Effect of genotype on Resting State Connectivity during Methamphetamine Administration

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Relevance to Veterans and the VA Mission: Methamphetamine is one of the most common addictive disorders among veterans today. Research seeking to understand the causes and maintenance of addiction are highly relevant to the VA's mission of serving the healthcare needs of the Veteran.

Specific Aims and Rationale: This proposal will determine the effect of a common variant (CV) synonymous single nucleotide polymorphism (SNP) of the gene for the human trace amine associated receptor 1(TAAR1) on the neural and behavioral response of subjects with methamphetamine (MA) use disorder (MUD) to acute MA administration. The SNP (rs8192620 on human [GRCh38.p7] chromosome 6 at 132,645,140 bp in *htaar1,* allelic frequency 22%) results from a change of adenine to guanine in a valine codon at amino acid 288 (v288v). MA is a potent agonist at the TAAR1 receptor (Reese et al., 2007), in addition to its actions at the dopamine transporter (Elliott and Beveridge, 2005) and the vesicular monoamine transporter (Fleckenstein et al., 2009). In rodents, a decrease in TAAR1 expression or non-functional TAAR1 receptor is associated with an increase in striatal dopamine (DA) signaling (Espinoza et al., 2015).

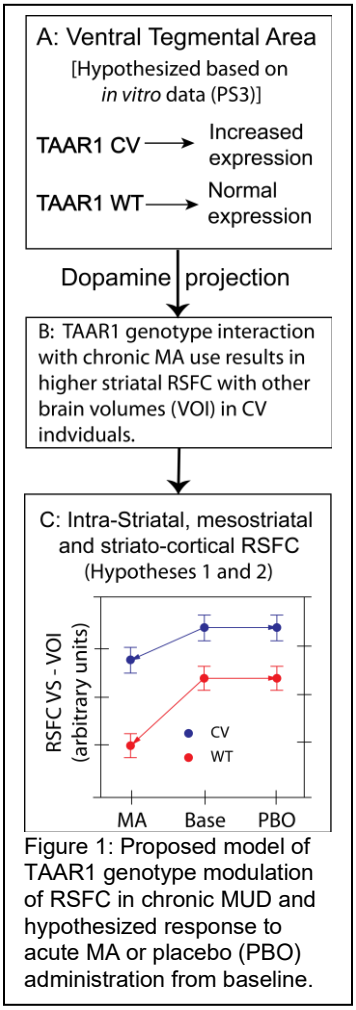

Figure 1: Proposed model of TAAR1 genotype modulation of RSFC in chronic MUD and hypothesized response to acute MA or placebo (PBO) administration from baseline.

The scientific premise of this project is based on 1) our preliminary findings that support a model that the CV alters RSFC of the striatum, a dopaminergic terminal region, and associated behavior in chronic MUD, 2) published reports that delineate the effect of TAAR1 on DA signaling and 3) preclinical evidence that TAAR1 influences sensitivity to rewarding and aversive effects of MA.

Furthermore, *this proposal will address questions that have important implications for understanding and treating patients with MUD,* as the TAAR1 receptor is implicated in MA self-administration. As an allele of the murine TAAR1 gene associated with an inactive receptor leads to increased MA intake in homozygotes (Harkness et al., 2015;Phillips and Shabani, 2015), *it is critically important to study the feasibility of exploiting human variant htaar1.*

We propose a model (Figure 1) based on this premise that makes testable predictions about the interaction of the CV with chronic and acute MA administration in MUD. Our preliminary data show that the CV causes over-expression of TAAR1 in cell culture. Stimulation of the TAAR1 receptor decreases dopaminergic signaling in mesocorticolimbic and corticostriatal networks (Pei et al., 2016;Berry et al., 2017). We propose that this effect *in conjunction with chronic MA use* causes neuroadaptations that result in the increased striato- and corticolimbic RSFC as well as increased drug craving observed in MUD subjects with the CV. We can indirectly test the hypothesis of decreased DA release due to ever-expression via MA administration. The effect of acute MA administration on RSFC in humans is not known but acute administration of S-amphetamine (Schrantee et al., 2016) and methylphenidate (Konova et al., 2013) reduce RSFC in salience attribution and default mode networks presumably via increased DA release. Stimulation of over-expressed TAAR1 should blunt this effect in CV carrying individuals compared to WT. There are no published reports on neural effects of the interaction between either chronic or acute MA administration and *htaar1* genotype in humans, therefore this proposal represents a unique opportunity to determine whether the RSFC response to acute MA administration in humans is mediated by genotype.

