10-20) to receive the HR. In contrast, amphetamine produced a dose-dependent, biphasic effect on choice behavior. A higher dose (0.5 mg/kg) decreased the preference for the HR lever during effort based decision making, whereas lower doses (0.125 or 0.25 mg/kg) actually increased the preference to exert more effort to obtain a larger reward. Risk-Based Decision Making: Dopamine receptor blockade with flupenthixol (0.25 mg/kg) made rats more risk-averse, reducing the preference for the high risk lever. Interestingly, amphetamine promoted risky choice in rats, increasing the preference for the high risk/HR lever at two doses tested (0.25 or 0.5 mg/kg). These effects were most pronounced during the highest risk blocks (25% and 12.5% probability of receiving 4 pellets), even though more reward would be obtained if they chose the LR lever that delivered a smaller but certain reward.
Discussion: These data indicate that dopamine receptor blockade alters both effort and risk-based decision making, reducing the preference to choose more effortful or risky response options that lead to larger rewards. However, increases in dopamine transmission induced by amphetamine can exert differential effects on decision making, in a task and dose-dependent manner. Lower doses of amphetamine biases an animal's choice behavior towards response options yielding larger rewards that come with either a greater effort or higher risk. In contrast, at higher doses, amphetamine can induce opposing effects on effort versus risk based-decision making, inducing a "lazy" but "risky" pattern of choice. Future studies are needed to clarify the specific dopamine receptor subtypes that mediate these effects.

24. Spontaneous Nicotine Withdrawal Produces Anxiogenic-Like Effects Reflected in Increased Light Potentiated Startle in Rats

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Sponsor: Past Travel Awardee, ADAA, 2005

Background: In humans, feelings of anxiety and irritability are consistently described after cessation of tobacco smoking. These effects are attributable to withdrawal from nicotine administration, as nicotine is one of the main psychoactive ingredients in tobacco smoke. Currently there are few animal models of this important aspect of nicotine withdrawal. Establishing animal models of these aspects of the nicotine withdrawal syndrome will aid in (1) investigations of the neurobiology of the anxiety-like and irritability-like responses associated with cessation of nicotine administration and (2) drug discovery efforts for development of novel compounds to facilitate smoking cessation and maintain abstinence from tobacco smoking. Here we tested the hypothesis that nicotine withdrawal exacerbates stress responding as measured by light-potentiated startle (LPS) in rats. LPS is a model of unconditioned anxiety, capitalizing on the innate fear of rodents for bright lights. Rodents exhibit significantly higher acoustic startle responses in the presence of bright light as compared to startle responding during darkness. In rats, LPS is reduced by anxiolytics such as buspirone and benzodiazepines, as well as antagonists for corticotropin releasing factor receptors. We predicted that during nicotine withdrawal, rats would exhibit increased sensitivity to LPS effects, supporting the hypothesis that nicotine withdrawal increases stress or anxiety-like responses.
Methods: Forty-two rats were prepared with osmotic pumps containing saline or 9 mg/kg/day nicotine tartrate (3.16 mg/kg/day nicotine base). To evaluate effects of precipitated nicotine withdrawal on LPS, rats were then split into two separate groups. Each group was treated with a different nicotinic acetylcholine receptor antagonist using a within-subjects Latin square design. One group received mecamylamine (0, 1, 2, 4 mg/kg) and the other received DHβE (0, 1.5, 3, 6 mg/kg). Twenty-eight days after exposure to nicotine/saline through the pumps, the pumps were removed. To determine effects of spontaneous nicotine withdrawal on LPS, all subjects were retested 24 hours after pump removal.
Results: No significant effects of mecamylamine or DHβE treatment were observed on LPS in nicotine or saline pump treated rats. Conversely, 24 hours after cessation of nicotine administration, nicotine treated rats exhibited significantly greater LPS compared to saline treated controls. Nicotine treatment had no effect on baseline startle during or after administration.
Discussion: These results indicate that spontaneous nicotine withdrawal selectively increased stress responding as measured by LPS in rats. Further studies are required to evaluate the mechanisms mediating the anxiety-like aspects of withdrawal reflected in augmented LPS. It is also unknown if nicotine withdrawal exacerbates similar stress-induced increases in startle reactivity in man. This rodent model of exaggerated anxiety-like responses during nicotine withdrawal may support translational studies of the effects of nicotine and tobacco cessation on anxiety.

25. CRH Signaling and the Dark Side of Addiction: Long-Lasting Hyper-Reactivity to Stress in Animals with a History of Ethanol Dependence

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Background: It is increasingly recognized that anti-reward systems (i.e. negative reinforcement through stress and fear systems) are progressively recruited during the development of alcoholism, and may constitute a key component in maintaining the dependent phenotype. Extra-hypothalamic CRH (corticotrophin releasing hormone) signaling is thought to be of crucial importance in this process. However, understanding the impact of the CRH mediated neurotransmission in ethanol dependence and its potential value as a candidate target for treatment of ethanol use disorders requires modeling the neuroadaptations which occur with prolonged exposure of the brain to ethanol. To this end we have recently developed an animal model, which based on repeated cycles of intoxication and withdrawal, mimics the natural history of alcoholism and triggers long lasting plasticity.
Methods: Male Wistar rats were exposed to either 4 or 7 weeks of daily cycles of ethanol vapor intoxication and withdrawal followed by 3 weeks of abstinence. Animals were then assigned to 3 separate experiments to investigate: 1) voluntary home cage ethanol consumption in a 2-bottle, free choice drinking paradigm; 2) fear-induced suppression of behavior in a punished drinking paradigm with or without pretreatment with a CRH receptor 1 antagonist; and 3) sacrificed for the study CRH and its receptors in the medial prefrontal cortex and the extended amygdala by in situ hybridization and receptor autoradiography.
Results: Only 7-weeks exposed animals show signs of withdrawal at the end of the exposure cycle and consume significantly more ethanol after the 3 weeks resting period ($p < 0.05$, 7-weeks exposed vs. control). Associated with the drinking phenotype was an increased fear response in the conflict test ($p < 0.01$), increased expression of CRH in the central amygdala ($p < 0.05$) and its receptor CRH-R1 in central ($p < 0.05$), medial ($p < 0.01$) as well as basolateral amygdala ($p < 0.001$) in 7-weeks exposed animals compared to non-exposed controls. There was a trend to significant increased fear- suppression also in animals with a history of only 4 weeks cyclic intoxication and withdrawal, but no alterations in CRH signaling. Furthermore, heightened fear response was still visible fourteen weeks after the induction of the high-drinking phenotype and was completely abolished by a specific, highly brain-penetrant CRH-R1 antagonist.
Discussion: Enhanced fear suppression seems to be an early onset and long-lasting phenotype in the development of ethanol dependence and is accompanied by long-term upregulation of CRH circuits in the amygdala. Together, these data support the hypothesis of an early recruitment of anti-reward systems in the descent into alcoholism and emphasize the potential of the CRH-R1 receptor as a treatment target for this disorder.

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

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Background: Gamma-hydroxybutyrate (GHB) is a putative neuromodulator involved in the regulation of sleep and used to treat narcolepsy. GHB is also used recreationally as a "club drug", and is often used together with alcohol. According to the popular press, this combination has synergistic effects. However, using rats trained to respond for food, we found that alcohol did not potentiate the response rate decreasing effects of GHB (Lamb et al., EJP 470:157, 2003). GHB is used also with other "club drugs", such as MDMA (Ecstasy), and the N-methyl-d-aspartate (NMDA) antagonists ketamine and phencyclidine (PCP). We found that the NMDA antagonist dizocilpine markedly enhances GHB-induced catalepsy in rats (Sevak et al., EJP 483:289, 2004; EJP 517:64, 2005). Conceivably, other NMDA antagonists also interact synergistically with GHB. Some of these NMDA antagonists (i.e., PCP, ketamine) are "club drugs", like GHB. Thus, our finding suggests the possibility of a synergistic interaction with PCP and ketamine in the recreational use of GHB and its precursors. The present studies are part of an effort to investigate the generality of our initial finding that the NMDA antagonist dizocilpine enhanced the cataleptic effects of GHB in rats. The studies examined whether this enhancement 1) can be produced by other NMDA antagonists, 2) can observed in species other than rats, 3) can occur with behavioral effects of GHB other than catalepsy, and 4) is specific to GHB, or can occur also with baclofen, which shares many effects with GHB and its precursors.
Methods: Catalepsy studies used a standard bar test in rats and mice. Studies on discriminative stimulus effects used a standard two-choice food-reinforced drug discrimination procedures in pigeons (trained to discriminate 178 mg/kg GHB from saline) and in rats (trained to discriminate 2 mg/kg PCP from saline, or trained to discriminate 3.2 mg/kg baclofen from saline).
Results: In rats, 1.78 mg/kg PCP and 17.8 mg/kg ketamine, which did not produce catalepsy when given alone, enhanced GHB-induced catalepsy. In mice, dizocilpine, PCP, and ketamine enhanced the cataleptic effects of GHB at maximally effective doses (i.e., 0.178, 5.6 and 17.8 mg/kg, respectively) that correlated strongly ($r=0.94$) with their affinities for PCP binding sites at the NMDA receptor complex. In pigeons trained to discriminate GHB from saline, 10 mg/kg ketamine shifted the dose-response curve for GHB's discriminative stimulus effects 4 to 5-fold to the left. In rats trained to discriminate PCP from saline, 178 mg/kg GHB, which did not produce PCP-appropriate responding when given alone, shifted the dose-response curve for PCP's discriminative stimulus effects 2 to 3-fold to the left. In contrast, 3.2 mg/kg baclofen did not shift PCP's dose-response curve. In rats trained to discriminate baclofen from saline, 2 mg/kg PCP shifted the dose-response curve for GHB's baclofen-like discriminative stimulus effects 2-fold to the left, but did not shift baclofen's dose-response curve.
Discussion: The observation that dizocilpine enhanced GHB-induced catalepsy in rats appears to have considerable generality: this enhancement is observed with other NMDA antagonists, in other species, and occurs also with discriminative stimulus effects. The drug discrimination results suggest that PCP and ketamine may potentiate the subjective effects of GHB, and vise versa. Our results are further evidence of interactions of the glutamatergic system with the neuropharmacological systems involved in the behavioral effects of GHB, and of the important role of glutamatergic systems in modulating/mediating effects of drugs of abuse. Supported by USPHS Grants DA14986, DA15692, and DA17918 (Senior Scientist Award to CPF)

27. Polymorphisms of the Apolipoprotein E Gene Which Alter Risk for Alzheimer's Disease Also Affect Cortical Morphology in Children and Adolescents

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Sponsor: Travel Awardee, Young Investigator Memorial, 2006

Background: Alzheimer's disease (AD) is characterized by a sweeping wave of cortical degeneration which starts in the entorhinal regions of the medial temporal lobes. Alleles of the apolipoprotein E (APOE) gene modulate risk for AD, with the ε4 allele increasing, and the ε2 allele possibly decreasing risk. We hy-

pothesized that possession of a ε4 allele would confer children with a neural substrate which renders them at risk for AD. By contrast, carriers of the ε2 allele might have a 'protective' cortical morphology. We predicted these structural differences would localize to regions where the earliest, presymptomatic changes of AD occur- specifically the entorhinal cortex and parahippocampal gyrus.
Methods: 239 healthy children and adolescents were genotyped and had repeated neuroanatomic magnetic resonance imaging (total 529 scans). Mixed model regression was used to determine if the developmental trajectory of the cortex differed by genotype.
Results: There was a significant stepwise increase in cortical thickness in the entorhinal cortex (right β=0.087mm, standard error (SE)=0.04, p=0.02; left entorhinal β=0.097, SE=0.04, p=0.03) and right parahippocamapal cortex (β=0.074, SE0.03, p=0.02). ε4 carriers had the thinnest, and ε2 carriers the thickest cortex, with ε3 homozygotes occupying an intermediate position. No such genotype effect was seen in the remaining cortex. The neuroanatomic effects were fixed and non-progressive with no evidence of accelerated cortical loss in healthy young ε4 carriers.
Discussion: Alleles of the apolipoprotein E gene have distinct neuroanatomic signatures, detectable in childhood. The thinner entorhinal cortex in those with the ε4 allele may contribute to risk for AD.

28. Heritability of Cortical Thickness During Childhood and Adolescence

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Background: Quantification of the relative contributions of genetic and environmental factors to the development of cortical structure may be a valuable method for exploration of the genesis of neuropsychiatric disorders. Twin studies are a method of measuring these factors in human populations. Here we used magnetic resonance images from a large sample of pediatric twins to assess heritability of cortical thickness during childhood and adolescence.
Methods: An extended twin design was used to estimate genetic (A), common environmental (C), and unique environmental (E) components to variance of cortical thickness. Study sample: 214 monozygotic twins, 94 dizygotic twins, 164 non-twin siblings of twins, 112 singletons; mean age = 11.08 (SD 3.43); 332 males, 268 females. All subjects underwent extensive screening to rule out medical or psychiatric morbidity(1). A T1 weighted magnetic resonance image was obtained from each subject using the same scanner and protocol (3DSPGR; 1.5mm axial slices; TE/TR/FA = 5/24/45; 1 NEX; 256x192 matrix; 24cm FOV). Cortical thickness was measured at 40,973 vertices using an automated method described elsewhere(2). Structural equation modelling was used to estimate variance components(3). Age effects were modeled using an AE model as C did not have significant effects in the first analysis. Variance components were expressed as coefficients of variation to avoid scaling effects related to changes of cortical thickness with age.
Results: Cortical thickness showed significant heritability in several regions, including frontal pole, dorsolateral and orbital prefrontal cortices, primary sensory cortex, angular and superior temporal gyri, and the superior parietal cortex. Unique environmental factors were the primary determinants of variance in the remaining regions. Shared environmental factors did not reach significance. Dorsal prefrontal cortex was heritable on the right but not left, whereas language associated regions were heritable on the left but not right. Variance components had significant interactions with age. Total variance of cortical thickness averaged across the cortex decreased as age increased, driven primarily by falling contributions from the environmental component. Environmental components of variance decreased in prefrontal and orbitofrontal, temporal, and superior parietal regions, and increased in primary and motor regions. The genetic component increased in left superior frontal and temporal regions.
Discussion: Cortical regions associated with language, executive function, and social cognition showed a higher impact of genetic factors on variance of cortical thickness than did primary motor and sensory regions. Decreasing environmental contributions with maturation in association regions may indicate these areas have less plasticity towards environmental influences during adulthood. These findings demonstrate that genetic and environmental factors affect variance of cortical thickness in a regionally specific fashion which changes over the course of childhood and adolescence. Refs: (1)Giedd et al Cerebral Cortex (1996); (2)Lerch et al Neuroimage(2005); (3)Neale & Cardon, Methodology for genetic studies of twins and families. Kluwer Academic (1992)

29. The Class III Allele of the Insulin Gene VNTR Promotes a Seasonal Thrifty Phenotype in Women with Seasonal Affective Disorder (SAD)

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Sponsor: Shitij Kapur

Background: We have recently shown that a spring birth interacts with the hypofunctional 7-repeat allele of the dopamine-4 receptor gene (DRD4) to promote obesity in women with SAD. This novel gene-environment interaction may reflect a "seasonal thrifty phenotype" that is programmed epigenetically during later gestation. The signal for this process might be a particular pattern of melatonin secretion passing from mother to fetus in the winter months before a spring birth. The ultimate function of such a phenotype would be the anticipation of seasonal famines for organisms likely to live their life at a northern latitude. Such a process would have been highly adaptive over the course of evolution, and might explain the positive selection the 7R allele over the last 40,000 years. Based on the fundamental role of insulin in early growth and development, and in long term energy regulation, we speculated that a functional VNTR polymorphism of the Insulin gene might also contribute to this seasonal thrifty phenotype. We explored this hypothesis by examining a functional VNTR polymorphism of the insulin gene in our model.
Methods: In 182 female probands with SAD we tested a General Linear Model predicting maximum lifetime body mass index (BMI) with 1. the exon-3 VNTR polymorphism of the dopamine-4 receptor gene (DRD4) 2.season of birth and 3. a functional VNTR of the insulin gene (any class III vs. class I-homozygotes).
Results: There was a significant three way (DRD4 x Insulin gene x birth season) interaction predicting maximal lifetime BMI in these SAD probands(F=3.63, df=3, 163, p=.014). Further analysis revealed that our prior finding of a 7R allele/spring birth interaction predicting maximal BMI was highly significant in the subgroup of 82 probands with at least one class III allele (F=6.01, p=.001). However, the same 7R/spring birth interaction failed to meet significance in the larger group of 95 class I homozygotes (F=1.52,p=.22).
Discussion: Sometime around birth, a functional insulin gene VNTR polymorphism appears to interact with both the DRD4 7R allele and an unknown seasonal factor to promote adult weight gain in the context of SAD.These results further support the existence of a "seasonal thrifty phenotype" in women with SAD. Of great interest is the fact that class III alleles of the insulin gene have previously been associated with both fetal growth and with weight gain and obesity in young girls. These various findings are highly consistent with a fetal programming hypothesis of seasonal weight gain in women with SAD.

30. Genetic and Neurodevelopmental Underpinnings of Individual Differences in Emotional Reactivity

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Sponsor: Travel Awardee, Young Investigator Memorial, 2006

Background: Inborn differences in emotional reactivity strongly influence how individuals respond to stress, and may predispose certain individuals to develop psychiatric disorders, such as depression, anxiety, or drug addiction. We have selectively bred rats exhibiting extreme differences in "novelty-seeking" behavior, a dimension of emotional reactivity. High Responder (HR) rats vigorously explore a novel environment, while Low Responder (LR) rats are inhibited, showing much less activity. HR rats are thought to model some aspects of human impulsivity and risk-taking behavior, and exhibit several other interesting behavioral differences compared to the LR animals, including reduced baseline anxiety, exaggerated hormonal stress response, a predisposition to self-administer psychostimulants, and increased incidence of aggressive behavior. While HR/LR differences are well-established in adult animals, there is practically no information regarding genetic and neurodevelopmental factors that give rise to these distinct phenotypes. Thus, we initiated a series of studies to explore the genetic basis of the HR/LR traits, and also track the developmental time-course for when these phenotypes begin to emerge.
Methods: To evaluate genetic factors which contribute to the HR-LR traits, we cross-mated male and female rats from the HR and LR lines (HR female/LR male OR LR female/HR male), and compared their offspring with "pure-bred" HR and LR offspring. A separate study examined the developmental emergence of the HR/LR phenotypes. Weanling (25-day-old) HR and LR pups were tested to assess novelty-induced locomotor activity and anxiety behavior. Brain tissue was dissected from a parallel set of animals sacrificed at multiple developmental timepoints (postnatal days 7, 14, and 21). Tissue from the hippocampus and nucleus accumbens was analyzed via Affymetrix Microarrays to examine HR/LR gene expression differences over the early developmental period.
Results: Interbreeding produced an intermediate phenotype, where cross-bred offspring were less active than HR controls, and more active than LR controls. Interestingly, the two cross-bred families behaved differently from one another. Male offspring from an HR mother/LR father were significantly more active than offspring of an LR mother/HR father. Since we previously found that HR and LR mothers behave differently towards their pups, we are currently using a cross-fostering paradigm to determine whether these differences are related to maternal care, or due to genetic contribution. Our behavior studies in developing animals showed that weanling HR pups, like HR adults, are more active in a novel environment, show less anxiety-like behavior, and exaggerated neuroendocrine stress response compared to LRs. Results from the microarray experiments revealed substantial HR-LR gene expression differences in the hippocampus, particularly at postnatal days 7 and 14. The most profound HR-LR differences involved genes critical for synaptogenesis and plasticity.
Discussion: Phenotypic HR/LR differences are already established in early life, and appear to be strongly influenced by genetic factors. Microarray findings point to dramatic HR/LR gene expression differences occurring in the hippocampus during the first 2 weeks of life, suggesting that the formation of hippocampal circuits may powerfully influence innate differences in novelty-seeking and emotionality. Ongoing studies will evaluate hippocampal structure, morphology, and function in developing HR and LR animals. Supported by Office of Naval Research N00014-02-1-0879, NIH Grant No. 5 P01 MH42251, Conte Center Grant #L99MH60398, RO1 DA13386, to HA and SJW.

31. Association of the Oxytocin Receptor Gene (OXTR) in Caucasian Children and Adolescents with Autism

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Sponsor: Past Travel Awardee, NIMH, 2005

Background: The oxytocin receptor gene (OXTR) has been studied in autism because of the role of oxytocin (OT) in social cognition. Linkage has been demonstrated to the region of OXTR in a large sample of families with autism. Single nucleotide polymorphisms (SNPs) in the OXTR have been associated with autism in the Chinese Han population. We hypothesized that the same SNPs would be associated with autism in a Caucasian sample.
Methods: Probands met clinical, ADI-R, and ADOS criteria for autism. We genotyped the two previously associated SNPs (rs2254298, rs53576) in 57 Caucasian autism trios. Next, we explored this gene region for allelic diversity using a tagSNP approach in HapMap (minor allele frequencies > 5%). TagSNPs representing clusters of SNPs in substantial LD ($r2 > 0.8$) were selected using Tagger (HaploView) to test for association.
Results: Significant family-based association was detected at rs2254298 ($p = 0.03$). The G allele was overtransmitted to autistic probands. In the previous report on the Chinese Han, the A allele was overtransmitted. In both samples, G was more frequent than A. However, in our Caucasian autism trios and the CEU Caucasian HapMap samples the frequency of A was less than that reported in the Chinese Han and Chinese in Beijing HapMap samples. The haplotype test of association did not reveal excess transmission of rs2254298/rs53576 haplotypes from parents to affected offspring. Four tagSNPs selected from other LD blocks spanning the gene were not significantly associated with autism.
Discussion: These preliminary findings provide support for association of OXTR with autism. Association with different alleles in different populations may be due to false positives or phenotypic heterogeneity. Alternatively, overtransmission of different alleles may be due to a different pattern of linkage disequilibrium between the marker rs2254298 and an as yet undetermined susceptibility variant in or near OXTR. We are currently testing whether this finding replicates in a larger, independent Caucasian sample. A more comprehensive tagSNP and resequencing approach is being pursued to further localize putative autism susceptibility variant(s) in OXTR.

32. Visual Information Processing of Faces in Body Dysmorphic Disorder

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Sponsor: Katharine Phillips

Background: Body dysmorphic disorder (BDD) is a severe psychiatric condition affecting 1-2% of the population in which individuals are preoccupied with perceived defects in their appearance. Clinical observation and neuropsychological testing suggest that BDD patients focus primarily on details, usually of their own appearance, at the expense of global or configurational aspects. No functional imaging studies have tested the patterns of visual information processing in BDD patients nor compared BDD to controls in any manner. The objective of this study was to determine whether BDD patients have a different pattern of brain activation from healthy controls with respect to level of detail when visually processing others' faces.
Methods: The participants were twelve medication-free males and females with BDD and twelve control subjects who were matched by age, gender, handedness, and level of education. Subjects were

scanned using functional magnetic resonance imaging (fMRI) while performing matching tasks of face stimuli. Stimuli were neutral-expression photographs of others' faces that were a) unaltered, b) altered to include only high spatial frequency (high detail), or c) altered to include only low spatial frequency (low detail). The main outcome measure was blood oxygen level-dependent fMRI signal changes in the BDD vs. control group during tasks with each type of stimuli.
Results: BDD subjects showed greater ventral and left visual cortex activity for unaltered face and low detail face tasks, while controls showed greater dorsal and bilateral visual cortex activity. Controls also showed greater right dorsal visual cortex activity for high detail face tasks. BDD subjects activated the left amygdala to a greater degree than control subjects, yet only for the high detail face tasks.
Discussion: BDD subjects demonstrated fundamental differences from controls in visual processing; they engage regions specialized for greater detail relative to configurational processing and may activate an automatic emotional response to high-detail faces. These abnormalities in visual processing of others' faces may be associated with apparent visual perceptual distortions experienced by BDD patients. The fact that these findings occured for visual processing of others' faces suggests fundamental differences in visual processing, beyond any perceptual distortions they may have for their own appearance.

33. Longitudinal Mapping of Lobar Cerebral Cortical Asymmetry in Children and Adolescents with and Without Attention Deficit Hyperactivity Disorder

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Sponsor: Judith Rapoport

Background: The typically developing human brain is characterized by structural and functional hemispheric asymmetries, some of which are thought to play an important etiological role in several neurodevelopmental disorders, such as attention-deficit hyperactivity disorder (ADHD). We aimed to examine the developmental trajectory of cerebral cortical asymmetries in children with ADHD and typically developing children. We hypothesized that ADHD would be characterized by anomalous asymmetries of the frontal and parietal grey matter, which have been consistently implicated in attentional processing.
Methods: 139 children and adolescents (81 males and 58 females) with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)–defined ADHD and 156 unrelated healthy controls (92 males and 64 females) who had no personal or family history of psychiatric or neurological disorders took part in this study. All subjects had at least one neuroanatomic magnetic resonance image (mean age 10y ± 2.9y), 62% had two, 31% had three and 6% had 4 scans, with a mean interscan interval of 2.7y ± 1.54y. Quantification of MRI images was performed via a 3-part fully automated image analysis process that determines the volumes of gray and white matter compartments in frontal, temporal, parietal, and occipital lobes with excellent test-retest reliability. Asymmetry indices were calculated for each region using the formula (2 x (left - right) / (left + right)) x 100 where left and right are the volumes of the (l)eft and (r)ight regions of interest. Longitudinal analytic methods were used to examine growth patterns of the white and gray components of the 4 major lobes.
Results: At baseline scan, there was no difference between the ADHD and healthy controls in the asymmetry index for any lobar compartment (all $p>0.05$). However in the longitudinal analyses a significant difference in the trajectory of the asymmetry index emerged for the parietal grey matter ($F=5.4$, $p=0.005$). Throughout the entire age range the ADHD group showed less asymmetry for the parietal grey matter. This effect became more marked with age and by late adolescence the asymmetry showed by the healthy control group was largely absent in the ADHD group. In the longitudinal analyses, there was a sex by diagnosis interaction in the trajectory of asymmetry index for parietal grey matter ($t=4.0$, $p<0.0001$). While healthy males showed little change in asymmetry with age, the males with ADHD showed a distinctive trajectory characterized by a decrease in asymmetry with age. Indeed by late adolescence ADHD males reversed the normal pattern of asymmetry completely, and had greater right than left parietal grey matter volumes. In contrast, ADHD females showed little developmental change in asymmetry, while their healthy female counterparts showed some decrease in asymmetry with age. There was no other diagnosis by sex interaction in the determination of the trajectories of the remaining lobes, nor main effects of diagnosis or sex.
Discussion: These findings suggest that underlying structural asymmetries which emerge during development are differentially sensitive to the effects of age and sex, and may provide clues to the underlying pathophysiology of ADHD.

34. DTI Measures in the Insular Region: Relationship to Autonomic Indices, Laterality and Apoe E4 in Healthy Elderly

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Sponsor: Steven H. Ferris

Background: The insula is known to regulate autonomic activity. Lesions in the left insula may be more likely to result in increased sympathetic activity and greater cardiovascular mortality than right-sided lesions. There is also evidence of early insula involvement in AD. We conducted a diffusion tensor imaging (DTI) study in cognitively intact elderly to determine the relationship between white matter integrity in the insula area and cardiovascular indices to examine a possible association between insula abnormalities and the increased autonomic disturbances associated with aging. The effect of APOE ε4, which is associated with increased AD pathology, was also examined.
Methods: All participants (aged 60-77) were medically healthy, cognitively intact with MMSE scores ≥28 and included 14 APOE ε4 carriers and 15 non-carriers. Pulse and BP were determined in the supine position, after 5 minutes of sitting, and upon immediate standing. DTI (8 directions) was collected at 1.5T. Images were normalized and ε4 effects were tested using voxelwise t-tests only for white matter voxels located between the surfaces of the insula and the striatum. Fractional anisotropy (FA) from white matter voxels deep to the insular cortex was used in the analysis. Regions of interest were defined by three clusters from the thresholded t-maps showing an effect of the epsilon 4 allele on FA. Average FA from these clusters was evaluated in relation to pulse rate, systolic and diastolic blood pressure in each position with Pearson correlations.
Results: Two of the three significant clusters were located in homologous regions of the insula and each showed higher FA in ε4 carriers. The homologous voxels extended from a coronal level containing the anterior commissure and approximately 10mm anterior. The right-sided cluster extended anteriorly an additional 5 mm. The third cluster of interest was located at a more ventral and anterior position and showed decreased FA in ε4 carriers. Highly significant inverse correlations were found between FA in the left but not right insula and systolic BP (sitting and standing) and diastolic BP (supine, sitting and standing). These effects were only present in ε4 carriers. FA also was positively correlated with the change in systolic BP from supine to sitting position when the entire cohort was evaluated. There were no significant right-left differences in FA or ε4 effects on FA asymmetry.
Discussion: Our data indicate that increased sympathetic activity may be associated with disruption of white matter connectivity in the area of the left insula. Subtle abnormalities in the left insula may thus contribute to increased sympathetic activity and increased risk for adverse cardiovascular events in the elderly especially in those who are ε4 carriers.

35. Estimation of Baseline DA D2 Receptor Occupancy in Striatum and Extrastriatal Regions in Humans using PET with [18F] Fallypride

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Sponsor: Robert M. Kessler

Background: Previous alphamethylparatyrosine (AMPT) studies with SPECT and PET have studied baseline DA D2 receptor (DAD2r) occupancy in striatal regions; yet dopaminergic neurotransmission in cortical and limbic regions is believed to be involved in psychosis,drug abuse and cognition. Most imaging studies suggest that extrastriatal DAD2r are the site of antipsychotic drug actions. We therefore undertook PET [18 F] fallypride studies with AMPT to examine whether [18 F] fallypride can be used to estimate DAD2 baseline occupancy in striatal and extrastriatal regions. [18F] fallypride is a benzamide with a high affinity for DAD2/3r which has been used to quantitate levels of DAD2r in both striatum and extrastriatal regions.
Methods: Six normal subjects (3 females and 3 males, ages 23 to 38 years) were studied prior to and following oral administration of AMPT (71.4 mg/kg p.o. over 26 hours) using 5.0 mCi [18F] fallypride and PET scanner. ROIs- caudate, putamen, ventral striatum, medial thalamus amygdala, temporal cortex, substantia nigra- were delineated on MRI scans and transferred to the coregistered PET scans. Regional DAD2r b.p and parametric images of DAD2r b.p. were calculated using the reference region method. Using an elastic deformation algorithm, parametric images of mean percent change were calculated. Probability maps were calculated using 2-tailed t-tests on a voxel by voxel basis and corrected for multiple comparisons.
Results: A repeated measure ANOVA of the ROI data with treatment status, region, and side as factors revealed significant effects of treatment and region ($p<0.001$), but no overall effect of side, treatment x side, or treatment x side x region interactions. As no overall effect of side was seen, the right and left regions were combined for further analysis. Given the significant effects of treatment and region, paired two-tailed t-tests and Wilcoxon rank sum tests were used to examine the effect of treatment on each region. Both tests demonstrated significant increases in b.p. following AMPT treatment ($p<0.001$) for the caudate (8.83±5.42%, S.D.), putamen (11.20±4.53%), ventral striatum (10.64±6.61%), substantia nigra (12.69±6.40%), and medial thalamus (3.83±4.91%); no significant effects of treatment were seen in the amygdala (1.00±5.91%) or temporal cortex (0.11±2.80%). Parametric images revealed a cluster of significant increases in b.p.'s subcortically involving the putamen, caudate, ventral striatum extending into the region of the hypothalamus, substantia nigra bilaterally, and into the subthalamic region and the inferomedial thalamus on the right at the level of and anterior to the posterior commissure. No significant clusters were seen in cortex. The mean depletion of plasma HVA levels was 70.6% ± 15.2%.
Discussion: These results demonstrate that [18F]fallypride PET studies performed prior to and following AMPT depletion of cerebral DA can be used to estimate the baseline, i.e. tonic, occupancy of DAD2r in the caudate, putamen, ventral striatum, substantia nigra and medial thalamus. The unexpected baseline occupancy of DAD2r in the substantia nigra, the highest of any region despite microdialysis data showing that extracellular levels of DA in primate substantia nigra are 5 to 10 fold lower in the nigra than in the putamen, may be related to two factors. First, DAD2r in the nigra are autoreceptors in the high affinity state while DAD2r in the striatum are in the high and low affinity states. Second, recent PET studies in baboons suggest that nigral DAD2r are predominantly DAD3 receptors which have 20 fold higher affinity for DA than high affinity state D2 receptors. These observations may explain the greater unmasking of DAD2r in the nigra than in the striatum despite the lower levels of extracellular DA.

36. Neurophysiological Mechanisms in Panic: Alterations of Cerebral Metabolism with Yohimbine-Induced Panic Attacks

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Background: Multiple lines of evidence, including several studies employing the α2-AR antagonist yohimbine, suggest involvement of noradrenergic mechanisms in the pathophysiology of panic disorder (PD). However, the neural mechanisms underlying this potential noradrenergic hypersensitivity have not been investigated using state-of-the-art functional imaging techniques.
Methods: In a randomized, placebo-controlled, double-blind crossover trial, medication-free PD patients and control subjects received intravenous yohimbine (0.4 mg/kg over 10 minutes) on one occasion and a saline infusion on another (temporally separated by 1-2 weeks to avoid carry-over effects). [F-18]FDG injection for PET imaging was timed so that maximum tracer uptake would coincide with yohimbine's peak effect. Behavioral assessments using the Beck Anxiety Inventory (BAI), Panic Symptom Scale (PSS), and Visual Analog Scale (VAS) were conducted at baseline and serially until +120 minutes. Heart rate and GSR were continuously monitored throughout the procedures. For region of interest (ROI) analysis of PET measures of regional cerebral glucose metabolism, ROIs were placed bilaterally in the amygdala (AMYG), anterior hippocampus (HC), anterior insula (AI), anteromedial prefrontal cortex (AMPFC), anterior temporal polar cortex (ATPC), orbital cortex (OC), posterior cingulate cortex (PCC), pregenual anterior cingulate cortex (PGACC), subgenual ACC (SGACC), and ventral striatum (VS). Voxel-by-voxel analyses were run using SPM.
Results: Significantly more panic subjects experienced a panic attack with yohimbine than control subjects (11/13 vs. 0/14, respectively). Behavioral ratings based on the PSS and BAI were significantly higher after yohimbine administration, and patients had higher ratings than controls after yohimbine. Significant drug x time interactions were found for GSR and heart rate, with no effect of diagnostic group. A trend ($p=.057$) was noted for a drug x group interaction in whole-brain metabolism, with a yohimbine-induced metabolic decrease of 11% in PD while controls remained unchanged. ROI analysis, normalized for whole-brain metabolism, reached significance for a drug x side x group interaction in the AMYG (driven predominantly by the effect of Yoh in the patient group) as well as a drug main effect in the AMPFC, a drug by group interaction in the ATPC, main effects of drug and group in the PC, a drug x side x group interaction in the PGACC, and a drug main effect in the SGACC. Voxel-by-voxel analysis in the PD group revealed significant increases with yohimbine vs. placebo in the L AMYG, PGACC, dorsal ACC, middle cingulate, cerebellum, medial OC, medial parietal, and medial and lateral cerebellum. Yohimbine-induced decreases in the patient group were located in the parahippocampal gyrus, posterior HC, PCC, R ATPC, brainstem, R perirhinal cortex, L precentral gyrus, L medial parietal, and infratemporal cortex. Significant increases in control subjects with yohimbine were localized in the R lateral cerebellum, R and L posterior OC, and R precentral gyrus; decreases were significant for inferior occipital gyrus, medial parahippocampal gyrus, superior parietal lobule, and superior temporal gyrus.
Discussion: These data are consistent with previous evidence of increased sensitivity to a noradrenergic challenge in PD versus controls. Specifically, we have found evidence for increased sensitivity of emotional and limbic (e.g., in ACC, AMYG) but not autonomic responses in patients versus controls.

37. Cortical Substrates of Mood and Anxiety in Normal Healthy Boys

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Background: Depression and anxiety are two of the most common psychiatric disorders and share many common features. The neural underpinnings of depression and anxiety in humans have become increasingly realized over the previous two decades, with converging evidence from several methodologies implicating a few critical brain regions. A remaining question to be answered is whether the structural and personality differences seen in clinical disorders is clearly delineated from the normal distribution in the population or if the structural and personality differences represent the extreme tail of a normal distribution.
Methods: To address this question, we studied 61 normal healthy boys ages 7 – 17 years. No subject had identified any current or previous diagnoses or assessment for depression or anxiety. Structure of selected regions of the prefrontal cortex were obtained from high resolution MRI scans using a program segmenting the cortex into functionally specific regions. Rating of mood and anxiety were obtained from a behavioral rating scale completed by both parents and teachers.
Results: 1) Three regions implicated in depression and anxiety correlate with behavioral measures of depression and anxiety: medial orbital frontal cortex, caudal anterior cingulate, and rostral anterior cingulate. 2) Measures of ratings of depression and anxiety were inversely correlated with the surface area of these cortical regions indicating that greater mood scores were associated with smaller volumes [Spearman r (p): left medial orbital frontal = -0.336 (0.008), right caudal anterior cingulate = -0.254 (0.048), right rostral anterior cingulate = -0.288 (0.024) and left rostral anterior cingulate -0.356 (0.005)].
Discussion: This provides preliminary support for the notion of continuity in the spectrum of behavioral and anatomical variation in the population with respect to depression and anxiety. Further analysis will include adding information on family history of depression as well as a completion of the same study design on a complementary sample of healthy girls.

38. Ventral Frontal Cortex in Healthy Children: Relationships Between Sex, Morphology, and Social Cognition

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Background: Females have been shown in a number of studies to be more adept in social perception compared to males. In addition, studies have reported that brain regions important in interpretation of nonverbal social cues, such as the ventral frontal cortex (VFC), are morphologically different between genders. In a previous study in our lab, the straight gyrus (SG), a subregion of the VFC, was found to differ in size between men and women and also to correlate with better performance on a test of social cognition and with higher identification with feminine characteristics. This study was designed to investigate these same issues in a sample of normal healthy children.
Methods: To investigate the relationship between the structure of the developing VFC and social cognition in children, gray matter volumes of the VFC were measured on MRI scans from 37 boys and 37 girls ranging in age from 7 to 17 and matched for age and IQ. The VFC was subdivided into the orbitofrontal cortex (OFC) and the straight gyrus (SG). To assess social function subjects were administered the Interpersonal Perception Task (IPT), a test of social perceptiveness. The Children's Sex Role Inventory (CI) was administered to obtain measures of femininity and masculinity.
Results: In contrast to our findings in adults, no differences were found between males and females in VFC subregion gray matter volumes. However in girls, smaller SG volumes correlated with better performance on the IPT and identification with more feminine traits on the CI. These relationships were not significant in boys. The volume of the straight gyrus was significantly and negatively correlated with age, representing the maturational process of pruning. Therefore, the correlation social perception and femininity with smaller SG is interpreted as higher scores on the IPT and more feminine scores on the CI are associated with a smaller, more mature SG.
Discussion: As seen in a previous study of adults, a specific region of the orbital frontal cortex, the straight gyrus, is directly related to measures of social cognition as well as to femininity. Sex differences in the morphology of this region are modified by the developmental process of pruning such that the correlations between this region of the brain and social perception and femininity in children are opposite that seen in the adult study, but yielding the same conclusions regarding brain and behavior relationships.

39. The Effects of Sadness on the Brain Circuitry of Attentional Bias Towards Reminders of the Deceased in a Bereaved Population

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Sponsor: J. John Mann

Background: Bereavement is a universal psychological reaction to the death of an attachment. One basic feature of early grief is elevated attentional bias towards reminders of the deceased, experienced subjectively as yearning; a second is sadness over the loss. The reduction of both sadness and attentional bias are used clinically as markers of grief resolution. An important question is why sadness and attentional bias are correlated. Two plausible causal relationships have been suggested. The 'disengagement' model hypothesizes that sadness reduces attentional bias, an effect that is predicted to be helpful in accelerating the recovery process. The 'reunion' model suggests that sadness increases attentional bias, and thereby delays resolution of grief. We tested the hypothesis that in a bereaved population sadness should produce a decrease in attentional bias towards reminders of the deceased, correlated with a decline in BOLD signal in regions associated with reward processing and attention, including the brainstem, anterior cingulate cortex, orbitofrontal cortex, and medial prefrontal cortex.
Methods: 8 subjects with no Axis I history by SCID I who had lost a beloved pet within the past 3 months were recruited. Grief intensity was scored using the Texas Revised Inventory of Grief (TRIG). Baseline attentional bias towards reminders of the deceased was measured with an Emotional Stroop (ES) task. A sadness episode was induced, and then the ES task was repeated. Emotional stimuli were words that reminded subjects of their deceased pet; the neutral control stimuli were words that reminded them of their house. Sad emotion was induced through autobiographical memories of the pet. Intensity of mood was assessed on a 10-point Likert scale were gathered immediately after scanning. Images were acquired on a 1.5T GE MRI.
Results: Subjects demonstrated slower reaction times to attachment-related than neutral control words at p=.01 both prior to and following sadness. ANOVA analysis of reaction time by emotion condition revealed a time by condition interaction at p=.04; reaction times were statistically elevated to pet-related words relative to neutral words prior to but not following sadness. On fMRI, at a z-stat cutoff of 1.6 and a cluster value of p=.05 brain areas that showed elevated BOLD signal in response to emotional words both prior to and following sadness induction included the medial prefrontal cortex and left insula. Regions that showed elevated BOLD signal prior to but not after sadness induction included the subgenual ACC, pregenual ACC, and posterior cingulate cortex.
Discussion: Consistent with the 'disengagement' model of sadness, a completed sadness episode caused a persistent decrease in attentional bias towards reminders of the deceased. Bereaved subjects demonstrated attentional bias towards reminders of the deceased that corre-

lated with BOLD activity in brain regions known to be involved in the mediation of emotional conflict, particularly the subgenual and pregenual ACC. A completed episode of sad emotion resulted in decreased attentional bias towards these stimuli and correlated with decreased BOLD activity in these regions, while regions involved in attention including the medial prefrontal cortex continued to mediate attention towards emotional but not neutral words. This is consistent with the interpretation is that sadness episodes downregulated the activity of these regions. It is plausible that with a reduction in emotionality or conflict associated with pet-related words, attention was mobilized for improved task performance. In healthy subjects, sadness may play a role in facilitating adjustment to loss. This has significant implications for the clinical management of bereavement.

40. Abstract Withdrawn

41. Voxel-Based Morphometry Predictors of Treatment Response in Psychotropic Drug-Naive Pediatric Patients with OCD

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Background: Several functional neuroimaging studies have implicated localized metabolic changes in brain regions comprising cortical-striatal-thalamic-cortical circuits in OCD following administration of serotonin reuptake inhibitors (SRIs) or behavioral treatment. There have been few prior studies examining the relationship between brain grey matter structure and treatment response in OCD.
Methods: In this study 44 (20M/24F) psychotropic drug-naive pediatric outpatients with OCD received monotherapy with a selective SRI or cognitive behavioral-therapy for 16 weeks. Patients underwent MR imaging scans consisting of 124 contiguous T1-weighted coronal SPGR MR images (slice thickness = 1.5mm) at pre-treatment baseline. Treatment response was defined as the change in Yale Brown Obsessive Compulsive Scale (YBOCS) from pre- to post-treatment. All patients met DSM-IV criteria for OCD using the Schedule for Affective Disorders and Schizophrenia for School Age Children - Present and Lifetime (K-SADS-PL) versions as determined by a board-certified child and adolescent psychiatrist (DRR). Mean age of the sample was 11.5 years (SD=3.2) and mean age at onset was 8.5 years (SD = 3.2). MR images were acquired in the coronal plane using a 3D spoiled gradient echo pulse sequence on a GE 1.5 Tesla whole body superconducting imaging system. This sequence produced 124 contiguous coronal slices (slice thickness = 1.5 mm) through the whole head with nominal in-plane resolution of .94mm x .94mm in a 256 x 256 matrix. We employed optimized voxel based morphometry to identify pre-treatment brain grey matter regions that significantly predicted subsequent treatment response. Using this approach we created a study-specific template and then re-incorporated volume information lost during the transformation process. Modulated grey matter images were smoothed with an 8-mm FWHM isotropic Gaussian kernel prior to analysis using voxelwise t-tests. Alpha was set to .001 using 100 contiguous voxels as the extent threshold. Percentage change in YBOCS score from pre-treatment baseline to followup was correlated with brain structure measures.
Results: Significant ($p<.001$; 100 voxels, uncorrected) correlations were identified between more grey matter in the anterior cingulate gyrus, dorsolateral prefrontal cortex, frontal pole and temporal cortex and greater reduction in OCD symptom severity. Moreover, these correlations remained significant when we controlled for changes in depression and anxiety over the treatment trial. In contrast, there were no regions where less brain grey matter predicted change in YBOCS score.
Discussion: These findings suggest that pre-treatment measures of brain grey matter structure may predict subsequent treatment response. The clinical utility of such measures will be an important area for subsequent research.

