A Phase One Study Investigating the Tolerability and Effects of AZD0530 on Functional Neuroimaging Response in Individuals With or Without a Family History of Alcoholism

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"Functional Neuroimaging of Alcoholism Vulnerability: Glutamate, Reward, Impulsivity, and Pavlovian-to-Instrumental Transfer (PIT), Part II - Saracatinib"

1. **Introduction**:

The purpose of this pilot study is to evaluate the role of Saracatinib in clarifying the neurobiology of alcoholism risk. This is a 1-site, randomized, within subjects, counterbalanced double-blind study of one dose (125 mg) of Saracatinib and placebo. This project explores the effects of 1 dose of Saracatinib (an experimental Fyn-Src family protein tyrosine kinase inhibitor drug (AZD0530)), in a double-blind, randomized, counterbalanced manner on alcoholism risk-relevant tasks. Drug/placebo will be administered on 2 separate visits separated by 1 week following an initial screening visit. More specifically, this project examines 4 functional MRI tasks related to different aspects of reward and/or impulsivity-related behavior in different contexts, compares the underlying neural circuitry across tasks, and uses a pharmacologic probe of the glutamatergic system to examine N-methyl-D-Aspartate and Dopamine (NMDA/DA) interactions. The combined measures provide the opportunity to advance our understanding of specific aspects of brain function related to familial alcoholism vulnerability in an already well-characterized population as some members evolve into alcohol abuse. In addition, as well as conventional within-task analyses, functional network connectivity and allied approaches will be used to examine brain networks across the above tasks.

2. **Background**:

The Yale Center for the Translational Neuroscience (CTNA), of which this is one project, examines Alcoholism Common Risk Factors that may act, in part, through synaptic pathology involving the convergence of glutamate and dopamine inputs in the ventral striatum and related "motivation" circuitry. We hypothesize broadly that, from a cognitive/behavioral neuroscience perspective, the inherited vulnerability to alcohol abuse is expressed, in part, as impairment in the normal ability to engage cortico-limbic motivational circuitry by delayed rewards and punishments, biasing individuals toward immediate rewards, exemplified by alcohol use and impulsive behavior. The proposed studies test the hypothesis of DA/NMDA imbalance in reward circuitry as a risk factor for alcoholism and sheds light on potential therapeutic interventions.
This current study builds upon our existing IRB-approved research protocol "Functional Neuroimaging of Alcoholism Vulnerability: Glutamate, Reward, Impulsivity, and Pavlovian-to-Instrumental Transfer (PIT)" study. The following additional background will be helpful in understanding the current application:

- The current research is part of project 2 (PI, Pearlson) of Dr. John Krystal's overall NIDA P01 center grant, (Center for the Translational Neuroscience of Alcoholism-4), to be funded by NIAAA in 2016.
- The overall study examines alcoholism vulnerability, (which is presumed to result in in part from dysfunctional interaction between NMDA receptors and dopamine D2 receptors in the brain's reward system), by blocking the activity of NMDA glutamate receptors.
- The existing IRB-approved study CTNA Project 3 within the existing CTNA-3, uses memantine, a non-specific NMDA receptor blocker, in an attempt to restore the presumed abnormal balance between an overactive NMDA and an underactive DA system,

(presumed to underlie alcoholism vulnerability), in individuals at risk for alcoholism by virtue of a positive family history in one or more first-degree relatives, compared to those who have a negative family history. Brain abnormalities related to this dysfunctional NMDA/DA imbalance are measured experimentally in terms of abnormal brain activation responses to specific functional MRI tasks and out of scanner behavioral tasks that we have previously documented [131-134], and that can be probed using pharmacologic agents that interact in known ways with DA/NMDA circuitry. A major thrust of this project, is that this circuitry is not "broken" but differentially dysfunctional depending on task context (presumably from a combination of differing afferent input from distributed neural networks and possibly reflecting differing cellular engagement not resolvable using fMRI). A corollary of this is that the system can be reset either more broadly via NMDA-R blockade by memantine (as demonstrated in CTNA-3), or in a more fine-tuned, specific, and possibly more effective way using the Fyn kinase inhibitor, Saracatinib, as proposed here. Alcoholism risk: Parental alcoholism is a significant (2- to 4-fold) risk factor for alcoholism in offspring, and is in part mediated through intermediate behavioral traits such as impulsivity[23]. Impulsivity is a multi-factorial set of linked behaviors consisting of several interrelated cognitive/behavioral phenomena including both reward sensitivity and "rash impulsiveness" [1,25,26,33,34,61,98,111,112]. It has been defined both as a "predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences . . . to the impulsive individual or others,"[92] and a failure of response inhibition, to contextually inappropriate, prepotent behavior[51]. Impulsivity is an alcohol risk factor in youth[5] persisting in adult alcoholics[11]. Alcohol/drug abusers score high on impulsivity measures[2,62,70,68]. Impulsive choice biases selection of abused substances in favor of long term rewards[9,33,53,91,101] and higher preference for small, immediate rewards over larger, delayed ones[20], a feature of normal adolescence, ADHD, and addiction.

Alcoholism Common Risk Factors act, in part, through synaptic pathology involving the convergence of glutamate and dopamine inputs in the ventral striatum and related "motivation" circuitry. This anatomically and neurochemically specified hypothesis complements and builds on earlier information processing models as reviewed by Petrakis[99] and data gathered during CTNA-2. We hypothesize broadly that, from a cognitive/behavioral neuroscience perspective, the inherited vulnerability to alcohol abuse is expressed, in part, as impairment in the normal ability to engage cortico-limbic motivational circuitry by delayed rewards and punishments, biasing individuals toward immediate rewards, exemplified by alcohol use and impulsive behavior. The suggestion is that disturbances in the interaction of dopamine and glutamate in the ventral striatum are related to reward and motivational processes associated with the risk for persistent heavy drinking, including impulsivity[23,22,83,96]. A major thrust of Project 3 is that this circuitry is not "broken" but differentially dysfunctional depending on task context (presumably from a combination of differing afferent input from distributed neural networks and possibly reflecting differing cellular engagement not resolvable using fMRI), as exemplified in the pilot data on the MID task, where NAcc may over- or under-activate depending on task phase.

This project builds directly on our prior CTNA research demonstrating that non-alcohol-abusing individuals with a family history of alcoholism (FHP) have a) enhanced responsiveness and

differential cortico-striatal activation compared to controls in response to the prospect and anticipation of monetary rewards and b) abnormal responsiveness to response inhibition. These inherent, possibly genetic, differences in reward processing and response inhibition may underlie the vulnerability of these individuals to alcoholism.

More specifically, this pilot examines functional MRI tasks related to different aspects of reward and/or impulsivity-related behavior in different contexts, compares the underlying neural circuitry across tasks, and uses a pharmacologic probe of the glutamatergic system to examine NMDA/DA interactions. The combined measures provide the opportunity to advance our understanding of specific aspects of brain function related to familial alcoholism vulnerability in an already well-characterized population as some members evolve into alcohol abuse. In addition, as well as conventional within-task analyses, functional network connectivity and allied approaches will be used to examine brain networks across the above tasks.

2a. Characteristics of the Study Drug and Rationale for Choice.
The FDA has granted an IND for the study of Saracatinib as proposed to the overall CTNA study PI, Dr. John Krystal at Yale. AZD0530 (Saracatinib) has been extensively studied previously in human subjects, including healthy individuals, patients with solid tumors and elderly patients with Alzheimer's disease and controls. It is a fyn kinase inhibitor, and the only clinically available drug in its class.