In Specific Aim 1 (**SA 1**)**,** we will confirm and extend our preliminary RSFC findings in *chronic* MUD using seed-based and data-driven precision brain mapping approaches. The latter are made possible by extended (40 minute) acquisition of functional connectivity data. We will investigate genotype and drug x genotype interactions with full connectivity matrices as well as topological RSFC measures including connection density and strength, network segregation, global efficiency, rich club coefficients, and global segregation in MA users at baseline and after MA administration. In **SA 2**, we will examine how *htaar1* genotype modifies the effects of *acute* MA administration on neural and behavioral measures in MUD. This provides an indirect test of Figure 1A that genotype modifies TAAR1 expression in the ventral tegmental area (VTA) and thus DA release in the striatum.

SA 1. Determine the influence of *htaar1* CV vs. wild type (WT) genotype on RSFC and craving in *chronic* MUD.

Hypothesis 1: CV vs. WT will exhibit higher cortico-striatal and striato-limbic and intrastriatal RSFC (Figure 1B and C: Base) and report higher craving for MA at baseline.

SA 2: Determine the effect of *acute* oral MA or placebo (PBO) administration on the interaction of *htaar1* CV vs. WT genotype on RSFC, craving, cognitive control, attention and subjective experience in MUD.

Hypothesis 2: Acute MA administration will lower RSFC in both genotypes, with a blunted decrease in the CV group (Figure 1C: MA and PBO).

Hypothesis 3**:** The CV group will exhibit, compared to WT, blunted effect of MA administration on craving, subjective experience and tests of attention and cognitive control.

Experimental Design:

Recruitment: MUD and control subjects will be recruited by advertisement from VAPORHCS, OHSU, community assistance programs. Advertisements will also be posted online externally utilizing Craigslist, the VAPORHCS web page, the quarterly newsletter (Veteran Connection), the VA Facebook page OHSU's Research Opportunities pages, the OHSU website (MARC page or dedicated lab page), Indeed.com, Ziprecruiter, Google Jobs, Localwise.com, Skoll.org, and community news publications (Street Roots, Portland Mercury, Willamette Weekly and possibly others). Approved flyers will be distributed throughout the community (retail locations, community assistance programs, primary care clinics, emergency departments, dental clinics, community outreach programs). All Craigslist ads, other job boards and social media will have email reply turned off so that potential participants will have to call the study team. Facebook posts will have a link to a PDF of the approved flyer, which will direct any subjects to contact the study team. All content published for both internal and external promotion will utilize the approved flyer or other approved language so that anyone interested in the study will have to call the study team for more information. Newspaper, job board and social media ads will utilize the approved Craigslist ad language unless other language is specifically approved. If potential subjects are referred by their VA providers, the provider will first ask permission from the subject to discuss the research project. If the subject gives permission, the provider will document this either in a CPRS note or encrypted email to the study team. VA providers may also send out our approved flyer with their regular occurring mail outs to their clients.