42. Systemic Lipopolysaccharide (LPS) Produces Regional Changes in Sigma-1 Receptors as Measured with [^{18}F]2-Flouropropyl-[(4-cyanophenoxy)methyl]piperidine ([^{18}F]FPS) in the Rat CNS

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Sponsor: Dean F. Wong

Background: Sigma-1 receptors are expressed throughout the mammalian immune, reproductive and central nervous systems. Sigma-1 receptor agonists potentiate NMDA modulated neuronal responses and are linked to cognitive and depressive behaviors in animals. Recent studies have linked sigma-1 receptors with immune system responses, including modulation of specific interleukins. Systemically administered LPS produces a well-documented cascade of behavioral symptoms termed "sickness behavior" in animals and in humans. The associated mechanisms are not well defined but might be important in specific psychiatric or neurological illnesses. This study tested the hypothesis that peripheral LPS challenge would induce changes in sigma-1 receptors that could be measured with the sigma-1 receptor selective radiotracer, [^{18}F]FPS.
Methods: [^{18}F]FPS was synthesized and formulated in sterile saline as previously described (Waterhouse et al. Nucl Med Biol 1997, 45-51). LPS (100 μg/kg in 400 μl saline, ip) or saline (400 μl, ip) were administered to conscious male rats (290-350g), followed 1 hr (n = 4) or 4 hr (n = 5) later by [^{18}F]FPS (20-25 μCi, 100 μl saline, iv), a highly selective sigma-1 receptor radiotracer. After 60 min, animals were humanely killed, and the concentration (%ID/g) of [^{18}F]FPS in blood, heart and select brain regions (striatum, cerebellum,, hippocampus, thalamus, hypothalamus, frontal cortex, temporal cortex and medulla/pons) were determined post-mortem. In addition, tissue-to-blood %ID/g ratios were calculated and compared between groups. Statistical analysis was performed with student's t-test.
Results: [^{18}F]FPS was prepared with specific activity of 1,250 mCi/μmol and radiochemical purity of > 99%. As expected, LPS, but not saline, induced fever by 1 hr after administration. Regional brain [^{18}F]FPS uptake was 14–34% higher in all brain regions in both 1 hr and 4 hr LPS groups vs saline controls, whereas blood activity remained unchanged. In the 4 hr LPS group, a significant increase in [^{18}F]FPS radioactivity concentration was observed in the thalamus (saline: 0.80 ± 0.14 %ID/g; 4 hr LPS: 1.05 ± 0.12 %ID/g, p = 0.04) and hippocampus (saline: 0.51 ± 0.02 %ID/g; 4 hr LPS: 0.65 ± 0.11 %ID/g, p = 0.04). The 1 hr LPS group exhibited tissue-to-blood ratios were significantly increased in all brain regions except the hypothalamus and temporal cortex. In the 4 hr LPS group, there was a strong trend towards increase in tissue-to-blood ratios for all regions, reaching significance only in the thalamus (saline: 31.8 ± 3.3 %ID/g; 4 hr LPS: 44.2 ± 6.6 %ID/g, p = 0.03)
Discussion: This study is the first to demonstrated that an acute immune challenge increases the uptake of a sigma-1 receptor tracer in the heart and brain. Such models should be valuable to map changes in the sigma receptor system that occur under as a result of immune system activation, and may provide evidence for a role such changes in "sickness behavior", depression, and cognitive distrubances often associated with these conditions. Studies to further explore these findings are warrented, including a determination of whether the increased [^{18}F]FPS binding is due to a change in tracer affinity or increased sigma-1 receptor availability.

43. Dopamine D2 Receptor Levels in the Substantia Nigra, Cortex, Limbic Regions, Thalamus and Basal Ganglia in Off Medication Schizophrenic Subjects

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Background: It has been hypothesized that in schizophrenia a hypodopaminergic state in cortex produces dysfunction of glutamatergic pyramidal neurons which project to the substantia nigra resulting

in increased striatal dopamine (DA) release. The hypothesized hypodopaminergic state in cortex has been related to cognitive deficits in schizophrenia; the increased striatal DA release has been correlated with positive symptoms. While a number of imaging studies and post mortem studies of dopaminergic neurotransmission in schizophrenic subjects are consistent with this hypothesis, significant questions remain concerning the role of nigral/VTA, cortical and limbic dopaminergic neurotransmission in the pathophysiology of schizophrenia. . The current study utilized PET with [18F]fallypride to examine DA D2 receptor (DAD2r) levels in substantia nigra, cortex, limbic regions, thalamus as well as striatum in off medication schizophrenic subjects.

Methods: PET [18F]fallypride studies were performed in 11 schizophrenic subjects (6 M, 5 F; mean age of 30.5 ± 8.0 (S.D.) years, age range of 20–45 years) who were either never treated (N=4) or were off medication for at least three weeks as well as 11 healthy subjects (5M, 6F, mean age of 31.6 ± 9.2 (S.D.) years, age range of 21 -45 years) age matched to schizophrenic subjects. DAD2r binding potentials (b.p.s) were calculated using the reference region method. All subjects had high resolution MRI scans which were used to delineate regions of interest (ROIs); these included the caudate, putamen, ventral striatum, medial and posterior thalamus, substantia nigra, amygdala, anterior cingulate, hippocampus, and temporal cortex. Parametric images of DAD2r levels were calculated and voxel based analyses performed using SPM.

Results: A repeated measures MANOVA of the ROI data revealed a significant group x region interaction, $F(7,13) = 6.00$, $p<0.005$ which was due to increased b.p.s in the substantia nigra ($p=0.0008$) and decreased b.p.s in the left medial thalamus ($p=0.03$) in off medication schizophrenic subjects. Voxel based analysis demonstrated multiple clusters of increased DAD2r levels in the frontal and inferior parietal cortices bilaterally, left superior temporal gyrus as well as in the anterior cingulate bilaterally in schizophrenic subjects. Voxel based analyses also demonstrated increased levels in the substantia nigra and dorsal midbrain. Clusters of decreased DAD2r levels were seen in the basal ganglia bilaterally.

Discussion: Previous imaging studies of extrastriatal DAD2r in schizophrenic subjects have not reported receptor levels in the substantia nigra or midbrain. Nigral DAD2r are autoreceptors on DA neurons. Post mortem studies have reported increased levels of DAD2r, tyrosine hydroxylase, tyrosine hydroxylase mRNA, and homovanillic acid in the substantia nigra. Taken together, the current finding and previous post mortem studies suggest dysfunction of nigral DA neurons in schizophrenia. The resolution of the PET scanner used in this study is insufficient to distinguish nigral from VTA neurons. The increased DAD2r levels in frontal, inferior parietal, superior temporal and cingulate cortices and the decreased levels seen in the basal ganglia on parametric image analysis are consistent with consistent with the previously hypothesized hypodopaminergic state in cortex and increased striatal DA release. The current study is the third PET study to report decreased DAD2r levels in the left medial thalamus. The results of this study indicate that there are widespread changes in DAD2r levels in schizophrenic subjects which appear to involve dopaminergic innervation of multiple portions of frontal/striatal/thalamic circuits as well as parietal and superior temporal association cortices.

44. Effects of Weight Recovery on Brain Structure in Adolescent-Onset Anorexia Nervosa

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Sponsor: Adolf Pfefferbaum

Background: Anorexia nervosa (AN) is associated with abnormalities in brain structure, including reductions in gray- and white-matter volumes and increases in cerebrospinal fluid (CSF) volumes. These findings are apparent in the acute stages of the illness and are known to diminish in severity with clinical recovery. However, whether they persist despite weight-recovery and whether they impact on functioning remains controversial as most studies to date have been limited by small sample sizes. This study was undertaken to determine whether weight-recovery from AN is associated with persisting deficits in brain structure and cognitive functioning.

Methods: This cross-sectional study included 67 women (age=21.3±2.3 years) with a history of adolescent-onset AN who had been treated 6.5±1.7 years earlier. A group of 42 healthy volunteers matched for age (age=20.7±2.5 years) and sex were recruited as a control group. All participants underwent an MRI scan of the brain as well as a clinical and neuropsychological assessment. Subjects with a history of AN whose BMI was greater than 19.5 kg/m2 at the time of study were categorized as "weight-recovered" (n=53) while those whose BMI remained below were considered "low weight" (n=14). Scores from the Woodcock Johnson III - Tests of Cognitive Abilities and Achievement, Hopkins Verbal Learning Test, and Wechsler Memory Scale - Revised were obtained. Images were acquired with a 1.5T MRI system (G.E., Milwaukee, WI). A three-dimensional, inversion-prepped, radio-frequency fast spoiled-gradient recalled-echo (IR-FSPGR) sequence was used (TI=300ms, TR=12ms, TE=5ms, flip angle=20°, FOV=20cm, matrix=256x256 pixels), yielding 124 contiguous 1.5 millimeter thick coronal sections. Images were normalized to MNI-Talairach space, resliced to 1.0mm isotropic voxels, and classified into gray matter, white matter, and CSF voxels.

Results: Neither weight-recovered nor low weight patients differed from the control group in total gray matter, white matter or CSF volumes. Compared to the control group, patients had significantly larger lateral and third ventricles. Moreover, the lateral and third ventricles of low weight subjects were significantly larger than those of weight-recovered subjects. AN patients performed worse on cognitive tests than controls with statistically significant between-group differences apparent in weight-recovered patients on tests of verbal ability, cognitive efficiency, math skills and verbal memory. Cognitive functioning was not associated with the degree of weight recovery.

Discussion: This study confirms the increase in ventricular volume previously reported in weight-recovered patients with a history of AN. However, persisting differences in gray matter and white matter were not detected. Our results suggest that increases in ventricular volumes may be a more sensitive indicator of persisting changes in brain structure. The results of cognitive testing suggest that significant differences in cognitive functioning remain apparent in the absence of detectable differences in brain tissue volumes. Whether these differences predate the development of AN or are a consequence of the disorder remains to be established.

45. Decreased Regional Cerebral Blood Flow in the Medial Prefrontal Cortex During Non-Traumatic Stressful Imagery in Vietnam Veterans with PTSD

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Background: Neuroimaging research has shown that the medial prefrontal cortex (mPFC) is hyporesponsive during emotional processing and trauma-specific symptomatic states in posttraumatic stress disorder (PTSD). Relatively decreased activation in the prefrontal cortex has been associated with autobiographical traumatic reminders (Shin et al., 1999; Lanius et al., 2001), as well as traumatic stimuli that are non-autobiographical (traumatic pictures and sounds, Bremner et al., 1999). Individuals with PTSD also have shown decreased mPFC activity when presented with emotional, but non-trauma specific stimuli such as emotional faces and pictures (Shin et al., 2005; Phan et al., 2006). In a previously reported positron emission tomography (PET) study in our lab (Shin et al., 2004) we found that PTSD subjects, relative to non-PTSD subjects, exhibited decreased regional cerebral blood flow (rCBF) in medial frontal gyrus

during the recollection of personal, PTSD-related traumatic vs. neutral events using a script-driven imagery paradigm. In the current study, we analyzed data from the same cohort to test the specificity of decreased mPFC activation by examing regional cerebral blood flow (rCBF) during the processing of stressful autobiographical stimuli that were unrelated to the index traumatic experience.
Methods: Participants were 35 right-handed Vietnam veterans: 17 participants met DSM-IV diagnostic criteria for current PTSD (PTSD group, 7M:10F, mean ± SD age =51.73 ± 3.46 yrs.) and 18 participants had no current or lifetime PTSD (non-PTSD group, 9M:9F, mean ± SD age = 53.24 ± 2.78 yrs.). Participants provided descriptions of two neutral, two Vietnam-related traumatic, and two non-traumatic stressful autobiographical events. Whereas results from the traumatic vs. neutral comparison were reported by Shin et al., 2004, herein we report the results of the non-traumatic stressful vs. neutral comparison. Psychophysiologic data were acquired to assess the extent to which participants experienced emotional arousal during the script-driven imagery. PET data were gathered by a 15-slice, whole-body tomograph. Statistical analysis of the PET data was conducted using the SPM99 software package. We hypothesized that the previous finding of decreased rCBF in mPFC in PTSD subjects during recollection of traumatic events would generalize to non-traumatic stressful events.
Results: For the three simultaneous physiological measures, viz., heart rate, skin conductance, and left lateral frontalis electromyogram (EMG) responses, there was a significant Group x Condition interaction, with PTSD subjects showing higher responses during non-traumatic stressful vs. neutral imagery ($F(1,53)=3.0$, $p<0.05$. With regard to rCBF, the non-traumatic stressful vs. neutral comparison yielded no significant rCBF increases within either group. However, relative to non-PTSD subjects, the PTSD group had significantly decreased rCBF in medial frontal gyrus (z=3.66; Montreal Neurological Institute (MNI) coordinates, +8, +60, 0) and anterior cingulate cortex (z=4.45; MNI coordinates, +12, +38, +26), during the non-traumatic stressful vs. neutral imagery.
Discussion: These results extend the rCBF findings of Shin et al. (2004) during mental imagery of traumatic events to rCBF during emotionally stressful, but non-traumatic, personal life events. Veterans with PTSD, compared to those without PTSD, exhibited rCBF decreases in mPFC during imagery of such events. These results suggest, but do not prove, that mPFC hyporesponsivity represents a trait in individuals with posttraumatic stress disorder, rather a specific product of the traumatic experience. These results indicate that functional neuroanatomical models of PTSD must account for the generalization of mPFC hyporesponsivity to emotional stimuli that are not trauma-specific.

46. Effect of Escitalopram on Decision Making Tasks in Patients with Major Depression and Generalized Anxiety: An Imaging Study

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Sponsor: Roland Griffiths

Background: Ahedonia in depression may be modified in presence of anxiety by reducing stress tolerance. Using fMRI, we investigated the effect of decision making tasks that differ in levels of reward in patients with major depression and generalized anxiety before, and after, treatment with escitalopram. The aim of the tasks was probing the responsiveness of frontal-subcortical and frontal-parietal networks implicated in both decision making and emotion.
Methods: Ten drugfree patients diagnosed with major depression and generalized anxiety, were imaged using BOLD fMRI before and after 8 weeks of treatment with escitalopram. During functional imaging, subjects completed three decision making tasks that differed, unpredictably, in the probability of earning or loosing monetary rewards. During the tasks, subjects had to choose between 2 squares of different colors. The choice of one square was always associated with a 50% chance of winning or loosing money. When choosing the other square the chances of winning were 100%, 70% or 50%.
Results: Clinically, patients improved significantly on investigator- and self-rated scales of depression and anxiety and on ratings of quality of life. Nine patients remained on escitalopram after termination of the study. Performing the task with highest chance of reward led, after treatment, to increased bilateral activation of medial prefrontal gyri and anterior cingulate, the left dorsal and lateral nucleus of the thalamus and right parahippocampal gyrus. The slope of activation from 50% to 70% to 100% probabilities to gain money became significantly less steep from pre to past treatment bilaterally in medial prefrontal and superior temporal regions, the left superior parietal gyrus, the left parahippocampus and brain stem.
Discussion: The higher after treatment activation of medial prefrontal and subcortical regions during the task with highest monetary gain indicates greater involvement in the task due to improvement in mood. After treatment changes in the slope of activation between the tasks indicate decrease in brain activation during adverse conditions and a more positive response to challenge due to lower levels of anxiety.

47. fMRI of Mu and Kappa Opioid Agonists in Non-Human Primates

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Background: Functional magnetic resonance imaging (fMRI) has emerged as a promising new technique to non-invasively image drug-induced changes in brain function. In our laboratories, we are developing technical and data analytic procedures for use of fMRI to study drug effects in awake, non-human primates. Studies in non-human primates are of interest because (a) non-human primates can be tested with a wider range of drugs, drug doses, and drug treatment regimens than can be tested in humans, (b) non-human primates are phylogenetically closer to humans than are many other common laboratory animal species (e.g. rodents), which may contribute to predictive validity, and (c) monkeys have larger brains than rodents, which is advantageous for evaluation of drug effects in small brain regions such as nucleus accumbens. In addition, an extensive literature exists on the effects of many drug classes in non-human primates, and this foundation of data can be used to design and interpret results of pharmacological fMRI experiments. Initial studies are comparing the effects of vehicle, the selective, high-efficacy mu agonist fentanyl (0.00032 and 0.0032 mg/kg) and the selective, high-efficacy kappa agonist U69,593 (0.00032 and 0.0032 mg/kg). Mu and kappa opioid agonists produce distinct profiles of physiological and behavioral effects in non-human primates, and we hypothesized that these drugs would also produce dose-dependent and neuroanatomically distinct fMRI effects.
Methods: Studies were conducted in three adult male cynomolgus monkeys. Prior to the initiation of scanning sessions, monkeys were gradually acclimated to restraint in the sphinx position in a custom-built, MRI-compatible restrainer (Insight Neuroimaging, Worcester, MA). Imaging sessions were conducted using a Siemens Trio 3 Tesla scanner (Malvern, PA). Single shot gradient-echo echo planar scans were used to map blood-oxygen-level dependent (BOLD) signal responses to IV saline and drug injections. Saline and each drug dose were tested twice in each animal, and successive scans were spaced by >1 week apart to minimize tolerance effects. Blood samples were collected before and after saline control sessions to assess plasma levels of the stress-related hormones ACTH and cortisol. Imaging results were analyzed with BrainVoyagerQX 1.6.3 and corrected for differences in brain size and positioning via a Talairach-like transformation. BOLD data were adjusted for subject motion, the hemodynamic response function, and scanner gradient heating effects.

Results: Restraint for the duration of the imaging session (~1.5hr) produced modest elevations in plasma levels of the stress-related hormones ACTH (122% increase over baseline) and cortisol (73% increase) similar to or less than elevations produced by restraint of acclimated macaques in standard restraint chairs used for behavioral studies (ACTH-226% increase; Cortisol-120% increase). Thus, by this measure, the tight restraint required for fMRI studies produced stress levels no greater than those produced by looser restraint commonly used for behavioral studies in non-human primates. Preliminary analysis of imaging results indicates that fentanyl produced dose-dependent positive BOLD signals in a number of brain regions bilaterally including the anterior temporal lobe/amygdala and insula. Analysis of results with U69,593 is underway.
Discussion: These data suggest that it will be possible to use this awake-macaque model to systematically characterize and compare brain effects of opioids and perhaps other drugs using fMRI in non-human primates. Supported by NIDA grants DA17324, DA14013, DA09448, DA015116, DA014178, and the John and Virginia Taplin Foundation.

48. Dopamine-Transporter Genotype Interacts with Familial Risk for Attention-Deficit/Hyperactivity Disorder and Striatal Activity
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Background: The dopamine-transporter (DAT1) gene has been implicated repeatedly in ADHD, although the mechanism by which it exerts its effects remains unknown. The polymorphism associated with ADHD has been shown to affect expression of the transporter in vitro and in vivo. Dopamine-transporters are predominantly expressed in the striatum, although they are also present in the cerebellar vermis. Stimulant medication is often effective in ADHD and is believed to exert its effects by blocking dopamine transporters in the striatum. We hypothesized that DAT1-genotype would affect brain activation patterns in a manner similar to stimulant medication, with the lower expressing allele mirroring its effects.
Methods: We investigated DAT1-gene effects on brain activation patterns in a sample of sibling-pairs discordant for ADHD and controls (N=29). All subjects participated in an fMRI session using a go/no-go paradigm, and provided a DNA-sample for analysis.
Results: We found that dopamine-transporter genotype affected activation in striatum and cerebellar vermis. Genotype interacted with familial risk for ADHD in striatum, but not vermis.
Discussion: These results suggest that dopamine-transporter gene effects in striatum may be involved in translating genetic risk for ADHD into a neurobiological substrate. This may point towards long-term possibilities for tailoring individual therapies by DAT1-genotype: If DAT1-genotype has differential effects on striatal activation, it may become possible to use this as a surrogate endpoint in individualized treatments targeting genotype/fMRI-activation profiles.

49. PET Predictor of OCD Response to Anterior Cingulotomy: Replication of Findings Suggests Potential Clinical Utility
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Background: Several studies have sought to identify predictors of treatment response for various therapies with respect to their corresponding psychiatric indications. To date however, there are few examples of replicated findings indicating reliable correlations between a pre-treatment brain imaging index and subsequent response to a specific treatment. To our knowledge, none thus far represent promising tests with respect to clinical utility, based on the risk/cost-benefit profile of the index and the corresponding treatment. Neurosurgical treatments for psychiatric disorders in general, and anterior cingulotomy for severe, refractory obsessive compulsive disorder (OCD) in particular, represents a setting where reliable predictors of response have the potential to be of great clinical value. Pertinent issues include the fact that the treatment is costly and carries surgical risks, while the likelihood of significant therapeutic benefit is only modest (~35% full responders). In an effort to identify candidate imaging predictors of response, we previously studied 11 patients (7M:4F) undergoing anterior cingulotomy for OCD using positron emission tomography with fluorodeoxyglucose (PET-FDG). Using statistical parametric mapping methods (SPM99), we found that pre-treatment regional cerebral metabolism at a locus within right posterior cingulate cortex (PCC) was significantly positively correlated with % improvement of Yale-Brown Obsessive Compulsive Scale (YBOCS) scores at ~6 months post-operative follow-up (Rauch et al, Biol Psychiatry 2001;50:659-667). In the current experiment, we sought to replicate the prior findings in an independent cohort of patients.
Methods: Using equivalent PET-FDG methods, we studied 13 patients (10M:3F; mean ± SD age = 34.9 ±10 yrs.) undergoing anterior cingulotomy for severe, treatment-refractory OCD. Pre-treatment normalized regional brain metabolism was tested for correlation with % improvement in YBOCS score at follow-up, on a voxel-wise basis using SPM99 for statistical parametric mapping. A priori, we sought to replicate the previous results by searching for significant correlation within the right PCC.
Results: In accord with prior results, we found a significant positive correlation between pre-surgical regional metabolism at a locus within right PCC and subsequent %YBOCS improvement at follow-up.
Discussion: Taken together, these findings suggest that pre-operative PET-FDG may be used to measure right PCC regional metabolism as an index to predict subsequent response to anterior cingulotomy for OCD. It is hoped that refinements of this application may help identify and exclude candidates who are unlikely to derive benefits from the operation, thereby functionally enhancing effectiveness rates of anterior cingulotomy for OCD, as well as its risk/cost-benefit profile.

50. Creatine Kinase Increase During Hyperventilation: Implications for Panic Disorder
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Sponsor: David L Dunner

Background: Research to date strongly suggests biological factors in panic disorder (PD) (1). There is evidence that the disorder may be genetically transmitted (2). Individuals with PD are susceptible to having panic attacks during metabolic challenges ranging from sodium lactate infusion(1), caffeine ingestion (3), CO2 inhalation (4), or hyperventilation (HV)(5). Although CO2 inhalation and lactate-infusion are most effective, individual subjects are not equally susceptible to challenge types (6). When measured at rest, PD subjects often display lower end tidal CO2 (pCO2) and have variable breathing patterns compared to controls and other anxiety groups (e.g. GAD (7)). These alterations largely persist after treatment (8,9). While HV is not sufficient or necessary for panic attacks to occur (10) it may bias the system toward metabolic instability. Neuroimaging studies in panic disorder often demonstrate altered lactate increases to HV(11) or lactate infusion (12). We have been studying how the healthy brain responds to HV, to infer what effects baseline hypocapnia might have. During HV, phosphocreatine (PCr) decreases (13). It is possible that creatine kinase (CK), responsible for catalyzing the

transfer between PCr and ATP, also changes in rate. To examine HV-effects on CK, eight healthy control subjects were studied.
Methods: Eight healthy adult control subjects (6 males, 2 females) were studied using 31P spectroscopy at 4T (Varian, Palo-Alto, CA). All subjects gave written informed consent for participation, approved by the Harvard/McLean Hospital Review Committee. The HV protocol consisted of a 10-min baseline, a 20 min HV to 20mm Hg, and a 30 min recovery. Slab-selective, pulse-acquire scans (0.5s pre-acquisition delay, 90 degree tip-angle, TR=6s) were collected from a 5cm thick brain slab in 2 min blocks, interleaving a BISTRO pulse train to irradiate gamma ATP (S) and a control acquisition (C). Analysis: The forward rate of CK was computed from PCr, kf=(1/PCr_T1)*((C-S)/S)).
Results: Marked pH increases (.05 units), PCr decreases (5%) and CK forward rate increases (14%) were observed during HV. These changes returned to baseline levels by the end of the recovery period.
Discussion: Consistent with past work (13), robust pH increases and PCr decreases were observed during HV. The forward rate of CK was also increased with HV. Hypocapnia at rest may be associated with a similarly altered CK rate, that, if present, may bias the system toward atypical metabolic response to challenge. References: 1. Liebowitz MR, Gorman JM, Fyer AJ, et al (1985): Arch Gen Psychiatry 42:709-719. 2. Torgersen S (1983): Arch Gen Psychiatry 40:1085-1089. 3. Uhde TW, Boulenger JP (1989): New Directions in Affective Disorders, pp. 410-413. 4. Papp LA, Klein DF, Martinez J, et al (1993): Am J Psychiatry 150:250-257. 5. Maddock RJ, Carter CS, Gietzen DW (1991): Psych Research 38(3):301-311. 6. Gorman JM, Fyer MR, Goetz R, et al (1988): Arch Gen Psychiatry 45:31-39. 7. Wilhelm FH, Trabert W, Roth WT (2001). Biol Psychiatry 49:596-605. 8. Shear MK, Fyer AJ, Ball G, et al (1991): AM J Psychiatry 148:795-797. 9. Fyer AJ, Liebowitz MR, Gorman JM, et al (1985): Psychiatry Res 14:143-148. 10. Papp LA, Klein DF, Gorman JM. Am J Psychiatry. 1993 Aug;150(8):1149-57. 11. Dager SR, Strauss WL, Marro KI, et al (1995): Am J Psychiatry152(5):666-672. 12. Dager SR, Friedman SD, Heide A, et al (1999): Arch Gen Psychiatry 56:70-77. 13. Friedman SD, Jensen JE, Frederick BB, et al (2006): JCBFM (doi:10.1038/sj.jcbfm.9600383).

51. Alterations in Affective Response to Masked Faces in Chronic Marijuana Smokers: An fMRI Study

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Sponsor: Deborah Yurgelun-Todd

Background: More than 94 million Americans have tried marijuana at least once, and it remains the most widely used illicit drug in the nation. Investigations of the cognitive effects of marijuana have reported alterations in brain function, most notably during tasks that require executive control, inhibition, and decision-making. Further, endogenous cannabinoids have been shown to regulate a variety of emotional responses, including anxiety, mood control, and aggression, nevertheless little is known about smokers' responses to affective stimuli. The anterior cingulate cortex has been shown to play a key role in affective regulation and the inhibition of impulsive behavior, and studies using both PET and fMRI techniques have demonstrated changes within this region in marijuana smokers. Given the alterations in mood and perception often demonstrated by individuals who smoke marijuana, we hypothesized altered cingulate response in chronic marijuana smokers relative to control subjects during the viewing of masked affective faces.
Methods: Thirteen chronic heavy marijuana smokers (mean age 25.1 years) who reported smoking at least three thousand joints in their lifetime and 13 control subjects (mean age 26.2 years) who reported smoking not more than five times in their lives completed the study. Imaging data was acquired on a 3.0 Tesla Siemens MRI scanner, motion corrected, and analyzed in SPM99 (height threshold $p<.005$, extent k=20 voxels). The fMRI stimuli consisted of black and white photographs of males and females posing in two affective conditions (happy and angry). Each trial consisted of an emotional target face presented for 30 ms, followed immediately by a neutral masking face of the same poser for 170 ms. Subjects were instructed to indicate the sex of each of the faces during each condition, and were not aware of the backward masked nature of the paradigm.
Results: Direct comparison of the imaging data of the cingulate cortex for the two groups indicated that during the viewing of masked angry faces, control subjects produced significantly more activity of the anterior cingulate (MNI coordinates -2, 20, 30) than marijuana smokers, who produced greater activity than controls in a posterior cingulate gyral region (MNI coordinates 2, -36, 42). The viewing of masked happy faces produced greater activity in normal control subjects relative to marijuana smokers, again within the anterior cingulate cortex (MNI coordinates 10, 14, 32) while marijuana smokers had greater activity in a more posterior region (MNI coordinates -14, -38, 42) of the cingulate gyrus.
Discussion: These findings indicate that marijuana smokers demonstrate altered activation of the anterior cingulate, an area noted to play a key role in affective regulation and the inhibition of impulsive behavior while viewing masked facial affect. This finding is consistent results from autoradiograhic studies which have reported high CB-1 receptor density in this region. The activation patterns noted between the groups during this masked affective task underscore the likelihood that individuals who have smoked marijuana process emotional information in a different way from those who do not smoke, which may result in negative consequences. Data from this investigation suggests differences in affective processing in chronic marijuana smokers even when the stimuli are presented below the level of conscious processing.

52. Imaging Nicotine-Initiated Brain Signal Transduction via Arachidonic Acid in Unanesthetized Rats

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Background: Nicotine exerts its central effects by activating nicotinic acetylcholine receptors (nAChRs), which can lead to the direct activation of Ca2+-dependent cytosolic phospholipase A2 (cPLA2) to release the second messenger, arachidonic acid (AA 20:4n-6), from membrane phospholipid, or to the indirect activation of cPLA2 via release of neurotransmitters acting at their own receptors. We hypothesized that nicotine-induced signaling via AA could be quantitatively imaged in unanesthetized rats by measuring regional brain AA incorporation coefficients, k*, following the intravenous infusion of [1-14C]AA, and that k* responses would show concentration dependency and desensitization. We have shown that regional k* responses represent cPLA2-mediated release of AA from membrane phospholipids (1, 2).
Methods: Nicotine (0.1 or 0.7 mg/kg s.c.) or saline s.c. was injected 2 or 10 min prior to the intravenous infusion of [1-14C]AA, and k* for AA was measured in 79 brain regions by quantitative autoradiography. Mecamylamine (1.0 mg/kg s.c.), a nAChR antagonist, was administered alone or 15 min before nicotine (0.7 mg/kg).
Results: Nicotine 0.1 and 0.7 mg/kg compared to saline, administered 2 min before [1-14C]AA, increased k* significantly in 36 and 43 regions, including the nucleus accumbens. Increases at 2 min following 0.7 mg/kg nicotine were completely blocked by pre-administration of mecamylamine. When given 10 min before tracer, nicotine (0.7 mg/kg) compared with saline increased k* in only 3 regions.
Discussion: Effects of nicotine on brain AA signaling at 2 min following drug injection can be imaged and are widespread in unanesthetized rats. The rapid disappearance of these effects is consistent

with the known rapid desensitization of nAChRs. nAChR saturation likely occurred at the 0.1 mg/kg dose of nicotine, as a higher dose did not markedly increase k*. Plasma nicotine levels from the 0.1 mg/kg nicotine infusion are equivalent to plasma nicotine levels produced by smoking 1 cigarette in humans, which is reported to lead to > 88% of nAChR occupancy in the human brain (3). The nicotinic dose and k* response relations in rats suggest that signal transduction involving AA can be imaged in the human brain with positron emission tomography by a method that we have put into place (4), in relation to cigarette smoking. Refs. 1.S. I. Rapoport, J Pediatr 143, S26 (2003). 2. M. Basselin et al., J Neurochem 96, 669 (2006). 3. A. B. Brody et al., Soc Neurosci Abstr 35th Annual Meeting, 683.7 (2005). 4. G. Giovacchini et al., J Cereb Blood Flow Metab 22, 1453 (2002).

53. Altered White Matter in Williams Syndrome: Preliminary Findings with DTI

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Background: Williams Syndrome (WS) is caused by a hemideletion on chromosome 7 and results in specific cognitive and affective alterations. We previously showed failure of activation with functional magnetic resonance imaging (fMRI), reduced cerebral blood flow with positiron emission tomography (PET) and structural deficits with voxel based morphometry (VBM) in various areas of gray matter (Meyer-Lindenberg et al.; Kippenhan et al.). We hypothesized that the white matter underlying these cortical regions would also be altered and used diffusion tensor imaging (DTI) in individuals with WS to test this notion.
Methods: We studied 5 high functioning individuals with WS (1F, 4M, ages 19-37, IQ ranging from 77 to 95) and 5 age, gender and IQ matched controls (NC). DTI was performed with 2 mm isotropic resolution and all images were aligned in Talairach space with a rigid body transformation in order to be able to compare the average direction of principal eigenvectors (e1) across subjects. Trace (D), a measure of diffusivity, was calculated, and e1 was represented on a red-green-blue color scale with an index of anisotropy (lattice index: LI) determining the brightness of the direction encoded color maps. We drew spherical regions of interest (ROI) of 10 mm diameter around areas of reduced sulcal depth/gray matter volume or hypoperfusion (the intraparietal sulcus, collateral sulcus, the ventral portion of the cingulum bundle [VCING] and the orbitofrontal cortex). The position of the spheres was determined automatically, based on the location of sulcal depth reduction previously reported by Kippenhan et al. in these same individuals, except for the VCING. The mean Trace and e1 for each color in the white matter of the ROIs for both hemispheres were entered in two separate ANOVAs with hemisphere and color intensity as the repeated measures and diagnosis as the categorical factor.
Results: There was a significant hemisphere x diagnosis interaction effect for LI [$F(1,8)=11.7$, $p=0.01$], with NC having larger LI in the left than in the right hemisphere while in WS this asymmetry was lost. There also was a significant effect of diagnosis for Trace [$F(1,8)=13.6$, $p=0.006$: NC>WS] and a significant interaction of e1 direction x diagnosis [$F(2,16)=12.2$, $p=0.001$], with WS having increased longitudinal and reduced transverse orientation of e1 as compared to NC.
Discussion: The significant hemisphere by diagnosis interaction for LI may indicate the presence of altered lateralization processes in the white matter development of individuals with WS. The reduction in Trace is consistent with an alteration in cytoskeletal function, although many other explanations are possible. The most interesting results, though, are the changes in orientation of the principal eigenvector. This, together with concomitant evidence from tractography and from unusual midline abnormalities observed in the same sample, seems to indicate that short range transverse fibers (likely corresponding to the U fibers) may be deficient in WS, while long range longitudinal fibers prevail. This presentation would be compatible with a disorder of neuronal migration during the late stages of embryonic development, leading fibers that would have normally connected two adjacent gyri to deviate longitudinally. This may happen especially in the right hemisphere, thus explaining the loss of asymmetry in LI. This hypothesis needs to be confirmed in a larger group of individuals and in animal models of the genetic haploinsufficiency of WS.

54. Social Information Processing Reveals Cortical Midline Abnormalities in Schizophrenia

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Background: Social and emotional information processing is carried out in cortical midline structures, such as the anterior medial frontal cortex (aMFC) and the posterior medial cortex (pMC). Although schizophrenia typically presents with significant disturbances in socio-emotional behavior, relatively few investigations have targeted these 'socioemotional' neurocircuits, in spite of data demonstrating abnormalities of the aMFC region (including the anterior cingulate cortex, ACC) during rest states and cognitive challenges. Recently, we reported a hyperactive fMRI BOLD signal in the aMFC of patients with persistent psychosis in response to a mildly stressful visual stimulus, in the same region activated by NMDA antagonists and associated with positive symptom of psychosis (Holcomb et al, 2005). We also noted reduced aMFC activity while viewing non-stressful, salient visual stimuli. In the current study, we extended our investigation of aMFC and pMC activity with a set of emotional faces, testing the hypothesis that patients would have an exaggerated aMFC response to negative (mainly fearful) emotional faces.
Methods: Twenty-one stable, schizophrenic/schizoaffective patients (7 females; Age: 40.8±9.3) and 21 matched healthy controls (6 females; Age: 40±9.6) viewed emotionally salient faces — positive, negative (primarily fearful) and neutral. They indicated preference judgments about each face (like/dislike) or identified the gender (GI) with a button press. Pseudo-randomized blocks of each type were separated by passive baseline blocks. BOLD-sensitive fMRI scans were obtained using a reverse spiral sequence. Realigned and normalized images were analyzed in a standard, random effects model.
Results: During scan acquisition, there were main effects of group (SZ > HC: $p=0.002$) and task (Preference > GI: $p<0.001$) for reaction time measures. Relative to GI, preference engaged aMFC and posterior MFC in both groups. In response to negative facial stimuli during the preference task (-GI), the patients showed a greater signal in the pMFC (ACC, Brodman area 32: 9, 24, 42; $Z=4.29$, $k=249$), but not in aMFC. Relative to baseline, the patients exhibited less aMFC activity than the controls for both preference (12, 54, 45; $Z=3.82$; $k=39$) and GI (0, 33, 36, $Z=3.15$, $k=14$; 0, 21, 57, $Z=3.31$, $k=14$), and less posterior cingulate activity for preference (-3, -57, 24; $Z=3.92$; $k=201$) and GI (0, -45, 27; $Z=3.32$; $k=49$).
Discussion: The results demonstrate significant deficits in activation of socioemotional neurocircuits in schizophrenic/schizoaffective patients, particularly when contrasted to a baseline condition. Because the aMFC and pMC are thought to play key roles in the integration of salient social stimuli with ongoing representations of subjective reality, these results reinforce the importance of these brain structures to psychotic processes.

55. Pharmacotherapy Effectiveness for Body Dysmorphic Disorder in a Prospective Observational Study: Preliminary Propensity-Adjusted Results

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Background: SRIs appear efficacious for body dysmorphic disorder (BDD), a relatively common disorder. However, only two random-

ized controlled efficacy studies, no fixed-dose efficacy studies, and no prospective effectiveness studies have been conducted. Therefore, in this prospective observational study, we examined SRI effectiveness for a broadly inclusive sample of individuals with BDD who were largely treated in the community. By design, this study observes, but does not manipulate, treatments received by subjects. Observational studies such as this can provide clinically useful information that complements results from randomized controlled trials, which often have tightly controlled and limited treatment options, and which typically exclude many patients seen in clinical practice (e.g., suicidal patients or those with comorbidity). However, because treatment is not randomized in observational studies, treatment effectiveness analyses must account for the non-equivalent nature of the comparison groups to reduce the impact of selection bias. We used the propensity adjustment, adapted for longitudinal data, which accounts for characteristics associated with receiving treatment (e.g., SRIs) and thereby reduces the impact of selection bias. The longitudinal approach addresses methodologic challenges such as multiple courses of treatment per subject.

Methods: 185 individuals with DSM-IV BDD participated in a prospective, observational, longitudinal study of BDD's course (mean follow-up duration=3.0 +/- 0.9 years). Using the Longitudinal Interval Follow-up Evaluation (LIFE), weekly information was obtained on BDD symptoms, medications received, and doses. The analyses included 579 courses of treatment (including none). Improvement in BDD was defined as >1 point decrease in pre-post treatment ratings on the LIFE BDD-PSR, a reliable 7-point measure of BDD severity.

Results: The propensity for treatment intensity model (using mixed-effects ordinal logistic regression analyses) indicated that subjects who received more intensive SRI treatment (higher doses) tended to be male and older. Treatment effectiveness analyses using mixed-effects logistic regression models were then conducted, separately for each propensity quartile; because there was no propensity-by-treatment interaction, these quartile-specific results were pooled. After controlling for propensity for treatment intensity, subjects who received lower SRI doses (<125 mg/day of sertraline, <20 mg/day of escitalopram, <40 mg/day of fluoxetine, paroxetine, or citalopram, and <150 mg/day of fluvoxamine or clomipramine) were significantly more likely to have improvement in BDD than those who received no SRI (odds ratio=1.49; 95% CI: 1.03-2.14; p=.034). Subjects who received higher SRI doses were not significantly more likely to improve than those who received lower SRI doses or no SRI.

Discussion: Longitudinal propensity-adjusted analyses indicated that subjects who received a lower-dose SRI were more likely to report improvement in BDD symptom severity than untreated subjects over the course of treatment. These SRI doses are generally within the range often used for depression, but lower than often recommended for BDD. Longer follow-up and more courses of treatment will increase power and could improve the quality of prospectively observed variables included in the propensity model, which would further reduce selection bias. This will enable us to better examine whether higher SRI doses are more effective for BDD, as suggested by clinical experience and retrospective data from this sample.

56. Treatment Outcomes in Older Depressed Patients with Earlier versus Late Onset of First Depressive Episode: A STAR*D Report

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Sponsor: A. John Rush

Background: There is a growing literature that earlier onset and late onset geriatric depression my have different etiologies. (Alexopoulos et al 1997; Coffey et al 1989a; Coffey et al 1989b; Figiel et al 1989; Figiel et al 1991; Krishnan 1993; Krishnan et al 1997) Whether earlier versus late onset of the first episode of depression predicts outcome or speed of recovery from a depressive episode in older patients is unclear. In order to address this question, data was used from the NIMH funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) research project. The study enrolled over 4,000 outpatients age 18-75 years old with major depressive disorder from 23 psychiatric and 18 primary care settings.

Methods: Data from participants treated with citalopram in the STAR*D trial were used to determine whether the age of onset of the first major depressive episode (MDE) affected the likelihood or timing of remission in depressed patients age 55-75 years. Participants were outpatients seeking treatment for non-psychotic major depression with a baseline 17-item Hamilton Depression Rating Scale (HDRS17) score of ≥ 14. The patients were openly treated with flexible doses of an SSRI, citalopram, for up to 14 weeks utilizing a measurement-based care approach (Trivedi et al., 2006). Outcomes were obtained by a central pool of research outcome assessors using telephone interviews. The groups were defined as earlier onset (age <55) of first depressive episode and late onset (age ≥ 55) of first depressive episode. Baseline characteristics, remission rates (QIDS-SR16 ≤ 5), and side effect measures were compared for the two groups.

Results: Of the 579 participants aged ≥ 55 years, 419 (72.4%) had earlier onset and 160 (27.6%) had late onset depression. No differences in remission rates (30.7% and 31.9%, respectively) using the QIDS-SR16 were found. To determine if there was an independent effect of age of onset - analyses were performed adjusting for baseline characteristics that were different except for employment status and level of education which were measuring the same factor captured by insurance status. Once again, there were no differences in rates of remission (QIDS-SR16). To determine whether the late onset or earlier onset groups took longer to reach remission, a survival analysis was performed, but no significant difference (p=0.71) was found. There were no differences in serious adverse events (SAEs), which were few in both groups (19/419 for earlier onset group; 11/160 for late onset group).Of the 579 participants aged ≥ 55 years, 419 (72.4%) had earlier onset and 160 (27.6%) had late onset depression. No differences in remission rates (30.7% and 31.9%, respectively) using the QIDS-SR16 were found. Analyses were performed adjusting for baseline characteristics that were different in order to determine if there was an independent effect of age of onset. Once again, there were no differences in rates of remission (QIDS-SR16). To determine whether the late onset or earlier onset groups took longer to reach remission, a survival analysis was performed, but no significant difference (p=0.71) was found. There were no differences in serious adverse events (SAEs), which were few in both groups (19/419 for earlier onset group; 11/160 for late onset group).

Discussion: In patients over age 55, the reported age at onset of first major depressive episode did not predict outcome or time to remission.

57. Aripiprazole Therapy in Older Adults with Bipolar Disorder

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Background: Bipolar disorder in older adult populations has gained increasing attention due to the growing proportion of elderly in the U.S. and worldwide. A continuing unmet need is the identification of agents that are generally well tolerated and effective in later life bipolar disorder. Aripiprazole is an atypical antipsychotic compound which is FDA approved for the treatment of bipolar mania and for the long-term treatment of bipolar disorder. This is an open-label prospective trial of aripiprazole therapy in 20 older adult patients with bipolar disorder.

Methods: Older adults with bipolar disorder I who were currently sub-optimally responsive to their treatments received 12 weeks of

open- label aripiprazole added on to existing mood stabilizer medication treatment. Aripiprazole was initiated at 5 mg daily and increased as tolerated. Efficacy outcomes included psychopathology scores (Young Mania Rating Scale/YMRS), Hamilton Depression Scale/ HAM-D), extrapyramidal symptom assessments, and level of functioning measurement (Global Assessment Scale /GAS).
Results: Twenty older adults (mean age 59.6 years, range 50-83 years) received aripiprazole therapy. The majority of individuals had bipolar depression. On preliminary analysis, individuals had significant reductions in depression scores (Hamilton Depression Rating Scale/HAM-D base =13.4, HAM-D end (LOCF) = 7.5, p<. 001), as well as mania scores (Young Mania Rating Scale/YMRS base= 8.4, YMRS end (LOCF)= 5.6, p<. 03). There were also significant improvements in functional status as measured by the Global Assessment Scale/GAS (p= .001) Mean daily dose of aripiprazole was 10.26 mg/day SD ± 4.9, range 5-20 mg/day. Overall, aripiprazole was well tolerated in this older adult population.
Discussion: Aripiprazole appears efficacious and well tolerated in older adults with bipolar disorder. Of particular note, aripiprazole therapy was associated with improvements in bipolar depression in this older population. However, larger, controlled trials are needed to confirm these preliminary findings.

58. Effect of Long-Acting Risperidone on Suicidality in Patients with Frequently Relapsing Bipolar Disorder
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Sponsor: Ross J Baldessarini

Background: Suicide is the leading cause of increased mortality for patients with bipolar disorder (BPD). More than 25% of patients with BPD attempt suicide at least once, and nearly 15% die of suicide. Currently, lithium is the only treatment for BPD that has strong evidence of reducing risk of completed suicide and of attempts in BPD. Atypical antipsychotics are increasingly used for treatment of manic symptoms of BPD, and some may limit recurrences of BPD illness. An ongoing double-blind, placebo-controlled trial was designed to investigate the long-term efficacy of adjunctive treatment with risperidone long-acting injection (RLAI; RISPERDAL® CONSTA®) to limit recurrences of mood episodes and reduce suicidal thinking and behavior in patients with frequently relapsing BPD (FRBD). Data presented are from suicidal measures during the initial 16-week, open-label stabilization phase.
Methods: Patients meeting DSM-IV criteria for Type I or II BPD, with ≥4 episodes requiring clinical intervention within 12 months and ≥2 episodes within 6 months (FRBD; N=275), received open-label augmentation of treatment-as-usual with RLAI for 4 months. Measures of suicidal thinking included the InterSePT Scale for Suicidal Thinking-Revised (ISST-R) and the Montgomery-Åsberg Depression Rating Scale-Item 10 (MADRS-10).
Results: Subjects given ≥1 biweekly injected dose of RLAI (N=275) were included. Multiple logistic regression identified factors significantly associated with baseline suicidality as ongoing substance abuse (odds ratio [OR]=3.40; P = 0.028) and baseline MADRS total score (OR=1.13; P < 0.001). Country effect (USA/India) was analyzed by univariate logistic regression (OR=1.93 [95%CI=1.09–3.41]; P = 0.025). Baseline ISST-R and MADRS-10 scores were highly correlated (r_s = +0.635; P < 0.001). The mean (±SD) baseline MADRS-10 score was 1.5 ± 1.4 for subjects with initial suicidality (baseline ISST-R ≥1) and 0.2 ± 0.5 for nonsuicidal subjects (ISST-R = 0). Prevalence of ISST-R suicidal subjects decreased by 40% from baseline to endpoint (23.0% to 13.9%; n=230, McNemar P < 0.01), and mean MADRS-10 suicidal ideation scores also decreased by 40% (from 0.50 ± 0.10 to 0.30 ± 0.10; n=225, P = 0.001).
Discussion: These preliminary observations indicate a major decrease of suicidal ideation ratings during adjunctive treatment of FRBD patients with long-acting risperidone for 4 months.