There is wide agreement that both DA and glutamate signaling are critical to reward circuit dysfunction associated with the risk for alcohol use disorders, but little understanding about these two systems intersect to yield family history positive for alcoholism (FHP) reward network dysfunctions documented by our group and others. This project tests a specific mechanism through which disturbances in DA signaling previously described by CTNA in FHP and AUDs might contribute to signs of increased NMDA-Receptor (NMDA-R) function in FHP. Fyn inhibition reduces the insertion of NR2B subunit-containing NMDA-Rs into synaptic membranes (136, 137). For this Project, Fyn inhibition is superior to uncompetitive NMDA-R antagonists such as memantine, that we have studied previously:
1) whereas uncompetitive NMDA-R antagonists such as memantine block <u>all</u> brain NMDA-Rs, Fyn inhibition limits down-regulation of NMDA-Rs to those synapses where DA signaling might up-regulate NMDA-Rs via enhancements in D1-R signaling (as in the striatal direct pathway) or reductions in D2-R signaling (as in the striatal indirect pathway (135); 2) whereas available uncompetitive NMDA-R antagonists block all subtypes of NMDA-Rs, Fyn inhibition limits the NMDA-R down-regulation to NR2B-containing NMDA-Rs (136) and 3) whereas uncompetitive NMDA-Rs directly interfere with normal NMDA-R-mediated signaling, Fyn inhibition reduces receptor number but otherwise leaves NMDA-R signaling intact. Drugs such as Saracatinib are thus much more specific, "fine-tuned" probes of the glutamate system.

In view of the above, this proposal will evaluate whether Fyn inhibition normalizes reactivity to reward-related cues (MIDT), and the reactivity to specific alcohol cues (ACRT) without impairing GNG performance. Thus, this project will deeply characterize the potential therapeutic impact of Fyn inhibition for AUDs from a cognitive neuroscience perspective. Further, by identifying the extent to which FHPs activate striatum during reward (D1-R, direct pathway) and punishment (D2-R, indirect pathway) learning in contrast to more basic reward

operations or motor inhibition as examined in CTNA-3, the current project will shed light on whether the benefits of Saracatinib are related to its ability to attenuate the downstream signaling effects of D1-R signaling or promote the downstream signaling effects of D2-R. This will shed light on dopaminergic contributions to alcoholism risk and, possibly, treatment.

Safety data collected to date: AstraZeneca has extensive safety data of this drug in human subjects (138-140). More recently, the doses of Saracatinib that are being used in the current study have been safely used in over a 4 week period in older patients with Alzheimer disease (by our collaborator Dr. Strittmatter; see pilot section).

AstraZeneca has extensive safety data of this drug in human subjects where data were collected from 7 Phase I studies in healthy male volunteers and 5 Phase I studies in patients with solid tumors and advanced solid malignancies; 608 subjects have received single or multiple once-daily oral doses of Saracatinib in AstraZeneca sponsored studies. Notably, in a multiple ascending dose study, Saracatinib doses of 60 mg to 185 mg were well tolerated, and although adverse events were noticeably more frequent and severe at the 250 mg dose, no major safety issues were identified from adverse events at any of the doses studied. In a multiple ascending dose study, the MTD was 250mg. In patients with advanced cancer, the MTD was 175mg. In clinical oncology, the duration of Saracatinib treatment has been 2-12+ weeks in most trials. Importantly, with Saracatinib monotherapy, febrile neutropenia or other serious hematologic adverse events have not been documented in doses equal to or lower than 175 mg. In the phase 1 trials, no major safety issues were identified from adverse events in any of the doses studied, up to 250 mg daily. There is a potential for a mild decreases in values for both white cell count and platelets but this only occurs at doses of above 125 mg, but these abnormalities never fell below reference levels, and levels normalized while patients remained on the drug. Thus, the doses proposed in this study, ranging from 50-125 mg have generally been well tolerated in both healthy volunteers, and in patients with advanced solid tumors. The most common adverse events at these doses have included rash, headache, and diarrhea. Less common adverse events have included nausea, vomiting, anorexia, anemia, palpitations, fatigue, influenza-like symptoms, and abnormal liver function tests (138-140).

Previous animal studies that have tested the effects of Saracatinib at doses that produced plasma levels significantly higher than those used in the current project, or for longer periods of time, have shown that the drug can cause problems with the heart, liver, blood cells, and digestive system (including the stomach and intestines). These harmful effects have included irritation of the digestive system (which can lead to symptoms of vomiting and diarrhea). Other side effects include lower blood pressure, higher heart rate, lower white blood cell counts (infection-fighting cells), and higher liver enzymes (which can be a sign of damage to the liver). It is not known for sure if Saracatinib would produce the same harmful effects in humans that it has with long-term doses in animals. However, we will rule out anyone who has any pre-existing conditions that could put them at risk for any of these changes through the use of our extensive screening

criteria. In addition, animal studies suggest that taking Saracatinib during pregnancy could result in eye defects in the fetus; therefore we will also rule out women who are pregnant or breastfeeding and ask all female and male (who could possibly pass along drug in sperm) participants to take appropriate birth control measures.

This proposal is the first human study to try to correct FHP-related reward circuit dysfunction by manipulating the molecular cross-talk between DA and NMDA-R signaling, i.e., by inhibiting Fyn. It differs from prior studies of dopamine receptor agonists and antagonists, because: 1) DA-R receptor agonists and antagonists modulate both canonical (cAMP-, PKA-, Fyn-dependent) and non-canonical (i.e., beta-arrestin-dependent) signaling whereas Fyn inhibition only modulates DA signaling via the canonical pathway.; 2) within the canonical signaling pathway dopamine modulates many downstream signaling mechanisms (DARPP-32, etc.) whereas Fyn is proximal to the desired consequence, i.e., regulation of NMDA-R insertion into neural membranes; and 3) DA receptors are widely distributed throughout the brain while PDE10A is most densely localized to the striatum and related forebrain structures [125]. Because of Saracatinib (AZD0530)'s selective inhibition of Src family kinases, with high specificity for Fyn kinase, the drug provides a precise tool in terms of its activity on NMDA-Rs. The drug was originally developed by AstraZeneca for the treatment of solid tumors, because these kinases also play a role in tumor invasion and proliferation, and has been found safe and well tolerated in both phase 1 and phase 2 clinical trials (AZ Investigator's Brochure). However, the Src family kinases (SFKs) are highly expressed in brain and have major effects on synaptic plasticity. Through well-described molecular mechanisms, Fyn inhibitors reduce the phosphorylation of NR2B subunits and thereby reduce the insertion of NMDA-Rs into neural membranes (see Research Strategy). Saracatinib has good central nervous system (CNS) penetration in rodents after oral dosing and this has been verified in human studies of patients with Alzheimer's disease by Dr. Steven Strittmatter at Yale. However Saracatinib, or any other Fyn kinase inhibitor, has not previously been used in the investigation or treatment of alcoholism.

Saracatinib has been extensively studied in healthy individuals and patients with solid tumors and more recently in patients with Alzheimer disease (AD). For our "proof-of-concept" trial, we chose to use the two doses, a lower dose of 50 mg and a higher dose of 125 mg, which have most commonly been tested in most trials (including those by our collaborator Dr. Strittmatter with AD patients) and shown to be safe. AZ has completed 7 Phase I studies in healthy volunteers and 5 Phase I studies in patients with solid tumors and advanced solid malignancies. AZD0530 doses of 60 mg to 185 mg were well tolerated, and although adverse events were more frequent at and above 250 mg, no major safety issues were identified. In patients with advanced cancer, the MTD was 175mg. In clinical oncology, the duration of AZD0530 treatment has been 2-12+ weeks in most trials. Importantly, with AZD0530 monotherapy no serious hematologic adverse events have been documented in doses lower than 175 mg. There is a potential for mild decreases in values for both white cell count and platelets at doses of above 125 mg, but these abnormalities never fell below reference levels, and levels normalized while patients remained on the drug. Thus, the doses proposed in this study, 50 and125 mg, have not only been used safely in healthy volunteers and patients with cancer and AD, but have also been used for significantly longer periods than the small number of single acute doses proposed in the current project. AstraZeneca will provide the proposed doses of AZD0530 and matching placebos.