Research Match and OHSU OCTRI Research Volunteer Registry will be used to recruit potential subjects. An IRB approved description of the study will be sent to individuals by Research Match who meet criteria for the study. If the individual indicates they are interested, their contact information (i.e. name, mailing address, email, phone number) will be sent through Research Match to the Hoffman Lab Research Match account. This information will remain in the ResearchMatch system and/or be exported to the OHSU RDS server. OHSU OCTRI Research Volunteer Registry will provide contact information of individuals who meet study criteria and this information with be stored on the OHSU RDS server. Research assistants will contact these individuals using phone or email to set-up a phone screen. Subjects will be emailed via hoffmanlab@ohsu.edu to set up a phone screen. The Hoffman lab has substantial capacity and expertise to recruit MUD participants. Per NIDA guidelines, MUD subjects who have been referred to appropriate VA or community treatment facilities but will not be in drug treatment (court-mandated or otherwise) when recruited or while participating in the study (if subjects choose to join a treatment program during their participation in the study they will be withdrawn from the study and will not be administered methamphetamine). The community assistance programs we work with interact with precontemplative methamphetamine users regularly. Subjects may also be recruited by calling participants who previously consented to being contacted for future research after enrollment into the MARC study (eIRB 8702). As the IRB previously approved, these subjects will be pulled directly from the MARC study, not from a contact information repository. CPRS will not be accessed for screening purposes. Subjects who call in response to advertisements are screened with a telephone script to verify likelihood of meeting criteria and, if indicated, given an initial appointment. Additional questions will be asked to screen for recent exposure and symptoms of COVID-19. If recent exposure or symptoms are disclosed, and the subject otherwise qualifies, we will wait to schedule them until they have self-isolated for two weeks from time of exposure and/or when their symptoms have completely resolved. Our screening criteria already excludes those who are at increased risk of severe illness from COVID-19; however some subjects who *might* be at an increased risk may still qualify to participate during modified operations including smokers and those with well-controlled moderate-to-severe asthma, hypertension, and/or high blood pressure. These subjects will be informed that they may be at higher risk for COVID-19 infection and they may not want to put themselves at risk by participating in research. A VA waiver of informed consent and authorization for screening/recruitment purposes will be requested to collect subject names, phone numbers, and email before potential subjects give formal informed consent. Email addresses will be collected on the screening form for scheduling purposes and, if the potential subject agrees, email will be collected to send an appointment confirmation email (Azure). Each subject will provide written informed consent before any data collection or additional screening takes place. Up

to 100 current users of methamphetamine (MA) who meet DSM-V criteria for MA use disorder (MUD) and 100 controls will be recruited for this project and 36 from each group will complete all study procedures (we anticipate many will screen out based on their genetic screening for TAAR1). These 72 will break down into 4 groups of 18:

- MUD Wild Type (WT) Group: MUD individuals who are WT for the TAAR1 gene
- MUD Common Variant (CV) Group: MUD individuals who are hetero- or homozygous for the V288V SNP on the TAAR1 gene
- CS WT Group: Healthy controls who are WT for the TAAR1 gene
- CS CV Group: Healthy controls who are hetero- or homozygous for the V288V SNP of the TAAR1 gene

Data (including MRI scans) and specimens (saliva) may be pulled from the MARC Biorepository (mIRB 3164) to supplement subjects enrolled into this study for data analysis. Data and specimens will be coded and will not include any identifiers. A Waiver of Process of Informed Consent/Authorization will be obtained for analysis of these data/specimens and a DUA will be fully executed before data/specimens are removed from the repository. Repository data shared with this project may be sent to the University of Minnesota for analysis as described below in **Specific Outcome Measures and Hypotheses**. This data will be a Limited Data Set that includes imaging data (defaced), demographics such as age (no one over age 89), sex, treatment assignment (meth and placebo), TAAR1 genotype, substance use variables and survey scores. Data will be shared with study team members currently approved by the VA/OHSU joint IRB for this protocol. As this data is being shared from the repository (Sender) to Minnesota under this protocol (Recipient), a DUA between the repository and University of Minnesota will be fully executed before data is removed.

Inclusion/ Exclusion criteria: Entry criteria will be assessed based on self-report questionnaires, medical history and psychiatric diagnosis**.** Data/specimens pulled from the MARC biorepository will have come from subjects with very similar relevant inclusion/exclusion criteria which will be evaluated before inclusion.