59. Olanzapine Plus Carbamazepine versus Carbamazepine in the Treatment of Mania: A 6-Week, Double-Blind, Randomized Trial
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Background: The concomitant use of olanzapine (olz) and carbamazepine (cbz) occurs commonly in clinical practice. There is a potential for a drug-drug interaction between these two compounds. This study assessed efficacy and tolerability of olz (≤30 mg/d) plus cbz (400–1200 mg/d) vs cbz (400–1200 mg/d) in patients with manic/mixed episodes.
Methods: This was a 6-week, double-blind, randomized trial. Primary efficacy measure was baseline-to-endpoint changes in YMRS total. Tolerability measures included adverse events (AEs), laboratory analytes, and weight. Plasma concentrations of olz, cbz, and the 10,11 epoxide metabolite of cbz were measured.
Results: The groups (olz+cbz , n=58; cbz, n=60) did not statistically significantly differ in baseline-to-endpoint changes on any efficacy measures (LS mean, olz+cbz vs cbz: YMRS total, –15.49 vs –15.25; MADRS total, –1.22 vs –1.00; CGI-BP overall, –1.29 vs –1.35; response, 63.8% vs 66.1%; remission, 55.2% vs 59.3%; switch to depression, 10.2% vs 14.0%). Statistically significantly more olz+cbz patients reported increased ALT as an AE (6.9% vs 0.0%; p=.05). Baseline-to-endpoint changes in WBC, cholesterol, or fasting glucose were not statistically significantly different between the groups, whereas such changes in triglycerides were statistically significantly higher in olz+cbz than in cbz (LS mean, mmol/L: 0.60 vs 0.02; p=.008). Olz+cbz patients gained statistically significantly more weight from baseline to endpoint than did cbz patients (LS mean, kg: 3.1 vs 0.6; p<.001). Olz did not affect olz+cbz vs cbz treatment cbz (6.29 vs 6.27 ug/mL) or metabolite (0.79 vs 0.86 ug/mL) concentrations. The known effect of cbz on metabolic enzymes decreased the dose-normalized concentrations (C/D) of the steady-state olz by approximately 50%.
Discussion: Compared with cbz patients, olz+cbz patients had similar improvement in manic symptoms, but statistically significantly higher weight gain and triglyceride levels. While olz did not affect cbz pharmacokinetics, lower C/D olanzapine resulted from cbz induction of metabolism.

60. Mediation of Exaggerated Serotonin Syndrome-Like Behaviors and Temperature Responses in Serotonin Transporter Knockout Mice by 5-HT_{1A} and 5-HT_7 Serotonin Receptors: A Possible Model and Mechanism for Differential Human Vulnerability to the Serotonin Syndrome
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Sponsor: Dennis L. Murphy

Background: Administration of two serotonin-enhancing drugs, most often a serotonin reuptake inhibitor (SRI) and a monoamine oxidase inhibitor (MAOI), even weeks apart, can result in the development of the serotonin syndrome. This syndrome is associated with neuromuscular hyperactivity (e.g. tremor, myoclonus), autonomic hyperactivity (e.g. temperature change) and altered mental status (Gillman 2006). Following administration of the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP), which increases serotonin levels, serotonin transporter (SERT) knockout (-/-) mice display an exaggerated temperature response and exaggerated serotonin syndrome-like behaviors compared to SERT wildtype (+/+) and heterozygous (+/-) mice (Fox & Murphy 2006).
Methods: In the current research, the effects of the selective 5-HT_{1A} antagonist WAY 100635 and the selective 5-HT_7 antagonist SB 269970, either alone or in combination, on 5-HTP-induced hy-

pothermia and serotonin syndrome-like behaviors were examined in SERT +/+, +/- and -/- mice.
Results: As hypothesized, both the temperature and behavioral responses to 5-HTP were exaggerated in SERT -/- mice. In SERT +/+ and +/- mice, administration of either WAY 100635 or SB 269970 alone decreased 5-HTP-induced hypothermia, and the combination of these two drugs additively decreased this hypothermic response to near-baseline levels. In SERT -/- mice, SB 269970 significantly decreased the hypothermic response to a larger extent than that observed in SERT +/+ and +/- mice. However, WAY 100635 administration had only a small effect on hypothermia in SERT -/- mice. Further, WAY 100635 blocked several of the exaggerated serotonin syndrome-like behaviors observed in SERT -/- mice following 5-HTP administration, whereas SB 269970 had no effect on these behaviors.
Discussion: Previous research implicates a role for 5-HT_{1A} receptors in both temperature regulation (hypothermia) and serotonin syndrome-like behaviors in mice (Bert et al 2006), in addition to a role for 5-HT_7 receptors in temperature regulation (Hedlund et al 2003). The current findings confirm a role for 5-HT_7 receptors in 5-HTP-induced hypothermia in mice, and also confirm that presynaptic 5-HT_{1A} receptors are downregulated in SERT -/- mice, as the hypothermic response observed in SERT -/- mice was not affected by the 5-HT_{1A} antagonist WAY 100635. This is consistent with previous research showing that the effects of 5-HT_{1A} agonists acting on presynaptic 5-HT_{1A} receptors are attenuated or absent in SERT -/- mice (Li et al 1999). The current study also shows that postsynaptic 5-HT_{1A} receptors mediate the serotonin syndrome-like behaviors observed in SERT -/- mice, as these behaviors were blocked by WAY 100635. These findings are potentially relevant to humans, as human SERT polymorphisms, such as the "SS" genotype of the SERT 5-HTTLPR and some SERT SNPs can reduce SERT expression/function by ~50-90%. SERT mutant mice thus constitute an appropriate model for humans at potentially greater genetic risk for the serotonin syndrome. The current research impacts our understanding of the serotonin syndrome, and may contribute to the development of more targeted therapeutic approaches for its treatment.

61. Self-Regulation of Emotion: Modulation via Coordinated Dorso-Rostral Cingulate Activity in MDD

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Background: Evidence from neuroimaging studies suggest the ACC is central to the etiology of depression as a function of its role in coordination of cortico-limbic activity and imperative to modulation of cognitive control/ self-regulation [dorsal] and processing of emotional salience [rostral]. Prior findings suggest independent activity in these subdivisions. Alternatively, coordinated activity across the dorso-rostral axis may serve as the basis for self-regulation of emotion (SRE)/evaluation of prior behavior to adapt to future context. The current study evaluated the independence of activity in the dorso-rostral axis by context, using an attention-constrained task in patients with MDD and healthy controls. In addition, time-course analysis was performed to ascertain pattern and evaluate effectiveness of SRE in conjunction with behavioral performance.
Methods: Eleven healthy volunteers and eight patients diagnosed with MDD performed a gender identification variant of the Eriksen flanker task of selective attention using selected Ekman faces as stimuli. Scans were acquired on a 3T Philips Intera Achieva scanner at the Vanderbilt University Institute of Imaging Sciences. High-resolution structural images were acquired in the axial plane using a 3D-SPGR sequence (TR 10.1, TE 4.2, slice thickness 1.2mm) [TR=450ms, TE=17, FOV=24cm and slice thickness =4mm]. Twenty-eight axial interleaved 4.0 mm functional slices (with a 0.5mm skip) were acquired parallel to the AC-PC using a gradient echo spiral in/out pulse sequence providing whole brain coverage (T2*-weighted images sensitive to BOLD signal changes; TR=3000 ms, TE=28 ms, FOV= 24 cm, flip = 90 and slice thickness= 4mm). Three trial types were presented (neutral, congruent and incongruent). Affective valence (i.e., neutral, positive and negative), was alternated across runs and each valence was presented twice. Each subject performed 12 blocks of 9 trials, alternating between level of task difficulty and fixation. Only incongruent trials are presented here. Activation maps for the two groups were created separately, and regions of interest (ROIs)defined. Temporal data and beta values for ROIs within the ACC were extracted.
Results: Among controls, both dorsal and rostral ACC activation was noted across affective conditions ($p<.016$). Rostral activity was detected in BA32, whereas dorsal activity was more diffuse across both BA32 and BA24. Dorsal activation was also more robust than rostral activation for the neutral condition; in contrast, the negative and positive conditions elicited more robust rostral activation. These patterns did not hold true for the patient population. Rostral activity was restricted to BA24. Across all three conditions, rostral ACC activation was more robust than dorsal. For the positive condition, no dorsal ACC activity was elicted. With regard to time-course, presentation of the stimulus for each condition for controls lead to increased BOLD signal in ACC that peaked to maximum around 5 seconds then declined to baseline by ~15 seconds. For patients, during the negative condition, there was a sustained increase in BOLD signal in rostral ACC that did not revert to baseline until ~27.
Discussion: Current findings contradict the notion of independent activity across the dorso-rostral axis of the ACC for either patients or controls, suggesting instead, a network of coordinated activity. The pattern of these data did differ between patients and controls with the most robust response to aversive stimuli for patients, whereas the response amongst controls was less variant across conditions. Lastly, the absence of dorsal cingulate activity for the positive condition in patients and delayed dorsal activity in the other conditions suggest a basis for impaired self-regulation of emotion, particularly in response to positive contexts.

62. Duloxetine as an Effective Treatment for Adults with Generalized Anxiety Disorder: A Pooled Analysis

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Sponsor: Smriti Iyengar

Background: Selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine serotonin reuptake inhibitors (SNRI) have been recommended as first line choices for pharmacological treatment of generalized anxiety disorder (GAD). The present work summarizes the efficacy of duloxetine, a SNRI, across three independent clinical trials.
Methods: All studies were randomized, double-blind, placebo-controlled multicenter trials conducted in adult outpatients who met DSM-IV criteria for GAD. Two studies were 10-week flexible-dose treatment with duloxetine 60-120mg; 1 study was 9-week, fixed-dose treatment with duloxetine 60mg or 120mg. Inclusion/exclusion criteria and measures were consistent across studies to allow pooling of data for a comprehensive analysis. The primary efficacy outcome measure was mean change from baseline to endpoint in Hamilton Anxiety Scale (HAMA) total score. Secondary efficacy measures included HAMA Psychic and Somatic factor scores, HAMA response and remission rates, Hospital Anxiety Depression Scale (HADS) subscale scores, and Clinician and Patient Global Impressions-Improvement (CGI-I, PGI-I) scales. Response was defined as ≥50% reduction in HAMA total score from baseline to endpoint, and remission was HAMA total score ≤7 at endpoint. Functional outcome was assessed by the Sheehan Disability Scale (SDS) global functional and domain scores (work, social life, home/family responsibilities). Adverse events

(AEs) were queried at every visit in each study. Analyses were based on the intent-to-treat sample. For continuous efficacy variables, treatment group differences were performed using an analysis of covariance model with treatment and study as main effects, and baseline score as the covariate. Comparison of treatment groups for categorical efficacy measures was analyzed using a Cochran-Mantel-Haenszel test controlling for study.
Results: Across the studies, patients were randomized to duloxetine (N=668) or placebo (N=495). Mean age was 42.4 yrs, and 753 (65%) were female. Duloxetine-treated patients had significantly greater mean reduction on the HAMA total score (M= -11.1) compared with placebo-treated patients (M= -8.0) ($P \leq .001$). On each secondary measure, the duloxetine group was significantly improved compared with the placebo group: HAMA Psychic factor ($P \leq .001$), HAMA Somatic factor ($P \leq .001$), HADS subscales ($P \leq .001$),CGI-I ($P \leq .001$) and PGI-I ($P \leq .001$). Greater HAMA response and remission rates were observed with duloxetine treatment (51% and 30%, respectively) than with placebo treatment (33% and 20%, respectively, $P \leq .001$ both comparisons). Duloxetine-treated patients also showed greater functional improvement than placebo-treated patients on the SDS global functional and domain scores ($P \leq .001$). Overall rate of discontinuation was 34% for duloxetine and 31% for placebo. Discontinuation was more likely to occur for duloxetine-treated patients due to AEs ($P \leq .001$) and to occur for lack of efficacy for placebo-treated patients ($P \leq .001$). The treatment-emergent adverse events (occurred ≥5% and twice the placebo rate) were nausea, dizziness, dry mouth, fatigue, constipation, insomnia, somnolence, hyperhydrosis, and decreased libido (duloxetine vs placebo, all comparisons, $P \leq .001$).
Discussion: Within a pooled sample size of over 1100 patients with GAD, duloxetine was an efficacious treatment for reducing the severity of anxiety symptoms associated with GAD and for increasing patients' overall role functioning.

63. A Randomized, Double-Blind, Placebo-Controlled Trial of Flexible-Dose Desvenlafaxine Succinate in Adult Outpatients With Major Depressive Disorder

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Background: Desvenlafaxine succinate (DVS), a novel serotonin-norepinephrine reuptake inhibitor that is the isolated major active metabolite of venlafaxine, has shown promise for the treatment of MDD in preclinical studies.
Methods: In this 8-week, multicenter, randomized, double-blind, placebo-controlled trial conducted in the United States, adult outpatients (aged 18 to 75 years) with a primary diagnosis of MDD were randomly assigned to treatment with flexible-dose DVS (100 mg/d to 200 mg/d) or placebo. The primary efficacy outcome measure was the 17-item Hamilton Depression Rating Scale (HAM-D17) total score at the final on-therapy evaluation. The Clinical Global Impressions-Improvement (CGI-I) scale was the key secondary efficacy measure. Other secondary efficacy measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions–Severity (CGI-S) scale, Visual Analog Scale-Pain Intensity (VAS PI) overall pain score and subcomponent scores, and rates of HAM-D17 response (defined as a ≥50% reduction in HAM-D17 total scores from baseline) and remission (defined as HAM-D17 ≤ 7). Mean scores at the final on-therapy evaluation for all continuous measures were analyzed using ANCOVA with baseline score as covariate, except for the CGI-I (ANOVA). Response and remission rates were analyzed using logistic regression.
Results: A total of 247 patients were randomized to treatment, 234 of whom comprised the intent-to-treat (ITT) population (13 patients were excluded from the ITT population because they did not take study drug, or did not have post-baseline data or a primary efficacy evaluation while taking therapy). Between days 14 (after the initial titration period) and 56, mean daily doses ranged from 179 mg to 195 mg in the patients treated with DVS. At study endpoint, there were no significant differences in scores between the DVS (N=120) and placebo (N=114) groups on the HAM-D17 total score (primary efficacy endpoint) or the scores on the CGI-I (key secondary endpoint). However, patients who took DVS had significantly greater improvement in the MADRS total scores (P=0.047), VAS-PI overall pain (P=0.008), back pain (P=0.006), and arm, leg, or joint pain scores (P<0.001) compared with the placebo group at the final evaluation. The remaining secondary efficacy measures, including CGI-S, HAM-D17 response rate, and HAM-D17 remission rate, did not differ significantly between treatments. Treatment-emergent adverse events (TEAEs) observed in this study were in line with the SNRI class and as expected. Adverse events led to discontinuation of treatment for 3% (n=3) of patients in the placebo group and 11% (n=13) of patients in the DVS group.
Discussion: DVS was generally safe and well tolerated in this population. In this study, a flexible dosage of DVS was not statistically different from placebo for the primary or key secondary efficacy endpoints. However, DVS demonstrated efficacy on an alternate depression rating scale as well as a visual analog scale measuring overall pain associated with MDD.

64. Analysis of Relapses in Mixed Episode Patients Treated with Aripiprazole: Post-Hoc Analysis of a 26-Week, Double-Blind, Placebo-Controlled Trial

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Sponsor: Andrew Nierenberg

Background: Patients with bipolar I disorder presenting with a mixed episode are a challenging subpopulation of patients to treat, and this subpopulation appears to have a high propensity to relapse to depressive episodes (Tohen et al. Am J Psych. 2003;160:2099-2177). In a 26-week, double-blind relapse prevention study, aripiprazole treatment significantly delayed time to relapse as compared with placebo in patients with a recent manic or mixed episode with bipolar I disorder (Keck et al. J Clin Psych. 2006;67:626-637). In this trial, more subjects whose index episode was mixed were randomized to the aripiprazole arm, possibly increasing the chance of observing a depressive relapse in that group. A post-hoc analysis was carried out to study the relapses that occurred in mixed episode patients treated with aripiprazole versus placebo.
Methods: In the 26-week study, subjects with a recent manic or mixed episode were stabilized for 6 consecutive weeks (YMRS ≤10 and MADRS ≤13), and then randomized to 30 mg/day or 15 mg/day aripiprazole (n=77) or placebo (n=83). For this post-hoc analysis, the incidence of relapse into a mood episode (manic, depressive, or mixed) was assessed for mixed episode patients (placebo: n=18; aripiprazole: n=30).
Results: A frequency analysis showed that there were significantly more mixed episode patients in the aripiprazole treatment arm (30/77 [39%]) than in the placebo group (18/83 [22%]) p=0.024 (Fisher's Exact test). In 26 weeks of double-blind treatment for mixed episode patients, the frequency of no relapses was 77% (23/30) for the aripiprazole group vs 61% (11/18) for placebo, odds ratio (OR) 95% confidence interval (95% CI) = 2.09 (0.59, 7.45). For overall relapses, the frequency was numerically lower for the aripiprazole group (7/30 [23%]) vs placebo (7/18 [39%]), OR (95% CI) = 0.48 (0.13, 1.70). The frequency of manic relapses was also numerically lower for the aripiprazole group (1/30 [3%]) vs placebo (3/18 [17%]), OR (95% CI) = 0.17 (0.02, 1.80). The frequency of mixed episode relapses was 13% (4/30) for the aripiprazole group vs 11% (2/18) for the placebo, OR (95% CI) = 1.23 (0.20, 7.51). The frequency of depressive relapses

was 7% (2/30) for the aripiprazole group vs 11% (2/18) for placebo, OR (95% CI) = 0.57 (0.07, 4.46).
Discussion: In this study, the aripiprazole-monotherapy group contained significantly more mixed episode patients than the placebo group. Since mixed episode patients appear to have a higher risk for depressive relapse than patients who present with a manic episode (Tohen et al., 2003), the aripiprazole arm might have the potential for more depressive relapses than the placebo arm. Similar to the overall population (Keck et al. J Clin Psych. 2006;67:626-637), aripiprazole treatment in the mixed episode population demonstrated a lower relapse rate for manic relapses, and aripiprazole did not increase the rate of relapses into a depressive episode as compared to placebo. Given the importance of preventing depressive relapse in bipolar disorder, a trial designed and powered to prospectively monitor relapses in mixed episode patients treated with aripiprazole is warranted to confirm these post-hoc results.

65. Suicidality in Adult Paroxetine Depression Studies

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Background: To compare the incidence of suicidality (ideation or behavior) between paroxetine (PAR) and placebo (PBO)-treated adults in depressive disorder studies.
Methods: The dataset comprised 5,980 patients (PAR N=3,720; PBO N=2,260) from all GSK sponsored acute PBO-controlled trials of PAR in Major Depressive Disorder (MDD, N=19), Dysthymia (N=1), Bipolar Disorder (N=2), and Intermittent Brief Depression (IBD, N=2). MDD trials contributed the majority of patients (3455/3720 [92.9%] for PAR; 1978/2260 [87.5%] for PBO). An expert panel blindly reviewed and categorized all potential cases detected by search of adverse events (AEs) as definitive suicidal behavior or ideation or as non-suicidal. Incidence rates were calculated for all depressive disorders combined and for each disorder separately. Results are presented as odds ratios (OR) with 95% confidence intervals (CIs) and p-values (adjusted for trial using exact inference methods). Efficacy in MDD was assessed by improvement on HAMD/MADRS scores, using both change from baseline as well as responder analyses (percent of patients with ≥50% reduction in total score). The number-needed-to-harm (NNH) and number-needed-to-treat (NNT) were calculated.
Results: For definitive suicidal behavior or ideation (DSBI; the primary endpoint), there was no significant difference between PAR and PBO overall (66/3720 [1.8%] vs. 47/2260 [2.1%]; OR = 1.1 [95% CI 0.7, 1.7]; p=0.671). Similarly, for definitive suicidal behavior alone (DSB) there was no difference between PAR and PBO (43/3720 [1.2%] vs. 36/2260 [1.6%]; OR = 1.2 [95% CI 0.7, 1.9]; p=0.613). In the MDD dataset, there was no significant difference between PAR and PBO for DSBI (31/3455 [0.9%] vs. 11/1978 [0.6%]; OR = 1.3 [95% CI 0.7, 2.8]; p=0.493). There was, however, evidence of increased suicidal behavior alone for PAR (11/3455 [0.3%] vs. PBO (1/1978 [0.1%]); OR = 6.7 [95% CI 1.1, 149.4); p=0.058). All cases of DSB for PAR in the MDD dataset were suicide attempts, with 8/11 events occurring in patients ≤ 30 yrs of age (3 events were in patients 18-24 yrs of age and 5 events were in patients 25-30 yrs of age). The overall incidence of DSBI in MDD patients 18-24 yrs of age was 2.2% for PAR (5/230) and 0.0% (0/104) for PBO. In comparison, the overall incidence of DSBI in MDD patients age 25 and older was 0.8% for PAR (26/3225) and 0.6% for PBO (11/1874). There were no completed suicides in the MDD dataset. MDD patients receiving PAR demonstrated significant improvement compared to PBO based on change from baseline in HAMD (-10.9 vs -8.4; p<0.001) and MADRS (-12.2 vs -8.5; p<0.001) total scores, as well as percentage of responders (52.3% vs 37.1%; OR=1.8 [95% CI=1.6, 2.0]; p<0.001). Of note, the efficacy of PAR in young adults (18-24 yrs of age) was less robust than among older adults. Across age groups of patients with MDD, the NNH for DSB was 345.2 while the NNT for responders was 7.2.
Discussion: An increased risk of suicidal behavior for PAR vs PBO was observed in the MDD dataset, with proportionally more events occurring in younger adults. The trend for more events in young adults is consistent with findings from previous analyses in adolescents, but the extent to which the risk seen in pediatric patients may extend beyond age 18 is unclear. The incidence of DSBI was similar between PAR and PBO, both overall and in the MDD dataset alone. Considering the evidence for efficacy, the overall risk:benefit of PAR in the treatment of adult MDD patients remains positive. These data continue to highlight the need for careful monitoring of patients at risk for suicide.

66. Functional and Structural Correlates of Conditioned Fear in Human Dorsal Anterior Cingulate Cortex

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Sponsor: Scott L. Rauch

Background: Convergent data from rodents and humans indicate that the amygdala is a critical structure in the acquisition and expression of conditioned fear. Recent preliminary rodent studies have begun to implicate the prelimbic (PL) region of the medial prefrontal cortex in fear conditioning (Quirk, pending). For example, electrical microstimulation of PL during extinction training enhanced conditioned freezing, and retarded extinction. Inactivation of PL in rats during fear acquisition interferes with the expression of conditioned freezing, suggesting that in addition to the amygdala, this brain region is also involved in mediating conditioned fear responses. Previous human studies suggest that the dorsal anterior cingulate cortex (dACC) may play a similar role to PL in mediating fear responses. For example, it has been previously reported that intra-operative electrical stimulation of dACC induces feelings of intense fear. The present study aimed to examine the role of the dACC during conditioned fear acquisition in healthy humans using magnetic resonance imaging.
Methods: Two separate experiments were performed using independent samples of 14 healthy subjects each. Experiment 1: subjects underwent a fear conditioning protocol during which a conditioned stimulus (CS+, picture of a virtual light) was paired with an unconditioned stimulus (US, an electric shock). Skin conductance response (SCR) magnitude was the behavioral index of conditioning. Participants underwent magnetic resonance imaging scans to obtain structural images, from which cortical thickness was measured. We performed a vertex-based analysis across the entire cortical surface to measure cortical thickness and map correlations between this measure and SCR. Experiment 2: subjects underwent fear conditioning while fMRI (at 3T) and SCR data were obtained. FMRI analyses included: 1) contrasting the CS+ vs. CS- (a different color of light not paired with shock) during fear acquisition; 2) voxel-wise correlational analysis between SCR and functional activation across the entire brain using SPM2; and 3) functional connectivity analysis (in which the dACC region found to be activated during fear acquisition was taken as seed, see below) using SPM2.
Results: Experiment 1 showed that cortical thickness at a locus within dACC was positively correlated with SCR magnitude during conditioning (r = 0.70, p = 0.005). Experiment 2 showed: 1) significant activation in the dACC to the CS+ relative to the CS-; 2) significant correlation between activation in the dACC and SCR magnitude (r = 0.84, p = 0.0001); and 3) dACC activation was positively correlated with amygdala activation (r = 0.83, p = 0.0002).
Discussion: These convergent results from two different cohorts of healthy controls and across the various analyses strongly suggest that the dACC may function in concert with the amygdala to mediate conditioned fear responses in humans. It is worth noting that this region of the dACC found to be structurally and functionally correlated with increased expression of conditioned fear approximates the target of

anterior cingulotomy, an ablative surgical treatment for patients with intractable obsessive compulsive disorder. Thus, the current findings in healthy humans together with recent findings in rodents and psychiatric neurosurgical experience implicate this territory as a potential target for future anti-anxiety therapies.

67. P2RX7: A Susceptibility Gene for Mood Disorders

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Background: Major depression and bipolar disorder, among the most prevalent mental disorders, are influenced by environmental and genetic factors. Previous results from our genetic analyses in a French Canadian population suggested that the interval delimited by markers D12S86 and D12S378 on chromosome 12 was the most probable genomic region to contain a susceptibility gene.
Methods: Association studies using case/control samples from the French Canadian population (n=423) or from a German population (n=1000). P2RX7 gene expression studies in transfected and/or transformed cells.
Results: Association results revealed significant allelic associations between the bipolar phenotype and a marker located in intron 9 of the P2RX7 gene. Following analysis of the surrounding genomic region in bipolar families for the presence of polymorphisms in regulatory, coding and intron/exon junction sequences, the strongest association was observed at the non–synonymous SNP rs223091 (p-value = 0.000708), which results from an over-transmission of the mutant G-allele to affected offspring. In a follow up study we investigated 29 single nucleotide polymorphisms (SNPs) within the P2RX7 gene and adjacent genes in a sample of 1000 German Caucasian patients suffering from recurrent major depressive disorder (MDD) and 1000 controls. The same non-synonymous coding SNP in the P2RX7 gene (rs2230912), previously found to be associated with bipolar disorder, was significantly associated (p=0.0019) with MDD. Psychosocial stress factors are the major cause for onset of affective disorder and exposure of cell lines to glucocorticoids resulted in a down-regulation of P2RX7 mRNA levels.
Discussion: P2RX7 is a purinergic ATP-binding calcium channel expressed in neurons as well as in microglial cells in various brain regions. The Gln460Arg polymorphism (rs2230912) occurs at an amino acid that is conserved between human and rodents and is located in the C-terminal domain of the P2X7 receptor, known to be essential for normal P2RX7 function, suggesting that it might play a causal role in the development of depression. In keeping with a role of P2RX7 in the aetiology of mood disorders, its expression is diminished by glucocorticoids and modified by both antidepressant agents and mood stabilizers. While studies interrelate immunity and depression and the role of the purinergic receptor P2X7 in immune responses is well documented, the relationship of this to BP MDD remains to be elucidated.

68. Predator Threat Induces Behavioral Inhibition, Pituitary-Adrenal Activation and Changes in Amygdala CRF System Gene Expression

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Sponsor: Ned H. Kalin

Background: Behavioral inhibition (BI) is an adaptive defensive response to threat; however, extreme BI is associated with anxiety-related psychopathology. When rats are exposed to a natural predator they display stress- and anxiety-related behavioral alterations and physiological activation. To develop a preclinical rodent model to study mechanisms underlying human BI and anxiety, we examined the extent to which ferret exposure elicits anxiety-related BI and HPA and amygdala activation of the CRF system.
Methods: In the first experiment, BI and other behaviors were assessed in the presence or absence of the ferret. In the second experiment, ferret-induced corticosterone release and changes in amygdala c-fos expression were assessed. In the final experiment, gene chip and quantitative real time-PCR (qRT-PCR) analyses were performed on amygdala tissue from control and ferret-exposed rats.
Results: We report here that ferret exposure increased BI and submissive posturing, as well as plasma corticosterone, and the number of Fos-positive cells in several subnuclei of the amygdala. Gene expression analysis revealed increased amygdala CRF-binding protein mRNA and a trend for an increase in CRF_1 receptor mRNA, but no change in CRF_2 receptor or CRF mRNA.
Discussion: These results demonstrate that ferret exposure can be used to elicit anxiety-related BI in rats that is associated with HPA and amygdala activation. Since the amygdala and the CRF system have been implicated in adaptive and maladaptive anxiety responses in humans, these data support use of our rodent model to further investigate mechanisms underlying anxiety-related psychopathology.

69. A Candidate Gene Study of Thalamic Volume in Pediatric Obsessive-Compulsive Disorder

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Sponsor: Past Travel Awardee, ADAA, 2004

Background: A previous neuroimaging study conducted by our group demonstrated increased thalamic volume in pediatric patients with obsessive-compulsive disorder (OCD) compared with age-matched controls. The purpose of this study was to determine if candidate genetic variants previously studied in OCD were associated with thalamic volume.
Methods: We studied 25 medication-naïve children and adolescents with OCD, who had been scanned using magnetic resonance imaging (MRI).Genotyping was performed on 12 polymorphisms in the following four candidate genes: the glutamate transporter SLC1A1, Glutamate Receptor Ionotropic N-methyl-D-aspartate 2A (GRIN2A), GRIN2B, and the dopamine 1 receptor (DRD1). Variants were selected based on results from earlier candidate gene studies in OCD. For each variant, genotype groups were examined using Analysis of Covariance (ANCOVA) for differences in volume of the thalamus after controlling for age and total intracranial volume.
Results: Two genotypes were associated with increased total thalamic volumes: SLC1A1- rs3056 G/G (p=.02) and DRD1-1251 G/G (p=.006). These findings were both consistent with previous family-based studies conducted by our group in which the same alleles were over-transmitted to OCD probands.
Discussion: These results, which were not corrected for multiple comparisons, provide preliminary evidence that SLC1A1 and DRD1 sequence variation may be associated with increased total thalamic volume in pediatric OCD. Taken together, the genetic and neuroimaging data suggest that thalamic volume warrants further study as a potential endophenotype of OCD. Replication in larger samples is needed to confirm these findings.

70. Adult Outcome in Children with Obsessive-Compulsive Disorder

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Background: OCD occurs from 1-3% in pediatric and adult populations alike. The majority of cases of adulthood OCD begin in the late

teenage years. Thus, it appears that many of the childhood onset cases of OCD may remit by early adulthood. A meta-analysis of long-term outcome studies suggests that between 40% and 59% of childhood onset OCD cases will remit by adulthood. However, previous pediatric OCD long-term outcome studies have had follow-up intervals that ranged from only 1-5 years and many have been retrospective in design and thus are prone to recall bias. We conducted this study to determine the adulthood outcome of children who had been treated for OCD at the Yale Child Study Center 10 or more years ago.
Methods: We interviewed 61 adults (45 male, average age=20.8 +/-3). Participants were recruited from a list of individuals who had been evaluated and treated for OCD at the Yale Child Study Center 10 or more years ago. Original evaluation included measures of OCD severity, tics and ADHD severity, and focused neuropsychological evaluations, and/or 1.5-T structural MRI scans. Follow-up clinical interviews consisted of measures of OCD current and worst-ever symptom severity, comorbid tics, ADHD, depression, anxiety and global psychosocial functioning. We conducted this study to determine the rate of symptom remission by adulthood in childhood onset OCD. Remission was defined as Y-BOCS score <12, clinical OCD as Y-BOCS ≥12, and severe OCD as Y-BOCS ≥24.
Results: At follow-up only 37.7% (n=23) of the sample had clinically significant OCD symptoms (Y-BOCS>12), while only 10% (n=6) had severe symptoms (Y-BOCS≥24). Average Y-BOCS score at follow-up in adulthood was 10.2 +/- 9 compared to 27.6 +/- 8 at worst-ever (age=11.8 +/- 3). 50.8% (n=31) of our sample experienced remission of OCD symptoms and they did so at an average age of 15.9 years. At the time of follow-up, 26% (n=16) had discontinued use of SSRI's that they had used in childhood, while 64% (n=39) of sample continued using SSRI's. 24% (n=15) of our sample at follow-up had a history of MDD. One participant was diagnosed with Bipolar disorder and one Aspergers at follow-up.
Discussion: OCD symptoms greatly improved by adulthood in this large cohort of patients with childhood-onset OCD. 77% of patients reported that they were "very much" or "much improved" on the Patient-Rated Global Improvement compared to their childhood symptom severity. These results largely confirm those of the meta-analysis by Stewart et al. (2004) that 30-59% of childhood OCD cases remit by adulthood. Further research is needed to determine predictors of adulthood remission in children with OCD. Based on previous literature we specifically hypothesize that earlier age of onset, increased severity of childhood OCD symptoms, increased IQ and presence of a comorbid tic disorder may be associated with poor outcome in childhood OCD. Further studies are needed to test these hypotheses.

71. A Normative Study of Neuropsychological Performance in Treatment Resistant Depression

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Background: Treatment resistant depression (TRD) is a significant mental health problem leading to substantial morbidity and mortality. Despite the disability that is associated with this condition, there is little information available about the determinants of this disability, with essentially no information available about the cognitive impairments seen in TRD. As cognitive impairment is a major determinant of disability across neuropsychiatric conditions, understanding the role of cognitive impairments in TRD, including both the profile and severity of these impairments, is clinically important.
Methods: In a large, multinational study of atypical antipsychotic treatment of TRD, a structured baseline cognitive assessment was performed on 297 of the 489 patients in the trial. This computerized assessment measured multiple cognitive domains including processing speed, working and episodic memory, and executive functioning. Normative data for healthy comparison subjects matched to the TRD population in age, education, and gender were also collected using the same assessment methodology.
Results: The profile and severity of performance relative to the healthy comparison sample will be described. Using regression-based techniques, standard scores will be calculated for each of the performance domains and for the overall composite score. These results will be used to examine the previously presented data on cognitive response following antipsychotic treatment.
Discussion: Evaluating the severity and profile of cognitive impairment in TRD will be a substantial step in understanding the determinants of disability in this condition. This information will be useful for interpreting the results of later, probably smaller studies, of TRD as well.

72. Distinct Electrophysiological Effects of Paliperidone and Risperidone on the Firing Activity of Rat Serotonin and Norepinephrine Neurons

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Background: Paliperidone is the 9-hydroxy metabolite of the atypical antipsychotic risperidone and both drugs share similar in vitro receptor binding profiles. Risperidone was shown to reverse the escitalopram-induced inhibition of locus coeruleus (LC) norepinephrine (NE) neuronal firing activity mainly through a serotonin (5-HT)2A receptor mediated action (Biol Psychiatry, Epub: August 23, 2006). Thus, non-response to SSRIs in some patients with major depression may be explained by a decreased NE tone and the beneficial effect of atypical antipsychotics by its reversal. The present study was first aimed at determining if paliperidone exerts distinct in vivo effects on 5-HT and NE neuronal activity from those of risperidone, and second, to determine if paliperidone acts in a similar manner on the firing activity of 5-HT and NE neurons as risperidone when it is combined with the SSRI escitalopram.
Methods: Extracellular single unit recordings were carried out from rat dorsal raphe and locus coeruleus under chloral hydrate anesthesia (400 mg/kg, i.p.).
Results: Acute administration of risperidone (0.4 mg/kg, i.v.) produced a robust inhibition (about 70 %) of firing rate of dorsal raphe nuclei (DRN) 5-HT neurons. This inhibition was partially reversed by the NE reuptake inhibitor desipramine (5 mg/kg, i.v.) and completely overturned by the 5-HT1A antagonist WAY 100635 (0.05 mg/kg, i.v.) given after desipramine. The same degree of inhibition of 5-HT neurons was observed after 2 or 14 days of risperidone administration (1 mg/kg/day, s.c.). However, the same regimen of paliperidone did not alter the firing rate of 5-HT neurons neither after 2 or 14 days of administration. Escitalopram administration for 2 days (10 mg/kg/day, via osmotic minipumps implanted subcutaneously) decreased the firing activity of 5-HT and NE neurons, as previously reported. After 14 days of sustained administration of escitalopram, the firing activity of 5-HT, but not of NE neurons, recovered to the value of control animals. Neither risperidone nor paliperidone modified the escitalopram-mediated inhibition of 5-HT neuronal firing activity. Paliperidone, as observed with risperidone, did not alter the firing rate of NE neurons when given by itself but reversed the escitalopram-induced suppression of NE neuronal firing. However, differently from risperidone, paliperidone co-administered with escitalopram did not initially elevate the firing rate of NE neurons above the value of control animals after 2 days of concomitant administration, although both drugs normalized the firing rate of NE neurons after 14 days of escitalopram treatment.
Discussion: It can therefore be concluded that paliperidone and risperidone do not alter the activity of 5-HT and NE neurons in a similar manner. Risperidone, unlike paliperidone, inhibits in a sustained manner the firing of 5-HT neurons most likely by enhancing 5-HT release in the DRN and by antagonizing excitatory α1-adrenoceptors on 5-HT neurons. This is supported by the reversal of the inhibitory action of risperidone by a 5-HT1A autoreceptor antagonist

and by a NE reuptake inhibitor. The capacity of both paliperidone and risperidone to reverse the SSRI-induced inhibition of NE neuronal firing rate, albeit paliperidone not producing an initial overshoot of firing, suggests that paliperidone may be beneficial in SSRI-resistant depression. This would result from a reversal of the suppressant effect of SSRIs on NE neuronal firing without attenuating the firing activity of 5-HT neurons.

73. Sustained Remission in Bipolar I Disorder: An Post-Hoc Analysis of an Aripiprazole Bipolar Study

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Sponsor: John March

Background: Remission is a key goal after treating an acute episode of bipolar I disorder. An analysis was carried out to differentiate symptomatic point remission vs. sustained remission using standard criteria of Young Mania Rating Scale (YMRS) ≤12 and more rigorous criteria. A study with olanzapine using more rigorous criteria to define remission showed that clinically meaningful symptomatic remission is achieved slowly and maintained for ≥8 weeks by only some patients within an average of 7 months of continuous treatment (Chengappa et al. Bipolar Disord. 2005;7:68-76). In the present study, remission rates from a 26-week, double-blind, placebo-controlled study (Keck et al. J Clin Psych. 2006;67:626-637) were analyzed in patients diagnosed with bipolar I disorder.
Methods: For the 26-week trial, subjects with a recent manic or mixed episode were stabilized for 6 consecutive weeks and then randomized to 30 mg/day or 15 mg/day aripiprazole (n=77) or placebo (n=83). For this remission analysis, symptomatic remission rates were assessed using 2 different criteria: 1) YMRS ≤12 and 2) YMRS ≤7, Montgomery-Asberg Depression Rating Scale [MADRS] ≤10, and Clinical Global Impression-Bipolar scale (CGI-BP)-Improvement =1. Sustained remission rates used these same criteria and included a time component of ≥ 8 consecutive weeks.
Results: For symptomatic point remission in a 26-week trial, 86% (66/77) of aripiprazole subjects achieved a YMRS ≤12 at Weeks 8, 16, and 26 (LOCF analysis). For symptomatic point remission at Week 8 using the more rigorous criteria (YMRS ≤7, MADRS ≤10, and CGI-I =1), 79% (61/77) of aripiprazole subjects achieved a YMRS ≤7. Of this cohort, 79% (48/61) achieved a YMRS ≤7 and a MADRS ≤10, but only 21% (13/61) of this cohort achieved all 3 criteria. For Week 16, 78% (60/77) of aripiprazole subjects achieved a YMRS ≤7. Of this cohort, 77% (46/60) achieved a YMRS ≤7 and MADRS ≤10, and 18% (11/60) achieved all 3 criteria. For Week 26, 75% (58/77) of aripiprazole subjects achieved a YMRS ≤7. Of this cohort, 74% (43/58) achieved a YMRS ≤7 and MADRS ≤10, and 16% (9/58) achieved all 3 criteria. Using YMRS ≤12, sustained remission rates in a 26-week trial for all visits at Weeks 8, 16, and 26 were 75% (58/77), 73% (56/77), 71% (55/77), respectively (LOCF analysis). Using the more rigorous criteria, the sustained remission rates at Weeks 8, 16, and 24 were lower than the rates assessed with YMRS ≤12. Of the cohort sustaining a YMRS ≤7 at Week 8, 95% (42/44) and 93% (41/44) sustained this remission rate at Weeks 16 and 26, respectively. At Week 8, 64% (28/44) of the cohort sustaining YMRS ≤7 also sustained a MADRS ≤10. At Weeks 16 and 26, 79% (22/28) and 75% (21/28) of the cohort sustaining YMRS ≤7 and a MADRS ≤10 at Week 8 continued to sustain both remission criteria.
Discussion: Defining clinically meaningful symptomatic remission has yet to be validated in the bipolar population. However, Chengappa and colleagues (2005) in an open-label study, using more rigorous criteria than the standard YMRS ≤12, have shown that remission is slow to attain and even more difficult to sustain. In double-blind conditions, these data confirm that sustaining remission is difficult, and indicate that there is fluctuation in symptomatic stability in the bipolar population. Finally, sustained remission at 8 weeks appears to be a good predictor for continued remission as shown by the high retention rate of sustained remission at Weeks 16 and 26 in aripiprazole-treated subjects.

74. Quetiapine Monotherapy Improves Anxiety Symptoms in Bipolar Depression: Results from Two Randomized, Double-Blind Placebo-Controlled Studies

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Background: Patients experiencing depressive episodes of bipolar disorder frequently experience anxiety symptoms. Quetiapine has previously demonstrated efficacy in improving depressive symptoms and anxiety symptoms in the first quetiapine monotherapy study, BOLDER I (Calabrese, et al 2005; Hirschfeld, et al 2006) in patients with bipolar depression. A confirmatory study, BOLDER II, has now also demonstrated similar results. The current analysis evaluated the effect of quetiapine monotherapy on anxiety symptoms in patients with bipolar depression within the two BOLDER studies.
Methods: A post-hoc analysis of anxiety symptoms in patients with bipolar I or II depression (as defined by Diagnostic and Statistical Manual of Mental Disorders, fourth edition [DSM-IV]) who entered either of two double-blind, randomized, placebo-controlled 8-week studies of quetiapine monotherapy (300 or 600 mg/d; once-daily, evening dosing) was conducted. Anxiety symptoms were assessed using Hamilton Rating Scale for Anxiety (HAM-A) total scores, and HAM-A psychic (items 1-6, 14) and somatic anxiety (items 7-13) factor scores. Change from baseline in these scores at each assessment was evaluated using Mixed Model Repeated Measures (MMRM) analysis.
Results: Data are from a total of 1051 patients (quetiapine 300 mg/d: n=353, quetiapine 600 mg/d: n=349, and placebo: n=349). Mean baseline HAM-A total scores were similar across the treatment groups (quetiapine 300 mg/d: 18.9 [SE=0.4]; quetiapine 600 mg/d: 18.6 [SE=0.4]; placebo: 18.6 [SE=0.4]), and were consistent with mild to moderate anxiety. There was a significantly greater improvement from baseline in mean HAM-A total scores at the first evaluation (Week 1) in both quetiapine groups compared with placebo (change from baseline 300 mg/d: –4.59, P<0.001; 600 mg/d: –4.10, P=0.003 vs placebo: –2.77). These improvements were sustained through to Week 8 with both quetiapine doses (300 mg/d: –10.12, P<0.001; 600 mg/d: –10.48, P<0.001 vs placebo: –6.88). The therapeutic effect sizes for quetiapine 300 and 600 mg/d were 0.56 and 0.62, respectively. Eleven of 14 items of the HAM-A were significantly improved with both quetiapine doses compared with placebo after 8 weeks of treatment. At Week 8, in both dose groups, there were also significant improvements from baseline in HAM-A psychic (both P<0.001) and somatic (both P<0.01) anxiety factor scores in the quetiapine 300 mg/d and 600 mg/d groups compared with placebo. Significant reductions in mean score were observed in the core items of anxious mood and tension following quetiapine treatment (P<0.001, both groups vs placebo). Improvement in depressive symptoms measured by the MADRS was also significantly greater in both quetiapine groups versus placebo (P<0.001) starting at first assessment (Week 1). Common adverse events included dry mouth, sedation, somnolence, and dizziness. These adverse events were generally mild to moderate in intensity.
Discussion: Quetiapine monotherapy is effective and generally well tolerated in the treatment of co-morbid anxiety symptoms in patients with bipolar depression. Supported by funding from AstraZeneca Pharmaceuticals LP. Literature References: Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al (2005). A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 162: 1351-1360. Hirschfeld RMA, Weisler RH, Raines SR, Macfadden W (2006). Quetiapine in the treatment of anxiety in patients with Bipolar I and II depression: a secondary analysis from a randomized,

double-blind, placebo-controlled study. J Clin Psychiatry 67: 355-362.