Consideration of Alternatives: With supporting documentation from AstraZeneca we have already obtained an IND from the FDA to conduct the current study which involves acute dosing with Saracatinib. We have also discussed and obtained feedback from the FDA regarding the design and safety monitoring as described in the current project. We recognize that there are sufficient safety data to preclude observing serious or unexpected adverse events. However, we will monitor all subjects carefully for safety throughout and following the conclusion of the proposed study; if we identify any safety concerns then we will have the option of modifying the current proposed project by reducing the dose of Saracatinib.

Choice of drug Doses. We selected the 125 mg dose of Saracatinib for the current proposed studies based on a careful review of data that showed that this dose produced target CSF levels, and had an excellent safety profile in Dr. Strittmatter's ongoing Yale Alzheimer disease study. Specifically, CNS penetration is excellent (plasma/CSF ratio=0.4). Following oral dosing, 125mg produced brain concentrations of 8-46nM (estimated), simultaneously producing physiologic effects associated with Src/Fyn inhibition without adverse effects on behavior, or significant change in vital signs, EKG or key lab values. Additionally, the use of 125 mg is supported by the preliminary analyses of our pilot study which evaluated the effects of 50mg vs 125mg of AZD0530, suggesting that the 125mg dose produced maximum effects compared to 50mg. Because we are providing single acute doses in the proposed experiments, we thought it reasonable to utilize 125 mg.

Thus, overall, the safety profile of the doses of AZD0530 proposed in this project is excellent. Patient safety will be evaluated clinically and by laboratory measures including complete blood count and serum chemistries with calcium, magnesium, and phosphate, liver function tests, B12 and TSH. These will be obtained at baseline and at each of the 2 weekly drug visits to detect any unexpected adverse event. Participants will be evaluated every day while on study medication. During the visit, vital signs will be recorded hourly, and if needed, they will receive a medical examination by a study physician or nurse practitioner. Patients will also have 24-hour access to a research line where potential adverse events can be reported and addressed. Specific parameters for intervention discontinuation are detailed below.

3. Major Aims:

The current study consists of ~7-8 hours of screening on one day, and 2 subsequent, separate 6 ½-7 hour study days, each separated by ~ 1 week. It proposes to examine 90 subjects (45 FHP, 45 FHN), using the experimental Fyn-Src family protein tyrosine kinase inhibitor drug Saracatinib, (AZD0530), which blocks the glutamate system more specifically and predictably than memantine. AZ0D530 was developed by Astra Zeneca as an anti-cancer drug in which is currently in clinical trials. The relevant Investigator's Brochure is appended. Dr. Krystal is obtaining permission from Astra Zeneca to use this new drug in the context we describe by being added to Astra Zeneca's existing approved IND. We will use one dose of the new drug, (125 mg versus placebo in random assignment single-blind fashion), administered 90 minutes prior to the MRI and other measures, in three separate experimental study visits. We will compare family history positive for alcoholism (FHP; i.e., affected parent plus other close relatives) to matched family history negative (FHN; i.e., no affected first-degree relative). This project explores the

effects of 125 mg of Saracatinib vs placebo in a single-blind, randomized, counterbalanced manner on alcoholism risk-relevant tasks.

4. MAJOR HYPOTHESES:

1. AZ0D530 trial with functional MRI Monetary Incentive Delay (MID) Task.
During the A1 (reward prospect) phase of the fMRI MID task, via Saracatinib blockade of NMDA receptors, compared to placebo, dopaminergic imbalance in reward circuitry of FHP will be "reset" such that excessive nucleus accumbens (NAcc) activation during the A1 phase will be normalized and more closely resemble that of matched FHN individuals on placebo.

Importance: tests hypothesis of DA/NMDA imbalance in reward circuitry as a risk factor for alcoholism and sheds light on potential therapeutic interventions. Logical extension of suggestive preliminary data gathered in prior phase of CTNA with memantine.

2. AZ0D530 trial with functional MRI Go/No-Go (GNG) Task.
The GNG task measures the ability to inhibit response to a pre-potent stimulus, assessing an orthogonal aspect of behavioral impulsivity to the MID task, but one also hypothesized to be related to alcoholism risk.
AZOD530's blockade will act to "reset" dopaminergic imbalance in extended reward system circuitry of FHP so that abnormal NAcc, ACC, and DLPFC activation during response inhibition will be normalized and more closely resemble that of matched FHN individuals in the placebo condition.

Importance: tests hypothesis of DA/NMDA imbalance in response inhibition circuitry as a risk factor for alcoholism. Logical extension of data gathered in prior phase of CTNA.
Extended network analysis using functional connectivity approaches will show interrelationships among neural circuits responsible for response inhibition (GNG) and motivation (MID) and additionally their alteration by Saracatinib in FHP (exploratory).

3. AZ0D530 trial with fMRI Alcohol Cue Reactivity (ACR) task (AKA 'NAC' task). The ACR task in alcohol users is related to the brain's response in reward-related regions to wanting and craving of alcohol versus matched soft drink stimuli. Prior data also suggest that Saracatinib will suppress cue-induced alcohol craving, perhaps more markedly in FHP. **Aim**: to examine NAcc response to alcohol-related versus control images using an existing ACR task.

Major hypothesis. FHP who use alcohol will respond with greater NAcc BOLD signal to alcohol-related cues vs. non-alcohol cues than matched FHN who use alcohol. **Subsidiary hypothesis**. Alcohol-using subjects in general will show a reduced response to alcohol images in the ACR task during the Saracatinib condition, but more markedly in FHP.

Importance: examines additional forms of responsiveness likely relevant to initiation into alcohol misuse.

4. Pilot Task: Pavlovian-to-Instrumental Transfer (PIT) Elaboration of MIDT

Brain responses to the prospect of reward (A1) phase of the MIDT may be considered to reflect a process of Pavlovian-to-Instrumental Transfer (PIT); that is, the phase of the task following the trial-type cue but before the imperative stimulus indicates the impending necessity for a speeded instrumental response in order to gain a reinforcer; a process that we hypothesis is functionally equivalent to PIT. The enhanced striatal responding during this phase that we observed in FHP in pilot data strongly suggests that aberrations of the effects of cues on instrumental choice may underpin the increased risk of alcoholism observed in the FHP group. We propose to test this hypothesis with a novel **fMRI PIT MIDT**. Outside of the scanner, we will train Pavlovian predictors of monetary reinforcement; color-based visual cues that predict monetary reward irrespective of the subject's behavior. Within the scanner we will superimpose these cues on the A1 (reward prospect) phase of the MIDT fMRI task, e.g. the "Win $5" notification could be colored with a predictor shade of e.g. red. If neural response to cues signaling reward are "PIT-driven," then Pavlovian predictors of monetary reward should further invigorate behavioral and neural responding, ie fMRI BOLD signal in reward areas will increase further. Such a finding would link our current project aims by identifying a neural mechanism that bridges cue reactivity and reward system-related impulsivity branches of alcoholism to neurobiological vulnerability research.

Major hypothesis: Cues that predict monetary reward will act as Pavlovian incentive stimuli, enhancing striatal responding during fMRI MIDT A1 phase, and by decreasing reaction-time to imperative stimuli. We expect this effect to be stronger in FHP than FHN and related to our second impulsivity factor that consists of scores on the Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ) and Padua inventory.

Importance: This task dissects a component of the MID, testing the hypothesis that A1 responding is a form of PIT. Moreover, it provides an imaging assay of a transfer-like process that can be related to real-world drinking behavior, thus informing upon and extending the key finding from CTNA-2.

Exploratory Aims:

5. Probabilistic Selection fMRI task (PST).

Saracatinib effects on this task will be explored with support of the Clinical Core to reinforce efforts of other projects to dissect the role of Fyn in the striatal direct (D1-R) and indirect (D2-R) pathways [141,142]

Major hypothesis: Deficient learning of negative reward contingencies (i.e., punishment) will be associated with reduced dorsal striatum activation in FHP compared to FHN due to deficits in D2-R signaling and downstream enhancement of NMDA-R signaling. Reducing NMDA-R signaling with Saracatinib is predicted to normalize, relative to FHNs, the striatal activation during punishment learning.