75. Nocturnal Panic and Depression: Relationship to Sleep in Panic Disorder

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Sponsor: Travel Awardee, ADAA, 2006

Background: Patients with panic disorder often complain of sleep disturbances. In addition, they have high co-morbid depression and almost 65-70% of PD patients report history of nocturnal panic attacks. It is possible that both nocturnal panic attacks and depression could be contributing to other sleep disturbances in panic disorder. In this study we examined the complex association between nocturnal panic attacks, depression, and other sleep disturbances using the National Institute of Mental Health Panic Disorder Questionnaire (NIMH-PQ).
Methods: NIMH-PQ was administered to individuals with diagnosed or suspected panic disorder and data have been collected over the past 16 years. For the purpose of this study, we report information on 773 individuals who met DSM-IIIR/IV criteria for panic disorder, with or without agoraphobia, and also completed all probes related to nocturnal panic attacks, lifetime depression, insomnia, and sleep duration.
Results: Among the whole group, significantly more panic disorder patients with nocturnal panic attacks report insomnia (p=.0001) and reported significantly fewer hours of sleep per night compared to panic disorder patients without nocturnal panic attacks (p=.0001). Likewise, significantly more panic disorder patients with lifetime depression report insomnia (p=.001) and sleeping significantly less number of hours (p=.005) compared to patients without lifetime depression. Because of the significant association between nocturnal panic attacks and lifetime depression on insomnia and subjective sleep hours, we evaluated the nature of these sleep disturbances in four subgroups [panic disorder patients without nocturnal panic attacks or lifetime depression (NP-Dep-), panic disorder patients with nocturnal panic attacks (NP+Dep-), panic disorder patients with lifetime depression (NP-Dep+), and panic disorder patients with both nocturnal panic attacks and lifetime depression (NP+Dep+)]. Subjects in these four subgroups did not differ in age, gender, and age at first panic attack. In all the four subgroups, significantly more patients reported insomnia. Among the four subgroups significantly more in the subgroup NP+Dep+ reported insomnia compared to other three groups. Even though, more patients in the subgroups NP+Dep- and NP-Dep+ complained of insomnia in comparison to the subgroup NP-Dep-, there was no difference. On comparing subjective report of sleep duration among these four subgroups (NP-Dep-, NP+Dep-, NP-Dep+, NP+Dep+), the NP+Dep+ subgroup reported significantly decreased subjective sleep duration compared to other three subgroups. On further analysis using ≤ 5 hrs as a criteria for moderate sleep restriction, approximately 20% in the subgroup NP+Dep+ and approximately 10% of patients in the subgroups NP+Dep- and NP-Dep+ reported sleeping 5hrs or less. In contrast, only 2.5% of subjects in the subgroup NP-Dep- reported sleeping 5 hrs or less.
Discussion: These results indicate that nocturnal panic attacks and lifetime depression have an independent as well as additive/interactive effect on subjective sleep in panic disorder. Possible explanation for these associations will be discussed within the context of future research.

76. Risperidone Treatment Of Resistant Depression: A Double-Blind Randomized Trial

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Background: Many patients with major depressive disorder (MDD) are suboptimally responsive to antidepressants. A variety of pharmacologic strategies are used in these patients, although relatively few have been tested systematically. Based on the effects of risperidone on monoaminergic systems, we hypothesized that it would enhance the pharmacologic effects in patients with treatment resistant depression.
Methods: Adult outpatients with DSM-IV MDD who had an incomplete response to ≥8 weeks of antidepressant treatment were randomly assigned to the addition of risperidone or placebo for 6 weeks in a double-blind multicenter trial. The dose of risperidone (or placebo equivalent) was 0.25 mg for the first 3 days, 0.5 mg on days 4 to 15, 1.0 mg on days 16 to 28. On day 29, patients could continue the 1.0 mg dose, or, in those considered by the investigator to have an insufficient response, the dose could be increased (to 2.0 mg/day), or patients could discontinue the study and receive open-label risperidone. The primary efficacy endpoint was change from baseline to week 4 (last observation carried forward, LOCF) in the least squares mean (LS mean +/- standard error [SE]) 17-item Hamilton Rating Scale for Depression (HRSD-17) total score. Remission (defined as HRSD-17 total score ≤7) and response (defined as ≥50% reduction from baseline in HRSD-17) at week 6 LOCF was calculated. Other outcomes measured at week 6 LOCF included the Clinician's Global Impressions of Severity (CGI-S) scale, and patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Patient-rated Global Improvement Scale (PGIS), and the Sheehan Disability Scale (SDS).
Results: A total of 274 patients were randomized to risperidone (n=141) or placebo (n=133). There were no significant between-group differences in demographics or symptom measures at baseline. During the 6 week study, the mean modal dose of risperidone was 1.12 (Standard Deviation [SD]=0.46) mg/day with that of placebo being 1.17 (SD=0.47) mg/day equivalents. The reduction in HRSD-17 (LS Mean +/- SE) was greater in the risperidone than the placebo group at week 4 LOCF (-8.8 +/- 0.63 vs. -7.07 +/- 0.68, respectively; p=0.027) and week 6 LOCF (-10.5 +/- 0.68 vs. -8.06 +/- 0.68, respectively; p=0.004). The percentages of patients attaining the HRSD-17 criteria of remission and response at week 6 LOCF were greater in the risperidone than the placebo group (remission: 19.7% vs. 9.5%, respectively; p=0.016; response: 40.9% vs. 28.6%, respectively; p=0.017). The risperidone group showed significantly greater improvement at week 6 LOCF in the clinician-rated CGI-S (p=0.002), and patient-rated Q-LES-Q (p≤0.002), PGIS (p=0.016) and SDS (p≤0.001). Adverse events reported in ≥5% of risperidone or placebo patients, respectively, were dry mouth (5% and 1%), headache (9% and 15%), and somnolence (5% and 2%).
Discussion: Augmentation of antidepressant therapy with risperidone produced significantly greater effects than placebo in depression severity, disability, functioning and quality of life. These results suggest that in those patients with an insufficient response to antidepressants, the use of combination therapy with placebo or risperidone improves clinician-rated as well as patient-rated responses, with the effects being greater with risperidone augmentation. Supported by funding from Janssen, L.P.

77. Aberrant Regulation of Endogenous Ouabain-Like Factor in Bipolar Subjects

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Sponsor: David Garver

Background: Ill phases of bipolar illness are associated with abnormalities in ion regulation and intracellular ion concentrations. Previously, it has been reported that mania is characterized by lower circulating levels of ion-regulating endogenous cardenolides, and that bipolar subjects lack the normal seasonal variation of these factors.

Methods: Since endogenous cardenolides are elaborated in settings of extensive physical activity, euthymic bipolar (n=14) and psychiatrically normal control (n=10) subjects were asked to exercise to exhaustion on a treadmill at 70% of their maximal capacity. Plasma concentrations of endogenous cardenolides and salivary cortisol were measured at baseline, 60 minutes, peak exercise, and post-recovery utilizing enzyme-linked immunoassays.
Results: Ouabain-like immunoreactive factor (OLF) was lower at baseline (0.005 ± SD 0.13 pg/mL in bipolar vs. 0.072 ± 0.058 pg/mL in normal control subjects, P = 0.019, power = 0.94), lower at 60 minutes (0.007 ± SD 0.1 pg/mL in bipolar vs. 0.075 ± 0.063 pg/mL in normal control subjects, P = 0.029), and trending to be lower at peak exercise (0.009 ± SD 0.122 pg/mL in bipolar vs. 0.149 ± 0.22 pg/mL in normal control subjects, P = 0.15, power = 0.83) in bipolar subjects compared to non-psychiatric controls. Other endogenous cardenolides and salivary cortisol did not vary significantly at any of the time points.
Discussion: The endogenous cardenolide, OLF, appears to be aberrantly controlled in bipolar illness. This factor may also be important in sleep-deprivation and may serve as the bridge between environmental events and biochemical changes.

78. Aripiprazole for Relapse Prevention in Bipolar Disorder: A 100-Week, Double-Blind, Placebo-Controlled Study

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Background: There are minimal long-term clinical data available on atypical antipsychotics for the treatment of bipolar disorder. A 26-week, double-blind relapse prevention study compared aripiprazole treatment with placebo in maintaining the stability of patients with bipolar I disorder (Keck et al. J Clin Psych. 2006;67:626-637). This same trial was prospectively designed to continue monitoring patients in a double-blind, placebo-controlled fashion for an additional 74 weeks, beyond the initial 26 weeks. The safety and efficacy of aripiprazole in preventing relapses of a mood episode in patients with bipolar I disorder with a recent manic or mixed episode was, therefore, evaluated for 100 weeks.
Methods: Patients with bipolar I disorder who had recently experienced a manic or mixed episode underwent an initial stabilization phase, in which they received open-label aripiprazole treatment 15–30 mg/day (starting dose of 30 mg/day) for 6–18 weeks. Patients achieving stabilization criteria (YMRS ≤10 and MADRS ≤13 for 6 consecutive weeks) entered the maintenance phase of the study, where they were randomized to double-blind treatment with aripiprazole or placebo for 26 weeks. The primary endpoint was time to relapse for manic, mixed, or depressive symptoms, defined as discontinuation due to lack of efficacy (requiring a dosing change in psychotropic medications other than study drug, or hospitalization for manic or depressive symptoms). Patients who completed the 26 week pivotal phase of the trial continued in a double-blind fashion with aripiprazole or placebo for an additional 74 weeks.
Results: In all, 161 patients met the stabilization criteria and were randomized to aripiprazole (n=78) or placebo (n=83). At 26 weeks, the time to relapse was significantly longer with aripiprazole treatment than with placebo (hazard ratio[HR]=0.52; 95%CI: 0.30,0.91; p=0.020). At 100 weeks, time to relapse was also significantly longer with aripiprazole-treated patients than with placebo-treated patients (HR=0.53; 95%CI: 0.32,0.87; p=0.011). Additionally, time to a manic relapse was significantly longer with aripiprazole-treated patients vs placebo (HR=0.35; 95%CI: 0.16,0.75; p=0.005). Over the 100 weeks, the adverse events reported with aripiprazole treatment vs placebo (≥5% incidence and twice placebo), respectively, were flu syndrome (5.2%, 0%), pharyngitis (5.2%, 2.4%), abnormal thinking (5.2%, 2.4%), vaginitis (6.4%, 0%), weight gain (6.5%, 0%), dry mouth (7.8%, 1.2%), akathisia (7.8%, 1.2%), and tremor (9.1%, 1.2%). Weight gain (≥7% increase) occurred in 15 (27%) aripiprazole-treated and 3 (5%) placebo-treated patients. Mean weight change from randomization to endpoint at 100 weeks (LOCF) for aripiprazole- and placebo-treated subjects was 0.38±0.84 kg and -1.94±0.83 kg, respectively.
Discussion: This study, to our knowledge, is the longest double-blind, placebo-controlled trial investigating the treatment of an atypical agent in patients with bipolar I disorder. Over the 100 weeks, aripiprazole monotherapy continued to delay the time to relapse in patients initially stabilized with aripiprazole for 6 consecutive weeks. Aripiprazole maintained a safety and tolerability profile consistent with other aripiprazole, placebo-controlled trials. Using the most stringent criteria for stabilization to date (YMRS ≤10 and MADRS ≤13 for 6 consecutive weeks), these data are in strong support for the safety and efficacy of aripiprazole in the long-term maintenance of stability in patients with bipolar I disorder.

79. Genetic Association Study of Treatment Response with Olanzapine/Fluoxetine Combination or Lamotrigine in Bipolar I Depression

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Sponsor: Alan Breier

Background: To evaluate common genetic variations for association with treatment response of bipolar I depression with olanzapine/fluoxetine combination (OFC) or lamotrigine.
Methods: We assessed response in 108 OFC-treated and 103 lamotrigine-treated bipolar I depressed patients in the seven-week acute period of a randomized, double-blind study comparing OFC (6/25, 6/50, 12/25, or 12/50 mg/day: N=205) with lamotrigine (titrated to 200 mg/day; N=205). Single nucleotide polymorphisms (SNPs) were genotyped in a set of candidate genes corresponding to known sites of activity or reported predictors of response for olanzapine, fluoxetine, and lamotrigine, as well as others previously associated with psychiatric disease states. Primary outcome was baseline-to-endpoint reduction in Montgomery-Asberg Depression Scale (MADRS) total score, and analysis utilized repeated measures analysis with terms for visit, genotype, genotype by visit interaction, and baseline score as a covariate.
Results: SNPs within the dopamine-D2 receptor, histamine H1 receptor, and glucocorticoid receptor (NR3C1) genes were associated with statistically significant differences in response to lamotrigine. SNPs within the Dopamine-D3 receptor gene, including the coding ser-9-gly SNP rs6280 previously associated with psychotic symptom response to olanzapine in schizophrenia, and neuronal NPAS3 transcription factor gene were significantly associated with response to OFC.
Discussion: SNPs in specific candidate genes differentially predicted response to OFC or lamotrigine treatment of bipolar I depression. Replication in other data sets is needed.

80. Olanzapine for the Treatment of Borderline Personality Disorder: Two 12-Week Randomized Double-Blind Placebo-Controlled Trials

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Background: These are the largest randomized, controlled trials to date evaluating pharmacotherapy for patients with borderline per-

sonality disorder (BPD). Two trials examined the safety and efficacy of treatment with olanzapine; the first utilized variable dosing, and the second compared fixed dose ranges.
Methods: Both multi-center, double-blind trials were 12 weeks long involving patients 18-65 years of age with a DSM-IV-TR diagnosis of BPD. Patients in the variable dose study were randomized to either olanzapine (OLZ2.5-20mg/day; N=155) or placebo (PLA N=159), while those in the dose comparison study were randomized to either 2.5mg/day (OLZ2.5, N=150), 5-10mg/day (OLZ5-10, N=148), or placebo (N=153). The primary efficacy measure was change from baseline to last-observation carried forward endpoint (LOCF) Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD) total score. Response was defined as ≥50% decrease from baseline at any time on the ZAN-BPD total score. Patients were seen in the clinic every two weeks, with a telephone visit between clinic visits.
Results: In the variable dose study, 314 patients were randomized, 71% were female, 86.9% were Caucasian, and the mean age was 31.8 yrs. Approximately half of the OLZ2.5-20 patients had a modal daily dose of 5mg or less, with the most frequent dose being 2.5mg. Baseline ZAN-BPD total scores were indicative of moderate symptoms (OLZ2.5-20: 17.01; PLA: 17.70, p=0.156). ZAN-BPD total scores decreased significantly for both treatment groups, but the magnitude of change did not differ significantly at endpoint (OLZ2.5-20: -6.56; PLA: -6.25, p=.661). Response rates did not differ significantly between groups (OLZ2.5-20: 64.7%; PLA: 53.5%, p=.062), but time to response was significantly shorter for OLZ2.5-20 relative to PLA (p=.022). In the dose comparison study, 451 patients were randomized, 74% were female and 65% were Caucasian, and the mean age was 33.0 yrs. Baseline ZAN-BPD total scores were indicative of moderate symptoms (OLZ2.5: 17.01; OLZ5-10: 17.42; PLA: 17.07, p=0.724). Relative to placebo, treatment with OLZ5-10 was associated with significantly greater decreases in ZAN-BPD total score (-8.50 vs -6.79, p=.010), while the OLZ2.5 group approached significance (-8.02 vs -6.79, p=.06). Response rates were significantly higher for OLZ5-10 relative to OLZ2.5 (73.6% vs 60.1%, p=.018) and PLA (73.6% vs 57.8%, p=.006). Time to response was significantly shorter for OLZ5-10 relative to PLA (log-rank test p=.028). Treatment-emergent adverse events reported significantly more frequently among olanzapine-treated patients included somnolence, sedation, increased appetite and weight increase. Mean weight change was significantly different for olanzapine- relative to placebo-treated patients (OLZ2.5-20: 2.86kg; PLA: -0.35kg, p<.001; OLZ2.5: 2.09kg; OLZ5-10: 3.17kg; PLA: 0.02kg, p<.001). Rates of treatment-emergent abnormal levels of fasting glucose and fasting lipids did not differ significantly between treatment groups.
Discussion: In the dose comparison study, treatment with 5-10mg/day of olanzapine was associated with significantly greater improvements in overall symptom severity, whereas the study using variable dosing did not show a significant difference compared to placebo. The types of adverse events observed in the olanzapine treatment groups appeared similar to those observed previously in adult populations.

81. Transcranial Magnetic Stimulation: Effectiveness and Safety in a Randomized, Controlled, Multisite Clinical Trial and an Open-Label Extension Study

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Background: Transcranial magnetic stimulation (TMS) uses pulsed magnetic fields to induce electrical currents in targeted cortical regions. Prior work suggests TMS may have therapeutic potential in the treatment of major depression. However, definitive conclusions of true efficacy of TMS have been hampered by limitations in prior study designs, including variable dose selection, insufficient duration of treatment, single center study design, inferior sham condition and inadequate sample size. In this report, we describe the outcome of a large, multsite (23 site) randomized controlled clinical trial of 6 weeks duration, administered at fixed treatment parameters over the left dorsolateral prefrontal cortex, compared to a sham TMS condition. Patients who failed to receive clinical benefit were offered entry into an open-label extension study, without unblinding their randomized treatment condition.
Methods: Eligible patients (N=301) met DSM-IV criteria for unipolar major depression, and had failed to receive benefit from at least one but no more than four antidepressant treatments in their current episode (ATHF criteria). All patients were medication-free during the course of the acute treatment period. Treatment parameters were standardized at 120% of motor threshold, 10 pulses/sec, with a 4 sec on/26 off cycle, for a total of 3000 pulses per session. Coil position was determined by external landmarks using a mechanical coordinate system. The sham coil was identical in appearance, acoustically similar, and held in the same manner as the active coil. Outcome was determined by blinded clinician and patient rated instruments. Safety was assessed by adverse event report and by targeted assessment of cognitive function and auditory threshold.
Results: Active TMS showed a significant benefit over sham TMS on continuous outcome measures at 4 and 6 week time points (MADRS total score: P = 0.057 and 0.058, HAMD24 total score: P=0.012 and 0.015, HAMD17 total score: P=0.006 and P=0.005). Similarly significant outcomes for contrasts between active and sham TMS were observed on categorical responder rates at 4 and 6 weeks (MADRS: 4 weeks, 18.1% v 11.0% meeting response criteria, P=0.045 and 6 weeks, 23.9% vs 12.3%, P=0.007; HAMD24: 4 weeks, 19.4% vs 11.6%, P=0.030 and 6 weeks, 23.9% vs 15.1%, P=0.042; HAMD17: 4 weeks, 20.6% vs 11.6%, P=0.018 and 6 weeks, 24.5% vs 13.7%, P=0.015). Patients who failed to receive benefit from treatment in the randomized trial were offered enrollment in the open-label extension trial without unblinding of prior treatment assignment. Patients crossing from prior treatment with sham TMS achieved response rates ~42-44% after 6 weeks of active TMS. Discontinuation rates due to adverse events were less than 5% and of similar incidence in either active or sham treatment groups.
Discussion: TMS was superior to sham for patients with major depression who failed to receive benefit from at least one medication trial. TMS was well-tolerated, with a low discontinuation rate due to adverse events. Disclosure: This study was sponsored by Neuronetics, Inc (manufacturer of the TMS device used in the study). One author (MAD) is an employee of the company. Many of the authors have received honoraria and consulting fees from the company.

82. Predictors of Response to Deep Brain Stimulation for Treatment Resistant Depression

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Background: Emerging data from the STAR*D series of publications support growing concerns about the prevalence of treatment resistant depression (TRD; Fava et al, 2006). Among the emerging somatic therapies for TRD, Deep Brain Stimulation (DBS) represents one experimental option. DBS is an established safe and effective functional neurosurgery for Parkinson's disease and Essential Tremor (Lozano & Mahant, 1998; Benabid, 2003), combining advances in magnetic resonance imaging and precision positioning of stimulation leads. This group (Mayberg et al, 2005) previously described the effectiveness of DBS to cingulate area 25 (Cg25) in 6 TRD subjects. The purpose of this analysis is to extend previous results and carry out a preliminary exploration of favorable response predictors.

Methods: All subjects (N=15) met DSM-IV-TR criteria for Major Depressive Disorder (MDD) and additional criteria for TRD. Subjects received DBS to Cg25 and were followed on a monthly basis for at least 6 months. In addition to demographic, social support, and illness related variables, the following baseline assessments were examined: Hamilton Rating Scale for Depression (HRSD-17), Montgomery-Asberg Depression Rating Scale, Beck Anxiety Inventory, and the NEO-Five-Factor Inventory. Statistical analyses were performed to determine predictors of outcome.
Results: There was a significant reduction in depression and anxiety scores at 6 months compared to baseline. Eight out of the 15 subjects achieved response (reduction in HRSD-17 score by >50%). The total HRSD-17 scores, as well as core melancholic and sleep sub-factors, were significantly improved in responders compared to non-responders by 3 months ($t=2.24$, $df=13$, $p<0.05$) and these differences were sustained for the 6 month follow-up period. Preliminary analyses suggest that a melancholic (8/12 responders) vs. atypical (0/3 responders) depression predicts response (Mantel-Haenszel Chi-square = 4.0, $p < 0.05$). Demographic and illness-related variables, including age, gender, marital status, age of onset of illness, number of depressive episodes, duration of illness, baseline HRSD17 score, Axis I comorbidity and previous transient response to ECT, did not predict outcome. Lower scores on the Agreeableness domain of the NEO-FFI were associated with favorable outcome ($t=2.37$, $df=12$, $p<0.05$).
Discussion: More than 50% (8/15) of subjects with treatment-resistant depression who received DBS to Cg25 achieved a greater than or equal to 50% reduction in their depressive symptoms at 6 month follow-up, as measured by the HRSD-17. The antidepressant effect of DBS in this population was seen at 3 months and was sustained in our 6 month follow-up data. DBS to Cg25 may preferentially improve core melancholic and sleep symptoms. Two-thirds of individuals with a melancholic depression were responders at 6 months compared to none of those with atypical depression, suggesting that depressive subtype may be a predictor of response. Demographic and illness-related variables, including duration of illness, number of episodes and previous transient response to ECT were not predictors of response in this cohort at 6 months. The conclusions of these analyses are limited by the small number of patients, and require replication in an expanded sample. There is a need for further work in elucidating predictors of response to DBS for TRD, to assist in the process of patient selection for this procedure.

83. Panic Attacks More Likely to Include Autonomic Symptoms in Patients with Hypertension than in Normotensives – A Comparison of Symptoms, and Factor Analysis

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Sponsor: Past Travel Awardee, ECNP/ACNP Fellow, 2005

Background: Hypertension is associated with panic attacks and panic disorder [Weissman et al, 1990, Davies et al, 1999]. The mechanism underlying this link is unclear but autonomic nervous system dysfunction may be implicated. Having ascertained the prevalence of panic attacks and panic disorder by DSM-III-R criteria in hypertensive patients in primary care and hospital clinics and normotensive primary care controls [Davies et al, 1999], here we determine whether there was an excess of autonomic symptoms: "sweating", "flushes" and "racing heart" occurring in attacks experienced by hypertensives compared with attacks experienced by normotemsives. Using factor analysis, we examined the further hypotheses that autonomic symptoms may cluster together as a distinct factor in panic attacks, and that this factor is more prevalent in hypertensive than normotensive patients with panic.
Methods: We analysed all 346 questionnaires completed by patients in our previous study whose had experienced a full (n=287) or limited symptom panic attack (n=59) (268 diagnosed as having hypertension, and 78 never having had hypertension). Data relating to symptoms occurring during the worst attack experienced were abstracted. Frequency of the symptoms prospectively selected as primary endpoints (sweating, flushes, and racing heart) as being most likely to be of autonomic origin based on their occurence in phaeochromocytoma, were compared between hypertensive and normotensive patients. Principle components analysis was performed using STATA version 8. Factors were selected based on eigenvalues > 1 and inspection of a scree plot, and subject to varimax orthogonal rotation. Using logistic regression, odds ratios were calculated for the association of factor scores with hypertension.
Results: Of the primary endpoints, "sweating" was significantly more common among hypertensive patients than normotensives (65% v 46%, difference +18.4%, 95% CI +5.94% to +30.9%, p=0.003). For "flushes" the difference was also significant (55% v 40%, difference +15.1%, 95% CI +2.72% to +27.5%, p=0.019). There was no statistically significant difference between groups for frequency of "racing heart" (74% v 68%), or any of the remaining ten panic symptoms analysed as secondary endpoints. Principle components analysis yielded four factors with eigenvalues > 1.0. The scree plot indicated that all should be retained. Factor 1 was dominated by autonomic symptoms, notably sweating and flushes, which had loadings of 0.68 and 0.61 respectively. 'Shaking', not considered classically autonomic in our a-priori hypothesis, but sometimes of autonomic origin, was present with a lower loading of 0.57. The non-specific symptom 'feeling sick' appeared with a loading of 0.62. The remaining three factors were dominated by respiratory, cognitive and freezing symptoms respectively. On logistic regression only Factor 1 showed a significant association with hypertension, the odds ratio for hypertension being 1.37 (95% C.I. 1.05 to 1.77, p=0.018).
Discussion: Among patients who had experienced panic attacks those with hypertension were significantly more likely than normotensives to have experienced two of three autonomic symptoms, sweating and flushes, during their worst recalled attack. Factor analysis revealed these and a further symptom of possible autonomic origin, shaking, cluster together dominating a principle factor in the distribution of panic symptoms in hypertensives and normotensives. Autonomic dysfunction may contribute to the association of panic with hypertension. Further research is required to explore the utility of autonomic symptoms, especially sweating and flushing, occurring in the context of panic attacks, as markers of excess blood pressure reactivity and susceptibility to hypertension.

84. Relationship Between the 5HTTLPR Polymorphism and Behavior in Rhesus Macaques During a Separation Paradigm

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Sponsor: Kenner Rice

Background: Traumatic experiences during childhood are consistently associated with a high risk for developing depression, anxiety, posttraumatic stress disorder, and substance abuse disorders. Rhesus macaques raised without adults in a group of peers (peer-only rearing, PR) rather than with their mothers (mother-reared, MR) have been proposed as a model to study the consequences of early life stress exposure. Together with an environmental component, genetic predisposition is likely to account for inter-individual differences, since some individuals are very sensitive to stressors, while others seem to be more stress resilient. Studies investigating the influence of candidate genes in susceptibility to anxiety and depression in humans have suggested an association with a length variant in the regulatory region of the serotonin transporter gene (5-HTTLPR). The 5-HTTLPR short (s) allele has been shown to diminish transcription rela-

tive to that from the long (l) allele and to increase the risk of developing depression in individuals exposed to stressful life events. Studies from our laboratory have demonstrated that an orthologous variant in rhesus macaques (rh5-HTTLPR) is associated with increased stress axis activity in response to social separation, particularly among animals with a history of adversity in the form of peer rearing. Here, we test the hypothesis that, in the context of early rearing history, length variation in the rh5HTT gene regulatory region is also associated with differential behavioral responding to social separation.
Methods: At 6 months of age, animals were subjected to 4-day long social separations. This manipulation was performed for 4 consecutive weeks, with 3 days of reunion in between. Data were collected during both the acute and chronic phases of separation, and averages were taken over the four weeks. Factor analysis was performed on the behavioral data collected during separation, and rotated factor scores were used as dependent measures in ANOVA. Three behavioral factors were generated for each phase of separation. For acute separation, "Despair," Resilience," and "Anxiety" and, for chronic, "Despair", "Agitation", and "Behavioral pathology".
Results: Our results show that PR animals with the l/s genotype exhibit higher levels of "Anxiety" during the acute phase of separation ($P < 0.001$) and were more likely to exhibit "Behavioral pathology" during the chronic phase ($P < 0.005$). PR monkeys homozygous for the l allele show higher levels of "Despair" compared to the other three groups, during both phases of social separation ($P < 0.03$).
Discussion: These findings indicate that early stress affects the behavioral response to separation differently as a function of rh5-HTTLPR genotype and suggest that carriers of the s allele are not only more anxious, but may be more vulnerable to developing behavioral pathology in the face of chronic adversity. All research was carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals, as adopted and promulgated by the National Institutes of Health.

85. Variation in the rhNPY Promoter Region is Associated with Anxiety and Behavioral Pathology in Infant Rhesus Macaques
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Sponsor: J. Dee Higley

Background: Neuropeptide Y (NPY) is an anxiolytic peptide that is involved in modulation of stress response. As such, the NPY gene may be a good candidate for investigating genetic variation as it relates to individual differences in anxious responding and vulnerability to stress in nonhuman primates. We have identified a functional SNP (-1002T>G) in the rhNPY regulatory region, and previous studies in our lab have demonstrated the -1002 G allele to be associated with decreased CSF levels of NPY and increased alcohol consumption, but only among animals exposed to early adversity in the form of peer rearing (PR). In this study, we investigated the association between the -1002 G allele and the behavioral response to social separation stress in infant rhesus macaques.
Methods: At six months of age, subjects were separated from their attachment sources (either mothers or peers) for 96 hours for four consecutive weeks, with 72 hours of reunion in between each separation. Behavior was collected during two different phases of social separation (acute and chronic), and factor analysis was performed on the separation behaviors. Two-way ANOVA were performed on the output factor scores with rearing condition of subjects (mother-reared, MR, and peer-reared, PR) and SNP -1002T>G genotype entered as independent variables.
Results: PR G/G infants exhibited higher levels of "Agitated" behavior during both phases of separation ($P = 0.05$ for acute, $P = 0.02$ for chronic). While there was no association of the G allele with behavioral pathology (i.e., stereotypical behavior) among PR infants, follow-up repeated measures ANOVA revealed that the PR G/G subjects increased their levels of behavioral pathology as a function of stress exposure ($P = 0.003$).
Discussion: These findings suggest that NPY variation may increase anxiety in addition to vulnerability to behavioral pathology, especially among animals with a history of stress exposure. This research was carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

86. Changes in fMRI Brain Activation in Frequently Relapsing Bipolar Disorder Treated with Long-Acting Injectable Risperidone
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Background: Frequently-relapsing bipolar disorder presents a specific treatment challenge, since this course is often associated with treatment failure. Meeting this challenge requires a better understanding of how drugs influence the neurophysiology of this patient group. Properties of risperidone suggest that it may stabilize these patients, particularly in the long-acting injectable (LAI) form (Risperdal Consta®). In order to clarify the neurophysiological effects of LAI-risperidone, we examined changes in fMRI brain activation in frequently relapsing bipolar patients treated for up to 16 weeks.
Methods: Nineteen frequently-relapsing bipolar patients received open-label LAI risperidone added to treatment as usual (TUA) as part of a large, multisite clinical trial. MRI data were acquired with 4T Varian INOVA systems at U.C. and McLean Hospital. Sixteen healthy subjects were also studied. Standard gradient echo EPI images for fMRI were collected, and imaging data were processed with AFNI using standard methods to adjust for voxelwise comparisons. The identical-pairs (IP) and degraded-stimulus (DS) versions of the CPT were used as cognitive probes during fMRI acquisition. Changes between baseline and 16 weeks were examined.
Results: Contrasting baseline to week 16 of treatment, patients demonstrated significant decreased activation during the CPT-IP in thalamus and insular cortex, with increased activation in the DLPFC (BA 9) and superior frontal gyrus (BA10). Within this group, patients with clinical improvement exhibited greater activation in anterior cingulate (BA 32) and posterior attentional regions (BA 17,18). Similarly, with the CPT-DS, significantly decreased activation in orbitofrontal areas (BA 45,47) and increased activation in DLPFC (BA 46) were observed with treatment; clinical improvement was associated with the latter. Better task performance was associated with clinical improvement. Comparisons with healthy subjects suggested that these and other activation changes were consistent with normalization of brain responses during attentional tasks while receiving LAI-risperidone treatment.
Discussion: LAI-risperidone added to TUA may normalize fMRI brain activation patterns in frequently-relapsing bipolar disorder, which is associated with improved cognition and clinical improvement. This study was funded by Janssen, LP.

87. Differential Impact of Socioeconomic Status in Ethnic and Age Defined Suicides
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Background: Suicide risk has been associated with several demographic, social and psychiatric factors, yet little is known about the relative importance of these factors at various points in an individual's life or among specific racial groups. The role of socioeconomic status (SES) on suicide risk remains an open question. Reports from Europe describe increased suicide rates during times of high unemployment. Low SES is associated with poor antidepressant response

and a greater likelihood of suicidal ideation in the elderly. Obviously, further clarification of the association of SES with suicide for at-risk age groups is necessary.
Methods: Demographic and toxicology data (i.e. victim's age, gender, race, zip code, method of suicide, and alcohol and cocaine toxicology) on all declared suicides in Fulton County Georgia from 1/1/88 through 12/31/03 was extracted from autopsy records (n=1,377) of the Fulton County Medical Examiner's Office and combined with per capita income by zip code of residence for each suicide. Age groups were defined as adolescent (≤19 years), middle age (20-64 years), and elderly (≥65 years). Per capita income was dichotomized to indicate the upper (>$45,021) and lower (<$14,478) 20th percentiles. Associations between the various demographic and toxicology variables and suicide occurring within age- and race-defined groups were statistically tested.
Results: 80.6% (n=1,110) of records were fully informative. Of those, 69% were from white (n=767) and 31% from African American (n=343) victims. African American suicide victims were younger than whites (36.17±16.74 v. 46.64±18.99, t=8.82, p<0.0001). There was no difference between mean ages of victims from the poorest or richest areas after controlling for race. Compared to the respective ethnic populations of Fulton County, white suicide victims lived in poorer areas ($51,232 v. $35,893) while African Americans did not ($17,384 v. $18,179). Among adolescents, 58% were African American and 37% white compared to 28% African American and 69% white among adults ($\chi 2=33.78$; df=2; p<0.0001). Logistic regression revealed adolescent suicides were more likely to be African American (OR 3.04; 95% C.I. 1.73, 5.36) and not to have alcohol present (OR 3.13, 95% C.I. 1.52, 6.45). No associations were found with other variables, including income percentile of the area. Among elder suicides, 18% were African American and 81% white compared to 33% African American and 64% white in younger groups ($\chi 2=20.60$; df=2; p<0.0001). Logistic regression revealed suicide among the elderly was associated with being white v. African American (OR 2.81, 95% C.I. 1.78, 4.45), not using cocaine (OR 27.65; 95% C.I. 3.82, 200.05) or alcohol (OR 2.98, 95% C.I. 1.98, 4.49), and living in the poorest areas (OR 1.80, 95% C.I. 1.14, 2.84). Cox PH modeling using the Heaviside step function revealed that increasing log(per capita income) increased the risk of suicide among adolescents (HR 2.76; 95% C.I. 2.15, 3.53), particularly African Americans (HR 4.22; 95% C.I. 2.19, 8.11). Among the elderly, increasing log(per capita income) decreased the risk of suicide (HR 0.58; 95% C.I. 0.50, 0.68).
Discussion: Results of this study suggest SES is differentially associated with suicide risk among racial and age groups. White suicide victims, but not African Americans, lived in poorer areas than the respective ethnic population of Fulton County. Elderly victims were more likely to live in the poorest areas compared to younger victims. Increasing income mitigated suicide risk in the elderly, while for adolescents, particularly African Americans, suicide risk increased as income increased.

88. P2RX7, a Gene Coding for a Purinergic Ligand-Gated Ion Channel, Is Associated with Major Depressive Disorder

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Sponsor: Florian Holsboer

Background: The P2RX7 gene is located within a region on chromosome 12q24.31 that recently has been identified as a susceptibility locus for affective disorders by linkage and association studies. P2RX7 is a purinergic ATP-binding calcium channel expressed in neurons as well as in microglial cells in various brain regions. To investigate the implication of P2RX7 in major depressive disorder (MDD), we performed a case/control study in a sample of German patients with recurrent MDD and diagnosed healthy controls from the same population.
Methods: We investigated 29 single nucleotide polymorphisms (SNPs) within the P2RX7 gene and adjacent genes in a sample of 1000 German Caucasian patients suffering from MDD. These were contrasted with diagnosed healthy Caucasian controls from the same population (n=1029).
Results: A non-synonymous coding SNP in the P2RX7 gene (rs2230912), previously found to be associated with bipolar disorder, was significantly associated (p=0.0019) with MDD. Under the assumption of a "heterozygote disadvantage" model, i.e., contrasting both homozygous genotypes with the heterozygotes AG genotype, we observed an odds ratio of 1.402 with a nominal p-value of 0.0009938.
Discussion: We report genotypic association in the P2RX7 gene providing evidence that P2RX7 might indeed be a susceptibility gene for major depressive disorder. The polymorphism rs2230912 results in an amino acid exchange in the carboxy-terminal cytosolic domain of the P2RX7 channel protein suggesting that the observed P2RX7 polymorphism could play a causal role in the development of depression. Our data, in combination with the association data in bipolar patients, suggest the implication of P2RX7 in affective disorders and are consistent with the possibility that various mood disorders share some genetic commonalities. Being localized in the plasma membrane, P2RX7 is a potential drug target and thus represents an example for a possible pharmacological drug discovery strategy emerging from an unbiased genetic approach.

89. Resilience and Spirituality in Trauma-Exposed African Americans

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Sponsor: Lawrence Brown

Background: Resilience has been described as the capacity to thrive in the presence of adversity. Several characteristics have been posited to contribute to resilience, including spirituality. While clinicians have observed that spirituality is an important aspect of resilience in African Americans (AA), prior studies evaluating resilience and spirituality in this population are limited. Studies in other populations have found that personal competence and acceptance also promote resilience; these characteristics deserve further study in AA. We hypothesized that resilient (never ill) and recovered (remitted from illness) AA exposed to significant trauma would be more likely to use spirituality or have more religious involvement as compared to those who are currently ill. We also hypothesized that they would have higher personal competence and acceptance.
Methods: Patients were approached while waiting in the doctor office and were asked to complete a self-report questionnaire inquiring about their history of trauma exposure (Life Events Checklist), after obtaining written informed consent. Patients who identified at least one significant trauma were invited to participate in an in-depth diagnostic assessment that included the SCID-IV and the CAPS, conducted by trained interviewers. Of a total of 737 patients surveyed, 584 met criteria for trauma exposure. Of the 352 that were assessed, 327 had complete data. The participants were administered the Wagnild Resilience Scale-RS (1993)evaluating Personal competence and Acceptance of Self and Life. They were also administered questions derived from a Religiousness/Spirituality instrument (Fetzer Institute, 2003). Patients (n=260) were assigned to one of three groups, after excluding those with psychotic or bipolar disorders: a resilient group (n = 53) with no lifetime disorders, a recovered group with at least one past but no current disorder (n = 79), and a currently ill group with at least one current disorder (n = 128). Logistic regression analyses were conducted with the three pairs of groups as dependent variables (resilient vs. ill, recovered vs. ill, and resilient vs. recovered)

and demographic variables (sex, age, education), trauma type (assaultive vs. non-assaultive), resilience scores and religious/spirituality measures as predictors.
Results: Of the 260, 67% were female and predominantly AA (97%). Mean age was 42 years. A majority had graduated from high school (79%) and 45% had attended at least some college. Results indicated that females ($p < .001$) and a history of assaultive trauma ($p = .001$) significantly predicted resilient vs. currently ill group. In addition, there was a significant interaction between the RS score and sex ($p < .001$) in predicting resilient vs. currently ill status. Females in the resilient group had a higher score on the RS compared to the ill, while this relationship was not seen in males. The RS score significantly predicted recovered vs. currently ill ($p <.001$), with no significant interaction with sex in this comparison. Higher frequency of attendance to religious services also significantly predicted recovered vs. currently ill status ($p=.047$). None of the variables were significant in predicting resilience vs. recovered status.
Discussion: Higher resilience was associated with the absence of psychiatric illness or remission in AA. AA females that were never ill had higher resilience as compared with the currently ill. As a group, AA that have recovered from illness were more resilient than those who were currently ill. AA who had recovered from illness had attended more religious services. Prospective studies could help further evaluate whether pre-existing characteristics such as personal competence, acceptance and religious attendance are predictive of resilience after a traumatic event.

90. Effectiveness of Quetiapine in a Clinical Setting
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Sponsor: David Spiegel

Background: Highly structured pivotal randomized controlled studies suggest that quetiapine is efficacious for acute mania and acute depression in patients with bipolar disorder (BD). However, there are fewer data regarding the effectiveness of quetiapine in longer-term therapy of the more complex and diverse patients with BD commonly encountered in practice. We assessed the effectiveness of quetiapine in a heterogeneous group of patients seen in the Stanford Bipolar Disorder Clinic.
Methods: Open quetiapine was naturalistically administered to BD outpatients assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation, and followed with the STEP-BD Clinical Monitoring Form. Data were retrospectively reviewed and descriptive statistics were compiled.
Results: 96 (36 BD type I, 50 BD type II, 9 BD NOS, 1 Schizoaffective Bipolar Type) patients (mean age 42.3±13.8 years, 67% female) had a total of 99 quetiapine trials. Patients were taking a mean of 2.6±1.6 other psychotropic prescription medications and 0.9±1.4 other non-psychotropic prescription medications and received quetiapine for a mean duration of 374±357 days, with a mean final dose of 197±274 mg/day. 39/99 (39.4%) trials had quetiapine discontinued: 19/99 (19.2%) for central nervous system adverse effects (primarily sedation), 9/99 (9.1%) for inefficacy, 6/99 (6.1%) for nonadherence, 1/99 (1.0%) for nausea/vomiting, and 4/99 (4.0%) for other reasons. Thus, in 38/99 (38.4%) trials quetiapine was continued with no subsequent psychotropic added (quetiapine duration 313±335 days), in 22/99 (22.2%) trials quetiapine was continued but had subsequent psychotropic added (added subsequent psychotropic at 113±143 days, quetiapine duration 613±403 days), and in 39/99 (39.4%) trials, quetiapine was discontinued (quetiapine duration 299±295 days). The main reasons for subsequent additional pharmacotherapy were depressive symptoms > manic/hypomanic/mixed/cycling symptoms > anxiety/insomnia.
Discussion: Quetiapine had a moderate (39.4%) discontinuation rate and patients commonly continued taking quetiapine (60.6%), either without (38.4%) or with (22.2%) subsequent additional pharmacotherapy, suggesting effectiveness in a clinical setting. *This research was conducted with support from the Investigator-Sponsored Study Program of AstraZeneca.*

91. The Effects of a Glucocorticoid Receptor (GR) Antagonist on the Body Clock - A Pilot Study
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Sponsor: Travel Awardee, Young Investigator Memorial, 2006

Background: The suprachiasmastic nucleus (SCN) is the master pacemaker and timekeeper for the diurnal fluctuations in biological rhythms such as for cortisol, melatonin, changes in 24 hour diurnal blood pressure, activity cycles and renal function. Dim light melatonin onset (DLMO) is relatively free of masking effects and is considered a relatively pure marker of SCN timing. One of the strongest zeitgebers for resetting the timing of the SCN is light. Pulsing with light can be used to reset the timing of the clock. For example, morning light can effect an advance in DLMO, evening light can effect a delay in DLMO. A recent interesting study showed that light could also affect the rise of the awakening cortisol response (Leproult 1997). Herein, we explored the possibility that modifying activity of corticotropin-releasing factor (CRH) and cortisol pathways may be an intermediate step or alternate pathway to effect a change in SCN timing. A GR antagonist probe was used and its effect on DLMO was assessed as was its effect on cortisol and ACTH acrophase.
Methods: A thirty day pilot study to measure GR antagonist acute and 2 week post-medication effects was conducted. Subjects with chronic insomnia (5M, 5F, ages 41 to 61) were given a 5 day course of 600 mg of mifepristone versus placebo. Subjects with DSM-IV Axis I and other International Classification of Sleep Disorders (2000) were excluded. Dim light melatonin onset (<20 lux), cortisol and ACTH was measured at baseline, day 5 of treatment and two weeks post treatment. Blood samples were taken every 30 minutes, beginning at 1800 until 1100 to determine the nocturnal activity and awakening response. Subjects were kept in a light and activity controlled environment and caffeine intake was restricted throughout the study. Acute effects on circadian timing are reported herein.
Results: DLMO, as well as cortisol and ACTH acrophases were computed at baseline and on the fifth day of medication. Herein, DLMO is defined as the time when evening melatonin reaches a value equal to 25% of the height from baseline to its maximum. This technique compensates for inter-subject variation in peak nocturnal values. Compared to placebo, mifepristone tended to delay DLMO (effect size =0.4, SD=.35, n=5:4). Acrophase was chosen as the phase marker on the cortisol and ACTH rhythms as it is less affected by sleep and masking effects than is the nadir. ACTH acrophase was delayed (effect size = 2.77, SD=1.14, n=5:5) as was cortisol acrophase (effect size =.77, SD=1.1, n=5:5).
Discussion: This is the first study to measure mifepristone's effect on SCN timing. It is also the first study to show that modifying glucocorticoid activity may induce a change in SCN timing. The effect is analogous to the effects of evening bright light therapy. The exact mechanism for this change is not known. One possibility is that feedback loops for control of CRH and cortisol activity interact with circuits for control of melatonin from the pineal gland. Two potential locations of intersection may be the interaction with the pre-autonomic cells of the paraventricular nucleus of the hypothalamus, or indirect actions on the noradrenergic system along the pathways from the PVN, through the spinal cord and superior cervical ganglion on up to the pineal gland. A GR antagonist may have useful applications when rapid circadian shifts of several internal hormonal rhythms are needed. For example, it may be useful in travel from east to west as

well as in night-shift work. It may have applications in aspects of certain forms of depression as well. It may be useful in combination with timed administration of a melatonin agonist. Preliminary findings and effects sizes are quite interesting, yet additional study with larger sample size is needed to further explore and substantiate this effect, particularly with respect to DLMO.