6. Functional Connectivity.

Using approaches developed by the Human Connectome Project and imported into CTNA via the Translational Technologies Core, we will explore brain functional connectivity during rest and during task (within and across tasks).

Major hypothesis: We propose to replicate increased functional connectivity of the NAc in FHP compared to FHN, as reported by other groups[143,144]. We propose to determine whether Saracatinib normalizes NAc functional connectivity in FHP, which would suggest that enhanced signaling via Fyn and NMDA-R contribute to the distinct patterns of NAc functional connectivity in the two groups.

EKG: Screening day and subsequent drug administration days- Obtained at request of drug manufacturer (A-Z) for screening and safety monitoring.

Blood Tests: Screening and each subsequent experimental day (at end of the session); CBC, liver function, electrolytes, B12, - obtained per A-Z for study safety monitoring purposes.

5. METHODS:

5.1 Research design and sample size/statistical power:

Saracatinib has not previously been used in this context. The purpose of the current study is to assess the effect size of interventions with this medication compared to placebo.

5.2 Subjects:

Subjects will either have a family history of alcoholism (FHP) or no family history of alcoholism (FHN; N=45 per group, to a total of 90 subjects; males and females in equal numbers).We will recruit subjects from the general population by advertisement (e.g. in the Hartford Advocate or on Craig's List). Yale University will provide and pay for an encrypted, password-protected study cell phone to contact potential subjects via text message. Subjects will also have the opportunity to agree to text message appointment reminders in the informed consent form. Interested participants will also have the chance to respond to web based advertisements that include the option to call in to be screened for eligibility over the telephone or via a locked online survey database. If participants complete the online pre-screener and are found eligible they will then be contacted to be fully screened by the staff recruiter to determine complete eligibility.

The CTNA study coordinator screens all potential subjects obtained from the above sources, and a study FH status is determined using the family history approach operationalized by the Family History Assessment Module (FHAM), developed by COGA. FHPs are defined as having a parent and at least another first- or second-degree relative with alcohol dependence OR having at least a father with a history of alcoholism. If the affected parent is the mother, we will rule out possible fetal alcohol syndrome, using a standardized symptom checklist; FHN will have no affected first-degree relative. We will be selecting subjects from families with substantial risk for developing alcoholism, and this increased susceptibility probably reflects increased genetic liability.

5.3a Inclusion Criteria:

Inclusion criteria are equal numbers of men and women between the ages of 18 and 40 years. Recruitment will be through advertisement. On each test day, subjects will be first screened toxicologically for drugs of abuse (and for women of childbearing age, pregnancy) by urine testing, any positive test results in exclusion. Our participants will not come from a "vulnerable population" because participants will not be pregnant women, under legal coercion or restriction,

or mentally impaired so as not to understand the nature of the research. They will be able to understand the procedures as judged by their ability to clearly repeat back to the PI or his designee correctly, the purpose and content of the planned research, and willingly agree to participate. Despite this, if the PI has any doubt as to whether a participant's status precludes his/her ability to participate fully in the informed consent process, these subjects will be excluded from the study until such time that proper informed consent can be obtained.

5.3b Exclusion Criteria:

Exclusion criteria include:

1) A diagnosis of any mood, psychotic, or current anxiety disorders under DSM-V, using the SCID-V-RV psychiatric interview
2) A past and/or current diagnosis of:
    a. Alcohol dependence (past alcohol abuse is OK)
    b. Substance abuse or dependence;
3) Report of psychotic disorder in a 1° relative, auditory or visual impairment that interferes with test-taking;
4) Prenatal exposure to alcohol plus currently meeting criteria for features of fetal alcohol syndrome;
5) Not speaking English fluently or being a non-native English speaker, or being educated in a primary language other than English >grade 1;
6) Mental retardation (Full Scale IQ<70);
7) Traumatic brain injury with loss of consciousness > 30 minutes or concussion in last 30 days;
8) Presence or history of any medical/neurologic illness that may affect brain physiology (e.g., epilepsy, Multiple Sclerosis), including focal brain lesion seen on structural MRI (all structural scans are read by a licensed radiologist);
9) Current pregnancy (all females will be tested with urine screens on the day of MRI);
10) All participants will receive a urine screen for the presence of marijuana, cocaine, opiates and a breath screen to detect the presence of alcohol;
11) Inability to comprehend the consent form appropriately;
12) Other specific fMRI exclusions include metal devices, clips or fragments in body (orbital x-ray performed if needed);
13) EKG abnormality indicating severe cardiac pathology (e.g. atrial fibrillation, chronic ischemia);
14) Significant change in LFTs, electrolytes, or CBC.

Saracatinib-related exclusions are current use (within 30 days of screening) of specific psychoactive medications (e.g., typical antipsychotics, narcotic analgesics, antiparkinsonian medications, systemic corticosteroids, or medications with significant central anticholinergic activity). Current use of warfarin or the following medications (CYP3A4 substrates whose metabolism may be slowed by AZD0530, which is also metabolized by CYP3A4): colchicine, carbamazepine, cyclosporine, disopyramide, fluticasone, quinidine, vinblastine, vincristine, nifedipine. Also, to avoid potential drug interactions, subjects taking sildenafil, tadalafil, and vardenafil will be advised to stop taking these medications for the duration of the trial. Subjects cannot take the following substances which inhibit the CYP3A4 isoenzyme: cimetidine, cyclosporine, danazol, fluconazole, grapefruit juice, HIV protease inhibitors, itraconazole,

ketoconazole, macrolides, miconazole, nefazodone, omeprazole, ritonavir, docetaxel, aromatase inhibitors & verapamil. Other exclusions are absolute neutrophil count <2,000/micro-L, platelets <150x10^3/micro-L, AST, ALT, total bilirubin >1.5 x upper limit of normal (ULN); serum creatinine, >2 x ULN, significant EKG abnormality, or history of interstitial lung disease. Subjects will be administered a visual analog intoxication scale every 30 minutes by verbally stating symptomology on a rating scale, and heart rate and blood pressure will be checked hourly. At the end of each study day, subjects will only be allowed to be discharged when they have minimal subjective reports of intoxication or sedation, vital signs have returned to baseline, and they have been assessed by either an RN or MD. Participants will be questioned carefully regarding possible study drug-related side effects at each visit using a standardized screening checklist (the SAFTEE-see below) and be followed up 1 week after the final test day by telephone screen. The SAFTEE is a tool for systematic assessment of adverse effects in clinical trials which includes 1) open-ended questions about any changes in physical or health problems, appearance, or activity level, and 2) yes/no responses to a specific list of symptoms (which correspond to anticipated adverse events associated with Saracatinib). For each symptom reported, the date of onset, severity (minimal, mild, moderate, severe), whether it was drug-related, and action taken, is recorded. The SAFTEE will be administered at each dosing day and at post-study follow up, to monitor and document rates of adverse events in a standardized manner.

5.4 Timeline

1. Initial phone screening
   Screening day:
2. Informed consent/HIPAA
3. Pregnancy and toxicology screen
4. Determine eligibility
5. Core battery and neuropsychological testing
6. Blood draw and EKG
   Experimental days:
7. Pregnancy and toxicology screen
8. Saracatinib effects scale
9. Medication/placebo administration by RN or MD
10. Vital signs checked (every hour)
11. Rest in designated room while completing Core intake packet
12. Lunch
13. BART/ EDT
14. Genetic saliva sample
15. MRI
16. EEG
17. Blood draw and EKG
18. Subject is compensated for his/her time*
19. Sign out by MD
20. Cab home

- *Check EKG and blood lab results prior to scheduling each subsequent experimental day.*
- *Call subject by phone 1 week after completion of last experimental session to assess possible side effects.*

**As a result of high cancellation rates, subjects will be eligible to receive an incentive for keeping all four of their scheduled appointments. Upon completion of the study, subjects will receive a $50 gift card to a local establishment. This is an addition to the $25.00per hour compensation for their time participating in the study.*

Consent:
Will be completed by HIPPA trained staff on the study.