92. Onset of Early Antidepressant Effects of Vagus Nerve Stimulation

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Background: Moderate antidepressant effects of vagus nerve stimulation (VNS) have been demonstrated in two open-label studies after three months, in the D01 study 31% of the treated patients reached the response criterion at this time, 44% in the D03 study. After twelve months of chronic treatment a more impressive proportion of the patients responded, 45% in the D01 study and 58% in the D03 study. This documented slow onset of antidepressant activity compared to pharmacotherapy is difficult to reconcile given the limited knowledge on putative biological modes of action of the treatment. It is however important to differentially assess the time course of depressive symptoms in treatment responders and non-responders in order to compare this treatment to others.
Methods: To address this question we analyzed data from all 116 patients included in the D01 and D03 studies. Patients suffered from chronic or recurrent treatment-resistant depression and were implanted with the VNS system and followed up according to similar study protocols (D01 / D03). Severity of depression was assessed by the 28-item Hamilton Rating-Scale of Depression (HRSD28). The response criterion (≥50% reduction of baseline HRSD28 score) was defined a priori to define response after 10 weeks of active stimulation (end of the acute study phase). According to the study protocols severity of depression was assessed before implantation (baseline), after implantation (post implant) and at study visits after 1, 2, 3, 4, 6, 8, 10 weeks of active stimulation. According to scoring at the end of the acute study phase the sample was divided in responders and non-responders. Differences in depressive symptomatology in scoring in HRSD28-items at baseline, post implant and after 1, 4, 10 weeks of active stimulation were then analyzed.
Results: 37 % (N=43) of patients met criteria for response after 10 weeks of active VNS (end of acute study phase). All items of the HRSD28 were significantly different between the two groups except for lost of weight, insight, compulsive symptoms, hypersomnia and increased appetite. At baseline and at post implant only two items were significantly different between the two groups(responders/non-responders): mood ($F(1)=4.25$, $p=0.04$; $F(1)=5.4$, $p=0.02$) and general somatic symptoms ($F(1)=7.88$, $p<0.01$; $F(1)=4.01$, $p<0.05$). After one week of active stimulation the two groups differed significantly in five items: depressive mood ($F(1)=5.68$, $p<0.02$), suicidal ideation ($F(1)=5.43$, $p<0.02$), working abilities ($F(1)=5.63$, $p<0.02$), bodily symptoms ($F(1)=4.27$, $p<0.04$), loss of energy ($F(1)=5.39$, $p<0.02$) and increased appetite ($F(1)=4.44$, $p<0.04$). After 4 weeks of active stimulation the two groups differed significantly in ten items mood: ($F(1)=10.51$, $p<0.00$), feelings of guilt ($F(1)=9.44$, $p<0.00$), suicidal ideation ($F(1)=10.12$, $p<0.00$), working abilities ($F(1)=9.44$, $p<0.00$), anxiety psychological ($F(1)<11.32$, $p<0.00$), diurnal variation ($F(1)=9.05$, $p<0.00$), hopelessness ($F(1)=5.19$, $p<0.02$), worthlessness ($F(1)=5.13$, $p<0.03$), sensitivity to rejection ($F(1)=5.81$, $p<0.02$).
Discussion: The objective of this post-hoc analysis was to characterize onset of antidepressant action for vagus nerve stimulation therapy. The major deficiency of this study is the absence of either a sham or active comparator; it would be unwise to draw any conclusions regarding time to onset of effect when compared with other antidepressant treatments. Our data show, that both a higher level of depressive mood and somatic symptoms predict lack of response after 10 weeks of treatment. While the onset of antidepressant response to VNS therapy is significantly delayed, there are depressive symptoms, especially suicidal ideation and work activity that are positively influenced very early into the treatment. These symptom level improvements might be clinically significant in this very treatment resistant patient population.

93. Escitalopram, in Contrast to Citalopram, Enhances the Excitability of the Dopaminergic Reward System in Brain and, in Addition, Gacilitates Glutamatergic Transmission in the Medial Prefrontal Cortex

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Background: Substantial evidence indicates an inhibition of dopamine (DA) mediated neurotransmission in brain by selective serotonin reuptake inhibitors (SSRIs), which may contribute to obstruct recovery from depression as well as to cause extrapyramidal side effects, sexual dysfunction, galactorrhea and more rarely gynecomastia, but also impaired cognition. In fact, preclinical studies show that several SSRIs, i.e fluoxetine, citalopram, paroxetine, setraline and fluvoxamine, all may cause a slight inhibition of the firing rate mesocorticolimbic DA neurons in the ventral tegmental area (VTA, Prisco and Esposito, Br J Pharmacol 116:1923, 1995, Di Mascio et al, Brain Res Bull 46: 547, 1998). In contrast, several studies report a cognitive-enhancing effect of selective noradrenaline reuptake inhibitors, such as reboxetine (REBOX) and atomoxetine, and our previous results show that REBOX activates VTA DA cells with a preferential effect on burst firing (Linnér et al JPET 297: 540, 2001). Here we studied the effect of escitalopram (S-CIT), citalopram (CIT) and R-citalopram (R-CIT) on the firing patterns of midbrain DA neurons in the VTA by using extracellular recording in vivo. We subsequently also tested in vitro the effects of S-CIT, CIT and REBOX on glutamatergic transmission in pyramidal cells of the medial prefrontal cortex (mPFC), which can be enhanced by DA, acting via D1 receptors.
Methods: We used extracellular single cell recording techniques to analyze drug effects on the firing activity of brain DA neurons in the VTA, identified by their typical firing characteristics and by routine histological methods. Both effects on firing rate and burst firing were recorded, using a Spike2 program (Linnér et al, J Pharmacol Exp Ther 297:540, 2001). We also used intracellular voltage clamp recordings in prefrontal pyramidal cells in a brain slice preparation with bath application of drugs. NMDA was used to induce an inward current and drugs were subsequently applied to evaluate their capacity to potentiate this current (Jardemark et al, Int J Neuropsychpharmacol 8, 157, 2005).
Results: Low doses of S-CIT, but not CIT or R-CIT, activated the mesocorticolimbic DA neurons and caused a preferential stimulation of the glutamate-driven burst firing mode, an effect which was antagonized by R-CIT. These data parallel previous results with REBOX and are consonant with a facilitated glutamatergic transmission in the brain. S-CIT and REBOX, but not CIT, potentiated NMDA-induced responses in the pyramidal cells, in similarity with atypical, but not typical, antipsychotic drugs (APDs), such as clozapine (CLOZ, Ninan et al, Synapse 48:66, 2003). In analogy with the effect of CLOZ, the enhanced glutamatergic transmission by S-CIT was blocked by the D1 receptor antagonist SCH-23390.
Discussion: Our data indicate that S-CIT, in contrast to CIT and other SSRIs, enhances the excitability of the dopaminergic reward system and, in addition, like REBOX and atypical, but not typical, APDs facilitates prefrontal glutamatergic neurotransmission. These effects of S-CIT may serve to improve mood and cognitive functions, such as response inhibition, but also to avoid detrimental effects of conventional SSRIs on other cognitive functions,

such as probalistic learning (Chamberlain et al, Science 311, 861, 2006). By inference, our results also propose that adjunct treatment with S-CIT may improve the efficacy of typical APDs in schizophrenia.

94. Proteomic Analysis of Human Norepinephrine Transporter Complexes as a Tool to Identify Biomarkers for Antidepressant Development

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Sponsor: Randy Blakely

Background: The neurotransmitter norepinephrine (NE) regulates peripheral physiology including heart rate, cardiac output, vascular tone and metabolism, and modulates autonomic, cognitive, and emotional behavior in the CNS. The norepinephrine transporter (NET) terminates noradrenergic signals by clearing NE after synaptic release. NE clearance rate and NET activity are highly regulated in vivo. Dysfunction of NE clearance and/or altered NET density has been associated with attention-deficit, depression, and suicide, as well as cardiovascular disorders. NETs are targets of psychoactive agents including cocaine, amphetamines, the tricyclic antidepressants such as desipramine, and the norepinephrine-selective reuptake inhibitors (NSRIs). Chronic administration of desipramine has been reported to alter NET density and NE uptake in vitro and in vivo. However, the mechanisms supporting change in NET density in depression or in antidepressant therapy have not been identified. In this regard, understanding regulatory mechanisms that support NET activity and NE signaling is strategically important for elucidating compromised pathways in psychiatric disorders and to identify novel therapeutic targets.
Methods: To gain a more complete understanding of regulatory mechanisms for NET, NET-associated protein complexes were purified by immunoprecipitation from NET-transfected CAD cells and analyzed by LC/MS/MS (Liquid Chromatography coupled tandem Mass Spectrometry). CAD cells, derived from mouse locus coeruleus, were chosen as a host for NET because the cells express a number of other noradrenergic neuronal markers such as tyrosine hydroxylase (TH), vesicular monoamine transporter 2 (VMAT2), voltage- gated Ca2+ (L, N), Na+ and K+ channels, and produce catecholamines.
Results: In the analyses, we identified proteins known to interact with NET or monoamine transporters such as protein phosphatase 2A complexes and 14-3-3 adaptor proteins. We also identified numerous proteins that may interact with NET and are currently under investigation for the specificity of interactions and for the roles in NET regulation. For examples, proteomic analysis of NET complexes identified multiple peptides from calmodulin, CaMKI, and CaMKII, suggesting roles of CaMKs in NET regulation. Subsequently, pharmacological inhibition and RNA interference studies establish that CaMKI and CaMKII are critical for Ca2+ dependent surface trafficking of NET. As another example, MS analyses of NET complexes identified ubiquitin (Ub) system enzymes including E3 ligase Nedd4, E2 conjugating, and E1 activating enzymes. Further studies verified that NET associates with Nedd4 E3 ligase and that NET can be mono- as well as poly-ubiquitinated. Interestingly, NET can be ubiquitinated in a manner acutely modulated by PKC activation and GPCR stimulation, and chronically regulated by antidepressants. These findings suggest that ubiquitination may control NET density and that this process might be important for antidepressant-induced neuro-adaptations.
Discussion: Systemic analysis of transporter complexes will enhance our understanding of molecular basis of regulatory pathways and may provide therapeutic strategy for NET or NE associated neurological disorders. This work is supported by NIH awards MH073662 to U.S. and MH58921 to R.D.B.

95. Comparison of Efficacy and Safety of Continuing Olanzapine to Switching to Quetiapine in Overweight or Obese Patients with Schizophrenia or Schizoaffective Disorder

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Sponsor: David Bleakman

Background: Although switching antipsychotic medications may be one approach to lessen safety concerns, the impact of switching on psychiatric symptoms is less clear. In this study, time to relapse (primary objective) was compared in patients maintained on olanzapine (OLZ) drug therapy to those switched to quetiapine (QUE). Secondary objectives included treatment effects on metabolic parameters, discontinuation rates, symptomatology, functioning and safety.
Methods: Patients with schizophrenia or schizoaffective disorder who were psychiatrically stable on OLZ treatment and obese or overweight with metabolic disorders were randomized to continue OLZ treatment (n=68; 7.5-20 mg/day) or switch to QUE drug therapy (n=65; 300-800 mg/day) for 6 months. Relapse was defined as the occurrence of at least 1 out of 3 conditions: 1) hospitalization for psychiatric reasons, 2) 20% worsening on the Positive and Negative Syndrome Scale (PANSS) Total score and an increase in level of care for psychiatric reason, or 3) 20% worsening on the PANSS Total score and worsening of CGI-S by at least one level (CGI score ≥4). Additional psychometric scales and a standard panel of laboratory tests were performed. Due to poor enrollment, the study was terminated prior to breaking the blind when about 33% of the intended sample size was achieved. All patients who enrolled prior to study termination were followed up until the last scheduled visit or discontinuation.
Results: No significant difference in time to relapse was observed between OLZ and QUE treatment groups (log-rank test, p=.293). Significantly more patients remained on treatment in the group continued on OLZ treatment (70.6%) compared to the group who switched to QUE treatment (43.1%) (Fisher's exact test; p=.002). OLZ-treated patients had significantly lower rates of study discontinuation for lack of efficacy and occurrence of psychiatric adverse events (OLZ: 2.9% ; QUE: 15.4% ; p=.015) and for "all other reasons" capturing patient and clinician decisions, protocol violations and lost to follow-up (OLZ: 14.7%; QUE: 33.8%; p=.014), but not for nonpsychiatric adverse events (OLZ: 11.8% ;QUE: 7.7% ; p=.562). Switching from olanzapine drug therapy to quetiapine did not result in significant improvement in weight, body mass index (BMI), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, fasting glucose, or hemoglobin A1c. However, statistical comparisons were significantly underpowered due to limited patient enrollment, and significant differences in study completion rates were observed.
Discussion: For patients with schizophrenia or schizoaffective disorder who are psychiatrically stable on OLZ drug therapy but overweight or obese and with metabolic disorders, switching to QUE led to earlier and more frequent discontinuations from the study.

96. Mixed States (MS) as Predictors of Polarity of Relapse in Bipolar Disorder (BD)

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Sponsor: Charles L. Bowden

Background: BD is a common, severe and recurrent illness, associated with high rates of disability and mortality, including a 20-fold higher suicide risk than in the general population. MS are intrinsic to BD and constitute > 50% of all episodes of BD. Index mood states

have both therapeutic and prognostic implications, with MS being an indicator of treatment refractoriness, poor prognosis, and an increased risk of suicide. Index mood states also have predictive value for subsequent polarity of relapse, with implications for design of future maintenance studies as well as the development of future mood stabilizers. Evidence suggests that index depressive and manic episodes are associated with a higher probability of subsequent relapses to a mood state of the same polarity, in particular for depression begetting depression. However, there are limited data with regards polarity of subsequent episodes in patients with index MS. We present findings from the largest study conducted to date limited to patients with an index episode of mixed mania.

Methods: 40 subjects with an index episode of mixed mania, while taking lithium (≥ 0.5 mEq/l), valproate (≥ 45 [l l]g/ml), lamotrigine or any combination of the three who were maintained at a stable dose for at least 4 weeks, were treated with add-on risperidone (dosage range 0.5-8mg/day) in an open label study for 20 weeks. Behavioral measures at baseline and weeks 1, 2, 4, 8 12, 16, 20 were assessed using the following scales: Schedule for Affective Disorders and Schizophrenia, Change Version (SADS-C), Young Mania Rating Scale (YMRS), Montgomery Asberg Depression Rating Scale (MADRS), Global Assessment Scale (GAS), Overt Aggression Scale (OAS), Positive and Negative Symptoms of Schizophrenia (PANSS) modified Barratt Impulsivity Scale (BIS), Internal State Scale (self rated) (ISS), Treatment Emergent Symptoms Scale.

Results: Sixteen patients (40%) completed the entire duration of the study. Twenty-seven (67.5%) patients responded to adjunctive risperidone acutely, in both manic and depressive symptomatology domains. Fifteen of the 27 (55.6%) patients who demonstrated a bimodal response to risperidone subsequently developed a symptomatic/syndromal relapse during the course of 20 weeks. All symptomatic/syndromal were depressive in nature.

Discussion: These results indicate that adjunctive risperidone is an effective acute treatment for mixed mania and in sustaining relief from manic/mixed symptomatology. Additionally, the continued use of adjunctive risperidone was efficacious in delaying/preventing subsequent emergence of manic symptoms. The results also indicate that risperidone did not adequately prevent subsequent emergence of depressive symptoms following initial relief of an index episode of MS. Additional analyses will address whether the profile of symptoms at the point of study entry, or the point of acute response, differed between patients eventually relapsing to depression from those who did not. Whether a similar pattern of results would be seen with other drug regimens will require future study. If similar outcomes occurred with adjunctive use of other atypical antipsychotics, sustained control of the manic component of MS would be anticipated with adjunctive antipsychotic regimens, but prevention of depressive relapses might require use of other medications with a different spectrum of efficacy for prevention of new depressive symptoms., These findings have implications in our understanding of the long term course of MS, including the selection of components of the treatment regimen for MS.

97. Hyperforin: Antidepressant and Neurotrophic Properties via TRPC6 Channel Activation

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Sponsor: Alfred Freedman

Background: Hyperforin is active in many behavioral models indicative of antidepressant activity, alters brain levels of serotonin, norepinephrine, and dopamine, inhibits synaptosomal uptake of all three neurotransmitters, and induces beta-receptor down-regulationin the frontal cortex of rats after subchronic treatment. In contrast to classical antidepressants, hyperforin does not directly interact with the transporter molecules, but uptake inhibition is the consequence of an elevation of the intracellular sodium concentrations, as the uptake of all neurotransmitters is strongly depending on the sodium gradient. We have previously shown that hyperforin elevates the intracellular sodium and calcium concentration by activating TRPC channels. We now report that hyperforin specifically activates TRPC6 channels and additionally mediates neuritic outgrowth via this mechanism.

Methods: With RT-PCR and western blotting we were able to confirm TRPC6 expression in PC12 cells. To directly investigate the effect of hyperforin on TRPC6 channels, we transiently transfected TRPC6 channels in HEK293 cells and analyzed hyperforin induced cation influx with whole-cell patch-clamp inside out recording technique and calcium imaging experiments.To confirm specificity, HEK293 cells transfected with other TRPC channels (TRPC1-TRPC6) and PC12 cells transfected with a negative mutant of TRPC6 were used.

Results: Hyperforin only induced a rapid and robust increase of intracellular calcium in TRPC6 transiently transfected HEK293 cells while HEK293 cells transfected with TRPC1, C3, C4, and C5 channels as well as control HEK293 cells did not respond. Calcium imaging data for TRCP6 were confirmed by patch clamp measurements. Since TRPC6 channels are activated by BDNF via TrkB receptors and are essential for nerve growth cone guidance of BDNF, we investigated possible effects of hyperforin on axonal growth of PC12 cells, an effect well known for NGF. Very interestingly, rather low hyperforin concentrations (100 nM) showed substantial neuritic outgrowth. Maximal effects were seen at 300 nM hyperforin and were similar to the effects observed for NGF (100ng/ml). Hyperforins effects on axonal growth were inhibited by the TRPC 6 channel blockers Ga3+ or La3+.

Discussion: Our findings clearly show that hyperforin, the major active ingredient of St. Johns Wort, activates specifically TRPC6 channels. By this mechanisms, not only its antidepressant properties (via elevated intracellularNa+, reuptake inhibition, and elevation of extracellular monoamine concentrations) can be explained, but also NGF like neurotrophic properties. Thus, hyperforin repesents a novel antidepressant mechanism of action with additionally quite promising neurotrophic properties. Supported by Deutsche Forschungsgemeinschaft and Dr. W. Schwabe, Karlsruhe

98. Leptin Induces Antidepressant-Like Behavioral Effects and Activates Specific Signal Transduction Pathways in the Hippocampus and Amygdala of Mice

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Sponsor: Alan Frazer

Background: Leptin, a hormone secreted from adipocytes, is best known for its role in the regulation of energy homoeostasis and body adiposity. However, evidence is accumulating on the multifunctional roles of this adipokine. Our recent work in rats have shown that leptin has antidepressant-like properties (Lu et al., 2006). The aim of the present study was to investigate leptin's antidepressant-like efficacy in mice and further determine possible underlying mechanisms.

Methods: C57BL/6J mice were handled for 3 days and sham-injected before each experiment. For behavioral testing, mice received i.p. injections of saline, various doses of leptin (0.25-1.0 mg/kg) or fluoxetine (15 mg/kg), an SSRI antidepressant as a positive control. Behavioral responses in the tail suspension test were assessed at 30 min post-injection. The immobility and escape-oriented behaviors were videotaped for 6 min and subsequently scored. For the investigation of neuronal activation patterns, mice were injected with saline or leptin (1 mg/kg, i.p.) and perfused at 2 h post-injection. c-Fos expression in the brain was evaluated by immunohistochemistry. In addition, to assess leptin signal transduction pathways, phosphorylation of Akt,

p44/42 MAPK and STAT3 was determined using Western blot in the hippocampus and amygdala 30 min after injection of saline or leptin (1 mg/kg, i.p.).
Results: (1) Leptin decreased the duration of immobility in a dose dependent manner in the tail suspension test. (2) Leptin stimulated neuronal activation in the hippocampus and amygdala as indicated by c-Fos immunoreactivity. (3) Leptin induced Akt phosphorylation in the hippocampus and p44/42 MAPK phosphorylation in both the hippocampus and amygdala. In contrast, STAT3 phosphorylation was unaltered by leptin in either brain region.
Discussion: These findings indicate the antidepressant potential of leptin in mice. In addition, our results suggest that leptin may produce antidepressant-like effects through activating specific signal transduction pathways in the limbic structures hippocampus and amygdala.

99. Activation of Phospatidylinositol 3-Kinase (PI3K) and Expression of Its Selective Catalytic and Regulatory Subunits Are Altered in Postmortem Brain of Depressed Suicide Subjects
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Background: Phosphoinositide (PI) signaling has become a very important part of signal transduction research in recent years. PI3-kinase (PI3K)/protein kinase B is one of the key signaling pathways involved in many physiological functions in brain, including cell growth and differentiation, neurite outgrowth, membrane trafficking, and cytoskeletal organization. The PI3-kinase pathway is utilized by many growth factors to mediate cell survival, or inhibition of apoptosis, for several neuronal subtypes. The enzyme PI3K is a heterodimeric protein complex consisting of a 110-kDa catalytic subunit (p110) and an 85-kDa regulatory subunit (p85). When recruited to an activated cognate receptor by the p85 regulatory subunit, the p110 catalytic subunit phosphorylates its main substrate, PIP2, to generate PIP3. Thus, both catalytic p110 and regulatory p85 subunits are critical in mediating PI3K action. PIP3 then activates PI-dependent protein kinase-1 (PDK-1). Protein kinase B, also known as Akt, is the most important target of PI3-kinase. The present study examines whether PI3K is involved in the pathophysiology of depression.
Methods: This study was performed in postmortem brain of depressed suicide (n = 11) and nonpsychiatric control subjects (n = 11). Postmortem brain samples were obtained from the Maryland Psychiatric Research Center. The psychiatric diagnosis of subjects was performed according to DSMIV criteria. Activation of PI3K was determined by enzymatic assay, whereas mRNA and protein levels of various isoforms of regulatory (p85α, p85β) and catalytic(p110α, β, γ) subunits of PI3K were determined by competitive RT-PCR and Western blot, respectively.
Results: It was observed that catalytic activity of PI3K was significantly reduced in PFC and hippocampus of depressed subjects as compared with nonpsychiatric control subjects. Competitive PCR analysis revealed significantly and selectively reduced mRNA expression of only the regulatory p85β and catalytic p110α and p110γ subunits in PFC and hippocampus of depressed subjects. Reductions in these catalytic and regulatory subunits were accompanied by reductions in their respective protein levels. These changes were not related to postmortem interval, age, or gender of subjects.
Discussion: Our findings of reduced activation and expression of specific PI3K regulatory and catalytic subunits demonstrate abnormality in this signaling pathway in postmortem brain of depressed subjects and suggest possible involvement of aberrant PI3 kinase signaling in pathogenic mechanisms of depression. Supported by NIMH RO168777 to Dr. Dwivedi.

100. Support for the Vascular Depression Hypothesis: Treatment Outcome in Late Life Depression is Predicted by Executive Function and White Matter Hyperintensities
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Background: LLD is a heterogenous disorder with significant medical co-morbidity, especially with vascular risk factors. Research on "vascular depression" has identified two LLD subsets: one with executive dysfunction and a second subset with significant white matter hyperintensities (WMH) on MRI. Studies have shown that both executive impairment and WMH predict poor antidepressant response of LLD. In this study we aimed to evaluate the relationship in LLD of WMH, neuropsychological performance and clinical response in a prospective treatment trial using sertraline.
Methods: A 2-site study at Washington University and Duke University enrolled 222 subjects in a 12 week prospective study with sertraline. Patients age $\geq$ 60 met DSM-IV criteria for major depression, scored $\geq$ 20 on the MADRS and were screened to rule out severe medical disorders, primary neurological disorders, conditions or drugs that may cause depression. All subjects received a psychiatric evaluation, physical exam, vascular risk factor score (Framingham criteria), comprehensive neuropsychological testing and MRI scan on a 1.5T Siemens or GE scanner at WU and Duke, respectively. WMH were assessed blinded to treatment data using the modified Fazekas criteria. All ratings were conducted at Washington University School of Medicine by RCM and YIS. In addition a total Fazekas rating (0-9) was created by summing the 3 ratings from deep white matter, subcortical gray matter and periventricular ratings. Change in MADRS scores over 12 weeks was assessed. To accommodate missing values due to missed appointments and censoring due to dropout, a mixed model was employed. To assess the difference in trajectories, in a second analysis, the factor by time interaction was incorporated into the model.
Results: Using the mixed model to assess the impact of total Fazekas score on MADRS score as a function of time, with age, race and education as covariates there was a strong trend for a statistically significant effect on difference between the groups (0,1,2, vs 3-9) over time. Those with higher scores had an average 1.82 higher MADRS scores across time,($p = 0.056$). Using the same estimation model, controlling for age, education and race the following measures produced a statistically significant effect on the MADRS scores over time (with worse performance related to higher MADRS scores): Executive Function factor score, Wisconsin Card Sorting Test, Total Correct, Wisconsin Card Sorting Test, Conceptual Responses, Wisconsin Card Sorting Test, Categories Completed, Trails A, Trails B and Logical Memory, immediate and delayed recall (all p values ≤ 0.01). Baseline depression severity and time on sertraline were the most significant predictors of treatment outcome.
Discussion: The principal finding of this prospective antidepressant treatment study in late life depression was that both neuropsychological function, especially executive function, and total burden of WMH affected treatment outcome over a 12 week course of treatment. To our knowledge, this is the first prospective study to test both neuropsychological variables and WMH burden as predictors of outcome in vascular depression. Vascular disease may contribute to LLD by affecting frontal white matter pathways and subcortical structures involved in mood regulation. These data support the vascular depression hypothesis, defined both by executive dysfunction and by increased burden of WMH. This study was funded by a collaborative RO1s grant to Dr. Sheline (R01MH60697) and Dr. Doraiswamy (R01MH62158), and by a K24 Award (RR18192) to Dr. Sheline. Study drug was provided by Pfizer which had no role in design or analyses.

101. Excitatory Amino Acid Transporter and Transporter Interacting Protein Dysregulation in the Prefrontal Cortex in Schizophrenia

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Background: The excitatory amino acid transporters (EAATs) are a family of molecules responsible for synaptic glutamate reuptake. Expression and regulation of these transporters facilitate clearance of glutamate from the synapse and play a pivotal role in long-term potentiation and synaptic plasticity. Compelling evidence has implicated cortical abnormalities of glutamate transmission in schizophrenia, but the precise role of EAATs in schizophrenia remains unknown. We hypothesized that expression and regulation of EAATs are altered in the prefrontal and anterior cingulate cortices in schizophrenia in a pattern consistent with increased glutamate reuptake.
Methods: In postmortem tissue from patients with schizophrenia and a comprison group, EAAT1, EAAT2, EAAT3 and the EAAT interacting protein g-protein suppressor pathway 1 (GPS1) transcript and protein levels were measured using in situ hybridization and Western blot analysis, respectively. Interactions between EAAT2 and GPS1 were measured using co-immunoprecipitation. To determine whether typical antipsychotic exposure regulates these molecules, transcript expression for EAAT1, EAAT2, EAAT3, and GPS1 were measured in the frontal, parietal, and retrosplenial cortices of rats treated with haloperidol (2mg/kg/day) or vehicle.
Results: EAAT1 and EAAT3 transcript levels were increased in the anterior cingulate cortex in schizophrenia, while GPS1 protein levels were decreased in this region. No changes were detected for EAAT1 or EAAT3 protein expression, and no changes were detected for GPS1 transcript. No changes were detected for EAAT1, EAAT3, or GPS1 in the dorsolateral prefrontal cortex, and no changes were detected for EAAT2 in either region. EAAT1 protein levels and co-immunoprecipitation of EAAT2 with GPS1 data will be presented. In general, none of these transcripts were regulated by haloperidol treatment in the frontal, parietal, or retrosplenial cortices, with the exception of a downregulation of EAAT1 transcripts in retrosplenial cortex.
Discussion: Our data support the hypothesis that expression and regulation of EAATs are altered in the prefrontal and anterior cincgulate cortices in schizophrenia, but are more consistent with a pattern of decreased glutamate reuptake. These data contribute to a growing body of evidence that glutamatergic signalling may be altered in schizophrenia. Our findings could have important implications for neuronal plasticity in this illness as well as provide targets for the development of novel treatments.

102. Orientation and Cellular Localization of Membrane-Bound Catechol-o-Methyltransferase in Primary Cultures of Rat Cortical Neurons

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Sponsor: Daniel R. Weinberger

Background: A functional polymorphism (Val158Met) within catechol-O-methyltransferase (COMT) gene has been linked or associated with cognitive dysfunction in schizophrenia, which led to the hypothesis that higher enzyme activity of COMT-Val impairs cognitive function by increasing dopamine catabolism in prefrontal cortex and by this mechanism increases the risk for schizophrenia. In brain, membrane bound (MB) COMT is expressed primarily in neurons and is more abundant in prefrontal cortex and hippocampus than in striatum or in brainstem dopamine neurons, but its distribution, orientation and trafficking in neurons remain unknown.
Methods: Rat primary cortical neuron culture, immunocytochemistry, flow cytometry and COMT enzyme activity assay
Results: In this study, we demonstrated that the MB-COMT protein is distributed in both cell body and dendrite of rat E18 primary cortical neurons. Enzyme activity analysis on live cortical neurons showed that the catalytic domain in its C-terminal region is located in extracellular space. To confirm the orientation, we constructed a MB-COMT C-terminal GFP fusion gene by subcloning human MB-COMT (Val) to pAcGFP1-N1 vector, and transfected rat cortical neurons with the fusion construct. GFP surface staining and flow cytometry results showed that the C-terminus of MB-COMT in the transfected neurons was outside. Furthermore, the MB-COMT colocalized with the dense core vesicle (DCV)-marker secretogranin-II (Sg-II), Golgi marker TGN38, axonal marker TAU, dendritic marker MAP2, synaptic markers synaptotagmin and PSD95 in the transfected neurons.
Discussion: Our results suggest that MB-COMT is important for inactivation of synaptic dopamine in synaptic cleft of cortical neurons, and provide the cellular basis for the effect of the COMT genetic variation on cortical function and schizophrenia.

103. Imaging Structural and Functional Connectivty in Schizophrenia

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Sponsor: Kenneth L. Davis

Background: Despite the advances made with diffusion tensor imaging (DTI) in understanding altered connectivity patterns in schizophrenia, this imaging modality only provides an index of the anatomical integrity of white matter structures, which cannot be directly equated with their functional connectivity. It is an intriguing hypothesis that abnormalities in the structure of white matter tracts may be important to the observed reductions in activation of interconnected networks as demonstrated by functional magnetic resonance imaging (fMRI); however, the simultaneous study of DTI changes and functional brain activation in schizophrenia is lacking.
Methods: 21 medicated schizophrenic subjects received DTI on a 3T Allegra MRI scanner (Siemens, Ehrlangen, Germany) and BOLD fMRI on the same machine with a gradient echo-planar sequence in the same slice locations as the DTI. The specific effects of working memory load on brain activation was assessed with the N-Back working memory test.
Results: Functional activation of the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) were positively correlated with white matter integrity (as indexed by fractional anisotropy measures) of both left and right anterior cingulum bundle (CB). Moreover, these correlations were weaker on the left compared with the right for ACC ($r=.49$ vs $r=.86$, all $p<.05$). Although overall correlations with DLPFC were similar for left and right CB ($r=.66$ vs $r=.76$, all $p<.05$), the area of cortex which correlated was substantially smaller on the left.
Discussion: These findings show that the magnitude of event related activation of the ACC and DLPFC are related to the integrity of the CB in patients with schizophrenia. We are currently analyzing this data to determine if the magnitude of synchrony between DLPFC and ACC during working memory performance are related to DTI measures of the integrity of CB. These results will be presented as well.

104. Asenapine: Preclinical Evidence for Clinical Effects in Schizophrenia

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Sponsor: Torgny H. Svensson

Background: Asenapine is a novel psychopharmacologic agent with a unique human receptor binding profile being developed for the treat-

ment of schizophrenia and bipolar disorder. Relative to its D2 receptor activity, it has higher affinity for an ensemble of serotonergic (5-HT2A, 5-HT2C, 5-HT6, 5-HT7), noradrenergic (α2B), and dopaminergic (D3) receptors.
Methods: We evaluated the antipsychotic efficacy of asenapine in male Wistar rats using conditioned avoidance response (CAR), a preclinical test with high predictive validity. Using a catalepsy test, we also assessed the propensity of asenapine for causing extrapyramidal side effects. In parallel experiments, we measured the effects of asenapine on dopamine output in the medial prefrontal cortex and the nucleus accumbens using in vivo microdialysis in freely moving rats. We also investigated the effect of asenapine on N-methyl-D-aspartate (NMDA)-induced currents in pyramidal neurons of the medial prefrontal cortex in male SD rats using an in vitro electrophysiologic intracellular recording technique.
Results: Asenapine 0.05 to 0.2 mg/kg given subcutaneously (s.c.) induced dose-dependent suppression of CAR (at 0.2 mg/kg, 91.5±7.5% [median±semi-interquartile range]) but did not induce catalepsy at any time interval studied (30–120 minutes). No escape failures were recorded for any asenapine dose tested. In contrast, haloperidol 0.1 mg/kg s.c. induced comparable suppression of CAR but catalepsy was near maximal at this dose. In fact even at 0.025 mg/kg haloperidol induced catalepsy at 120 minutes. Similar to clozapine but not haloperidol, asenapine 0.05 to 0.2 mg/kg s.c. increased dopamine efflux in both the medial prefrontal cortex (maximal effect, 219.2±15.1% [mean±SEM] of control) and the nucleus accumbens (235.5±21.1%) in a dose-related manner. Like clozapine (100 nM), but at a considerably lower concentration (5 nM), asenapine potentiated the NMDA-induced responses in pyramidal cells of the medial prefrontal cortex (156±19% of control).
Discussion: These preclinical data suggest that asenapine may exhibit highly potent antipsychotic activity without inducing extrapyramidal symptoms. Its ability to increase both dopaminergic and glutamatergic activity in rat medial prefrontal cortex suggests that asenapine may have an advantageous effect not only on positive symptoms in patients with schizophrenia, but also on negative and cognitive symptoms.

105. Genetic Variation of the 5-HT_{2A} Receptor Predicts Severity of Anxiety in Schizophrenia

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Background: Accumulating pharmacological and genetic association data indicate that the genes encoding the serotonin (5-HT)$_{1A}$, 5-HT_{2A} and 5-HT_{2C} receptors are candidates for investigation in studies of anxiety and mood, which are features of many psychiatric disorders, including schizophrenia.
Methods: We have now examined variation in three serotonin receptor genes in two samples of Caucasian American patients (n=72 and n=184) and two samples of African American patients (n=31 and n=139) diagnosed with schizophrenia or schizoaffective disorder, in relation to severity of anxiety, depression and suicidality at baseline, measured by Brief Psychiatric Rating Scale and Hamilton Depression scale items or subscales. 5-HT_{1A} (-1019 C/G), 5-HT_{2A} (102 T/C, 452 His/Tyr) and 5-HT_{2C} (-1165 G/A, -997 G/A, -759 C/T, -697 C/G, 23 cys/ser) SNPs were genotyped and statistical analyses were conducted using ordinal logistic regression.
Results: The 5-HT_{2A} 452 His/Tyr change was associated with severity of anxiety but not depressed mood or suicidality in both Caucasian American groups but not African Americans at baseline. Caucasian American subjects with at least one Tyr452 allele had significantly lower mean psychic anxiety scores (1.8+/-1.5) compared with His/His homozygous subjects (2.6+/-1.5) (overall Wald=8.6, 1df, p=0.003). SNPs in the 5-HT_{1A} and 5-HT_{2C} genes were not associated with these symptoms in either ethnic group.
Discussion: The current data suggest that genetic variation of the 5-HT_{2A} receptor may play an important role in the development of anxiety in patients with schizophrenia and schizoaffective disorder. Possession of the 5-HT_{2A} 452 Tyr allele is predicted by *in vitro* studies to reduce G protein coupling and to produce more rapid desensitization of the 5-HT_{2A} receptor. Whether these findings generalize to other psychiatric disorders requires further study.

106. Neurocognitive Impairments in Schizophrenia Patients and Their First-Degree Relatives: Findings from the Consortium on the Genetics of Schizophrenia (COGS)

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Sponsor: Raquel E Gur

Background: The Consortium on the Genetics of Schizophrenia (COGS) is a 7-site, NIMH funded, collaboration investigating the genetics of quantitative endophenotypes related to schizophrenia. In addition to six primary candidate endophenotypes, a computerized battery developed at the University of Pennsylvania was included to characterize participants' neurocognitive functioning and to potentially generate additional endophenotypes. The purpose of this report is to provide preliminary results from the neurocognitive battery in the sample collected as of August 2006.
Methods: Schizophrenia patients (n=153, mean age=35.2, SD=11.2), their biological first degree relatives (n=371, mean age=46.1, SD=13.9) and community comparison subjects (CCS; n=202, mean age=37.7, SD=12.2) completed a battery of tasks assessing 7 neurocognitive domains: abstraction and flexibility (ABF), facial memory (FMEM), spatial memory (SMEM), working memory (WM), spatial ability (SPA), sensorimotor (SM), and emotion processing (EMO). The computerized format provided independent assessments of accuracy and response time (speed). Group differences were evaluated using mixed effects analyses, with family as a random effect.
Results: In comparison to CCS, schizophrenia patients demonstrated significantly reduced accuracy in all three memory domains (FMEM, $F=38.72$, df=353,1, $p<0.001$; SMEM, $F=30.28$, df=348,1, $p<0.001$; WM, $F=8.45$, df=336,1, $p<0.004$), and EMO ($F=41.28$, df=348,1, $p<0.001$), and significantly reduced speed in all domains (all p's <0.01) except WM. Although relatives were less accurate than CCS in only SMEM ($F=7.44$, df=304,1, $p<0.007$) and EMO ($F=18.6$, df=368,1, $p<0.001$), they were significantly slower than CCS in ABF ($F=17.9$, df=331,$p<0.001$), FMEM ($F=15.94$,df=382,1, $p<0.001$), SMEM ($F=10.71$, df=353,1, $p<0.001$) and EMO ($F=11.48$, df=393,1, $p<0.001$).
Discussion: The implication that relatives may sacrifice speed for accuracy underscores the utility of reliable assessment of response times in neurocognitive testing. EMO impairment in both patients and relatives indicates that emotion processing warrants further consideration as a candidate endophenotype of schizophrenia. Overall, the results support the use of particular neurocognitive abilities, especially memory and emotion processing, in studies of the genetics of schizophrenia.

107. Rat Strains Different in Their Gating-Disruptive Effects of Dopamine Agonists Do Not Differ in the Gating-Disruptive Effects of Corticotropin Releasing Factor

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Background: Albino Sprague Dawley (SD) rats are significantly more sensitive to the disruption of prepulse inhibition (PPI) by dopamine (DA) agonists, compared to hooded Long Evans (LE) rats. This effect

is heritable and neurochemically specific, and linked to heritable differences in D2-linked G-protein mechanisms in the nucleus accumbens. Recent reports indicate that PPI in rats is also reduced by the 41 amino acid polypeptide, corticotropin releasing factor (CRF); in some cases, this effect appears to be opposed by antipsychotic agents, suggesting that CRF's effect on PPI may be mediated via DAergic mechanisms. If this is the case, we would predict SD > LE sensitivity to the PPI-disruptive effects of CRF; such a model might provide insights into the neural basis for heritable mechanisms linked to the deleterious effects of stress on information processing and cognition. Here, we tested the sensitivity to the PPI-disruptive effects of CRF in SD vs. LE rats.
Methods: Outbred adult male SD and LE rats underwent stereotaxic implantation of cannulae for intracerebroventricular (icv) CRF administration. Acoustic startle and PPI were later assessed on 4 days in a balanced, within-subject design, after icv infusion of vehicle, 0.3, 1.0 or 3.0 μg CRF/2 μl saline. The test session consisted of 120 dB(A) startle pulses, and prepulses 3, 5 and 10 dB over a 70 dB(A) background; prepulse intervals were 100 ms. Comparable stimuli have been used to detect SD > LE potency in the PPI-disruptive effects of systemic or icv administration of DA agonists (but not the 5HT2A agonist, DOI). A subset of the test group (both SD and LE rats) exhibited a profound loss of startle after repeated icv infusions. Data for rats with mean startle magnitude ≥ 10 units were analyzed by ANOVA with alpha set at 0.05.
Results: PPI was disrupted in a dose-dependent fashion by icv CRF ($p<0.001$). This effect reached significance for the 1.0 μg ($p<0.04$) and 3.0 μg doses ($p<0.0001$). SD and LE rats exhibited comparable sensitivity to this effect (dose x strain interaction: $F<1$). Startle magnitude was initially increased in SD and reduced in LE rats, but across the test session CRF tended to reduce startle in both strains. These CRF effects on startle magnitude could not account for changes in PPI. Data will also be presented to demonstrate significant SD > LE sensitivity to the PPI-disruptive effects of DA agonists.
Discussion: If CRF disrupts PPI exclusively via changes in DAergic activity, then this is accomplished in a manner that is distinct from that of direct or indirect DA agonists, in that it does not appear to engage heritable nucleus accumbens D2-linked G-protein mechanisms known to distinguish SD and LE rats. An alternative explanation is that these gating-disruptive effects of CRF are mediated at least in part via non-DAergic mechanisms, including perhaps 5HTergic substrates of PPI known to exhibit comparable sensitivity in SD and LE rats. Supported by MH68366 & MH01436.

108. Effects of Amphetamine on Prepulse Inhibition of Acoustic Startle in Normal Women

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Background: Sensorimotor gating, as indexed by prepulse inhibition (PPI) of startle, is deficient in schizophrenia patients, and is disrupted in laboratory animals by dopamine (DA) agonists, including the indirect DA agonist, d-amphetamine (AMPH). We previously reported that AMPH also disrupts PPI in normal men, though this effect was limited to relatively short prepulse intervals (10-20 ms). Both PPI and AMPH sensitivity are sexually dimorphic. We now present preliminary findings from our ongoing studies of the effects of AMPH on PPI in normal women.
Methods: Female subjects (18-35 yo) were carefully screened to rule out psychopathology, substance use, medical illness and pregnancy, and to document robust acoustic startle magnitude. Screened subjects were then enrolled in a within-subject double blind comparison of placebo vs. 20 mg AMPH po on measures of startle and PPI, based on bilateral orbicularis EMG responses to 118 dB(A) 40 ms noise pulses alone, or preceded 10-120 ms by 20 ms bursts 16 dB over a 70 dB(A) background. Tests were conducted in early follicular phase, separated by approximately one month, with dose order balanced. Also recorded were personality inventories (TPQ, EPQ, SSS), as well as autonomic and self-rating scales for mood, alertness and malaise, and estradiol levels. Data presented here are from the first startle test, conducted 60 min after placebo or AMPH administration.
Results: ANOVA revealed no effects of AMPH on spontaneous blink rates, or on startle magnitude or habituation. ANOVA of PPI revealed a significant effect of AMPH dose ($p = 0.05$) and prepulse interval ($p<0.02$), but no dose x interval interaction. Inspection of the data suggests that, in contrast to men, the PPI-disruptive effects of AMPH in women are evident even at longer prepulse intervals (120 ms), despite substantially lower basal (placebo) levels of PPI in women (mean (SD) PPI in present study vs. male historical comparisons = 9.0 (23.2) vs. 30.0 (28.7)%; $d = 0.77$). Findings from personality, autonomic, self-rating and hormonal measures will also be reported.
Discussion: These preliminary findings suggest that PPI is reduced by AMPH in normal women, despite the low levels of PPI normally observed in women. While basal levels of PPI are sexually dimorphic (women < men), our findings suggest that women exhibit at least comparable sensitivity to the PPI-disruptive effects of AMPH. A similar pattern is observed in schizophrenia: despite sexually dimorphic levels of PPI in patients (women < men), both male and female patients exhibit PPI deficits compared to non-patient controls. The relationships between AMPH sensitivity and personality and hormonal measures in normal women will be discussed. Supported by MH59803 & MH01436.

109. A "Virtual" Comparison of Paliperidone ER and Oral Risperidone in Patients with Schizophrenia

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Background: Paliperidone Extended Release (ER) is an investigational agent using OROS technology to deliver 9-OH risperidone at a therapeutic dose with less plasma level fluctuations than immediate-release (IR) oral formulations. Placebo-controlled studies in schizophrenia demonstrated efficacy of paliperidone ER at 3-15 mg/day; 6 mg/day is the anticipated recommended dose for most patients. A virtual comparison of efficacy and tolerability was conducted by combining data from paliperidone ER and risperidone IR schizophrenia studies into one database for analysis. This methodology offers an advantage to meta-analytic techniques by using individual rather than group data.
Methods: All randomized placebo-controlled studies in adults with schizophrenia were identified from the manufacturer's database (3 per agent). Matched populations were selected from the larger database based on: age 18-65 years, exposure to a conventional antipsychotic within 90 days of study entry, and treatment with paliperidone, risperidone, or placebo (n=1103). Paliperidone ER doses anticipated to be commonly used in schizophrenia (6-12 mg/day) were compared to 4-6 mg/day risperidone. To also study doses hypothesized by pharmacokinetic data to provide similar medication exposure, 6-12 mg/day paliperidone ER was compared to 2-4 mg/day risperidone. Placebo group comparisons examined whether groups were similar across programs and identified cross-program differences. The primary efficacy endpoint was change in PANSS total score from baseline to week-6 (LOCF). Tolerability endpoints included weight and adverse event (AE) reports.
Results: The placebo(PALI n=145) and placebo (RIS n=215) groups had comparable mean PANSS scores at baseline (94.3 and 93.1, respectively; P=0.442) and changes at endpoint (-4.3 and -4.9, respectively; P=0.772). Some cross-program differences were noted in specific adverse event reports. Paliperidone ER 6-12 mg/day (n=275) vs risperidone 4-6 mg/day (n=174) had similar completion rates (67.6% and 65.5% respectively; 40.8% combined placebo group) and PANSS change scores at endpoint (-19.0 and -19.7, respectively; P=0.83). AE rates (adjusted for cross-program differences identified

in placebo groups), showed paliperidone ER was associated with lower percentages of patients reporting akathisia, restlessness, anxiety, insomnia, somnolence, dizziness, and gastro-intestinal effects. The mean±SD weight change was greater with risperidone (1.3±3.7) than paliperidone ER (0.67±2.7) (P=0.024). The comparison of paliperidone ER 6-12 mg/day and risperidone 2-4 mg/day (n=173) showed completion rates of 67.6% and 53.8%, respectively. There was a greater reduction in PANSS total score at endpoint with paliperidone ER (-19.0 and –11.4, respectively; p=0.003). Each active treatment group had a greater PANSS score reduction than placebo (P=.001). At these doses, paliperidone ER was associated with lower percentages of patients reporting akathisia, restlessness, insomnia, somnolence, dizziness, and gastro-intestinal effects, and more reports of tachycardia.
Discussion: Findings suggest that a virtual comparison is feasible and informative. Placebo groups were comparable across programs. Results suggest that paliperidone ER at 6-12 mg/day may be similarly efficacious to risperidone IR at 4-6 mg/day, with some tolerability benefits; and more efficacious than risperidone IR at 2-4 mg/day, with some tolerability differentials. In the absence of direct comparisons, such analyses can guide future research.

110. Akathisia in Schizophrenia Patients Treated with Aripiprazole, Haloperidol, or Olanzapine - Analyses of the First 12 Weeks of Three Double Blind, Long Term Trials
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Sponsor: Timothy Crow

Background: Second generation antipsychotics (SGAs) have an improved tolerability profile compared to first generation antipsychotics (FGAs). Most SGA clinical concerns focus on changes in metabolic parameters that can be induced by some drugs in this class. Extrapyramidal side effects, including akathisia, are less frequent with the SGAs compared to the FGAs. Aripiprazole has a different mode of action compared to other SGAs; its partial D2 agonism and lack of histaminergic and cholinergic receptor affinities account for its unique clinical characteristics, including its benign metabolic profile. It has been suggested through clinical experience that akathisia may be a side effect more frequently associated with aripiprazole than with other SGAs. Objective: This analysis was performed to quantify and qualify akathisia in schizophrenia patients receiving one of two SGAs, aripiprazole (Ari) or olanzapine (Olz), or a FGA, haloperidol (Hal), in the first 12 weeks of treatment.
Methods: A post hoc analysis of the safety dataset was conducted to assess akathisia characteristics in three double-blind randomized trials: a 52-week comparison of Ari 30mg/d (n=859) versus Hal 10mg/d (n=431); and pooled data from two trials (26- and 52-week) comparing Ari 15-30mg/d (n=504) and Olz 10-20mg/d (n=505). The following akathisia parameters were assessed: incidence rates, time to onset, duration and severity of symptoms, and scores on the Barnes Akathisia Rating Scale.
Results: In the Hal comparative trial, akathisia was reported by 12.5% in the Ari group and 24.1% in the Hal group. Akathisia occurred within the first 12 weeks after randomization in 89.6% of Ari-related events and 92.5% of Hal-related events. The median day of onset was 16.5 for Ari and 11.5 for Hal, with a median duration of 13 days for Ari and 17 days for Hal. In the Olz comparative trials, akathisia was reported by 10.7% of Ari-treated patients and 6.1% of Olz-treated patients. Akathisia occurred within the first 12 weeks in 94.4% of Ari-related events and 90.2% of Olz-related events. The median day of onset was 13 for Ari and 15.5 for Olz while the median duration was 7 days for both Ari and Olz. Akathisia was rated as mild or moderate by the majority of patients (≥ 80% of reports), with low discontinuation rates ranging from 0.2% (Olz group versus Ari group 1.2%) to 2.8% (Hal group versus Ari group 0.9%). The use of benzodiazepine among patients reporting akathisia was high in all treatment arms varying from 75% (Olz group versus Ari group 86.3%) to 86.5% (Hal group versus Ari group 77.1%). According to the BARS, the percentage of patients with akathisia (Item 4 – Global Assessment ≥ 2) at week 12 was significantly higher for Hal (24.5%) when compared to Ari (9.0%) (p<0.0001) and did not differ between Olz- (6.6%) and Ari-treated patients (9.4%) (p=0.1).
Discussion: Consistent with previous reports, the FGA haloperidol was associated with higher rates of akathisia than the SGAs aripiprazole and olanzapine. Under double-blind conditions, for all antipsychotics, akathisia occurred early in treatment, was time-limited, of mild to moderate severity, and associated with high rates of concomitant benzodiazepine use. Contrary to previous reports, akathisia was not associated with high rates of discontinuation. The high rates of benzodiazepine use in all treatment groups may have influenced its clinical presentation, as this class of drugs have been successfully used in the management of akathisia.

111. Feasibility of Quantifying Activity Energy Expenditure and Caloric Intake by Doubly-Labeled Water in Treated Patients with Schizophrenia
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Sponsor: Theodore Cicero

Background: Schizophrenia is associated with an average loss of 25-30 years of life vs. population norms. The major factor explaining this dramatic increase in mortality is an increased prevalence of cardiovascular disease in comparison to the general population. Overweight/obesity, a major risk factor for cardiovascular disease, occurs at a high prevalence among schizophrenia patients. Antipsychotic medications used in the treatment of schizophrenia can induce significant increases in weight and adiposity, with different medications associated with well-characterized differences in weight change. Less well characterized are the differential effects of specific antipsychotic medications on changes in regional adiposity, or on mechanisms underlying changes in adiposity. There are currently no in vivo experimental data from humans that quantify the degree to which antipsychotic medications alter caloric intake, physical activity level, or some combination of both. The doubly-labeled water (DLW) method has been recognized as the gold-standard measure of total energy expenditure, energy intake, and activity energy expenditure in humans. However, this method has never been applied to the evaluation of antipsychotic-induced increases in adiposity in treated patients.
Methods: This ongoing project uses DLW to quantify treatment-induced changes in Activity Energy Expenditure (AEE) and Energy Intake (EI) in schizophrenia patients during twelve weeks of prospective, randomized treatment with either olanzapine or ziprasidone. For this pilot study, chronically treated patients with schizophrenia undergo single DLW assessments to confirm the feasibility of engaging patients in the required procedures.
Results: Details on the procedure and calculations of AEE and EI will be presented. Symptomatic patients with schizophrenia can be successfully engaged in the required procedures. Relevant data will be presented.
Discussion: Preliminary data support the feasibility of using the gold-standard DLW method to assess the effects of antipsychotic treatment on caloric intake and energy expenditure. This information will be relevant to the interpretation of observed changes in adiposity during antipsychotic treatment, and critical for planning appropriate interventions to address this problem.

112. Improving Antipsychotic Adherence in Schizophrenia: A Randomized Pilot Study of a Brief CBT-Based Intervention

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Sponsor: Nina R. Schooler

Background: Most medication adherence strategies rely on the basic assumption that patients agree with the diagnoses for which they are being treated. However, many schizophrenia patients disagree with their diagnoses, even after multiple episodes. Therefore, such patients might benefit most from adherence strategies designed to bypass acceptance of a diagnostic label. Such an intervention can then facilitate adherence by working with, rather than against, patients' personal beliefs. Cognitive Behavior Therapy (CBT) model may be an appropriate platform to base an adherence intervention. CBT relies on a symptom-based rather than diagnosis-based approach. Our research group used a CBT treatment platform to develop and pilot a new intervention to improve antipsychotic medication adherence.
Methods: Schizophrenia patients who had recently relapsed and responded to oral antipsychotic therapy were screened and invited to participate in a pilot study of this CBT-based adherence intervention (CBT-AI). The CBT-AI is largely based on the CBT Insight Program (CBT-IP) developed by DT and studied in the UK. All consenting subjects continued with treatment as usual (TAU) at a public mental health outpatient setting. After baseline, patients were randomized to either 1) continue with TAU, or 2) add a 12-session course of CBT-AI to be given over the next 4 months. The CBT-AI was developed during and after an intensive 1-week CBT-IP training course provided to our research program by the original designer of CBT-IP (DT along with another UK CBT expert). The CBT-AI treatment manual was developed by PJW based on CBT-IP principles, and was then used for the pilot intervention. During the course of the pilot study, ongoing supervision was provided weekly with PJW for the adherence focus and DT for CBT techniques. All CBT-AI sessions were recorded, and each CBT-AI subject/clinician pair received 2 fidelity reviews. Major outcome measures were changes in adherence attitude between baseline and endpoint at 4 months post-randomization using the Rating of Medication Influences (ROMI) scale, and emergence of nonadherence behavior defined by time until first episode of 1 week of nonadherence. Other outcomes included changes in PANSS, CDRS, ITAQ, and satisfaction with CBT-AI.
Results: 88 patients were screened between 10/2004-3/2005; 41 were eligible, 19 consented and 16 randomized to CBT-AI (n=9) or TAU (n=7). The study subjects were relatively young (mean age 33.2 years), 58% men, and had been ill for 8.1 (SD 5.9) years. The mean number of sessions was 7 (SD 4.8) with 44% (n=4) completing all 12. The sessions were found consistent with CBT principles; all clinicians received passing CBT fidelity scores based on audiotaped sessions (mean score of 37.7; comparable to CBT-IP therapists certified in the UK with "passing" > 30). Adherence attitude outcome: the CBT-AI group was significantly more likely to endorse reasons for both adherence and nonadherence on the ROMI, a finding that was consistent with the *a priori* hypothesis. Adherence behavior outcome: At the 4 month assessment, 33% (3/9) of CBT-AI subjects had discontinued antipsychotic medication vs. 83% (5/6) of TAU, although in this small sample the difference failed to reach statistical significance.
Discussion: This pilot study cannot separate nonspecific effects of increased therapist attention from the effects of specific CBT techniques. It does confirm the feasibility of adapting CBT principles to address medication adherence. The changes in adherence attitudes as well as a trend in improved adherence behavior in the CBT-AI group support the hypothesis that a CBT platform can be adapted to improve medication adherence.

113. Cognitive Benefits of Ziparasidone vs. Clozapine in Treatment Resistant Schizophrenia: A Randomized Double-Blind Comparative Study

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Background: Recent data from the CATIE schizophrenia trial has suggested that there may be few differences in cognitive effects of antipsychotic medications. However, assessment of such effects can be complex, due a number of confounds, including subject characteristics and dosage of the treatments. In specific, treatment resistant patients may show a substantial dissociation between clinical and cognitive benefits, with clozapine sometimes showing fewer cognitive benefits. This study compared the cognitive and clinical benefits of clozapine and ziprasidone in patients with a history of failure to respond to previous antipsychotic treatments.
Methods: Patients with a documented history of either failure to respond to multiple previous adequate antipsychotic treatments or intolerance of treatment were randomized in double-blind fashion to either clozapine (n=74)or ziprasidone (n=73) in a single country (Italy), multi-site trial. Efficacy assessments included the Positive and Negative Syndrome Scale (PANSS) and a cognitive assessment battery examining episodic memory (RAVLT), executive functioning (Stroop test), and processing speed (Trail-making test Parts A and B).
Results: Both groups demonstrated statistically significant improvements ($p<.05$) in total PANSS scores and several of the PANSS subscales, with no differences between the groups. Analyses of the cognitive variables found statistically significant within group improvements for ziprasidone in learning and delayed recall and recognition on the RAVLT and Trail Making Part B. Clozapine treated patients improved on the RAVLT, but not on the trail making test and neither group improved on the Stroop test. Weight and total cholesterol were significantly lower at endpoint in the ziprasidone treated patients. When patients recruited for treatment resistance only were compared across treatments, there were no changes in the efficacy profiles.
Discussion: This study indicated that cognitive and clinical measures improved following treatment with ziprasidone in patients with a history of either treatment resistance or intolerance. While cognitive improvements were only found for a subset of items in the battery, processing speed and episodic memory may be related to functional disability. These findings are consistent with several prior comparative studies on the cognitive effects of atypical antipsychotics.

114. SSR504734, a Selective Glycine Transporter-1 (GlyT1) Inhibitor, Reverses Abnormally Persistent Latent Inhibition Induced by MK-801 or Neonatal Nitric Oxide Synthase Inhibition, Suggesting Potential Efficacy Against Negative Symptoms of Schizophrenia

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Background: Noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonists induce schizophrenic-like symptoms in humans, presumably by impairing glutamatergic neurotransmission. Therefore, a compound potentiating this NMDAR function, by increasing extracellular levels of glycine (a requisite co-agonist of glutamate), could possess antipsychotic activity. SSR504734 is a highly selective and competitive Glycine transporter-1 (GlyT1) inhibitor that has been demonstrated to increase extracellular glycine levels and potentiate glutamatergic neurotransmission, effects reflected in activity in a variety of rodent models of the positive symptoms of schizophrenia (Depoortere et al 2005).

Methods: To explore further the antipsychotic potential of SSR504734, we investigated its effects in the latent inhibition (LI) model, using two variants of the model, one using the administration of the NMDA receptor antagonist MK-801 to adult rats, and the second using the administration of the nitric oxidase synthase (NOS) inhibitor, L-NoArg, at the neonatal stage, to mimic the neurodevelopmental aspect of schizophrenia. LI is a cross-species process, which refers to retarded conditioning to a stimulus as a consequence of its non-reinforced pre-exposure. This interfering effect is reduced by amphetamine but becomes abnormally persistent following MK-801-induced NMDA receptor blockade, the latter considered to address the negative/cognitive symptoms of schizophrenia (Gaisler-Salomon et al, 2003; Weiner I. 2003). Similarly, neonatal NO inhibition, leads to post-pubertal emergence of abnormally persistent LI in male rats (De Levie A. Weiner I. (2006)).
Results: In the present experiments, saline-injected rats pre-exposed to 40 tones prior to being conditioned with 5 tone-shock pairings did not show LI, whereas rats injected with the NMDA receptor antagonist MK-801 exhibited LI in spite of strong conditioning. SSR504734 (3 and 10 mg/kg, i.p.) and glycine (0.8 g/kg, i.p.) reversed MK-801-induced abnormally persistent LI. In addition, SSR504734 (3 and 10 mg/kg, i.p.) potentiated LI in saline-treated rats. In the neonatal NOS model, SSR504734 (3 mg/kg, i.p.) reversed abnormally persistent LI observed in neonatally L-NoArg-treated rats. Furthermore, as was the case in the LI MK-801 experiment, SSR504734 (3 mg/kg, i.p.) potentiated LI when administered to vehicle-treated rats. The pharmacological profile displayed by SSR504734 in both models resembles closely that seen with atypical, but not typical antipsychotics.
Discussion: These findings suggest that SSR504734, in addition to its potential to alleviate positive symptoms of schizophrenia, may be useful in treating different aspects of the negative symptoms of this condition. Refs. : De Levie A. Weiner I. (2006), IBNS Annual meeting, Whistler, 15, 115 ; Depoortere R. et al (2005), Neuropsychopharm.; 30,1963-1985 ; Gaisler-Salomon I., Weiner I. (2003). Psychopharm.; 166:333-42 ; Weiner I., (2003) Psychopharm., 169:257-297

115. Could Neurotensin Receptor Antagonists also be Antipsychotics?

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Sponsor: Travel Awardee, NIMH, 2006

Background: The neuropeptide neurotensin (NT) modulates the mesolimbic DA system and has been hypothesized to be an endogenous antipsychotic. NT is localized in cell bodies of ventral tegmental area (VTA) DAergic neurons, as well as in their terminals and cell bodies in limbic regions. NT neurotransmission in the nucleus accumbens (NAcc) has been proposed to mediate the therapeutic effect of antipsychotic drugs (APDs). However, similar to APDs, NT receptor (NTR) blockade induces depolarization-block in DA VTA neurons. Although results from a recent clinical trial with a NTR antagonist in schizophrenia were inconclusive, it is possible that NTR blockade could produce antipsychotic-like effects. The role of endogenous NT neurotransmission in two different animal models of antipsychotic action, prepulse inhibition of the startle response (PPI) and drug-induced hyperlocomotion is not completely understood. In order to characterize the role of endogenous NT in the regulation of sensorimotor gating, further explore its influence on locomotion, and finally, to characterize the interaction of endogenous NT with drugs the influence DA and NMDA systems, we examined the effects of systemic blockade of NTRs on the effects of DA agonists and dizocilpine on PPI, locomotion and c-fos mRNA expression.
Methods: Adult male Long Evans rats were pretreated with the NTR antagonist SR 142948A or vehicle before apomorphine, amphetamine or dizocilpine challenge and tested for PPI and locomotor activity. One hour later, animals were killed and brains processed for assessment of c-fos mRNA expression. c-fos in situ hybridization was performed in prefrontal cortex, cingulated, lateral septum, insula, NAcc, thalamus, VTA and ventral subiculum.
Results: Pretreatment with SR 142948A dose-dependently prevented amphetamine and dizocilpine-induced PPI disruption with no effect on baseline PPI or on apomorphine-induced PPI disruption. In contrast, SR 142948A did not modify baseline locomotion or the hyperlocomotor effect of these drugs. All drugs that decreased PPI, increased c-fos expression in the dorsolateral prefrontal cortex, lateral septum and thalamus. SR 142948A decreased drug-induced c-fos activation in the dorsolateral prefrontal cortex.
Discussion: Endogenous NT modulates the disrupting effects of two different types of drugs used to model the pathophysiology of schizophrenia: DA agonists and NMDA receptor antagonists. NT neurotransmission selectively mediates the sensorimotor gating effects of these drugs, butnot locomotor behavior. C-fos data indicate that endogenous NT release within the prefrontal cortex may mediate psychotomimetic drugs-induced disruption of sensorimotor gating. These results suggest that global blockade of NT neurotransmission may share some of the behavioral effects of APDs which may be related to blockade in the dorsolateral prefrontal cortex. Direct comparison with c-fos activation related to NTR agonists is not available, however increased NT neurotransmission in the NAcc is known to have antipsychotic-like properties. NAcc and prefrontal cortex are primary targets for the antipsychotic action of atypical APDs, however a comprehensive view of NT neurotransmission in this regions is still lacking.

116. Neurocognitive Effects of Antipsychotic Medications in Patients with Chronic Schizophrenia in the CATIE Trial

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Background: Neurocognitive impairment in schizophrenia is severe and is an important predictor of functional outcome. The relative effect of the second-generation (atypical) antipsychotic drugs and older agents on neurocognition has not been comprehensively determined. Our objective was to compare the neurocognitive effects of several second-generation antipsychotics and a first-generation antipsychotic, perphenazine.
Methods: A double-blind design was employed to study patients with schizophrenia assigned to receive treatment with olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months as reported previously by Lieberman et al. Ziprasidone was included after its approval by the Food and Drug Administration. Fifty-seven sites participated, including academic sites and treatment providers representative of the community. From a cohort of 1460 patients in the treatment study, 817 completed neurocognitive testing immediately prior to randomization, and then after 2 months of treatment. The primary outcome was change in a neurocognitive composite score after two months of treatment. Secondary outcomes included neurocognitive composite score changes at 6 months and 18 months after continued treatment and changes in neurocognitive domains.
Results: At 2 months, treatment resulted in small neurocognitive improvements of z=0.13 for olanzapine (P<.002), 0.25 for perphenazine (P<.0001) 0.18 for quetiapine (P<.0001), 0.26 for risperidone (P<.0001), and 0.12 for ziprasidone (P< .06). with no significant differences among groups. Results at six months were similar. After 18 months of treatment, neurocognitive improvement was greater in the perphenazine group than in the olanzapine and risperidone groups. Neurocognitive improvement predicted longer time to treatment discontinuation, independently from symptom improvement, in patients treated with quetiapine or ziprasidone.

Discussion: After two months of antipsychotic treatment, all groups had a small but significant improvement in neurocognition. There were no differences among any pair of agents, including the typical drug perphenazine. These results differ from the majority of previous studies.

117. Galantamine for the Treatment of Cognitive Impairments in Patients with Schizophrenia

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Background: Patients with schizophrenia are characterized by a broad range of cognitive impairments. Areas of impairment include: attention/information processing; problem solving; processing speed; visual and verbal learning and memory; and working memory. Despite appropriate treatment with either conventional or second generation antipsychotics, patients continue to exhibit pronounced cognitive impairments. This has led to the investigation of adjunctive agents for the treatment of these impairments. The cholinergic system has been implicated in multiple cognitive processes. Cognitive effects may be mediated through the muscarinic or nicotinic receptor systems. Galantamine is an acetylcholinesterase inhibitor, which also acts as an allosteric modulator at the $\alpha 2\beta 4$ and $\alpha 7$ nicotinic receptors. Previous small-N studies have reported potential benefits of galantamine for cognition.
Methods: In the current 12-week, placebo-controlled, parallel group, RCT, the efficacy of galantamine for cognitive impairments was evaluated using paper and computerized assessments of attention, manual dexterity, processing speed, simple and complex reaction time, verbal and visual memory, visual recognition, and working memory.
Results: Seventy-nine patients with either DSM-III-R/DSM-IV schizophrenia or schizoaffective disorder were randomized to study drug (galantamine: 39/placebo: 40); 72 subjects completed the study (galantamine: 35/placebo: 37); and 62 subjects had valid cognitive assessments at baseline and 12 weeks (galantamine: 32/placebo: 30). The treatment effect for the overall composite cognitive summary score was not significant, but the analysis examining whether there was a heterogeneity of treatment effect was significant (chi-square=10.65, df=4, p=0.031). Follow-up analyses revealed that galantamine, compared to placebo, was associated with a significant improvement in verbal memory (chi-square=4.79, df=1, p=0.029), with a trend for improvement in processing speed (chi-square=3.81, df=1, p=0.074). In contrast, patients randomized to placebo, compared to galantamine, showed a significant improvement on the vigilance measure (chi-square=6.26, df=1, p=0.012). There were no significant between group differences in manual dexterity or working memory. The effects of galantamine on computerized simple and complex reaction time and visual recognition measures will be presented.
Discussion: Study results will provide a comprehensive evaluation of the efficacy of galantamine for cognitive impairments in patients with schizophrenia. Supported by the Stanley Medical Research Institute and P30 068580. Ortho-McNeil Neurologics, Inc. provided study medication.

118. Schizophrenia Collaborative Resource (CoRe) Program: Establishing a Partnership for Treatment Through Enhanced Communication and Education

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Background: Although diagnostic criteria exist for schizophrenia, the disease course is less well defined. Unlike many other chronic disorders, stages of illness are not well characterized for schizophrenia. This gap in understanding the course and stages of the illness impacts expectations, goal setting, recognition of measurable gains or losses, and ultimately overall patient management. This abstract describes a unique initiative aimed at optimizing patient care throughout the course of illness by enhancing patient/physician communication, defining stages of the illness, providing a resource for evaluating patients as they transition from one stage to another, and allowing physicians to track patient progress over time, creating a personalized profile at each stage. The development of an interactive tool will be discussed.
Methods: A group of clinicians expert in the treatment of patients with schizophrenia have been involved in the development of this tool. Efforts have included extensive literature searches to identify the current approaches to staging in schizophrenia and other disorders. Additionally, analyses of clinical data from acute, stable, and remitted patient populations have suggested symptom profiles and levels of functioning that are characteristic and definable for distinct stages, providing information to help shape the clinical definition at each stage of illness.
Results: A computer-based, interactive, educational tool capable of capturing information on multiple domains related to individual patient status has been developed. This interactive program enhances patient/physician communication via a question and answer algorithm focused on gathering information on current interventions, symptom severity, as well as several other domains (social functioning, stress tolerance, cognition, and physical health). At the initial visit, the patient is staged according to the level and type of intervention required and the intensity of symptoms. Four stages of illness have been tentatively defined based on both clinician input and data analysis: 1) acute, 2) stabilization, 3) stable, and 4) remission. At subsequent visits patients are reevaluated and improvements or set backs in symptom severity and other domains are measured, and the patient's stage is determined. These data are stored providing clinicians with a method to track patient progress over time. Physicians are also able to use these data to graphically depict the evolution of an individual patient's clinical profile over time, facilitating patient/physician communication. Supplemental resource materials for both physician and patient are provided to support effective intervention and help optimize outcome.
Discussion: This tool was created to provide physicians and patients a common point of reference in the management of schizophrenic illness. It assists in the development of positive goals by providing milestones for improvement throughout the course of illness toward which both the patient and clinician can direct their efforts. Additionally, the tool provides physicians a mechanism to capture patient data and record it for future reference to help manage a treatment course towards optimal functioning.

119. Altered Vesicular Glutamate Transporter Expression in the Anterior Cingulate Cortex in Schizophrenia

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Sponsor: John F. Greden

Background: Schizophrenia is a debilitating mental illness with emotional and economic burdens for afflicted persons and their families. Current advances have linked the pathophysiology of schizophrenia with glutamatergic neurotransmission. Elements of the glutamate system that have been implicated in schizophrenia are involved in neuroplasticity and include glutamate receptors and transporters. While numerous studies have found alterations of postsynaptic molecules in schizophrenia, a growing body of evidence implicates presynaptic factors. Three vesicular glutamate transporters (VGLUT1-3) have been identified and are known to package glutamate into vesicles in the presynaptic terminal for subsequent release into the synap-

tic cleft. Recent studies have shown that VGLUTs regulate synaptic activity via the amount of glutamate released. Accordingly, we hypothesize that VGLUTs are altered in schizophrenia, possibly contributing to dysfunction of synaptic activity.
Methods: Using in situ hybridization and Western blot analysis we investigated alterations in VGLUT1 and VGLUT2 transcript and protein expression in the anterior cingulate cortex (ACC) and dorsal lateral prefrontal cortex (DLPFC) in schizophrenia. To assess the effects of treatment with antipsychotic medications, we also measured cortical VGLUT1 and VGLUT2 transcript and protein expression in rats treated with haloperidol (2 mg/kg/day) for 28 days.
Results: We found an increase in VGLUT1 transcript and a reduction in VGLUT1 protein expression in the ACC of schizophrenic subjects. We did not detect changes in VGLUT1 expression in the DLPFC, and we did not find any changes in VGLUT2 mRNA or protein in the ACC or DLPFC. We did not find changes in VGLUT1-2 mRNA expression in the frontal cortex of rats treated with haloperidol. Western blot analysis of VLGUT1-2 protein expression in rats treated with haloperidol will also be presented.
Discussion: We found increased VGLUT1 mRNA and decreased VGLUT1 protein expression in the ACC in schizophrenia, suggesting an abnormality of presynaptic function in this region. There are several possible explanations for these potentially disparate findings. Changes in VGLUT1 protein expression could originate from intrinsic excitatory neurons of the ACC, from extrinsic presynaptic terminals expressing VGLUT1 protein, or both. If the change in protein expression is in the same population of neurons with increased VGLUT1 mRNA, then this would suggest a loss of coordination of mRNA and protein expression in these cells. This scenario could result from abnormalities of de novo protein synthesis or from an increased rate of VGLUT1 protein degradation. Alternatively, the loss of VGLUT1 protein could be due to diminished excitatory input to the ACC from other cortical regions. Since VLGUT expression levels may determine the amount vesicle filling and hence indirectly impact synaptic glutamate release, a reduction of VGLUT1 expression is consistent with a loss of excitatory neurotransmission in a region that integrates myriad cognitive functions, many of which are impaired in schizophrenia. Overall, our findings suggest that schizophrenia may be associated with decreased innervation of the ACC and suggest that the functional roles of VGLUTs and other presynaptic molecules may be important pharmacological targets for the diagnosis and treatment of schizophrenia.

120. Abnormal Kynurenine Pathway Metabolism in the Striatum of Individuals with Schizophrenia

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Background: The levels of two metabolites of the kynurenine pathway (KP) of tryptophan degradation, kynurenic acid (KYNA) and its bioprecursor L-kynurenine (L-KYN), are elevated in cortical regions in individuals with schizophrenia (SZ) (Biol. Psych., 50: 521, 2001). Nanomolar concentrations of KYNA, a preferential antagonist of NMDA and α7 nicotinic acetylcholine receptors, can reduce the extracellular levels of glutamate and dopamine in experimental animals. Increased levels of KYNA may therefore play a role in the pathophysiology of SZ. To examine if abnormalities in KP metabolism also exist in the striatum, another brain area implicated in SZ, we now measured the tissue levels of L-KYN and KYNA and the activity of several KP enzymes in samples from five distinct striatal regions [dorsal caudate (DC), ventral caudate (VC), dorsal putamen (DP), ventral putamen (VP) and nucleus accumbens (ACC)].
Methods: Brains from 15 SZ patients and 14 matched controls (CTR), obtained from the Maryland Brain Collection, were used in this study.
Results: KYNA levels were increased in all regions tested (overall ANOVA $p<0.001$, SZ vs. CTR), and significant differences were observed in the VC, DP and ACC using Fisher's LSD multiple comparison test ($p<0.05$). L-KYN levels, too, were elevated in all regions (overall ANOVA $p<0.001$, SZ vs. CTR), and these differences were also significant in the VC and DP after Fisher's LSD corrections were applied ($p<0.05$). Using the same tissues, we then determined the activity of several enzymes involved in KP metabolism [indoleamine 2,3-dioxygenase (IDO), tryptophan dioxygenase (TDO), kynurenine aminotransferases I and II, kynureninase, kynurenine monooxygenase (KMO), 3-hydroxyanthranilate dioxygenase and quinolinate phosphoribosyltransferase] to explore whether enzymatic abnormalities could account for the observed elevations in L-KYN and KYNA levels. IDO (+83%) and TDO (+61%) activity were increased in the SZ samples, while KMO activity was decreased (-26%) (overall ANOVA in all cases $p<0.001$, SZ vs. CTR). After Fisher's LSD corrections, significant differences ($p<0.05$) were seen in IDO (DC, DP, VP and ACC), TDO (all five regions) and KMO (DP and ACC). No other KP enzyme changes were observed.
Discussion: Our data indicate a pronounced impairment of striatal KP metabolism in SZ, where the synthetic machinery leading to L-KYN and KYNA is up-regulated, while a key degradative enzyme of L-KYN is down-regulated. These results justify a detailed study of the causes of these enzyme abnormalities, their relationship to elevated L-KYN and KYNA formation, and implications for various domains of SZ pathology and treatment responses.

121. Differential Effects of Allelic Variations in Apo C3 and Apo A5 SNP's on 1st and 2nd Generation Antipsychotic Effects on Serum Lipids in Patients with Schizophrenia

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Background: Increases in serum lipids are associated with some second generation antipsychotics, especially olanzapine and clozapine.We have previously demonstrated differential drug effects for serum triglycerides in olanzapine and clozapine treated patients with schizophrenia, compared to these treated with risperidone. Previous studies have shown that variations in serum cholesterol and triglycerides are influenced by genetic variations in several genes including SNP's in the ApoC3, ApoA5 and Lipoprotein Lipase (LPL) genes, but the interaction of these genetic variations with effects of antipsychotic drugs in schizophrenic patients has not been studied.
Methods: We investigated several SNP variations in these genes and their association with drug effects of antipsychotics, on fasting levels of triglycerides and cholesterol in a cross sectional study of 189 schizophrenic patients treated with a single antipsychotic drug olanzapine, clozapine, risperidone, or lst generation antipsychotic. Assays for cholesterol and triglycerides were done at the regional clinical chemistry laboratory of Nathan Kline Institute. Genotyping of the selected SNP's was performed using standard PCR based methods.
Results: Our results showed a differential effects of drug x SNP for some allelic variations. For serum cholesterol the ApoA5-1131 SNP showed a significant drug x gene interaction in a dominant analysis (drug x SNP [AA vs. AG or GG], interaction effect, $F= 6.830$, $df=2,181$ $P=0.011$), with the C allele tending to lower cholesterol in patients taking second generation antipsychotics and increasing cholesterol in patients taking first generation antipsychotics. For serum triglycerides the ApoC3-1100 SNP interacted in a complex way with the antipsychotic effects (drug x SNP [CC vs.CT vs. TT], interaction effect, $F=2.463$, $df=4,179$, $P=0.044$). For patients treated with clozapine or olanzapine the TT genotype was associated with decreased triglycerides whereas the presence of the T allele tended to

increase triglycerides slightly in the patients treated with first generation antipsychotics. Some haplotypes from ApoC3 SNP's showed significant drug x haplotype interaction effects. For cholesterol (Figure 2A), the ApoC3-CC haplotype showed a drug x haplotype interaction (F=2.924, df=2,182 P=.054); patients with the haplotype present showed decreased cholesterol (mean difference -50.4 mg/dL) if they were being treated with 1st generation antipsychotics (t-test P=.022) and no change or slightly increased cholesterol if they were being treated with second generation antipsychotics groups (P =ns). For triglycerides the ApoC3-TG haplotype showed a trend for a drug x haplotype interaction (F=2.740 df=2,182,P=.067). The olanzapine and clozapine treated patients with positive cases of haplotype present showed slightly decreased triglycerides compared to the negative cases (mean lg10 difference x 100 = -9.9 mg/dL; t-test P=.048).
Discussion: If these results are confirmed and extended in additional samples, they could point to ways to identify schizophrenic patients who would be at greater risk of developing serum lipid abnormalities when treated with second generation antipsychotics such as olanzapine or clozapine.

122. Schizophrenic Smokers and Nonsmokers - Comparison of Baseline Psychiatric and Neuropsychological Characteristics

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Background: Schizophrenics have a very high rate of cigarette smoking, with rates in hospitalized inpatients approached 80-95% in some studies, and rates in outpatients slightly lower. It has been hypothesized that nicotinic deficits may be involved in the pathophysiology of schizophrenia. Some studies have suggested differences in psychopathology or neuropsychological test performance between schizophrenic smokers and nonsmokers.
Methods: In the context of a research project investigating effects of smoking cigarettes and nicotinic nasal spray on cognitive performance, we also studied differences in baseline psychiatric symptoms and neuropsychological performance measures in schizophrenic smokers (current cigarette smokers), schizophrenic non-Smokers, and control (non-psychotic) smokers. Schizophrenic non-smokers were defined as patients who had not smoked cigarettes for at least a year when they were in environments which permitted cigarette smoking. This reports presents preliminary data on group comparisons in our experimental sample.
Results: There were no statistically significant differences between PANSS Total, PANSS Positive, or PANSS Negative, Hamilton Depression Total, or SANS Total scores between schizophrenic smokers and schizophrenic non-smokers, although schizophrenic smokers had slightly higher scores on some measures. There was no significant difference in the percent of schizophrenic smokers vs., schizophrenic non-smokers classified as meeting the criteria for the deficit syndrome. On baseline neuropsychological tests there were no differences between schizophrenic smokers and schizophrenic nonsmokers on several neuropsychological tests including CPT(attention vigilance), ANAM (spatial organization), Dot Test (visual spatial memory), Stroop, Wisconsin Card Sort (total errors perseverative errors), RANDT (verbal memory). As expected control smokers showed better neuropsychological performance than either schizophrenic smokers or schizophrenic nonsmokers on verbal memory (RANDT), executive function (WCS), STROOP, visual spatial memory (Dot Test, immediate and delayed mean), and CPT reaction time.
Discussion: The lack of difference between schizophrenic smokers and nonsmokers may be influenced by our relatively small sample size and the fact that our sample was composed primarily of hospitalized schizophrenic patients who may have had less opportunity to smoke cigarettes than schizophrenic outpatients.

123. Synaptic Organization of the Patch Matrix Compartments in Postmortem Striatum in Treatment Responsive vs. Treatment Resistant Subjects with Schizophrenia

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Sponsor: Robert Schwarcz

Background: The patch and matrix compartments of the striatum, which process limbic and cognitive information, respectively, are differentially affected in subjects with schizophrenia (SZ). Our previous studies have shown an increased density of synapses characteristic of corticostriatal inputs in the caudate matrix and putamen patch in a heterogeneous group of SZ. The purpose of this study was to determine if the synaptic organization in treatment resistant vs. treatment responsive subgroups of schizophrenia (SZ) was differentially affected. Our hypothesis is that psychotic SZ (either not responsive or off drug) would have more dramatic differences in synaptic density than treatment responsive SZ, and that these changes would be selective to the patches.
Methods: Postmortem striatal tissue was obtained from the Maryland Brain Collection from 8 normal controls (NC), 6 treatment responsive SZ cases (SZr), and 6 treatment non responders or off drug SZ cases (SZno). The mean ages and PMIs were NC, 43yrs and 5.0 hrs; SZr, 53yrs and 4.5 hrs; SZno, 44yrs and 5.7 hrs. Tissue was prepared for calbindin immunocytochemistry to identify patch matrix compartments, prepared for electron microscopy and analyzed using stereological methods. Data are presented as the mean synaptic density per 10u3 +/-SD. Data were analyzed with ANOVA and FLSD.
Results: In the caudate, synapses characteristic of corticostriatal inputs were significantly higher in density in SZno (2.5 +/-0.7) than in either SZr (1.8+/-0.2) or NCs (2.0+/-0.4). The same results were found in the putamen: SZno (2.5+/-0.6) vs. SZr (1.95+/-0.4) and NCs (1.8+/-0.5). In the caudate, synapses characteristic of thalmostriatal inputs were similar in density between the NCs (0.22+/-0.1) and SZno (0.21+/-0.12), while the SZr showed an elevated synaptic density (0.36+/-0.07). The same results were found in the putamen: NCs (0.22+/-0.13) and SZno (0.23+/-0.12), vs. SZr (0.35+/-0.11). These increases in synaptic density were confined to the patches, which process limbic information.
Discussion: These data suggest that corticostriatal inputs are abnormally dense in areas of the striatum which process limbic information in SZno. The failure to normalize this abnormality may play a role in treatment resistance and contribute to psychosis. These data also suggest that thalamostriatal inputs are normal in SZno, but are abnormally high in SZr. The increase may be compensatory and could play a role in treatment response.

124. High-Field (4-Tesla) Single-Voxel ^{1}H MR Spectroscopy of Left Superior Temporal Gyrus of Young Individuals Genetically At-Risk for Schizophrenia

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Background: Developmental changes in the brain prior to the typical age of onset of schizophrenia may be relevant to its etiopathology. The left superior temporal gyrus (STG), which plays a role in language, has been consistently implicated in schizophrenia and is believed to undergo maturational changes during adolescent years. Proton magnetic resonance spectroscopy (^{1}H MRS) permits the in vivo quantification of metabolites such as *N*-acetylaspartate (NAA; a marker of neuronal integrity), phosphocreatine plus creatine (PCr+Cr), glycerophosphocholine + phosphocholine (GPC+PC, a measure reflecting the turnover equilibrium of membrane phospho-

lipid metabolism), glutamate and myo-inositol. In this study, we examined the left STG in young individuals at increased genetic risk for schizophrenia and healthy controls using in vivo 1H spectroscopy with a hypothesis that HR will show reduction in NAA reflecting developmental abnormality consistent with our previous finding of reduced STG volumes in HR.
Methods: 20 non-psychotic offspring of schizophrenia patients (HR-age 10-20, M/F=13/7) and 18 healthy controls (HC-age 10-20, M/F=7/11) volunteered for this study. A short echo-time, single-voxel ^{1}H spectroscopy method was used to localize a 3.4 cm^3 voxel in the left STG posterior to the Heschl's gyrus on a 4 Tesla Bruker MedSpec MR scanner. The data were analyzed using LC model.
Results: With gender and age as covariates, the absolute GPC+PC level in HR (mean=0.51±0.08) was significantly lower (F=7.5 and P< 0.01) compared to HC (0.61±0.09). However, NAA levels as well as PCr+Cr, glutamate and myo-inositol were not significantly different.
Discussion: Although NAA was not significantly different, reduction in GPC+PC suggests an alteration in the turnover equilibrium of membrane phospholipid metabolism; possibly due to a reduction in the neuronal processes and synapses of the language related areas. These findings should be considered preliminary for several reasons; heterogeneous sample as many in the HR may not develop psychopathology, small sample size, differences in gender and age distribution and a lack of follow up data. Further studies are warranted to investigate whether this finding could be a marker of genetically mediated susceptibility for schizophrenia spectrum disorders.

125. Gabaergic Transmission Abnormalities in the Amygdala of Subjects Diagnosed with Bipolar Disorder or Schizophrenia

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Sponsor: Francine M. Benes

Background: Growing evidence supports a pivotal role for the amygdala in the pathogenesis of bipolar disorder (BD) and schizophrenia (SZ). Imaging and postmortem investigations on subjects affected by major psychoses have detected morphological, neurochemical and functional abnormalities within this temporal lobe nuclear complex. Consistent with evidence from other brain regions, some of these findings point to abnormalities relative to the GABAergic system in the amygdala (Reynolds et al., 1990; Benes and Berretta, 2001). With the present study we tested the hypothesis that GABA-immunoreactive neurons may be altered in the amygdala of subjects affected by BD or SZ.
Methods: Postmortem tissue blocks containing the whole amygdala from 12 subjects diagnosed with SZ, 12 with BD and 16 normal control donors (1 hemisphere/subject), matched by age, gender and postmortem time interval, were included in this study. Serial sections were processed for immunocytochemistry using an antibody raised against GABA (BSA-conjugated). Total numbers, numerical density of GABA-immunoreactive (IR) neurons, and density of GABA-IR neuropil (thresholded pixel count) were measured in the lateral (LN), basal (BN), accessory basal (ABN) and cortical (CO) nuclei and in the intercalated cell masses (ITCM) of the amygdala using computer-assisted light microscopy. Stepwise linear regression procedures, including as covariates age, gender, postmortem time interval, hemisphere, brain weight, cause of death, age of disease onset, duration of illness, and lifetime as well as last six months' exposure to antipsychotic and/or lithium, were used to test statistical significance of differences between groups.
Results: In BD, increases of numerical densities of GABA-IR neurons were detected in the BN (p=0.01) and in the CO (p=0.02). Total numbers of GABA-IR neurons were also increased in the same nuclei (BN, p=0.06; CO, p=0.01). Densities of GABA-IR neuropil were increased in the LN (p=0.05) and the ABN (p=0.02). In contrast, SZ showed a decrease of total number of GABA-IR neurons selectively in the ITCM (p=0.03), while the other amygdala nuclei investigated showed no changes.
Discussion: These results indicate that GABAergic transmission is altered in the amygdala of both BD and SZ. However, the pattern of these changes strongly diverges in these two diseases. In BD, increases of IR neurons and neuropil suggest an increase of GABA expression in inhibitory neurons. We propose that augmented inhibitory power of intrinsic circuits may result in disregulation of information processing within the amygdala. Opposite changes were detected in SZ. Our findings point to a defect of GABAergic transmission selectively in the ITCM of SZ. These clusters of inhibitory neurons are thought to modulate the information flow from the LN, BN, and ABN to the central nucleus as well as from the prefrontal cortex to deep and superficial amygdala nuclei (Berretta et al., 2003; Quirk et al., 2003; Pare et al., 2004). In SZ, these circuits may be disrupted as a consequence of a defect of GABAergic transmission in the ITCM. Such changes are consistent with decreases of GABAergic neurons in other brain regions in SZ (Benes and Berretta, 2001; Costa et al., 2001; Lewis et al., 2005). Our findings support the idea that the amygdalar GABAergic system may be differentially affected in SZ and BD.

126. WAY-163909, A 5-HT_{2C} Agonist, Enhances the Preclinical Potency of Current Antipsychotics

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Background: 5-HT_{2C} agonists, by decreasing mesolimbic dopamine without affecting nigrostriatal dopamine, are predicted to have antipsychotic efficacy with low extrapyramidal side effects (EPS). By combining 5-HT_{2C} agonists with low doses of existing antipsychotics, treatment efficacy could be increased while reducing treatment liabilities such as EPS (typical antipsychotics), and the propensity for weight gain (atypical antipsychotics with 5-HT_{2C} antagonist properties).
Methods: WAY-163909, a selective 5-HT_{2C} agonist, was administered with either the typical antipsychotic haloperidol, or the atypical antipsychotic clozapine, at doses that were ineffective on their own, were tested in several rodent behavior models predictive of antipsychotic activity (apomorphine-induced climbing/stereotypy, conditioned avoidance responding, and prepulse inhibition.
Results: In mice, there was a 0-15% reduction in apomorphine-induced climbing with 5.4 mg/kg WAY-163909, 0.17 mg/kg haloperidol or 5.4 mg/kg clozapine. Coadministration of WAY-163909 and haloperidol resulted in a 70% reduction in apomorphine-induced climbing while WAY-163909 plus clozapine reduced apomorphine-induced climbing by 60%, both without an appreciable decrease in apomorphine-induced stereotypy, or an increased occurrence of catalepsy. In the rat conditioned avoidance model, a 0.54 mg/kg dose of WAY-163909 was combined with either haloperidol (0.54 mg/kg) or clozapine (5.4 mg/kg). Individually, these compounds produced reductions in avoidance response on the order of 10%, but the combination of WAY-163909 and either of the antipsychotics resulted in a greater than 70% reduction in avoidance, with no evidence response failures. While neither haloperidol (1 mg/kg) nor clozapine (3 mg/kg) antagonized an MK-801 (0.1 mg/kg) induced deficit in prepulse inhibition, the combination of WAY-163909 (1 mg/kg) with either of these antipsychotics, resulted in a significant attenuation of the sensory gating deficit.
Discussion: Taken as a whole, these data support the notion that 5-HT_{2C} receptor agonists, when co-administered with other marketed antipsychotics, could increase patient compliance through improved treatment efficacy coupled with a more favorable side effect profile.

127. Effect of Food on Absorption of Ziprasidone

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Background: Orally administered ziprasidone shows a increase in bioavailability in the presence of food, and therefore administration with food is recommended in the label.1 In this report, we describe pharmacokinetic studies conducted to quantify the impact of food under various conditions on the absorption of ziprasidone.
Methods: The effect of food on ziprasidone absorption was examined in 2 clinical pharmacokinetics studies. In the first study, absorption of ziprasidone was investigated in an open-label, nonrandomized, 6-way crossover study in 8 healthy male subjects. Subjects received oral ziprasidone 20, 40, and 80 mg single doses in a fasting state (8-hour fast) or immediately following consumption of an FDA standard meal (ie, a high-fat breakfast). A second study explored the impact of dietary fat content on ziprasidone absorption in an open-label, randomized, 3-way crossover study in 14 healthy subjects. Subjects received ziprasidone 40 mg using a steady state regimen under 3 conditions: in the fasting state, with an FDA standard meal (60% fat content), and with a lower-fat meal (30% fat content).
Results: The AUC0-inf was greater in the fed state than in the fasting state at each dose tested (20 mg, +48%; 40 mg, +87%; 80 mg, +101%). The increases in AUC0-inf and Cmax with dose were nonlinear in the fasting state but linear in the fed state. Nonlinearity was attributed to dose-limiting absorption at the higher doses owing to fasting conditions during administration. Decreasing the fat content from 60% to 30% in test meals (using the 40 mg dose) had a modest impact on ziprasidone absorption. Compared with the fasting state, there was a 100% increase in AUC for the high-fat meal and an 80% increase for the lower-fat meal. These increases are attributed to enhanced ziprasidone solubilization secondary to food consumption leading to greater intestinal absorption.2 Less variability of AUC and Cmax values was observed in the fed state, suggesting more consistent absorption of ziprasidone when taken with food.
Discussion: These results demonstrate that the administration of ziprasidone with food is crucial to ensure linear pharmacokinetics and optimal absorption for consistent systemic exposure to ziprasidone. Food also reduced pharmacokinetic variability in drug absorption indicating that coadministration of ziprasidone with food will also provide greater consistency in daily systemic exposure to ziprasidone and thus, symptom control and patient tolerability.