***Pregnancy and toxicology screening*:**
Will be completed by HIPPA trained staff on the study, who are annually trained on each screening.

***Medication*:**
Astra Zeneca will provide the Saracatinib 125- mg doses, and the placebo will be masked by identical-appearing tablets by the drug manufacturer:
Prescriptions will be made yearly, and label will include discontinuation dates from the pharmacy. Dr. Pearlson and study RN will dispose of unused medications utilizing Hartford Hospital's pharmacy drug discontinuation system. Saracatinib will be stored in HH Pharmacy and the IOL Butler Building, room 222 at Hartford Hospital in a locked safe in a locked room. Medication will be dispensed by Dr. Pearlson. Medication sheets that document dispersion of Saracatinib are recorded. Medication: This drug is an experimental Fyn-Src family protein tyrosine kinase inhibitor, (AZD0530), which has a similar, but more specific action than memantine in blocking the glutamate system. AZ0D530 was developed by Astra Zeneca as an anti-cancer drug in which is currently in clinical trials. The relevant Investigator's Brochure is appended. Dr. Krystal has obtained permission from Astra Zeneca to use this new drug in the context, we describe by being added to Astra Zeneca's existing approved IND.

***EEG/ERP*:**
The EEG recording session is non-invasive, but requires us to maintain a clean contact between the electrode and the subject's scalp. We scrub the skin under each sensor placement. This procedure may be mildly uncomfortable, but not painful and may leave small red patches afterward that will disappear in a day or two. An additional risk lies in the possibility of transmission of infection. To minimize these risks, careful preparation of skin surfaces using sterile supplies is conducted before attachment of electrodes, and the elastic cap is sterilized after each use. There is a very low risk of developing an allergic reaction to the gel, which is essentially a thick salt-water. Some of the sounds subjects listen to in this part of the test may be loud or occasionally unexpected. Subjects may discontinue the session at any time if it becomes uncomfortable.

***Psychological Ratings/Interviews and Cognitive Tests*:**

All tasks forms are in study 126237, "Functional Neuroimaging of Alcoholism Vulnerability: Glutamate, Reward, Impulsivity, and Pavlovian-to-Instrumental Transfer (PIT)."

Two hours post drug administration subjects will complete the out of scanner version of BART and EDT (Go/ No-Go, IAT, AAT are completed on screening day) computerized impulsivity procedures, and approximately 4 hours post-drug administration, (the timing used in the prior Krupitsky study)[79], they will undergo the fMRI Monetary Incentive Delay, Go/No-Go and MID/tasks in counterbalanced order. Subjects' heart rate and blood pressure will be checked hourly.

In addition to the computerized tasks (Go/ No-Go, IAT, AAT, BART and EDT) and the fMRI tasks, subjects will complete paper and pencil measures derived from the CTNA Clinical Core, which consists of the, Clinical Core Accession and Demographic Questionnaire (CCADQ), Family History Assessment Module (FHAM), SCID-E Alcohol Summary (SCID-E),Timeline Followback Summary Sheet (TLFB), Sensation Seeking Scale (SSS), Barratt's Impulsivity Scale (BIS-11), Short Inventory of Problems (SIP-2R), Self Rating Effects of Alcohol (SRE), Alcohol Expectancy Questionnaire (AEQ), Negative Alcohol Expectancy Questionnaire (NAEQ), Depression Anxiety Stress Scale (DASS), Behavioral Inhibition Activation System (BIS-BAS),Columbia-Suicide Severity Rating Scale (CSSRS), , Childhood Trauma Questionnaire (CTQ), Drinking Motivations (DV), , Self Report Habit Index (SRHI), UPPS Impulsive Behavior Scale,, PROMIS Alcohol Use Form, and Experimental Delay Discounting Task (EDT). Other paper and pencil measures not derived from the CTNA Clinical Core include the COGA Family History Assessment Module which is used to screen for family history, the ONRC Health Questionnaire, Handedness, SPSRQ, Padua, the AUDIT, and a 14 question questionnaire that assesses how the participant is currently feeling while on the medications. A separate self-report, the Borderline Personality Questionnaire (BPQ), is being used to assess borderline personality traits that are often correlated with substance use. In addition to the IQ measures included in the CTNA Clinical Core, IQ will be assessed using the Vocabulary and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II). During the Vocabulary subtest of the WASI-II, subjects will be audio recorded so another member of the research team can double score the assessment. If the subject does not wish to be audio recorded then it will be arranged to have another member of the research team to sit in during that time.

Subjects may find the battery of psychiatric and psychological tests tedious and boring, or intrusive. If the former is the case, additional brief breaks will be given during assessment. The latter concern is addressed through use of trained interviewers who have experience discussing sensitive material with clinical research subjects. However, if a subject finds a topic too uncomfortable, those questions will be skipped, or with severe reactions, subjects will be reminded they can discontinue participation without penalty.

Following study completion, subjects will only be allowed to be discharged when they have minimal subjective reports of intoxication or sedation, their vital signs have returned to baseline, and they have been assessed by either an RN or physician.

MRI **:**

The FDA has approved the MRI system and the scanning protocols to be used. The MRI scanning procedure in a 3 Tesla system is safe in normal healthy humans. However, subjects who could suffer potential risks from the MRI scanning procedure include those with metal implants (pacemaker, metal rods, bone screws, orthodontics, metal flakes from metalworking). Subjects are told during the informed consent process about the need to carefully screen for metal implants or any other exposure to metal in the body. Subjects who could potentially suffer harm will be screened for metal prior to scanning using a HH Radiology Department screening checklist. Although there is no proven harm to developing fetuses, women will be screened for pregnancy before scanning. Subjects with claustrophobia may experience some anxiety symptoms, and will be discouraged from participating. Subjects who feel claustrophobic during the experiment will be encouraged to notify experimenters at any time to discontinue scanning. There are no known risks associated with the visual or auditory stimuli presented during recording of event-related fMRI.
Structural MRI: Performed on day 1 only.

Functional MRI tasks: (both study days)

The Monetary Incentive Delay (MID) Task:
MID tasks dissect anticipatory (motivational) from outcome (consummatory) components of reward. Anticipating rewards of many types, including abstract ones such as money, activates ventral striatum (VS); VS responds to learned appetitive cues, while medial PFC directs energy to appropriate goals[72,73], and more anterior OFC regions are activated by abstract rewards. Hommer's fMRI monetary incentive delay task (MID)[71] elicits anticipation of monetary reward or punishment. He exposed NAcc (VS) deficits during anticipation of reward in abstinent alcoholic individuals vs. age/sex matched controls during MID task performance; alcoholics activate VS less while waiting to work for reward, but they activate similarly to controls in posterior cingulate & ventral PFC in response to feedback about success[59]. To address whether the NAcc abnormality predisposes or is secondary to alcoholism, Hommer compared healthy adults & adolescents to adolescent children of alcoholic (COA) fathers. The MID task[12] identified increased VS activation during reward anticipation in young adulthood, but no change in brain states associated with successfully winning money. However, adolescent COA's and adult alcoholics[126, 6] show blunted VS activation compared to healthy FHN same-aged controls for reward anticipation, suggesting that motivational system hypo-activity precedes alcoholism and may be a risk marker, predisposing an individual to addictions. Thus, since its inception the MID has been used in alcohol risk studies; to date we have studied >700 subjects at 3T across multiple diagnostic groups (see preliminary data section).

Go/No-Go Tasks: An fMRI Paradigm to Explore Response Inhibition Circuitry.
Stop signal and Go/No-Go (GNG) fMRI tasks assess one aspect of impulsive decision making, namely withholding inappropriate choices[27]. The GNG task, in which the participant is required to refrain from responding to designated items within a series of stimuli, has frequently been used to examine cognitive control using fMRI in both healthy and psychiatric samples. Cognitive control processes, as embodied in the GNG, are a vital element in inhibiting the immediate pursuit of rewarding stimuli and in developing adaptive behavior patterns—both important factors in substance abuse[52]. The neural circuitry underlying the task has been carefully mapped in healthy populations. We have explored fMRI GNG tasks at 3T in detail[113] in >1800 total

subjects in our lab [113,114]. The GNG fMRI literature reveals that the same regions are consistently implicated. No-Go responses include anterior cingulate cortex (ACC)[16,56,61,65,66,85,89,116]; orbitofrontal cortex (OFC)[38,61,74,89]; dorsolateral prefrontal cortex (DLPFC)[4,7,16,21,38,48,65,66,74,89,122]; inferior parietal lobule (IPL)[4,7,16,38,89,61,122]; and pre-motor area BA6 and caudate[89,93,122]. ACC seems essential for conflict response, decision formation/action selection, and error monitoring [15,65,129-131] and ventrolateral prefrontal cortex plays a role in response inhibition[131] . Children activate these regions and amygdala more than adults[14], suggesting a less efficient response inhibition system. Impulsive normal subjects activate paralimbic areas and OFC more during response inhibition[61] likely to maintain behavioral inhibition. Substance abusers may show less task-related ACC and PFC activity[35, 64].

fMRI Alcohol Cue Reactivity (ACR) Task:

This Alcohol Cue Reactivity task[102], (15 min.) is programmed in E-Prime and consists of 44 (i.e., 22 alcohol and 22 matched soft drink/bottled water) beverage pictures derived from advertising images and 44 degraded stimuli, randomized with 15 fixation periods of 3 different durations (i.e., 2, 4, and 6 seconds to model the hemodynamic response). To improve contrast in the primary task condition and contrast of interest, alcohol and non-alcohol stimuli are programmed to be presented four times each (i.e., 88 trials per condition), while degraded stimuli are each presented once (i.e., 22 trials per condition). Each picture is presented for 750 ms with a 1250 ms inter-stimulus interval (i.e., blank screen) and intermittent fixation periods (i.e., screen with a centered fixation). The fixation and shuffled conditions provide the opportunity for the eventual fMRI studies to contrast activation to alcohol and/or non-alcohol pictures to a visual and rest baseline, respectively. The alcohol cue reactivity task is 8 minutes and 32 seconds in duration. There is a 12 second fixation period before stimuli is first presented. Ratings and reaction times are logged for statistical analysis. Task instructions are to press a key within 2000 ms of stimuli presentation in response to whether participants Like (left button), feel Neutral about (down button), or Dislike (right button) seeing the beverage picture. Participants are instructed to use the left, down, and right arrows in a laptop or computer while practicing the task outside the scanner. Once in the scanner, a button box is used. A practice task with non-beverage pictures was created for practice purposes.

fMRI Probabilistic Selection task (PST).

The PST will be employed as outlined by Waltz et al.[1] as successfully implemented by our collaborators at UC Davis, (Carter) that separately examines the function of both reward- (Go) or punishment-driven (No Go) learning, in that it enables the assessment of whether subjects have a bias for choosing frequently-reinforced stimuli, or for avoiding frequently-punished stimuli. In an acquisition phase, participants learn to choose between three different stimulus pairs presented in random order based on probabilistic feedback. The task, shown by Frank to be sensitive to DA-ergic manipulation[145], allows assessment of the effects of group and reinforcement probability on measures of contingency learning. The only differences from the originally-described 2007 design are that the training phase of this shortened (15 min) version consists of 2 (rather than 3) pairs of options, an AB pair (associated with positive/negative outcomes in 85/15% of trials where A is chosen and 15/85% for B) and a CD pair (associated with positive/negative outcomes in 70/30% of trials where C is chosen and 30/70% for D). On the test phase, participants choose between all possible pairs with A, B, C, and D. Go-learning is computed by averaging performance on AC and AD test trials. NoGo-learning is computed by

averaging performance on BC and BD test trials. Note that a full version of a (different) computerized version of the PST is administered out of scanner, as part of the behavioral Core battery.

***Out of Scanner Impulsivity and Other Tasks (all 3 experimental days)*:**

The Implicit Association Task (IAT)[139]
This task measures implicit affective associations with the alcohol. Using a computerized sorting task, individuals simultaneously classify two target conditions, 'alcohol' (ie., wine, beer, pint, vodka, whiskey, wine cooler) versus 'soft drink' (coca cola, juice, orange soda, root beer, sparkling water, 7-up) , and two affective categories relevant to drinking, 'pleasant' (ie. talkative, excited, cheerful, happy, funny, lively), versus 'unpleasant' (i.e., nauseous, listless, awful, miserable, sad, annoying).

The Approach Avoidance Task (AAT)[140]
This task measures approach bias for alcohol related stimuli. The subject pushes or pulls computer presented stimuli according to a content irrelevant feature, the tilt of the stimulus. Pushing the joystick gradually decreases stimulus size, while pulling gradually increases stimulus size. Pulling is related to more positive evaluations than pushing. The zooming feature also generates a sense of approach or avoidance.

The Balloon Analog Risk Task (BART)[144]
This is a computer decision-making task that measures risk taking. Participants are presented with a series of "balloons." The object is to earn as much money as possible by pumping the balloon without popping it. The point of explosion varies from trial to trial and costs participants the money they have earned in that trial.

Experiential Discounting Task (EDT)[145]
This delay-discounting task exposes participants to choice consequences during test administration. The EDT involves multiple blocks of choices, one for each delay. Choices are made between a standard amount that is delivered immediately and is certain and a probable amount that is delayed and uncertain. The EDT is sensitive to various levels of alcohol dosing (i.e., between 0 and 0.8g/kg)[145].

Go/No Go Task
In order to measure behavioral reaction times, we perform two runs of the go/nogo task, identical to that performed in the scanner and described earlier, out of the scanner as well.

PIT task
For the Pavlovian-to-Instrumental Transfer task (PIT) subjects will be asked to taste different stimuli. The stimuli will be delivered as liquids. Stimuli will be stored in a refrigerator and brought to room temperature before use. In brief, the liquid delivery consists of a computer running E-Prime, controlling a series of programmable syringe pumps with 60ml syringes and beverage tubing attached. New tubing and syringes are used for each subject. Our stimuli will contain either a taste (juice or bitter) or a neutral solution. The juice taste will be one of three different flavors of commercially available Gatorade that subjects choose. The bitter and neutral

solutions will be prepared in the laboratory using commercially available tastes such as: quinine sulfate, sodium bicarbonate and potassium chloride

Subjects are also asked to make ratings about their perceptions of these taste stimuli, for instance, to judge the intensity of a taste. All stimuli are commercially available products, or made from commercially available products. Subjects are then asked to complete several tasks on the computer that require learning how abstract cues might predict the delivery of a bitter, neutral, or juice solution. The entire session takes approximately 1 hour and 15 minutes.

Genetic Sample: **Specimen Collection of Saliva**

An oral fluid sample will be collected in an Oragene DNA container provided by DNA Genotek. This sample will be used for full genome analysis (GWAS) to show whether genes have a role in substance use, identify genes influencing behaviors and other characteristics of brain structure and function, and examining genetic variation across groups - comparing control subjects to the addicted population. To do this we will use Illumina Human1M-Duo Infinium Human1M BeadChips that feature > one million markers to interrogate human genetic variation using single nucleotide polymorphisms (SNPs) and copy number variation (CNV) probes. The BeadChip specifically targets genes, tag SNPs, copy number variation, and other high-value genomic regions, offering the most comprehensive genotyping available on a single microarray. The novel CNV content on the Human1M BeadChip was developed in collaboration with DECODE Genetics and features more than one million SNPs for genotyping and CNV analysis and an additional 52,167 markers designed to specifically target nearly 9,000 copy number variant (CNV) regions of the genome not currently available in any public database, for a total of over 1,070,000 usable markers for CNV analysis inover 14,000 total CNV regions. This will allow further definition of the genetic contributors to impulsive behavior, reward and punishment processing, and addiction.