128. Decreased Prepulse Inhibition of Startle and Increased Locomotor Activity After Administration of a Dopamine D2 Agonist in C3H/HeJ, SPRET/EiJ and CAST/EiJ Mice

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Background: Prepulse inhibition (PPI) and locomotor activity have been used to investigate the effects of antipsychotic and stimulant drugs and their underlying dopaminergic mechanisms. Whereas dopamine D2 selective agonists consistently decreased PPI and increased locomotion in rats in previous studies, we recently reported that these hallmark behavioral effects were not observed in several commonly used mouse strains. The objective of the present study was to extend these investigations to determine whether any mouse strains could be identified in which PPI deficits and locomotor hyperactivity after administration of a selective D2 agonist are consistently observed.
Methods: We selected the following 15 strains of mice for locomotor studies: Swiss Webster, CD-1 (ICR), C57BL/6J, DBA/2J, 129X1/SvJ, 129S6/SvEvTac, 129S1/SvImJ, Balb/cJ, Balb/cByJ, A/J, SJL/J, C3H/HeJ, FVB/NJ, SPRET/EiJ and CAST/EiJ. We also tested outbred Sprague-Dawley rats. Group sizes were 16 (half male and half female) for all strains and species, and doses were varied within subjects using a latin square design.
Results: The dopamine D2 agonist quinelorane (0.01 – 3.2 mg/kg IP) dose-dependently increased locomotion in Sprague-Dawley rats ($p<0.001$), as previously observed. In contrast to rats, quinelorane only decreased locomotion across a broad dose range (0.003 – 5.6 mg/kg IP) in those mouse strains most widely used in biomedical research including standard outbred strains (e.g., Swiss Webster, CD-1) as well as inbred strains commonly used to generate knockout and transgenic mice (e.g., C57BL/6J, 129X1/SvJ, 129S6/SvEvTac). Nevertheless, we identified the following three mouse strains in which the dopamine D2 agonist dose-dependently increased locomotor activity similar to those effects of quinelorane observed in Sprague-Dawley rats: C3H/HeJ, SPRET/EiJ and CAST/EiJ. In a second series of studies, we found that quinelorane (0.032 – 1.0 mg/kg IP) also dose-dependently decreased PPI in C3H/HeJ, SPRET/EiJ and CAST/EiJ mice ($p<0.05$). These effects of quinelorane on locomotor activity and PPI in C3H/HeJ, SPRET/EiJ and CAST/EiJ mice are in agreement with effects in Sprague-Dawley rats and contrast with effects observed in other more commonly used mouse strains such as Swiss Webster, C57BL/6J, DBA/2J and 129X1/SvJ (Ralph and Caine, JPET 312:733, 2005). Parallel studies with the dopamine D1 selective agonist R-6-Br-APB revealed a much more comparable behavioral profile between Sprague-Dawley rats and most mouse strains tested, yielding dose-dependent increases in locomotion and decreases in PPI, although the CAST/EiJ mice were remarkably unaffected by the D1 agonist across a broad dose range (0.1 – 18.0 mg/kg IP).
Discussion: In summary, similar to rats and unlike previous published reports in several commonly used mouse strains, we have now identified three strains of mice in which a D2-like agonist decreased PPI. Thus, the C3H/HeJ, SPRET/EiJ, and CAST/EiJ mice may more closely mirror the Sprague Dawley rat than most other mouse strains and may confer advantages in cross species behavioral pharmacology studies related to D2 receptor function.

129. Stress and Genetic Factors Interact to Modulate Effects of D-Serine, Sarcosine, and Guanosine on NMDA Receptor Function in Intact Mice: Relevance to Schizophrenia

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Background: Abnormalities of NMDA receptor-mediated neurotransmission are implicated in the pathophysiology of psychiatric disorders, including schizophrenia. Phencyclidine (PCP), a noncompetitive NMDA receptor antagonist, precipitates a schizophreniform psychosis, consistent with the hypothesis of NMDA receptor hypofunction in schizophrenia. Mouse strains differ in sensitivity to behavioral effects of MK-801 (dizocilpine), a PCP analogue; in particular, the BALB/c inbred strain shows heightened sensitivity. This heightened sensitivity could reflect combinations of NMDA receptor subunits with a higher proportion of open channels and higher affinity for MK-801 or both (combinatorial diversity). These factors may also explain differences between the inbred BALB/c and outbred NIH Swiss strains in stress-induced reductions in MK-801's antiseizure efficacy. The BALB/c mouse strain, "stressed" mice, and behavioral consequences of MK-801 administration represent models of altered glutamatergic neural transmission. We examined the ability of D-serine, sarcosine and guanosine to modulate the effects of MK-801 in an intact whole animal model of altered NMDA receptor-mediated neurotransmission. D-Serine is a naturally occurring glycine agonist that modulates the NMDA receptor, sarcosine is a naturally occurring glycine reuptake inhibitor and guanosine is a modulator of glutamate uptake.
Methods: Mice were forced to swim for up to 10 min in cold water (6 degrees Celsius) 24 h prior to testing the ability of MK-801 to raise

the threshold voltage for the precipitation of tonic hindlimb extension. D-Serine, sarcosine, guanosine or the saline vehicle control was injected 20 min prior to the injection of MK-801 or its vehicle, which occurred 20 min prior to electroconvulsive shock delivered via earclip electrodes. Nonstressed mice were handled identical except for the swim on day 1.
Results: 24 h after stress, the antiseizure efficacy of MK-801 was reduced in the outbred NIH Swiss and inbred BALB/c strains. In nonstressed outbred NIH Swiss mice, D-serine and sarcosine did not modulate MK-801's antiseizure efficacy, whereas guanosine reduced MK-801's antiseizure efficacy. D-Serine and sarcosine were also ineffective in outbred NIH Swiss mice 24 hours after stress. However, D-serine and sarcosine reduced MK-801's antiseizure efficacy in BALB/c mice 24 hours after they were forced to swim for up to 10 minutes in cold-water, although they were ineffective in nonstressed inbred BALB/c mice. Protocols were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.
Discussion: D-serine and sarcosine interact with stress to reduce MK-801's ability to antagonize electrically precipitated tonic hindlimb extension. Under conditions of stress, modulatory effects of these glycinergic interventions on the antiseizure effect of MK-801 are observed in BALB/c mice that are not apparent in the nonstressed condition. Additionally, these paradigms have demonstrated that in the intact animal, D-serine, sarcosine and guanosine modulate NMDA receptor-mediated neurotransmission; however, the interaction of stress and genetic strain affect the modulatory effects of these compounds. The results could be relevant to the development of these interventions for the treatment of neuropsychiatric disorders.

130. Pilot Study of an α7 Nicotinic Acetylcholine Receptor Agonist Adjuvant Therapeutic Strategy for Schizophrenia

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Background: Converging evidence implicates α7 nicotinic acetylcholine receptor (α7 nAChR) hypofunction in the etiopathogenesis of schizophrenia. For example, impairment of auditory sensory gating that is inherited as an autosomal dominant among schizophrenia patients and their unaffected biological relatives may be due to diminished hippocampal expression of this receptor. Unfortunately, development of a selective α7 nAChR agonist interventional strategy for schizophrenia is problematic because nAChRs in general desensitize rapidly upon exposure to agonist, resulting in an agonist becoming a functional antagonist. This would be especially problematic in the context of diminished expression of the α7 nAChR. Galantamine is a positive allosteric modulator of nAChRs that enhances the efficiency of coupling between binding of agonist and channel opening, and may preserve the receptor in a sensitive, as opposed to a refractory, state. Additionally, galantamine is an inhibitor of acetylcholinesterase and, thus, would lead to nonselective stimulation of both muscarinic and nicotinic acetylcholine receptors. Choline, the hydrolytic split product of acetylcholine (Ach) that is derived locally in the area of cholinergic synapses, is a selective α7 nAChR agonist, mimicking the agonist properties of ACh at this receptor. We hypothesize that the combination of galantamine and CDP-choline, a dietary source of choline, would obviate the limitations associated with administration of either galantamine (nonselective stimulation of muscarinic and nicotinic acetylcholine receptors) or CDP-choline (receptor desensitization) alone.
Methods: We studied the tolerability, safety and preliminary efficacy of the combination of CDP-choline (2000 mg/day) and galantamine (24 mg/day) in six schizophrenia patients with residual symptoms in a 12-week, open-label trial. The patients were maintained on stable dose regimens of antipsychotic medications for four weeks prior to study entry and throughout the duration of the trial.
Results: All enrolled patients reached the target doses of medication and completed the trial. Transient side effects were noted in all patients that resolved without slowing of dose titration. GI adverse effects (constipation, diarrhea, GI distress) were the most common adverse events seen. All patients showed reduction in CGI severity scores and three patients showed evidence of efficacy based on the Positive and Negative Syndrome Scale (PANSS) Total score. Three patients requested continuation of the adjunctive combination after the conclusion of the trial, including one patient who did not show objective evidence of efficacy with the PANSS.
Discussion: The results of this pilot study support further investigation of the "proof of concept" that the combination of CDP-choline and galantamine is an α7 nAChR agonist intervention that possesses adjuvant therapeutic efficacy in schizophrenia.

131. Two Year Outcomes on Risperidone and Olanzapine in Stable Patients with Schizophrenia

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Background: The goals of long-term treatment for schizophrenia include preventing psychotic relapse and improving physical health and functional outcomes. Recent trials including the NIMH-CATIE trial have underlined that effective management often requires complex decision-making regarding these different goals. We characterized these outcomes in patients with stabilized schizophrenia who were randomly assigned to double-blind risperidone or olanzapine.
Methods: : One hundred seven stable outpatients with schizophrenia or schizoaffective disorder were randomly assigned to receive double-blind olanzapine vs risperidone, and supported employment with and without a skills training module. (This report will focus on the drug conditions.) Using a double dummy design, clinicians were instructed to target doses of 4 mg of risperidone and 15 mg of olanzapine. (At one year year the mean risperidone dose was 6.3 (sd,3.1) mg/day and mean olanzapine dose was 17.1 (sd, 5.8) mg/day. Patients were followed prospectively for 24 months or until they discontinued their medication for lack of efficacy or adverse effects. Regular evaluations included measures of psychopathology, quality of life, and metabolic factors (body mass index, lipids, glucose, and glycosolated hemoglobin. In contrast to other studies, early evidence of weight gain, glucose or lipid elevations was considered an event leading to drug discontinuation. At study entry, 37% were taking olanzapine, 34% risperidone, 12% quetiapine, 5% clozapine, and 11% first-generation antipsychotics.
Results: Product limit survival estimates for all cause discontinuation was 54% vs. 47% at 12 months, and 37% vs. 33% at 24 months for olanzapine vs. risperidone respectively (p=ns). There were no significant differences in psychopathology ratings between the two drugs. We found a time by drug interaction indicating less weight gain on risperidone (p=0.04). However, weight gain on olanzapine in patients who remained in their drug condition was only about 1 kg for 24 months. We did not find significant medication effects on lipids or glycemic control. Entering the study on a first-generation antipsychotic or risperidone, or randomization to change medication to olanzapine, was associated with a significant increase in BMI.
Discussion: The findings indicate that olanzapine and risperidone demonstrated similar effectiveness in stabilized outpatients with schizophrenia. Our finding of relatively less weight gain and metabolic derangement than that reported in CATIE may reflect the impact of intervening before patients demonstrated serious metabolic disturbances.

132. Dysbindin-1 Is Reduced in Intrinsic Glutamatergic Terminals of the Hippocampal Formation in Schizophrenia

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Background: Significant associations have been reported between schizophrenia and certain haplotypes of single-nucleotide polymorphisms in the gene encoding dysbindin-1 at 6p22.3 in populations around the world.
Methods: In situ hybridization, immunohistochemistry, and quantitative microscopy and image analysis were used to map the distribution and levels of expression of dysbinidn-1, vesicular glutamate transporter 1 (VGluT-1), and other pre-synaptic proteins in two sets of postmortem tissues from patients with schizophrenia and controls.
Results: Compared with matched, non-psychiatric controls, 73-93% of cases in two schizophrenia populations displayed significant presynaptic dysbindin-1 reductions at hippocampal formation sites lacking neuronal dystrobrevin (i.e., β-dystrobrevin). The reductions occurred specifically in terminal fields of intrinsic, glutamatergic afferents of the subiculum, the hippocampus proper, and especially the inner molecular layer of the dentate gyrus. An inversely correlated increase in VGluT-1 occurred in DGiml of the same schizophrenia cases. Those changes occurred without evidence of axon terminal loss or neuroleptic effects on dysbindin-1 or VGluT-1.
Discussion: Our findings indicate that presynaptic dysbindin-1 reductions independent of the dystrophin glycoprotein complex are frequent in schizophrenia and are related to glutamatergic alterations in intrinsic hippocampal formation connections. Such changes may contribute to the cognitive deficits common in schizophrenia.

133. Asenapine Cognitive Function Effects in Acute Schizophrenia: a Placebo- and Risperidone-Controlled Trial

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Background: Neurocognitive impairment is a core characteristic of schizophrenia. Asenapine is a novel psychopharmacologic agent being developed for the treatment of schizophrenia and bipolar disorder. It has a unique human receptor signature characterized by high affinity for an ensemble of serotonergic, dopaminergic, and adrenergic receptors. A 6-week, randomized, double-blind, placebo- and risperidone-controlled, fixed-dose study was conducted to evaluate the efficacy and safety of asenapine in patients with acute exacerbation of schizophrenia. As previously reported, asenapine was superior to placebo on PANSS total score, PANSS positive and negative subscale scores, and CGI score; superior to risperidone on PANSS negative subscale score; and well tolerated, with a low risk of hyperprolactinemia or significant weight gain. Here, we report results of the cognitive assessments performed in this study.
Methods: Patients with acute exacerbation of schizophrenia were randomized to receive asenapine 5 mg BID (n=59), risperidone 3 mg BID (n=59), or placebo (n=62); a double-dummy placebo design was employed to maintain blinding. A comprehensive neurocognitive test battery was administered after the morning dose at baseline, week 3, and week 6 or last visit; last observations were carried forward for patients who did not complete the trial. The following domains were tested: speed of processing (Category Fluency, Verbal Fluency, Trails A and B, Digit Symbol Substitution Test [DSST]); working memory (Letter-Number Span); verbal learning and memory (Rey Auditory Verbal Learning Test, which includes Immediate and Delayed Recall and Delayed Recognition); visual learning and memory (Benton Visual Retention Test); and reasoning and problem solving (Wisconsin Card Sorting Test [WCST]). Placebo-corrected effect sizes (Dunlap's D) were calculated for individual neurocognitive tests to evaluate the impact of asenapine on neurocognitive functioning in schizophrenia.
Results: Asenapine-treated patients demonstrated improvements on tests of verbal learning and memory (Dunlap's D 0.45, 0.38, and 0.25 for Immediate and Delayed Recall and Delayed Recognition, respectively) and speed of processing (0.43, 0.34, and 0.31 for Trails A time, DSST, and Verbal Fluency, respectively). Risperidone-treated patients demonstrated improvements in speed of processing (Dunlap's D 0.31 and 0.24 for Trails A time and DSST, respectively), but their performance worsened in the domain of reasoning and problem solving (–0.35 and –0.31 for WCST percentage of perseverative errors and total number correct, respectively).
Discussion: Patients treated with asenapine showed improvements in domains of cognitive function that are particularly relevant to functional outcome in schizophrenia: the speed of processing and verbal learning and memory domains. Further studies are needed to confirm and generalize these observations.

134. A Randomized, Double-Blind, Placebo-Controlled Study of Bifeprunox, a Partial Dopamine D2 Receptor Agonist, in Patients with Acute Exacerbations of Schizophrenia

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Sponsor: Steven Potkin

Background: Objectives: To determine the efficacy, safety, and tolerability of 20 mg or 30 mg bifeprunox versus placebo in patients with acute exacerbations of schizophrenia.
Methods: In this 6-week double-blind, placebo-controlled, olanzapine-referenced, parallel-group, multi-center efficacy and safety study of bifeprunox, 604 patients with acutely exacerbated schizophrenia (DSM-IV-TR) were randomly assigned to treatment with bifeprunox 20 mg (n=154), bifeprunox 30 mg (n=150), placebo (n=150), or olanzapine 15 mg (n=150). Bifeprunox doses were titrated, beginning with a dose of 0.25 mg on day 1 and approximately doubled every day until 20 mg (day 7) or 30 mg (day 8) were reached, while olanzapine treatment began at 10 mg for the first 7 days, and subsequently maintained at 15 mg for the remainder of the study. The change in the Positive and Negative Symptom Scale (PANSS) total score, from baseline to endpoint (LOCF and OC), was used as the primary outcome measure. Secondary efficacy measures included: Clinical Global Impressions (CGI)-Severity of Illness, PANSS negative and positive subscale scores, and PANSS-derived Brief Psychiatric Rating Scale (BPRS) score. Safety and tolerability evaluations included extrapyramidal symptoms (EPS), weight gain, fasting glucose and lipid, and serum prolactin. Olanzapine was included for assay sensitivity.
Results: The 20 and 30 mg doses of bifeprunox showed improvement in PANSS total score at endpoint compared to baseline of -13.8 and -13.1, respectively, but were not statistically significant versus placebo (-10.7). Olanzapine was statistically superior to placebo. The observed case analysis demonstrated a decrease from baseline in total PANSS of -24.4 and -24.6 points for the bifeprunox groups, -22.3 for placebo and -29.1 for olanzapine. The reasons for the high placebo response rates are unknown. Discontinuation rates due to adverse events were 11% in placebo, 8% in each of the bifeprunox groups, and 6% in the olanzapine group. The most common adverse events (incidence >5% and twice placebo) included: nausea, vomiting and constipation. Abnormal movement rates were comparable among treatment groups. Both bifeprunox doses lowered prolactin ($P<0.0001$), and the 30 mg dose lowered triglycerides versus placebo ($P<0.05$). Both bifeprunox doses also showed decreases in weight and improvements in fasting lipid and glucose profiles, similar to placebo. Olanzapine demonstrated statistically significant increases in weight, fasting triglycerides, LDL, and VLDL versus placebo.

Discussion: No statistically significant improvement in PANSS score was observed with 20 mg or 30 mg bifeprunox compared to placebo. Bifeprunox treated subjects' metabolic profile was favorable and comparable to placebo. Based upon the safety profile presented here, bifeprunox may be a useful treatment for the long-term management of schizophrenia.

135. Predictors of Long-Term Outcome in Schizophrenia: A Double-Blind, 196-Week Study of Ziprasidone and Haloperidol

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Sponsor: William E. Bunney

Background: Recently published consensus-based operational criteria for remission in schizophrenia1 provide clinicians and researchers with a new, well-defined long-term treatment goal. Previous studies have shown improvement in indices of psychosocial function in patients attaining remission.2 A significant relationship between symptom remission and quality of life has been demonstrated using longitudinal analyses in a long-term (nearly 4-year) double-blind study comparing ziprasidone and haloperidol.3 The current analysis was conducted to identify predictors of remission in that study.
Methods: One hundred and eight six subjects completed an initial 40-week randomized, double-blind trial and enrolled in a 3-year, double-blind continuation study. We examined potential predictors at the pre-treatment baseline of the 40-week phase. The main predictor variables considered were treatment, diagnosis, socio-demographic factors, psychiatric history, family history of psychiatric illness, symptom severity and the Quality of Life Scale (QLS) score at baseline. The primary outcome variable was the likelihood of attaining full remission in the final 6 months of participation in the continuation study. Logistic regression was used to control simultaneously for multiple variables predicting remission, with adjustment for treatment duration.
Results: Treatment was a significant predictor of remission (p=0.015). The predictive model found that ziprasidone-treated subjects (N=139) had a 3-fold (adjusted odds ratio [OR] 95% CI 1.1-7.9) increase in the likelihood of remission than the haloperidol-treated subjects (N=47). After controlling for treatment effect, the following factors were significantly associated with sustained remission: better baseline QLS total score (p<0.001), Caucasian race (OR 4.5; p=0.006), schizoaffective diagnosis (OR 3.9; p=0.02), lower baseline symptom severity (p=0.02), younger age (p=0.038), no prior psychiatric hospitalization (OR 3.3; p=0.046), and no family history of psychiatric illness (OR 2.3; p=0.07). Single (never married) subjects were less likely to attain remission (p=0.035). Gender, education level, and age at onset of psychotic illness were not significant predictors in this analysis. The predictive validity of these findings was confirmed using the area under the receiver operating characteristic curve (ROC) (AUC 0.85, SE=0.03, 95% CI 0.8-0.9).
Discussion: These findings are consistent with previous reports showing that patients with relatively good prognosis may be less chronically ill (younger with fewer prior psychiatric hospitalizations) and have a schizoaffective diagnosis, lower symptom severity, history of close interpersonal relationship and a favorable global QLS score. Treatment with ziprasidone was a significant predictor for sustained remission, with an estimated 3-fold increase in the likelihood of attaining remission compared with haloperidol treatment. These results suggest the potential for enhanced symptom remission and long-term outcomes among patients treated with a second-generation antipsychotic.

136. Alpha 4 Beta 2 but not Alpha 7 Nicotine Receptor Subtypes Contribute to Augmentation of Mouse Correlate of Human P50

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Background: People with schizophrenia exhibit reduced P50 and N100 amplitudes following auditory stimuli. We examined the ability of nicotine to reverse both of these physiological deficits using event related potentials (ERP) in a mouse model of early sensory encoding. Similarly, mouse ERP models may be useful in elucidating the reinforcing properties of nicotine for early sensory encoding in smokers. These studies demonstrate preclinical screening measures for development of new medications for both schizophrenia and nicotine cessation.
Methods: All protocols were approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania and were conducted in accordance with NIH guidelines. ERPs were recorded in non-anesthetized animals one week after electrode implantation. Mice were treated with nicotine, the non-specific nicotine antagonist mecamylamine, the alpha 4 Beta 2 antagonist dihydro-beta-erythroidine (DHBE), the alpha 7 antagonist Methyllycaconitine (MLA) or the combination of each antagonist with nicotine.
Results: Nicotine increased P20 amplitude and caused a reduction in N40 amplitude. N40 reduction was reversed by mecamylamine, DHBE and MLA, suggesting that activation of multiple receptor types is required for suppression of the mouse correlate of the human N100. However, P20 augmentation was blocked by mecamylamine and DHBE but not MLA indicating that Alpha 4 Beta 2 but not Alpha 7 receptors participate in the beneficial effects on the mouse correlate of the human P50.
Discussion: Nicotine causes an increase in the P20 and decrease in the N40 in mice, replicating previous data in our group and suggesting that there are both beneficial and detrimental effects of nicotine on pre-cortical (P50 correlate) and cortical (N100 correlate) sensory processing. These data are consistent with human studies demonstrating increased P50 following smoking. Our data suggest that the beneficial effects of nicotine may be related to activation of Alpha 4 Beta 2 nicotinic receptors while the detrimental effects require activation of both Alpha 4 Beta 2 as well as Alpha 7 receptors. These data suggest that increased P20 amplitude without reduction in N40 amplitude could be achieved with an Alpha 4 Beta 2 agonist. Therefore, we propose that Alpha 4 Beta 2 agonists represent an appropriate target for smoking cessation and sensory encoding deficits in schizophrenia.

137. Cognitive Change After Treatment with Second Generation Antipsychotic Medications in First Episode Schizophrenia: Is It a Practice Effect?

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Background: It is generally accepted that cognitive impairment accounts for a significant share of the social and vocational morbidity associated with schizophrenia. Numerous recent studies have suggested that second generation antipsychotic medications significantly enhance cognition in schizophrenia. None of these studies included healthy controls undergoing repeated testing to assess the possibility that "improvements" actually reflect simple practice effects.
Methods: In this study of 104 first episode (FE) schizophrenia patients we were able to address several sources of bias or problematic methodologies which made interpretation of earlier results complex. 1. We directly compared two of the most widely prescribed second generations drugs in the US, olanzapine and risperidone in a randomized, blinded trial on key measures of neurocognition (increasing the generalizability of the result). 2.) The study was federally sponsored; 3. The large majority of patients were drug naïve at baseline (thus changes over the following weeks could not be attributed to a switch in medication or withdrawal from of medication as in studies that used washouts and pari passu, patients did not have long and/or complex histories of antipsychotic treatment that might play a role in drug response that cannot easily studied, not less quantified. 4. A healthy control group was assessed over repeated visits to measure practice effects. Fifty one FE patients were randomized to olanzapine

(modal dose 12.7 mgs) and 53 to risperidone (modal dose 3.7 mgs). Eighty four healthy controls received cogntive testing. Assessments occurred at baseline, six weeks later, and 16 weeks later. Neurocognitive tests included measures of working memory and attention, speed of processing, episodic memory, and executive function.
Results: No differential drug effects were observed. Of 16 cognitive measures, nine demonstrated improvement over time. Of these only two (visual memory for designs, trailmaking speed) demonstrated greater rates of change than that observed in the HC group undergoing repeated assessment. The composite effect size in the HC group was .33, in the FE patients, .36.
Discussion: Results suggest that cognitive change was consistent in magnitude to practice effects and thus does not reflect cognitive enhancement per se. We believe that these findings have important implications for drug discovery and the design of registration trials that attempt to demonstrate cognitive enhancement.

138. *ASPM* Influences Cerebellar and Cerebral Cortical Volumes in Two Independent Samples of Individuals with Schizophrenia

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Sponsor: Raymond Crowe

Background: The *ASPM* gene is expressed at spindle poles of mitotic peri-ventricular neural progenitor cells in the developing brain, influencing whether daughter cells remain as pluri-potent progenitors or enter terminal differentiation. *ASPM* mutations can cause autosomal recessive primary microcephaly, and common SNPs appear to have contributed to the increase in cerebral cortical volume that has characterized the evolution of the primate brain. We examined whether *ASPM* was associated with brain structure volumes in individuals with schizophrenia (SZ).
Methods: We examined 268 SZ individuals and 125 controls. Two SNPs in tight LD with each other were primary in the cortical evolution haplotype; we genotyped one of these, rs3762271, a C/A SNP. We imaged 263 of the SZ individuals with one of two MRI protocols: the first 135 with protocol 1 (PR1), and the next 128 with protocol 2 (PR2); 90 controls were imaged, 18 with PR1 and 72 with PR2. We tested gray, white, and total tissue volumes of the cerebral cortex, the 4 cerebral lobes, and the cerebellum, and ventricular CSF. In addition, 233 SZ individuals and all controls received cognitive testing across 5 domains of functioning: verbal memory, processing speed and attention, problem solving, language, and visual-spatial abilities. All SZ individuals were assessed for neurological, cerebellar, and soft sign abnormalities. ANCOVAs tested genotype effects on quantitative measures, with partial *r*2 as a measure of effect size. Relationships between genotypes and neurological abnormalities were assessed with chi-square tests.
Results: rs3762271 was not associated with SZ. Significant genotype effects, however, were found in **both** PR1 and PR2 on volumes of: cerebral cortex, parietal lobe, parietal WM, cerebellum, and cerebellar GM. Adjusted means for each genotype revealed concordant relationships: in both PR1 and PR2 for the cortical structures, AA < CA < CC, while for the cerebellum, AA > CA > CC. Treating genotype as a linear variable confirmed this observation—total cortex: PR1 (F=4.62, p=0.03), PR2 (F=7.59, p=0.007); total parietal lobe: PR1 (F=12.65, p=0.001), PR2 (F=11.10, p=0.001); parietal WM: PR1 (F=4.62, p=0.03), PR2 (F=7.59, p=0.0007); total cerebellum: PR1 (F=4.99, p=0.03), PR2 (F=12.70, p=0.001); and cerebellar GM: PR1 (F=8.82, p=0.004), PR2 (F=9.57, p=0.004). In combined analyses using MR protocol as a covariate, the effects, not surprisingly, became stronger. Partial *r*2 values ranged from 0.044 to 0.068. In the combined analyses, genotype also produced significant effects on cortical WM (F=7.09, p=0.008), frontal WM (F=4.85, p=0.03), and parietal GM (F=4.98, p=0.03). Significant linear genotype effects were also observed for problem solving (F=5.11, p=0.02) and language (F=8.37, p=0.004), with AA better than CA better than CC. SZ individuals with cerebellar signs had a different genotype distribution than SZ individuals without cerebellar signs, weighted toward the CC genotype (genotype chi-square=9.91, p=0.007). *No similar effects were found in controls for either imaging or cognitive measures.*
Discussion: We find that the *ASPM* SNP rs3762271 is associated with brain structure volumes in individuals with schizophrenia. The SNP produced concordant effects across two independent samples in multiple brain regions. The genotype effects were linear in opposite directions in cerebral cortical white matter as compared to cerebellar gray matter. Significant relationships were also observed between genotype and both cognitive abilities and cerebellar neurological abnormalities in directions concordant with the cerebellar brain structure relationships. The contrasting cerebellar and cortical effects may be due to differing times of expression of *ASPM* in these structures and/or to the unique embryonic derivation of cerebellar tissues.

139. Heritability and Multivariate Analyses of Endophenotypic Measures for Schizophrenia: The Consortium on the Genetics of Schizophrenia (COGS)

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Sponsor: David L. Braff

Background: The exploration of the genetic architecture of specific endophenotypes is a powerful strategy for understanding the genetic basis of schizophrenia. The Consortium on the Genetics of Schizophrenia (COGS) has undertaken a large 7-site study to characterize the genetic architecture of some key endophenotypic measures. The COGS assesses the automatic processing measures of Prepulse Inhibition (PPI) of the startle response and P50 suppression, as well as the effortful, controlled processing measures of the Antisaccade Task (AS), the Degraded Stimulus Continuous Performance Test (DS-CPT), the California Verbal Learning Task, Second Edition (CVLT-II), the Letter-Number Span (LNS) test, and several domains of the University of Pennsylvania Computerized Neuropsychological Battery.
Methods: At the time of this data analysis update, 184 probands with schizophrenia and their family members (N=871) have been assessed for these endophenotypes. Variance component models were used to assess heritability, as well as the environmental and genetic correlations among the endophenotypes in the first data release of 106 families (N=479). Additionally, probands and controls with complete data for all endophenotypic measures were selected for analysis with a novel multivariate method for testing the relationship between variation in a similarity matrix and ancillary information collected on a sample of individuals that obviates the need for cluster analysis by testing more global hypotheses about the patterns of similarity in the matrix. This method is also the perfect companion for heat map and tree-based representations of high-dimensional data organized by some feature or grouping factor meant to reveal the relationship between the variables used for their construction.
Results: All of the endophenotypes, with the exception of one domain from the Penn Battery, were found to be significantly heritable ($p<0.05$), with heritabilities ranging from 21 to 53%. Significant environmental and genetic correlations were also observed between many of the endophenotypic measures, providing some evidence for pleiotropy. Our multivariate approach has also revealed a number of interesting associations. In addition, it is clear form this and related studies that may of the endophenotypes are at least partially "normalized" by the use of atypical antipsychotic medication in schizophrenia

patients. Multiple strategies for making statistical corrections for thee medication effects will be discussed.
Discussion: This is the first large-scale, multi-site, family-based heritability study of a large collection of endophenotypes for schizophrenia families and suggests that endophenotypes will be important measures to consider in characterizing the genetic basis of schizophrenia. A major advantage of the use of endophenotypes is that they are likely to be more correlated with the genetic and neural substrate abnormalities than is the "fuzzy", qualitative DSM-IV diagnosis of schizophrenia itself.

140. Whole Genome Association in Schizophrenia Reveals Novel Risk Locus, Confirmed by Independent Sequencing Study
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Sponsor: Sam Siris

Background: The recent development of whole genome association (WGA) technology provides an opportunity to rapidly identify novel susceptibility genes for complex phenotypes. We report converging results of a WGA study in a case-control schizophrenia (SZ) cohort, and a gene sequencing study in an independent case-control cohort, which identify a novel susceptibility locus for SZ.
Methods: For the WGA study, SZ cases (n=178) and controls (n=144), drawn from a single geographic site were examined. Patients (65F/113M) and controls (63F/81M) did not significantly differ in sex distribution. All subjects self-identified as Caucasian non-Hispanic; testing of 210 ancestry informative markers (AIMs) revealed no evidence of population stratification. For the sequencing study, 71 cases (28F/43M), drawn from a US population of clozapine-treated SZ patients and 31 controls (18F/13M), all at least 90% Caucasian based on 76 AIMs were examined. For WGA, 500,568 single nucleotide polymorphisms (SNPs) were assayed using the Affymetrix 500K array. Quality control procedures yielded mean call rates of 97%, reliability (concordance across repeated samples) > 99%, and 439,511 high-quality SNPs available for analysis. Likelihood ratios (df=1) were analyzed for the best possible genotypic split (e.g., recessive or dominant models) for each SNP (excluding monomorphic and very rare SNPs), yielding 362,188 splits. Using Bayesian reasoning, the genomewide significance threshold was set to $p<4.2*10^{-7}$ (yielding an empirically-derived false discovery rate q<.05). Sequencing was performed on exons and flanking regions for two genes neighboring the most significant SNP from the WGA study. The sequencing reactions were carried out in both directions using M13F and M13R primers using BigDyeTM Terminator Cycle Sequencing, and electrophoresis was run on the ABI Prism 3700 DNA Analyzer.
Results: In the WGA study, one SNP demonstrated an association beyond the genomewide threshold ($p=3.7*10^{-7}$). Homozygosity for the common (C) allele at this SNP was significantly associated with SZ; 59% of cases (105/178), but only 31% of controls (44/143, one subject not called) were C/C homozygotes (odds ratio = 3.23; 95% confidence interval = 2.04-5.15; population attributable risk = 23.5%). In the sequencing study, we identified 8 novel, rare missense mutations. A total of 16 amino acid substitutions were detected in cases, with only 1 detected in controls (Fisher's exact p = 0.031). Additionally, common SNPs (minor allele frequency≥.10) were examined and three haplotype blocks were identified; two were significantly associated with SZ, as were 5 intronic SNPs within these 2 blocks.
Discussion: While there is some prior cytogenetic and linkage support for this chromosomal region, neither gene examined in this study has been previously implicated in SZ. Results are consistent with prior biological and epidemiological data in SZ, as will be discussed.

141. Neural Effects of Ziprasidone in First-Episode Schizophrenia: A Longitudinal Study Using Functional MRI and a Procedural Learning Paradigm
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Sponsor: Matcheri Keshavan

Background: We previously demonstrated deficient procedural learning and striato-thalamic dysfunction using functional magnetic resonance imaging (fMRI) and a relatively simple non-verbal sequence-learning task in a group of chronic schizophrenia patients on typical antipsychotics compared to healthy controls (Kumari et al 2002). In this study we examined procedural learning and its neural correlates as well as the effect of ziprasidone treatment on brain and neural responses in a longitudinal design in first episode schizophrenia patients.
Methods: A group of patients who were experiencing their first psychotic episode and had no or minimum exposure to antipsychotic medication underwent fMRI during the same blocked, periodic procedural learning task as used in our previous study at baseline and then after six weeks treatment with ziprasidone.
Results: We observed (i) significant procedural learning in patients but with a different pattern to that normally seen in healthy controls on this task, (ii) abnormal (rather than absent) neural activity in striatal and thalamic regions in patients at baseline, and (iii) normalization of neural activity in the striatal and thalamic regions after ziprasidone treatment.
Discussion: This study provides evidence for abnormal striatal and thalamic activation pattern in first-episode patients which appears to change towards normalization with six weeks ziprasidone treatment.

142. A Randomized, Double-Blind, Placebo-Controlled Trial of Sustained-Release Bupropion Combined with Transdermal Nicotine Patch for Smoking Cessation in Schizophrenia: Neuropsychological Predictors of Treatment Outcome
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Background: Cigarette smoking is highly prevalent in schizophrenia (58-88%) compared to the general population (~22%), and smokers with schizophrenia have great difficulty with smoking cessation. The goals of this study were to determine if: 1) the combination of sustained-release (SR) bupropion with transdermal nicotine patch (TNP) is safe, and superior to placebo and TNP for smoking cessation in schizophrenia, and; 2) whether baseline neuropsychological performance is associated with smoking cessation treatment outcomes.
Methods: In this 10-week, double-blind, placebo-controlled trial, fifty-three treatment-seeking cigarette smokers with schizophrenia received in bupropion SR (300 mg/day) of matching placebo in combination with open-label TNP (21 mg/24h) and weekly group behavioral smoking cessation therapy for smokers. In addition, prior to pharmacological treatment, neuropsychological performance was evaluated in a subset of patients (n=30), using a battery which included the Wisconsin Card Sorting Test (WCST), Visuospatial Working Memory (VSWM) task, Continuous Performance Test (CPT), Iowa Gambling Test (IGT), California Verbal Learning Test (CVLT), Digit Span of the WAIS-III, and Trail Making Test (TMT) Parts A and B.
Results: Treatment retention in the 10-week trial was ~65% and not significantly different between study groups; compliance with study medications in both groups was excellent (>70%). Smokers with schizophrenia assigned to the bupropion SR + TNP group (n=27)

were significantly more likely to achieve continuous smoking abstinence in the last four weeks of the trial (6/26, 23.1%) than those assigned (n=27) to the placebo + TNP group (1/27, 3.7%) [Fisher's Exact Test Statistic, p=0.05]; at 6-months post-TQD, 5/26 (19.2%) versus 0/27 (0.0%) remained abstinent (p<0.03). Neither bupropion SR nor smoking abstinence significantly altered the positive or negative symptoms of schizophrenia or depressive symptoms. Adverse events were modest, and comparable between groups. While there were no significant baseline demographic or clinical differences between quitters and non-quitters, non-quitters exhibited significantly greater deficits in performance on TMT (p<0.02) and Digit Span backwards (p=0.04) compared to quitters. No significant differences were found on VSWM, WCST, CPT, IGT and CVLT outcome measures.

Discussion: Our findings suggest that combination therapy with bupropion SR (300 mg/day) and TNP versus placebo bupropion SR and TNP leads to significant improvement in both short- and long-term smoking abstinence outcomes in refractory cigarette smokers with schizophrenia. Furthermore, deficits in working memory and executive function are associated with smoking cessation failure in schizophrenia. This may be important for the development of tailored smoking cessation treatments in this population. Supported in part by NIDA grants R01-DA-13672 and K02-DA-16611 (to TPG), and NARSAD (to KAS and TPG).

143. Modulation of PKA Activity in the Medial Prefrontal Cortex: Effects on Attention, Motor Activity and Reward

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Background: Attentional deficits characterize a number of neuropsychiatric disorders including bipolar disorder, schizophrenia, and attention deficit hyperactivity disorder. The contributions of each of the major transmitter systems to attention as measured in the 5-choice serial reaction time task (5CSRTT) are well characterized, but little is known about the intracellular signaling mechanisms that regulate attentional processes. In working memory paradigms, modulation of cyclic-AMP dependent kinase (PKA) activity within the medial prefrontal cortex (mPFC) modulates working memory in much the same way as modulation of D1 receptor activation in this brain area. Here, we assess the effects of PKA modulation on attentional performance in the 5CSRTT in Sprague-Dawley rats.

Methods: Rats were trained on a standard version (0.5-1.0 sec stimulus duration, 5 sec inter-trial interval) of the 5CSRTT until they reached criterion performance (>60% accuracy and <20% omissions) for 5 consecutive days prior to drug testing.

Results: Activation of PKA within the mPFC using Sp-cAMPS (2.1 nmol/side) increased omissions (a putative measure of attention) in the 5CSRTT whereas inhibition of PKA using Rp-cAMPS (21.0 nmol/side) reduced accuracy (a measure of attention) and increased omissions in the 5CSRTT. Premature responding (a measure of impulse control) and response latencies (measures of motivation) were both unaffected by modulation of mPFC PKA activity. Changes in omissions are difficult to interpret as they can increase as a result of attentional impairments, changes in motor activity, or reductions in motivation. Thus to further understand the effects of PKA modulation on performance in the 5CSRTT, the effects of PKA modulation on motor activity and brain stimulation reward using intracranial self-stimulation were also assessed. PKA activation within the mPFC had no effect on locomotor activity, whereas PKA inhibition within the mPFC dramatically increased locomotor activity. Further, preliminary data suggest that mPFC PKA activation attenuates the impact of rewarding brain stimulation, whereas mPFC PKA inhibition potentiates the impact of the stimulation.

Discussion: Together, these data suggest that reductions in the efficacy of rewards following PKA activation likely contribute to the increase in omissions observed in the 5CSRTT. In contrast, increased motor activity following PKA inhibition likely contributes to both the reduced accuracy and increased omissions observed in the 5CSRTT. Thus, inhibition of PKA in the mPFC causes a pattern of behavioral consequences (disrupted attention, hyperactivity, increased reward-driven behaviors) that is qualitatively similar to that seen during mania. Support: NARSAD

144. Assessing Functional Plasticity of Cortical Structures in Schizophrenia: fMRI Studies of Associative Learning

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Background: Schizophrenia is widely regarded as a disorder of inter-regional information integration (Tononi and Edelman, 2000). Associative learning is a basic building block of behavior and depends on the strengthening of synaptic linkages following synchronous neuronal discharges (Hebb, 1949). Therefore, associative learning paradigms that rely on the large scale integration of inter-regional neuronal signals may provide an ideal domain in which to investigate the pathophysiological correlates of disconnection in schizophrenia (Stephan et al., 2006). We present preliminary fMRI and behavioral analyses from a learning task (Buchel et al., 1999) in which subjects learned associations between nine objects and locations in a grid (3 x 3). Of particular interest were differences in rates of learning and the relationship between increases in the strength of associations and measurable activity in key structures such as the hippocampus.

Methods: fMRI was conducted using a 4T Bruker MedSpec with standard epi (TR=3 s, TA=1.5 s, TE=30 ms, 24 axial slices, 64 x 64 matrix). During the procedure, subjects alternated between blocks of encoding, rest and retrieval/retention. During encoding, nine equi-familiar objects were presented in sequential random order (3s/object) in grid locations for naming. Following a brief retention interval, memory for object-location associations was tested in retrieval blocks, during which subjects named cued locations (3s/cue). Eight blocks (each alternating between encoding, rest/retention and retrieval) were employed. fMRI analyses (smoothing, detrending, normalization, contrast images) were conducted using SPM2. To date, nine subjects including six controls (HC, age=24 yrs, 4 males) and three stable schizophrenia patients (SCZ, age=30 yrs, 2 males) participated.

Results: Consistent with expected patterns of learning (Gallistel et al., 2004), behavioral performance in HC (accuracy x block) exhibited negatively accelerated growth ($y= 40.35x^{0.4263}$; r^2=.85, $F_{1,6}$=33.9, p<.001), indicating rapid early learning followed by asymptotic performance. By contrast, performance in SCZ exhibited strictly linear behavior ($y= 9.37x + 27.98$; r^2=.97, $F_{1,6}$=271.9, p<.000). These differences were also expressed in a significant Group x Time (early vs. late blocks) interaction, $F_{1,66}$=3.45, p<.05 (one-tailed). Separate random effects analyses of the fMRI data indicated significant encoding (enc) and retrieval (ret) related activity in the hippocampus (enc), inferior temporal (enc, ret), extra-striate (enc, ret). superior parietal (enc, ret), dorsolateral prefrontal (ret) and inferior frontal (ret) structures (p<.005). Initial analyses focus on differences in the plasticity of the hippocampal response (measured by changes in mean percent signal change with time) between HC and SCZ. Whereas HC showed a highly plastic response across left and right hippocampus ($y = -0.09x + 0.57$, $F_{1,6}$=25.2, p<.002), with increased behavioral proficiency, trends in SCZ were notably absent, with only marginal and tonic supra-threshold changes in signal observed.

Discussion: SCZ patients appear to demonstrate deficits in the rate of associative learning coupled with relative dysplasticity of the response of key structures such as the hippocampus. Previous documentation of deficits in associative learning in SCZ is relatively sparse but the current findings are consistent with the widely hypothesized association between schizophrenia psychosis and hippocampal dysmorphometry and hypo-metabolism (Tamminga et al., 1992; Gur et al., 2000). These results have significant translational implications given the documented relationship between the N-methyl-D-aspartate (NMDA) receptor sensitivity and associative learning (Tang et al., 1999), and the presumed dysmodulation of the NMDA system in SCZ (Stephan et al., 2006).

145. Elevated ErbB4 Protein in the Prefrontal Cortex of Schizophrenic Patients

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Sponsor: Alfred Lewy

Background: Evidence linking schizophrenia to polymorphisms in the neuregulin-1 gene has prompted extensive investigation of the role of neuregulin-1 in this disease. Yet, few studies have examined schizophrenia pathology with respect to the putative neuregulin-1 receptor, ErbB4, in which genetic variations have recently been shown to influence schizophrenia risk as well. The present investigation compared amounts of cytoplasmic and nuclear full-length ErbB4 and its potential cleavage products among the prefrontal cortices of normal, bipolar, depressed and schizophrenic subject samples from the Stanley Consortium.
Methods: ErbB4 and its potential cleavage products were analyzed by immunoblotting tissue homogenates with an ErbB4 antibody that reacts with the receptor's c-terminal region, which can exist as part of full-length ErbB4 or as a component of ErbB4 cleavage products. We quantified a fragment detected at 180 kDa, corresponding to the molecular weight of full-length ErbB4, as well as ErbB4-preabsorbable bands detected at 60 kDa, 55 kDa and 21 kDa. The latter three bands were presumed to be ErbB4 cleavage products. Subject group differences in prefrontal cortical quantities of each fragment were determined by ANOVA techniques and post hoc comparisons for cytoplasmic and for nuclear fractions.
Results: Prefrontal cortical cytoplasmic full-length ErbB4 levels were approximately 30% greater in schizophrenic patients than in normal ($p<0.02$), in bipolar ($p=0.05$) and in depressed ($p<0.02$) individuals. In prefrontal cortical nuclear fractions, the 180 kDa fragment was increased by approximately 20% in schizophrenic subjects relative to bipolar ($p<0.02$) and to depressed ($p<0.02$) patients. Elevations in prefrontal cortical nuclear full-length ErbB4 were also observed in the schizophrenic group as compared to the normal group, although these differences were not significant. In terms of the 60 kDa, 55 kDa and 21 kDa products, none of the examined fractions displayed differences in these proteins among any of the subject categories. However, 55kDa/180kDa and 21kDa/180kDa ratios were decreased in prefrontal cortical cytoplasmic portions from schizophrenic patients relative to those from normal individuals.
Discussion: Previous studies have demonstrated elevations in specific ErbB4 mRNA isoforms in the prefrontal cortex of schizophrenic patients (Silberberg et al., 2006). Our investigation reveals that these increases may occur at the protein level and may be specific to schizophrenia as compared to other mental illnesses. Our findings also suggest that ErbB4 processing may be altered in the schizophrenic brain with respect to certain ErbB4 cleavage products. Finally, our observations may relate to the elevated prefrontal cortical ErbB4 signaling seen in post-mortem schizophrenic brains by earlier studies (Hahn et al., 2006).