To perform collection, subjects will spit into a disc shaped container until they have reached an approximate tablespoon level (takes about 2-5 minutes). Subjects will not be allowed to eat, drink, smoke or chew gum for 30 minutes before giving their saliva sample so as to not contaminate it. Genetic samples are assessed by Joel Gelernter, *MD* at Yale University. This sample will not be used for any diagnostic purpose and the lab will not know who individual subjects are, since randomly generated ID numbers are used to indicate samples. Oragene DNA containers made by DNA Genotek are used because of the easy storage, long shelf-life of samples and safer handling. It also makes obtaining genetic samples non-invasive vs blood draws, so there is much higher subject compliance.
The genetic results will not be made available to the subject under any circumstance, and will be released only to those outside the study team who have attained proper approval from their institution's IRB.

6. **DATA ANALYSIS**: note, as mentioned earlier, the current tasks are designed to assess effect sizes compared to memantine data gathered as part of the approved study, in order to estimate power for future planned large-scale studies.

***6a. General Task Analysis Approaches*:**

fMRI – Data Processing:

We will use a traditional massively univariate approach for block and event-related fMRI Analysis**.** Event-related responses are modeled using a synthetic hemodynamic response function composed of 2 gamma functions. Formulating the model in this way allows us to use standard procedures developed for analyzing serially correlated fMRI time-series that employ the general linear model and a sound theoretical correction for the comparison examined[37,125]. Reported statistical levels will be significant at the voxel level[125]. We use random effects models to account for between-subject variability. Functional images will be reconstructed offline and each run separately realigned using INRIAlign[37]. A mean functional image volume will be constructed for each session from the realigned image volumes, that is then used to determine parameters for spatial normalization into the Montreal Neurological Institute (MNI) standardized space employed in statistical parametric mapping (SPM). The normalization parameters determined for the mean functional volume will then be applied to the corresponding functional image volumes for each participant. Finally, the normalized functional images will be smoothed with a 12 mm full-width, half-maximum Gaussian filter. Appropriate task-relevant regions of interest will be selected using strategies employed in recent publications from our group e.g. [113, 114, 67].

Statistical Parametric Mapping (SPM5) analyses will test pre- to post-treatment differences in fMRI regions of interest (ROIs) during decision making for owned and control items on the symptom provocation task. The primary ROIs for treatment effects include bilateral NAcc, ACC and bilateral OFC. These and other task-relevant ROIs will be defined as 16 mm diameter spheres around x, y, z coordinates determined from our current data. Mean estimates of signal change (i.e., beta-weights from fMRI regression models) within each ROI will be examined separately using Bonferroni correction will be used to guard against alpha inflation due to multiple comparisons. As a secondary analysis, in the event that our new dataset shows somewhat different main effects of task (i.e., peak activation foci in slightly different regions), we can use the Wake Forest University toolbox to draw anatomically-based regions-of-interest. SPM analyses can then test these using averaged % BOLD signal change estimates from the entire region, or SPM small-volume correction to determine the peak group effect difference within the study ROIs.

Mapping Abnormal Responses Across fMRI tasks onto Functional Brain Systems

Distributed neural system dysfunction arises in psychiatric disorders either from weak structural interconnections or because available neural pathways are inappropriately/inefficiently engaged due to factors interfering with proper interregional communication (e.g., disordered cellular firing, or as hypothesized here, NMDAR/DA-D2 abnormalities. The recent emphasis placed on obtaining quantitative measurements of brain connectivity in psychopathology results from the recognition that complex cognition is not the product of isolated local neural processing; rather, it appears mediated by often widely distributed neural systems that are structured with dense local connections and weaker 'long-range' connections between nodes. Such a ‘small-world’ architecture appears to be an efficient, effective, and resilient property of neural control systems. Thus we will perform an extended network analysis to examine functional connectivity across task-related circuits. Multimodal fusion approaches are a powerful means to dissect such underlying abnormalities across different but overlapping functional brain circuitry, and are often based around Independent Component Analysis (ICA). Structural Equation Modeling (SEM) performs well preliminarily in this regard, as do allied analytic strategies, as shown in our papers and those of our collaborators[113, 114, 115, 30, 31, 69] that employ such approaches as Granger

causality**,** functional network connectivity (FNC), and ICA-DBN, which does not involve not SEM of ROI's directly, but is conceptually related and network based.

6b. Analyses Based on Specific Aims:

Aim 1
The primary outcome for this Aim will be BOLD activation during the A1 phase of the MID task. The effects of Saracatinib treatment on activation will be assessed using linear mixed models. In these models, BOLD response will represent the dependent measure and family history status (FHP vs. FHN) will represent a between-subjects explanatory variable, while treatment (placebo vs. Saracatinib) and ROI (NAcc vs. OFC) will be included as within-subjects factors. All 2-way interactions will be modeled and interpreted using graphical displays and appropriate post-hoc tests. In the above analysis, we anticipate a family history by treatment by ROI interaction explained by significant NAcc decreases and significant OFC increases in BOLD response due to Saracatinib treatment among FHP subjects. Secondary analyses will include the above analysis performed for activation levels observed during the A2 phase and examination of additional ROIs as well as dose and. Similar models as described, excluding phase as a factor, will be used to model BART and EDT outcomes (subsidiary hypothesis). In these models, we expect a family history by treatment interaction such that each of these impulsivity measures are reduced by Saracatinib treatment among FHP individuals.

Aim 2
BOLD signal activation in the anterior cingulate cortex (ACC) observed during False Alarms of the GNG task will represent the primary outcome in this Aim. The effects of Saracatinib treatment on activation will be assessed using linear mixed models with family history (FHP vs. FHN) included as a between-subjects factor and treatment (placebo vs. Saracatinib) and response type (false alarms vs. correct rejections) as within-subjects factors. A significant family history by treatment by response type interaction explained by increased BOLD activation due to Saracatinib during false alarms in both groups, but more markedly in FHN, will be supportive of our hypothesis. We will consider other regions (BA9, BA44/45, BA47, Insula, VS) represented as additional within-subjects factors in the model described above. In this analysis, we expect Saracatinib to reduce BOLD signal activation among FHP in each of the regions during correct rejections.

Aim 3
Linear mixed models will be used to evaluate the effects of family history on NAcc BOLD response during the ACR task. These models will include family history (FHP vs. FHN) as a between-subjects factor and type of Cue (ETOH-related vs. non-EOTH) as a within-subjects factor. We anticipate a significant group by cue interaction such that FHP subjects will respond with greater NAcc BOLD signal to alcohol-related cues vs. non-alcohol cues compared to matched FHN subjects and subsequently experience a greater reduction in NAcc BOLD response following Saracatinib administration.

Aim 4
The same statistical models described for Aim 1 will be used to evaluate the effects of Saracatinib and family history on NAcc and OFC activation during the A1 phase of the PIT-in

modified MID task. In these models, however, we will include Cue Type (PIT-related vs. Non-PIT-related) as an additional within-subjects variable. We expect a significant family history by treatment by cue type by region interaction explained by significant NAcc decreases and significant OFC increases in BOLD response due to Saracatinib treatment among FHP subjects, with these effects most exaggerated during the presentation of PIT-related cues. In addition, using regression we can test whether PIT responses (using the out-of-scanner version used in all data from study 126237) show the expected learning effect.

7. Risks and Data Monitoring Plan:

Under some circumstances, it can be a risk for genetic information about subjects to be known. Variation in some genes is known to be directly related to risk for certain illnesses. Other genes we will be studying in subject DNA may be shown at some point in the future to be related to illnesses. Since the results of these genetic tests may allow prediction of risk of illness in some cases, we will make every effort to keep the results confidential (only scientists working on this research project will know the results). We will not make any of our laboratory results available to subjects, nor will we add them to any medical record or release them to others.

Known risks may include but are not limited to issues related to insurability or employability or those subjects may become aware of information about themselves or family members that they would have preferred not to know. We will not make any of our laboratory results available to subjects, nor will we add them to subjects' medical record or release them to others. Additionally, the research DNA bank will contain DNA samples identified only by a random number to reduce the likelihood that the DNA data is connected to the individual from whom it was taken. When saliva is collected, subjects may experience dry mouth during the collection. No other physical risks are associated with this procedure.

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator, Dr. Godfrey Pearlson, will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. In addition, Dr. Pearlson will consult regularly as required with the DSMB (see paragraphs below) and seek guidance from them as required. Either the principal investigator, DSMB or Hartford Hospital IRB have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed moderate because we do not view the risks associated with the administration of AZD0530 as minimal.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Plan for Grading Adverse Events and Attribution of Adverse Events

Side effects/adverse experiences are collected on standardized forms, using the SAFTEE (Levine and Schooler, 1986). The SAFTEE includes 1) open-ended questions about any changes in physical or health problems, appearance, or activity level, and 2) yes/no questions on a specific list of symptoms (which correspond to anticipated adverse events associated with Saracatinib) for a specified time period. For each symptom reported on the SAFTEE a rater also records the date of onset, severity (minimal, mild, moderate, severe), whether it was drug-related, and action taken. The SAFTEE is administered at baseline, during the inpatient periods, and every other day during the outpatient treatment periods. We will monitor the number of patients experiencing symptoms and the severity of symptoms.

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Dr. Godfrey Pearlson, according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

The principal investigator, Dr. Godfrey Pearlson, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events, report to both the HH and Yale IRB's plus the DSMB and determine collectively if modifications to the protocol or consent form are required.

DSMB.

We will be accessing the Data and Safety Monitoring Board (DSMB) developed for Dr. Krystal's Alcoholism Center. The DSMB is multi-disciplinary and includes representatives with expertise in the primary components of the proposed trial. The following individuals will be on the DSMB as voting members:

Robert Swift, MD, PhD, Prof. Psych (Brown)/ VAMC Chmn., DSMB

Robert Stout, PhD, (Yale) Director, Decision Sci. Int., Statistician, DSMB
Howard Zonana, MD, (Yale) Dir., Dept. Psychiatry Ethics Committee, IRB Rep., DSMB
Lisa Newton, PhD, Prof. Applied Ethics, (Fairfield Univ). Ethicist, DSMB

This DSMB will follow the operational guidelines outlined in the YCCI plan for DSMBs.

Frequency of Review of Safety Reports

Subjects are recruited at a maximum rate of 2 per month; thus, the DSMB will review safety reports two times a year. More frequent meetings will be scheduled if indicated by interim findings.

Data Safety and Monitoring Plan (developed in accordance with the NIAAA guidelines)

The DSM plan must designate an experienced, qualified professional (usually the PI) who can distinguish a serious adverse event (SAE) from a non-serious adverse event (AE).

All staff are required to complete Hartford Hospital's CITI Training and receive passing scores on modules involving the detection and evaluation of adverse events, and reporting serious adverse events. The P.I. on the project, Dr. Godfrey Pearlson, is a trained MD psychiatrist. He is responsible for all overall project management and supervision, including subject clinical assessment and medical screening, and drug administration. Each subject who has an unanticipated adverse event is checked by the supervising nurse and/ or the Principal Investigator. Each event is logged, noted and a write up is placed in their folder. All events are reported to Hartford Hospital IRB during IRB renewal.

The DSM plan must indicate that serious adverse events will be reported to the local IRB and to the NIAAA project officer within 48 hours.

Hartford Hospital IRB has a computerized adverse event reporter found on all work stations in which the P.I. or designee must report any adverse events within 24 hours. The events are tracked, trended, analyzed and reported to the Quality Committees at HH. Serious Adverse Events will be reported to the NIAAA project officer within 48 hours.

The DSM plan must indicate that an annual report will be submitted to the NIAAA Project Officer summarizing all adverse events.

The annual Hartford Hospital IRB and Yale reports include all adverse event summaries during the time of the incident, as well as re-submission during the annual report. This summary will be submitted to the NIAAA Project Officer as part of the annual report on the project.

The DSM plan must specify that female subjects who are pregnant, nursing, or not using effective methods of birth control will be excluded from studies involving the administration of alcohol and/or drugs.

All females are pregnancy tested who are of child-bearing age. If they are currently nursing pregnant or planning on becoming pregnant within 6 months of intended study participation date, individuals will not be seen at that time. All women will be screened for pregnancy before the MRI scan, and will be excluded if pregnant.

The DSM plan must indicate that trained personnel will be present or on call when human laboratory studies of alcohol or other drug intake are conducted.

Common side effects for the Saracatinib medication include flu-like symptoms, nausea, diarrhea, headache, and skin rash. Individuals will be told prior to participation that they may not drive to or from the study procedure, but will either take a taxi cab or be driven by a friend/spouse. Following assessment, they will be administered either a 50 mg dose of Saracatinib, a 125 mg dose of Saracatinib, or an identical-appearing placebo either by an RN or physician investigator.

For studies in which alcohol is administered, the DSM plan must indicate that NIAAA guidelines for the administration of alcohol will be followed. These guidelines can be found at the following web address: http://www.niaaa.nih.gov/extramural/job22.htm

No alcohol is administered in this study.

If the study has a follow-up phase, there must be a specific plan for referral to treatment during follow-up of any patient requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms.

Other than a phone call from study staff one week post last study drug dose, the study does not have a follow up phase. The purpose of phone call is to follow-up on any symptoms participants may have to the study drug. Since the study drug does not affect alcohol consumption and is only provided at single doses, and since this study does not recruit subjects meeting criteria for DSM-IV alcohol dependence, careful monitoring post-last dose for adverse effects using EKG and biochemistry is sufficient as a safety monitoring plan for this drug.

The DSM plan must indicate that all adverse events during follow-up will be reported (SAEs within 48 hours) to the IRB and NIAAA.

This study does not have a follow up phase, other than a phone call one week after the last study dose. All participants have access to a 24 hour, 7 days/week line to the Principal investigator if participants experience any adverse symptoms.

The DSM plan must briefly describe the procedures for data quality assurance and confidentiality.

Confidentiality risks will be minimized by using randomly coded records and storing signed consent forms and other identifiable information in a locked file cabinet. We will maintain confidentiality by using procedures that are fully-HIPAA compliant and approved by HH and Yale Research Administrations. All information and data concerning volunteers are confidential and never released to anyone outside of the project without the volunteer's written authorization. The identity of participants is never revealed in research reports or conferences. A Certificate of Confidentiality will be obtained.

Protection of these data will be maintained through password protected databases and computer workstations, as well as with auto-locking room doors and locked file cabinets that contain this data. Overview by Dr. Pearlson and audits by Hartford Hospital, Yale University HIC, and NIAAA will ensure proper compliance with these and all confidentiality protocols.

Data quality is assured by careful training of staff members, use of forms designed to minimize errors and oversight from the data management component of the clinical core.

Data will be analyzed and made available to other qualified researchers on request. All data are kept in locked file cabinets in a locked office and all information entered into a database is password protected. Data are kept on average for 5 years following the completion of data analysis.

Phase III clinical trials must have an independent data and safety monitoring board.

This is not a phase III clinical trial.

ClinicalTrials.gov Requirements: The application includes a trial which requires registration in ClinicalTrials.gov.

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