146. Staged Genetic Analysis for Schizophrenia Risk Reveals Significant Main Effects and Interactions Between SNPs at Dopamine Transporter and Dopamine D3 Receptor Genes

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Sponsor: Shirley Hill

Background: Dysfunction in the dopaminergic (DA) neurotransmitter system has long been hypothesized in schizophrenia (SZ) genesis, but convincing proof is lacking. Genetic association studies may enable a test of the DA hypothesis. Prior studies have been inconsistent, possibly because genetic variation was investigated inadequately.
Methods: We have systematically evaluated associations between schizophrenia (SZ) and variants of genes in the dopaminergic (DA) neurotransmitter system. We used published meta-analysis of SZ linkage studies to prioritize our analyses in order to improve the prior probability of detecting meaningful associations. In phase I, we analyzed database SNPs from 18 functional DA genes among 150 case-parent trios and 280 control individuals. Phase II involved more comprehensive analyses using tag SNPs for an enlarged sample of cases (n=478) and a new control sample (n=500).
Results: In phase I, two genes met predetermined criteria for association after corrections for multiple tests ($p < 0.0028$ at SLC6A3 alias DAT and DRD3). For phase II analyses, we included DA genes localized to linked regions (COMT, DRD2, NR4A2, VMAT1), as well as SLC6A3 and DRD3. Tag SNPs ($r2>0.8$ between loci) were derived using HapMap data alone (DRD2, NR4A2, VMAT1, SLC6A3; 148 total SNPs/58 tags) or in combination with novel SNPs detected by sequencing known functional regions (COMT; 58 SNPs/20 tags). For DRD3, we sequenced the entire gene and flanking sequence to identify all common variation (DRD3; 69 SNPs, 15 novel SNPs/20 tags). A genomic control panel was also evaluated. Phase II analyses continued to implicate SLC6A3 and DRD3 ($p<0.05$; SLC6A3: 6 SNPs; DRD3: 5 SNPs). The associations could not be attributed to population substructure and are detectable using different analytic designs. Epistatic interactions were tested for SNPs providing suggestive main effects within SLC6A3 and DRD3. These analyses revealed significant intragenic interactions between four SLC6A3 locus pairs and six SLC6A3*DRD3 locus pairs.
Discussion: Our analyses support the DA hypothesis. They represent a comprehensive and novel evaluation of dopaminergic candidates in SZ genesis. An interaction between SLC6A3 and DRD3 has not been previously reported in SZ risk.

147. Reduced Center-Surround Interaction in Visual Motion Processing of Schizophrenia: Evidence for Altered Spatial Organization of the Visual System

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Background: Brain disorganization is hypothesized as a core dysfunction associated with schizophrenia. While generally consistent with findings in different fields such as compromised neural connection in postmortem schizophrenic brains and some clinical symptoms, this hypothesis needs to be tested by a link between specific behaviors and their underlying neural mechanisms in patients. In basic neurobiological studies of the visual system, center-surround interaction represents a ubiquitous neural mechanism of which neurons compares visual signals in one spatial region with those in the immediately surrounding region. This neural mechanism is characterized by antagonistic interactions between the responses to central and to surrounding visual stimuli. The perceptual correlate of the center-surround neural mechanism is a suppressive modulation of a surrounding visual stimulus on the perception of a central visual stimulus. The link between the neural mechanism and its perceptual

correlate provides an opportunity to evaluate the brain disorganization hypothesis.
Methods: We examined the suppressive effect of surround on the performance of motion perception at the center in schizophrenia patients (n=22), as well as in normal controls (n=25). Subjects judged the direction of a central circular random dot pattern (RDP, center) at various stimulus coherence levels (strength of motion signal), with and without presence of another concentric surrounding RDP (surround).
Results: The presence of the surround shifted the perceptual judgments of the center towards the opposite direction of the surround at low and intermediate coherence levels in both subject groups, but the magnitudes of the perceptual shift were significantly larger in the patients. The abnormally large perceptual shifts in the patients were not correlated with psychotic status (measured with PANSS scores) or antipsychotic medication (measured with CPZ equivalents), nor with neurocognitive function (measured with intelligence quotients).
Discussion: These results show that the normal suppression of the surround on motion perception of the center is weakened in schizophrenia. The weakened center surround interaction suggests that abnormal perceptual behaviors in schizophrenia patients can be linked to local neural interactions, which may involve special types of neurotransmission such as GABA-mediated inhibition. The link of the abnormal motion perception to the specific center surround neural mechanism provides evidence for altered spatial organization of the visual system in schizophrenia.

148. The GPR54 Ligand, Metastin/Kisspeptin, Selectively Activates Glutamatergic Neurons in the Medial Septum/Diagonal Band of Broca

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Background: Loss-of-function mutations in the gene encoding the G-protein coupled receptor, GPR54, in mice and humans are associated with hypogonadism and a failure to generate pulsatile LH and FSH secretions and reach puberty. Immunoreactive fibers containing metastin, the natural ligand for the GPR54 receptor, are widespread within the rodent medial septum/diagonal band of Broca.
Methods: The electrophysiological effects of the potent metastin amide (also known as kisspeptin-1or KiSS-1) on identified septal cholinergic, GABAergic and glutamatergic neurons, were studied in brain slices prepared from rats or from transgenic mice in which the vGluT2 promoter upstream from the vGluT2 sequence were used to drive GFP expression.
Results: A subpopulation of vGlut2-GFP neurons that could be clearly distinguished from other vGlut2-GFP neurons on the basis of their electrophysiological and pharmacological properties responded to KiSS-1 (30 nM-1 microM; 3-5 s; n=49) with a remarkably prolonged and profound increase in firing rate (control: 1.8 ± 0.39 Hz; KiSS-1: 8.6 ± 1.2 Hz; n=15) and/or membrane depolarization (11.4 ± 0.9 mV; n=26) that lasted 15 ± 1.5 min (n=28). Response to subsequent applications of KiSS-1 was significantly attenuated. KiSS-1 activation of vGlut2-GFP neurons persisted in TTX and in low Ca2+/high Mg2+-containing solutions suggesting a direct postsynaptic mechanism. The effects of Kiss-1 were associated with an apparent increase in input resistence and were blocked by external Ba2+, suggesting involvement of potassium channels. In contrast to its potent excitatory effects on glutamatergic neurons, KiSS-1 had no effect on either the septohippocampal GABAergic (n=69) or cholinergic neurons (n=10) located within the same nucleus.
Discussion: We speculate that KiSS-1 sensitive glutamatergic septal neurons may be directly/indirectly involved in LH and FSH release.

149. Altered Glutamate Dynamics in Dopamine D4 Receptor Heterozygote and Knockout Mice

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Background: Genetic studies have implicated certain alleles of the Dopamine D4 Receptor (DRD4) in patients with attention-deficit/hyperactivity disorder (ADHD). A DRD4 knockout mouse model has been developed that expresses different behavioral and novelty seeking characteristics. The DRD4 and the NMDA receptor are co-localized on both Glu terminals projecting from the cortex to the striatum, and on medium spiny neurons in the striatum. We have previously demonstrated altered DA dynamics in DRD4-/- mice, and hypothesized that these DA changes along with lack of the DRD4 would alter Glu dynamics in the Str, NAc, and PFC.
Methods: DRD4 knockout, wild-type, and heterozygote mice (all N-20 generation) were obtained from David Grandy at the Oregon Health Science University. Mice were anesthetized with 10% urethane and placed in a mouse stereotaxic adaptor for recordings from PFC, Str, and NAc. Ceramic-based microelectrodes were prepared to measure Glu on a second-by-second basis. Basal Glu, potassium-evoked Glu and clearance of exogenous were measured.
Results: Significant differences were found in the basal Glu, K+-evoked Glu, and (after amplitude matching of evoked signals) Glu uptake rate between wild type, heterozygote, and DRD4-/- mice. Glu pressure ejected locally in the striatum showed significantly slower clearance rates in the DRD4-/- vs wild type mice (10.3 ± 0.7 vs 12.1 ± 0.4 μM/sec, $p<0.05$) while heterozygotes demonstrated significantly faster rates (14.9 ± 0.6 μM/sec $p<0.001$,). Rise time was similar in wild types (1.43 ± 0.03 sec) and heterozygotes (1.41 ± 0.04 sec), but significantly increased in knockout mice (1.61 ± 0.06 sec, $p<0.01$).
Discussion: Mice that lack the DRD4, or which are heterozygote for DRD4, show significantly different Glu dynamics than litter-matched wild types. Taken together, these data support a role of DRD4s and DA in the regulation of Glu neurotransmission dynamics. Implications for the DRD4 and Glu in the pathophysiology of ADHD will be discussed.

150. Accelerated Degradation of Kinase Proteins in Depression

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Background: Prior research using both peripheral tissues and human post-mortem brain suggest reduced protein kinase A (PKA) activity and protein in a subset of patients with major depression. Specifically, we have shown abnormally low levels of the PKA subunit proteins RII-alpha, C-alpha, and C-beta. This study examined whether this was related to increased turnover rate (reduced half-life) of these proteins.
Methods: Fibroblasts were cultured from skin tissue samples obtained from persons with major depression with reduced PKA activity (n=6) and normal controls (n=6). The fibroblasts were subjected to pulse chase immunoprecipitation, which estimates protein turnover rates by measuring the incorporation of [35S]methionine in fibroblasts cultured in Met/Cys free medium, followed by application of unlabeled amino acid ("cold chase").
Results: C-beta protein from depressed patients had reduced incorporation of [35S]methionine of C-beta protein relative to controls (-33.8% reduced half-life [$p<0.02$]). There were no significant differences in rate of incorporation for RII-alpha or C-alpha.
Discussion: The reduced activity of PKA may be associated with an increased turnover rate of C-beta subunit proteins followed by a compensatory decrease in RII-alpha and C-alpha. Future research

will focus on oxidative stress that may be involved in C-beta protein degradation.

151. Serotonergic 5-HT1A and 5-HT7 Receptors Interact in the Control of Emotional Learning in the Passive Avoidance Task

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Background: Serotonin mediates its physiological actions via at least 14 receptor subtypes. A number of 5-HT receptors appear to play significant roles in various domains of cognition, including learning and memory. There is strong evidence for the view that the 5-HT1A receptor have a significant role in emotional learning, as studied in fear conditioning and passsive avoidance (PA) in mice (Stiedl et al 2000; Madjid et al 2006). Also studies with 5-HT1A receptor KO mice implicate the 5-HT1A receptor in emotional learning (Klemenhagen et al 2006). Recent evidence has also implicated the 5-HT7 receptor in the regulation of emotional memories (Roberts et al 2004). It has also been suggested that the behavioral effects caused by the preferred 5-HT1A receptor agonist 8-OH-DPAT are partly mediated via stimulation of 5-HT7 receptors (De Vry, 1995). The 5-HT7 receptor has been found to have both opposite and synergistic roles with 5-HT1A receptors, such as in regulation of hippocampal firing rate and in thermoregulation, respectively (Hedlund et al 2004). In view of these contradictory findings, the aim of the present study was to examine the potential interactions between 5-HT1A and 5-HT7 receptors in control of passive avoidance, an emotional memory task which is dependent on both the hippocampus and amygdala.
Methods: The studies were performed in male C57BL/6 mice (2 months old, body weight 22-27 g). The passive avoidance procedure was performed as described in detail previosly (Madjid et al 2006). MK-801 (0.2 mg/kg) and 8-OH-DPAT (0.3 mg/kg) were injected subcutaneously (s.c.) 15 minutes prior to PA training. SB-269970 (10 or 20 mg/kg) was injected intraperitoneally (i.p.) 30 minutes prior to training and AS 19 (5.0 mg/kg) was injected i.p. 20 minutes prior to PA training.
Results: As demonstrated earlier, administration of the 5-HT1A receptor agonist 8-OH-DPAT, produced a marked imparirment in PA retention. This impairment, which has been shown to be fully blocked by the 5-HT1A receptor antagonist robalzotan, was not blocked by the 5-HT7 receptor antagonst SB-269970. Importantly, SB-269970, by itself, failed to change PA retention performance, but significantly enhanced the impairments caused by 8-OH-DPAT. Administration of the 5-HT7 receptor agonist AS 19 did not change retention latencies by itself. As also demonstrated earlier, the NMDA receptor antagonist MK-801 caused a marked impairment in PA retention performance. This impairment was significantly reduced when AS 19 was coadministered with MK-801.
Discussion: The present results did not indicate that the impairment of PA induced by 8-OH-DPAT is mediated via 5-HT7 receptors. This finding contrasts with previous studies on hypothermia (Hedlund et al 2004), which indicated that the hypothermic effect of 8-OH-DPAT is mediated by both 5-HT1A and 5-HT7 receptors. However, there is evidence for a significant interaction between 5-HT1A and 5-HT7 receptors, in the control of PA. Thus, the 5-HT7 receptor antagonist SB-269970 enhanced the PA impairment caused by 8-OH-DPAT. This indicates that 5-HT7 receptor activity may have a facilitatory effect on this type of learning, under conditions when there exists activation of 5-HT1A receptor signaling. Importantly, the 5-HT7 receptor also seems to have a facilitatory role when there exists impairments in NMDA receptor transmission, since the 5-HT7 receptor agonist AS 19 reduced the deficit caused by MK-801. It is possible that the inhibition of glutamatergic NMDA receptors and stimulation of 5-HT1A receptors share similar mechanisms, which contribute to their impairing effects on learning processes. Importantly, 8-OH-DPAT has recently been shown to enhance the impairing effects of NMDA receptor blockade on memory (to be publiced).

152. Pharmacological Characterization of the Eantiomers of Doxanthrine at Dopamine and Adrenergic Receptors

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Background: Parkinson's disease is a common neurodegenerative condition that involves the death of dopamine neurons in the substantia nigra. Current therapy includes treatment with L-dopa, which is converted to dopamine within the brain. Direct-acting dopamine D1 receptor agonists are alternative treatments that show significant potential. Dihydrexidine (DHX) is a potent full dopamine D1 receptor agonist that has been examined both as a treatment for Parkinson's disease and in reversing the cognitive deficits of schizophrenia. Administration of racemic DHX was associated with a reduction in Parkinson's symptoms and as well as hypotension in humans. Although the mechanism of this hypotensive effect presumably reflects D1 receptor activity in the renal system, off-target effects at other catecholamine receptors may be involved.
Methods: In the present study we evaluated the pharmacological activity of the enantiomers of a novel D1-selective dopamine receptor agonist, doxanthrine (ODHX) in cultured cells expressing recombinant and endogenous receptors. ODHX is an oxygen-substituted analog of DHX that recently has been shown to have high affinity (Ki = 20 nM) for dopamine D1-like receptors, but low affinity at dopamine D2-like receptors (Ki = 4500 nM) in native striatal porcine tissue. The functional properties of (+)- and (-)-ODHX were evaluated at dopamine D1, alpha2C adrenergic, and beta1 adrenergic receptors.
Results: Racemic ODHX possessed full intrinsic activity compared to dopamine at recombinant human dopamine D1 receptors. Similar to DHX, (+)-ODHX was more potent than (-)-ODHX, with an EC50 of 40 nM in a heterologous expression system. Studies in MCF7 cells that express an endogenous human dopamine D1 receptor revealed that (-)-ODHX was a weak partial agonist/antagonist and suggested that the presence of (-)-enantiomer reduced the functional activity of racemic ODHX. Additional studies revealed that both enantiomers of ODHX showed weak partial agonist properties at beta1 adrenergic receptors. Surprisingly, (-)-ODHX had 10-fold greater potency than (+)-ODHX at the alpha2C receptor, with an EC50 of 10 nM that was similar to the prototypical alpha-2 agonist, clonidine.
Discussion: These findings indicate a reversed stereoselectivity for ODHX at dopamine and alpha adrenergic receptors. Further, the present data suggest that administration of the (+)-enantiomer of ODHX may reduce the likelihood of off-target effects in the treatment of Parkinson's disease or schizophrenia.

153. Dysregulation of X-Linked Gene Expression in Klinefelter's Syndrome and Association with Verbal Cognition

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Background: Klinefelter's Syndrome (KS) is a chromosomal karyotype with one or more extra X chromosomes. KS individuals often show language impairment. The phenotype might be due to over-expression of genes on the extra X chromosome(s). The concept of X chromosome gene expression and verbal functioning has not been formally tested.
Methods: We profiled mRNA derived from lymphoblastoid cell lines from 11 males with documented KS and 6 control males using the Affymetrix U133 2.0 microarray platform. Differential gene expression was also tested by quantitative PCR (QPCR) for genes that passed Benjamini-Hochberg false discovery. Exploratory analysis of gene expression and verbal cognition measures was conducted.
Results: There were 129 differentially expressed genes (DEGs) in KS group compared with controls after false discovery correction. The X

chromosome differentially expressed genes (DEGs) were significantly over-represented. Twelve DEGs showed significant correlation of expression with measures of verbal cognition in KS. A pseudoautosomal gene, GTPBP6 (GTP binding protein 6, putative) was inversely correlated with verbal IQ ($r = -0.86$, $p < 0.001$) and four other measures of verbal ability. The XIST gene was over-expressed in KS compared to XY controls. The microarray findings for 8 DEGs were validated with QPCR.
Discussion: Further examination of X linked DEGs, such as GTPBP6, TAF9L, and CXORF21, that show verbal cognition-gene expression correlations may establish a link between these genes, neurodevelopment, and language function. A small fraction of KS cases are currently recognized. A screen of candidate gene expression may lead to early diagnosis of Klinefelter's syndrome.

154. Serotonin Transporter Immunoreactivity in DRN Subnuclei in Schizophrenia, Major Depression, Bipolar Disorder and Controls

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Sponsor: Victoria Arango

Background: Serotonergic neurotransmission is altered in major depression (MDD), bipolar disorder (BD) schizophrenia (SZ) and suicide. The reuptake of serotonin by serotonin transporter (5-HTT) is the principal means by which serotonin is inactivated, and the dorsal raphe nucleus (DRN) is the region in the brainstem where the majority of serotonin synthesizing neurons reside. Binding to the transporter (5-HTT) may not reflect the amount of transporter protein. We therefore measured 5-HTT protein by immunoautoradiography (5-HTT-IR) in the DRN of subjects with MDD, BD, SZ and non-psychiatric controls (NPC).
Methods: Brainstem sections every 1 mm throughout the DRN and median raphe nucleus (MRN) from MDD, BD, SZ and NPC (15 per group) obtained from the Stanley Foundation Neuropathology Consortium were assayed for 5-HTT-IR, autoradiograms quantified using a computer-based image analysis system (MCID). DRN rostrocaudal levels were defined as 0 mm (at largest DRN area), -3 mm, -6 mm, -9 mm and -12 mm caudal to the 0 level. Twelve SZ subjects received neuroleptics, twelve MDD received antidepressants, thirteen BP patients received different psychotropic drugs (http://www.stanleyresearch.org/programs/brain_collection.asp).
Results: The area of 5-HTT-IR (mm2) at 0 mm was lower in BD, SZ and MDD compared to NPC ($p=.000$) with no independent effect of suicide ($p=.941$). At 0 mm the amount of 5-HTT-IR (μCi/g tissue) was lower in schizophrenia compared to the other 3 groups ($p<.05$) in the DRN dorsal (DRd) subnucleus while it was higher in BD compared to MDD and NPC in ventral (DRv) ($p<.05$) and compared to SZ and NPC in ventrolateral (DRvl) ($p<.05$) subnuclei. No differences in 5-HTT-IR were revealed among suicide and non-suicide psychiatric cases and NPC in the different DRN subnuclei at the rostral 0 mm level. Caudal subnucleus (DRc) area at level -3 mm was lower in SZ compared to BD ($p=.008$). DRc area at level -6 mm was also lower in BD, MDD and SZ compared to NPC ($p<.05$), with no independent effect of suicide ($p=.880$).
Discussion: Lower 5-HTT-IR and smaller area in DRd subnucleus in SZ is consistent with a role for serotonin in the pathophysiology of SZ and may indicate specific effects in target cortical regions related to the pathophysiology of psychosis. Lower 5-HTT-IR in DRd is consistent with lower 5-HTT binding in the prefrontal (Joyce et al., 1993; Laruelle et al., 1993) and cingulate cortex (Dean et al., 1995) in schizophrenia and suggests less serotonergic innervation of these regions. Although the number or size of tryptophan-hydroxylase-immunoreactive neurons does not differ in SZ compared to NPC (Craven et al., 2005), our results suggest lower expression of the 5-HTT gene in these neurons. Lower 5-HTT-IR distribution area in the largest rostral (0 mm) DRN and at the -6 mm caudal second DRN enlargement in MDD and BD may explain the lower brainstem 5-HTT PET binding in BD (Oquendo et al., 2006: Cannon et al., 2006) and MDD (Malison et al., 1998; Parsey et al., 2006). Higher ventral and ventrolateral subnuclei 5-HTT-IR in BD compared to MDD or SZ and NPC needs to be investigated and may not be detectable in in vivo PET studies, since the region's area is smaller. That difference might be related to specific target cortical areas functionality in BP compared to MDD, SZ or NPC. Given reports that SSRIs may inhibit 5-HTT gene expression, the low 5-HTT-IR, might be a medication or a disease effect. Further studies of the relationship of immunoreactivity to diagnosis and to treatment are important next steps. Supported by AFSP Young Investigator Award.

155. An Open-Label Trial of Aripiprazole in the Treatment of Autism and Its Correlation to Whole Blood Serotonin Levels and Serotonin Transporter (5HTTPLR) Function

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Sponsor: Richard Rech

Background: Autistic disorder (AD) is the fastest-growing developmental disability today, with a prevalence of 8-10/10,000. Some studies have suggested that disorders in the peripheral and central metabolism of serotonin (5-HT) may play a role in the pathophysiology of autistic disorder. Elevated whole blood serotonin levels have been found in 25-40% of individuals with autism. Recent studies have demonstrated the effects of(5-HTTLPR)on platelet 5-HT physiology in autism and on treatment response. More recent challenge studies have identified changes in whole blood serotonin may play a role as a biomarker in a subgroup of individuals. Linkage studies have identified the candidate gene WNT2 mutations, 5-TTPLR polymorphisms predicts genetic vulnerability to autism. Genetic association studies linking serotonin transporter and psychotropic response in AD although few, have yielded mixed results. Psychotropic agents are efficacious and safe for treating behavioral aspects of autism including impairment in social skills, problems communicating, and stereotypic ovements, irritability, aggression and hyperactivity. It does not appear to be as effective for the treatment of the core symptoms of autism. Choice of an agent that has minimal side-effect burden would optimize treatment outcomes. Amongst atypical antipsychotics, risperidone has shown some promise in autism. Aripiprazole has a unique pharmacological profile as a partial D2 receptor agonist with partial agonist activity at serotonin 5HT1A receptors and antagonist effects of 5-HT2A receptors and has a favorable side-effect profile compared to other atypical antipsychotics. Clinical experience with this agent in autism in real world clinical practice shown some promise in autism
Methods: A 12 week IRB approved study assessing the efficacy of aripiprazole in the amelioration of symptoms of AD in children with a sample size of 15 patients was conducted at the University of South Carolina. Subjects between the ages of 6-17 years with a clinical diagnosis by DSM-IV TR criteria for AD and/or a research diagnosis Autism Diagnostic Inventory (ADI-R). Routine labs and medical screening included vital signs (pulse, blood pressure, respirations and temperature), weight. Blood was also drawn to obtain whole blood serotonin (5-HT) and the 5-HT transporter polymorphisms. Outcome measure included: Aberrant Behavior Checklist (ABC), the SNAP-IV, the Social Skills Questionnaire (SSQ), and the Repetitive Behavior Questionnaire (RBS), CGI (S) & (I) severity and improvement were completed by the parents and research psychiatrist respectively. Subjects were assessed every two weeks for the duration of the study.
Results: 8 subjects have been enrolled in the study with 3 completers. Dose range used was 2-10mg of aripiprazole. Patients demonstrated

clinical improvement on the Aberrant Behavior checklist (ABC) and Repetitive Behavior Scale (RBS). However given the small sample size it failed to reach statistical significance. Responders did demonstrate an improvement in irritability, lethargy, stereotypy, hyperactivity, compulsive subscale on the ABC and RBS Scales. Clinical Global Impression Severity, CGI (S) and Improvement, CGI (I) did reach statistical significance ($p<0.019$ and $P< 0.007$ respectively). Although we did notice a trend towards a decrease in 5-HT post treatment in responders, it failed to reach statistical significance. The 5-HTTPLR results and its correlation to treatment response are pending.
Discussion: The study is ongoing with some of preliminary findings showing a positive correlation of whole blood serotonin to treatment response. 5-HTTPLR samples are being analyzed to see if 5-HTTLPR may influence individual responses to partial D2 agonist.

156. Sodium Oxybate for the Treatment of Fibromyalgia: A Double-Blind, Placebo-Controlled Trial
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Sponsor: Cynthia Kuhn

Background: No FDA-approved medication exists for treating fibromyalgia; however, preliminary evidence suggests sodium oxybate may provide therapeutic benefit for these patients. This proof-of-principle study examined the efficacy and safety of sodium oxybate as a treatment for fibromyalgia
Methods: 195 patients with primary fibromyalgia were randomized to receive 4.5 or 6 g sodium oxybate or placebo nightly for 8 weeks. The primary outcome variable (POV) was a composite of 3 co-primary measures: Pain Visual Analog Scale (PVAS), Fibromyalgia Impact Questionnaire (FIQ); and Patient Global Assessment (PGA). Secondary outcome measures included changes in sleep quality (SLP) and Total Tender Point Count (TTP) and quality of life (QOL) questionnaires. Safety measures included physical examinations, clinical chemistry and hematology parameters and adverse events.
Results: The ITT population included 188 patients; 147 (78%) completed the trial. Significant benefit in POV was seen with both doses of sodium oxybate vs. placebo (4.5g, $p = 0.005$); SLP and QOL also improved with both sodium oxybate dosages (4.5g, $p = 0.004$; $p = 0.01$, respectively); TTP improved with the 6g dosage ($p = 0.05$). Changes in PVAS were significantly correlated with SLP ($r = 0.55$; $p < 0.001$). Only nausea and dizziness occurred with significantly greater frequency than placebo; no unexpected adverse events occurred.
Discussion: Sodium oxybate therapy significantly improved the major symptoms of fibromyalgia and appears to be generally safe in this patient population. Improved sleep quality may contribute to pain reduction. Sodium oxybate may represent a novel therapeutic option for fibromyalgia, warranting further study.

157. Dopamine in Cost-Benefit Decision Making
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Sponsor: John F. Neumaier

Background: Throughout our lives we are constantly assessing the costs and benefits of possible future outcomes of our actions and using this information to guide behavior. In weighing up the costs of an outcome, one must consider how much physical effort is required, the delay before the outcome is presented, the certainty of the outcome and possible aversive consequences. In addition, we have evolved to respect social and financial costs. Decision-making dysregulation crosses diagnostic categories of psychiatric disorders and particularly prevalent are deficits in dealing with costs. These are manifested as traits such as lethargy, impulsivity, risk-taking and compulsion. There is accumulating evidence that dopamine may contribute to a fundamental component of this process: how rewards are compared with the costs incurred when obtaining them. Depletion or antagonism of dopamine in the nucleus accumbens is sufficient to lower the physical effort rats will make to obtain greater rewards. Similarly, rats will not tolerate time delays to gain larger rewards following systemic dopamine antagonism. These data suggest that one role of dopamine transmission is to overcome response costs in obtaining rewards. Dopamine neurons are phasically activated on presentation of predictors of future rewards; and this subsecond activity encodes the (average) expected reward. We propose that this transient activity should produce psychomotor activation to energize proximal behaviors and in this way surmount larger response costs when better rewards are expected. This simple computation should facilitate appropriate action selection either when single reward options or concurrent choices are available.
Methods: To test this hypothesis, we have established a series of operant decision-making tasks in rodents that allow us to assess cost-benefit analysis and normalize across different costs. Using fast-scan cyclic voltammetry we can measure subsecond dopamine transmission in terminal regions implicated in action selection while rats engage in these tasks. Our first studies examine the effect of obtaining food rewards when physical-effort response costs are imposed.
Results: In a two-lever operant task where responding on one lever delivered a higher reward (more food pellets) for the same response cost (number of lever presses), rats displayed a strong preference for that lever. When the levers were presented individually, we observed phasic dopamine release in the nucleus accumbens on lever presentation with amplitude monotonically related to reward magnitude. This indicates that dopamine transmission in the nucleus accumbens encodes the predicted value of the reward. When both levers delivered equal reward magnitude, but at different response costs, animals favored the lever yielding reward for the lower cost, demonstrating behavioral preference to the highest net-value outcome. However, under these circumstances, dopamine release in the nucleus accumbens was comparable for either lever presentation, indicating that dopamine encodes the absolute value of the reward, not the cost-discounted net value. In a concurrent-choice task where two levers yielded different rewards at different response costs, animals chose the high-reward option less frequently as the response requirement for that option was increased. Pharmacological antagonism of dopamine receptors also decreased the frequency of high-reward choices. However, once again, phasic dopamine transmission appears to encode the absolute rewards available regardless of the cost at which they are being offered.
Discussion: These data suggest that dopamine encodes the absolute utility of possible future rewards independent of their response cost. This information is used to assess a reasonable cost to endure to obtain reward that is compared to the available response requirement (encoded elsewhere) to direct action selection.

158. Attenuated Circadian Rhythms in Mice Lacking the Prokineticin 2 Gene
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Background: Circadian clocks drive daily rhythms in virtually all organisms. In mammals, the suprachiasmatic nucleus (SCN) is recognized as the master clock that synchronizes other central and peripheral oscillators to evoke circadian rhythms of diverse physiology and behavior. Prokineticin 2 (PK2), a secreted protein that is encoded by a clock-controlled gene, has been indicated as a candidate SCN clock output signal in regulating circadian locomotor rhythm.
Methods: To gain insight into the physiological role of PK2 in the circadian rhythm, we generated mutant mice (PK2-/-) with the PK2

gene disrupted by homologous recombination. A series of circadian-related behavioral, physiological and molecular examinations on PK2-/- mice revealed that PK2 plays an important role in the maintenance of robust circadian rhythms.
Results: Here we report the generation and analysis of PK2-null mice. The reduction of locomotor rhythms in PK2-null mice was apparent in both hybrid and inbred genetic backgrounds. PK2-null mice also displayed significantly reduced rhythmicity for a variety of other physiological and behavioral parameters, including sleep-wake cycle, body temperature, food intake, circulating glucocorticoid and glucose levels as well as the expression of peripheral clock genes. In addition, PK2-null mice showed accelerated acquisition of food anticipatory activity (FAA) during a day-time food restriction.
Discussion: We conclude that PK2, acting as a SCN output factor, is important for the maintenance of robust circadian rhythms.

159. Psychiatric and Drug Response Phenotypes in Rats with Neonatal Amygdala Lesions

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Sponsor: Travel Awardee, Young Investigator Memorial, 2006

Background: Independent lines of evidence implicate the amygdala in the pathophysiology of mental illness or substance use disorders. In order to elucidate the role of the amygdala in these disorders in a neurodevelopmental context, and as comorbid conditions, we tested the effects of neonatal amygdala lesions (NAL) vs. SHAM operated rats in mental illness and addiction-related paradigms.
Methods: In adulthood, NAL and SHAM rats were tested in a series of psychiatric phenotypic exams (novelty responding, elevated plus maze, social interaction at baseline and in response to odor and restraint stressors), followed by measurement of behavioral sensitization to repeated cocaine vs. saline injections, and finally, measurement of social interaction after drug exposure.
Results: Prior to drug exposure, adult NAL rats show hyperlocomotor responses to a novel environment, tend to show less fear responding in an elevated plus maze, and are refractory to the dampening effects of fear-inducing olfactory stimuli on social behavior. In response to repeated cocaine injections, NAL rats show elevated short-term locomotor sensitization patterns in comparison to SHAM rats. In a challenge session 2 weeks after the initial injection series, NAL rats with cocaine history show elevated activity compared to all SHAM rats and NAL rats with saline only histories. In subsequent social interaction testing, history of repeated cocaine injections differentially affected NAL rats compared to SHAM rats.
Discussion: These results suggest that the amygdala is an important neurocircuit component underlying substance disorder vulnerability in mental illness of developmental origins. NALs may represent a viable animal model of dual-diagnosis phenomena, in which psychiatric phenotype and addictive drug impact show bi-directional accentuation.

160. The Effects of a Single Evening Dose of Eszopiclone 3mg on Next Day Driving Ability and Cognitive and Psychomotor Function in Patients with Primary Insomnia

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Sponsor: Mark Pollack

Background: Eszopiclone is a non-benzodiazepine, cyclopyrrolone approved for the treatment of chronic and transient insomnia. In a previous study in normal healthy volunteers, a single evening dose of eszopiclone 3mg was not significantly different than placebo on an objective measure of car driving ability, on-the-road Brake Reaction Time (BRT). However, the effect of hypnotics on 'on-the-road' driving has not been studied in patients with insomnia. The aim of this study was to investigate the impact of an evening dose of eszopiclone 3mg, compared with placebo, on next day actual car driving ability (as assessed by on-the-road BRT) and cognitive and psychomotor performance in patients with primary insomnia.
Methods: Patients (18-55 years, n=31) with primary insomnia (as defined by DSM-IV criteria) completed this randomized, double-blind, placebo-controlled, 2-way cross-over study. Treatment was administered 30 minutes before bedtime, and next day driving ability was assessed by on-the-road Brake Reaction Time (BRT) in a dual controlled car on a closed circuit track the next morning (approximately 9.5 hours post dose). A cognitive test battery measured residual effects on information processing, divided attention, psychomotor tasks, working memory, and subjective ratings of morning sedation and sleep quality were also obtained. Overnight polysomnography was conducted to assess sleep architecture.
Results: There were no significant differences in BRT following night time administration of eszopiclone 3mg compared with placebo ($p=0.39$). In addition, there were no significant differences between treatments on objective cognitive tests of information processing, divided attention, psychomotor tasks and working memory as assessed by Critical Flicker Fusion, Choice Reaction Time, Continuous Tracking Task, Sternberg Short Term Memory Scanning Task, Rapid Visual Information Processing and Digit Symbol Substitution Test (p values > 0.15). Neither was there any significant effect on subjective next day ratings of morning sedation, co-ordination or mood as assessed by the LARS (p values > 0.22). There was significant improvement compared with placebo ($p<0.0001$) in subjectively rated ease of getting to sleep and quality of sleep the morning following dosing, and no perceived impairment of behavior following awakening or early morning awakenings as assessed by the LSEQ. Polysomnography demonstrated significant increases in total sleep time and sleep efficiency ($p=0.0005$), and significant reductions in time awake ($p=0.0037$), wake after sleep onset ($p=0.005$), sleep onset latency ($p=0.0001$) and latency to persistent sleep ($p<0.0001$).
Discussion: This study, the first to assess next day on-the-road driving in patients with primary insomnia following hypnotic use, demonstrated that night time administration of eszopiclone 3mg improved both objective and subjective measures of sleep onset and maintenance without any significant residual impairments on car driving ability or cognitive and psychomotor performance the next day.

161. Transmission Disequilibrium of Polymorphic Variants in the Dopamine Beta Hydroxylase Gene in Attention Deficit Hyperactivity Disorder

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Sponsor: Arieh Y Shalev

Background: Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, with high heritability. Candidate gene association studies have implicated several loci that exert small but significant effects on risk for ADHD. Dopamine beta hydroxylase (DBH) catalyzes the conversion of dopamine to norepinephrine. Genetic variation in this key enzyme may alter central catecholaminergic activity. Previous studies have examined the contribution of several genetic polymorphisms in the DBH locus to risk for attention deficit hyperactivity disorder (ADHD), with mixed results to date.
Methods: We examined a number of polymorphic loci in the DBH gene including the intron 5 TaqI site (rs2519152), a 5` region 19 base pair insertion deletion (ins/del) polymorphism, an exon 2 G/A substitution (rs1108580), and an exon 5 G/T substitution (rs4531), using

transmission disequilibrium test (TDT) in a family based trio sample of children affected with ADHD.
Results: Two of the four loci examined were found to show significantly biased transmission to affected children, including the exon 5 G/T (rs4531) (p=.014) and the 5` ins/del (p=.04) polymorphisms. The intron 5 TaqI (rs2519152) and the exon 2 G/A (rs1108580) sites did not show significantly biased transmission in our sample. A haplotype consisting of the two positively associated polymorphic variants showed significantly biased transmission to affected children (p=.008).
Discussion: Our results provide further support implicating the DBH gene with risk for ADHD. The positive associations detected may reflect linkage disequilibrium with an adjacent causative variation. A number of studies have previously implicated DBH gene variations with ADHD, as well as endophenotypes. However, results have been inconsistent, with several negative reports, including a large collaborative study, and the data can not be used to implicate a true disease susceptibility variant. Several factors including the likely small and variable contribution of implicated gene variations to risk, limited knowledge regarding functional relevance of allelic variants to central catecholamine function, and genetic and phenotypic heterogeneity, may contribute to these inconsistencies. Further work is required to define an actual causative variant, its functional impact on central catecholaminergic regulation, and a pathophysiological role in terms of alterations in endophenotypic correlates of the disorder.

162. Gene-Based Haplotype Analysis Reveals TPH-1 Gene Association with Psychiatric Disease

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Sponsor: Marie Asberg

Background: Tryptophan hydroxylase (TPH) is the rate limiting enzyme in serotonin biosynthesis, and has been associated with several psychiatric disorders. Two forms are currently known, TPH- 1 and 2. We have initiated studies aimed to use gene-based haplotypes for identification of risk gene variants in a case-control design, and applied our strategy to TPH-1.
Methods: Several psychiatric patient and control groups were analyzed. Six SNPs belonging to a single haplotype block spanning 23 kb of the total gene's 29 kb were genotyped in a total of about 750 individuals. Haplotype reconstruction and statistical association analyses was carried out. Bonferroni correction was used as a correction for multiple testing.
Results: We analyzed haplotype frequencies in various patient groups, and found association with major depression, schizophrenia, and borderline personality disorder. Risk haplotypes differed among disease groups.
Discussion: In our studies, gene-based haplotypes appear to be superior to single loci in a case-control design. Our data suggest that risk carried by individual haplotypes may be diagnosis-specific rather than pleiotropic.

163. Catechol-O-Methyltransferase (COMT) Val108/158Met Is Associated with the Personality Trait Extraversion and Interacts with 5-HTTLPR in Normal Subjects

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Sponsor: Past Travel Awardee, NIMH, 2005

Background: The functional Val108/158Met SNP in the Catechol-O-methyltransferase (COMT) affects enzyme activity and has been shown to affect behavior (e.g. personality), brain function (cognitive processing), and risk for mental illness (rapid cycling in Bipolar Disorder, Schizophrenia). One report found the Met allele associated with low scores of Extraversion and high scores of Harm Avoidance, especially in women. In this study, we investigated the association of COMT Val108/158 Met SNP and personality traits measured by the NEO-PI.
Methods: We evaluated the COMT Val108/158Met SNP (rs4680) in 573 individuals from 240 families (ascertained through a hypertensive proband but unscreened for psychiatric conditions) who have completed the NEO-PI questionnaire. Association was tested between this polymorphism and personality domains, taking familial relationships into account. We also tested statistical interaction of COMT and the 5-HTTLPR (previously genotyped and associated with Neuroticism) in this sample using ANOVA (which could not take familial resemblance into account). Genotypes were in Hardy Weinberg equilibrium.
Results: Individuals with the COMT Met/Met genotype showed higher scores of Extraversion (mean ± s.e.m) (110.14 ± 1.3; p = 0.004) compared to Val/Val (104.2 ± 1.58) with Val/Met in between (107.6 ± 0.98), with an even larger effect in women (p = 0.002), all p values corrected for testing multiple personality domains. The effect on Extraversion was mainly due to the facets Assertiveness, Warmth and Positive Emotions. In the absence of the 5-HTTLPR short allele, homozygote individuals for COMT Met/Met showed higher scores of Extraversion (mean ± s.d.) (114.55 ± 15.26) than individuals with either Val/Val or Met/Val (104.45 ± 18.31).This interaction between COMT x 5-HTTLPR was significant (p = 0.035).
Discussion: We found significantly higher Extraversion scores in individuals homozygote for the Met allele, and in the absence of the short allele in 5-HTTLPR, these scores are even higher, showing significant interaction. This finding is inconsistent with one report that found Met/Met associated with lower Extraversion scores. Compared to controls, Bipolar patients score higher in Extraversion. Two meta-analyses were reported in Bipolar, one with borderline significance and the other with a non-significant trend towards association with the Met allele. Further studies are necessary to establish the relationship of the genetic influence of the Met allele on Extraversion and Bipolar. Interaction of COMT x 5-HTTLPR has already been reported for Persistence, Novelty Seeking and life stressors in mood disorders.

164. An Animal Model of Individual Differences in "Conditionability": Relevance to Psychopathology

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Sponsor: Terry E. Robinson

Background: The way an individual responds to cues associated with rewards may be a key determinant of vulnerability to psychopathology. Stimuli in the environment can become imbued with incentive salience, gaining the power to control behavior. Incentive salience is considered the motivational component of reward, transforming sensory information about rewards and their cues into attractive and desired incentives. The ability of cues associated with reward to become motivational magnets and elicit approach towards them is an example of Pavlovian conditioned approach (PCA) behavior and can be studied in the laboratory using an autoshaping paradigm. The present set of studies investigates individual differences in PCA behavior in attempt to understand the neural substrates of "conditionability" and the relevance of this dimension to psychopathology.
Methods: The Pavlovian autoshaping procedures consisted of the brief presentation of an illuminated retractable lever (conditioned stimulus, CS) followed by the response-independent delivery of a food pellet (unconditioned stimulus, US). Multiple CS-US presentations typically elicit a conditioned response including lever-CS directed approach, followed by grasping and gnawing of the lever. This CS-directed response called sign-tracking develops even though no

response is required for the animal to obtain the reward. The alternative, and less studied response that can emerge is that of goal-tracking. Goal-tracking is directed towards the US rather than the CS, such that an animal that goal-tracks will respond to the presentation of the CS only by remaining at, or approaching the location where the reward will be delivered. We have found, using the same paradigm, that some animals sign-track and others goal-track. Thus, two phenotypes emerge: sign-trackers (ST) are those animals that respond to the CS by approaching it (i.e. the lever) and attempting to "consume" it; whereas goal-trackers (GT) respond to the CS by approaching the location where the US is delivered (i.e. the food receptacle). In ongoing studies, we have characterized animals as ST or GT based on their PCA behavior and are currently assessing the relevance of this phenotype to addictive- and gambling-related behavior using measures of psychostimulant sensitization, conditioned place preference and delayed-reinforcement paradigms. In addition, the neural substrates of "conditionability" are being investigated.

Results: In studying the way cues in the environment associated with reward control behavior we uncovered two phenotypes: ST are those animals that appear highly conditionable with approach to the reward-related cue; while GT remain at the location where the reward is to be delivered, exhibiting little, if any reaction to the reward-related cue. We have demonstrated ST and GT exhibit differences in gene expression of neurobiological markers associated with the dopaminergic system, the same neural system implicated in incentive motivational processes. Thus, we have established an animal model to investigate individual differences in the way incentive salience is attributed to environmental stimuli.

Discussion: The ST/GT phenotype reveals two distinct ways to interact with the surrounding environment. This dimension may be relevant to a number of activities in which context is associated with an event. One could therefore imagine the importance of this model to studying individual differences in susceptibility to psychopathology (e.g. PTSD, addiction, pathological gambling). Moreover, utilizing this model to understand the neural substrates of conditionability may prove invaluable to psychiatric medicine.

165. Neuronal Correlates of Repetitive Stereotypical Movements in Prefrontal Cortex and Striatum of Awake Rats

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Sponsor: Bita Moghaddam

Background: Tourette Syndrome (TS) is characterized by disinhibition of involuntary movements, a process that involves dysregulation of corticostriatal networks. Recent evidence suggests that prefrontal cortex (PFC), in interaction with its striatal targets, may play an important role in pathophysiology of TS and its comorbid disorders. We studied the dynamics of PFC and striatal activity and regional interactions during expression and suppression of tic-like stereotypies.

Methods: Ensemble single unit and local field potential recordings in awake rats were used to study the relationship between stereotypical tic-like movements, induced by amphetamine or the NMDA antagonist MK801, and the simultaneously recorded neuronal activity in PFC and striatum. Haloperidol and clonidine were used to study the neural correlates of tic suppression in the same population of neurons.

Results: We found that stereotypy was associated with diminished correlation in the activity of neurons within and between PFC and striatum, and an overall hyperactivity of striatal neurons. Furthermore, suppression of stereotypy by haloperidol was associated with reduction of striatal hyperactivity and re-establishment of correlations in the activity of PFC and striatum neurons. Likewise, the suppression of stereotypy by clonidine was associated with a reduction in striatal hyperactivity.

Discussion: These findings suggest that decreased coordination in PFC-striatum communications may serve as a neuronal substrate for induction of tics and other disinhibited behaviors. Alleviating these functional disruptions may contribute to the mechanism of action of anti-tic drugs.