Criteria for Inclusion:

All groups:

* 18 to 55 years old
* Homozygous or heterozygous for the hTAAR1 V288V genotype or wild type for hTAAR1 (Part 2)

MUD groups:

* Subjects must have a positive urine drug screen for methamphetamine during visit one
* Meets current criteria for methamphetamine use disorder
* Subjects should have been using at least 100mg of methamphetamine (not prescribed), 5 days per week for at least one year
* Abstinent from methamphetamine for 48 hours on days of scans

CS groups:

- At least one exposure to a stimulant, either recreational or prescribed

Criteria for Exclusion:

All groups:

* Allergies to stimulants or hypersensitivity to taking a stimulant in the past
* Diagnosis of a psychotic or mood disorders (past diagnoses of depression allowed) (DSM-V)
* Self-reported claustrophobia
* Women who are pregnant or breast-feeding
* Positive urine drug screen result at any point during the study (except for amphetamines except for verified medical reason)
* Intoxicated on study days (see Abstention from Methamphetamine below)
* Clinically significant neurological, cardiovascular, endocrine, renal, hepatic or systemic disease that could compromise safe participation or confound outcomes (including hepatitis C, HIV, severe anemia, or liver disease)
* History of glaucoma
* Metal in the body which is contraindicated for MRI or would compromise image quality
* Current prescription use of stimulants, anti-psychotic drugs or anti-Parkinson's drugs
* Use of monoamine oxidase inhibitors within 14 days
* Use of serotonin reuptake inhibiters, serotonin norepinephrine reuptake inhibiters, triptans, tricyclic

antidepressants, Fentanyl, lithium, tramadol, tryptophan, bispurone, St. John's Wort, insulin, phenothiazines, guanethidine, acidifying/alkalinizing agents, CYP2D6 inhibitors, proton pump inhibitors

MUD Groups:

- Positive urine drug screen at any point during the study (except for meth or marijuana)
- History of any severe substance use disorders within the last 5 years, except for methamphetamine use disorder or tobacco use disorder

CS Groups:

- History of any severe substance use disorders within the last 5 years except tobacco use disorder
- Positive urine drug screen at any point in the study (except for marijuana or verified medical reason)

Enrollment: We will enroll up to 200 individuals into Part 1. Individuals will then be screened into Part 2 based on their genotype and if they have no contraindications for methamphetamine administration or MRI. Subjects must have the WT Group or CV Group to screen into Part 2 and we will continue to enroll subjects into Part 2 until we have 18 completers in each of the 4 WT and CV groups.
Abstention from Methamphetamine: MUD subjects will be asked to abstain from using methamphetamine on the day of Visit 1 and 2 will be asked to abstain from using methamphetamine for 24 hours prior to Visits 3 and 4. If subjects come to their appointments intoxicated, they may be dropped from the study or rescheduled.
Subject selection and randomization: Dr. Aaron Janowsky's laboratory at the Portland VA will genotype the *htaar1* in Part 1 participants to identify all V288V variants (members of the Hoffman lab may also prep samples but will not read results). The CV Groups will be composed of subjects who are heterozygous or homozygous for the CV SNP without any other variant, while the WT Groups will include those who have the wild type genotype. The *htaar1* gene will also be sequenced in its entirety (the Janowsky lab will purify the DNA and then send it to the OHSU Core lab) so that individuals with rare non-synonymous *taar1* can be identified *post hoc* and analyzed separately. We will screen subjects until we have 18 subjects in each of the four CV Groups and the WT Groups balanced by age and sex (a research assistant not involved in the subject evaluations will check the balance and will adjust accordingly). As the population gene frequency is 23%, we expect to genotype up to 200 individuals to ensure two groups of age and gender matched subjects. We will replace dropouts until we have 18 completers in each group (for a total of 72 completers). The study team will be blind to genotype. The Janowsky lab will determine genotype and refer subjects back to the study team for inclusion in blocks of six subjects (three CV and three WT). If more than three CV or WT subjects are genotyped before three of the other group, then participants will wait for enrollment into Part 2 until the current block of six subjects is complete. Genotype data will be provided to the pharmacy to allow stratification by genotype during randomization.

Visit Number	**1**	**2**	**3**	**4**
	Part 1		**Part 2**	
Informed Consent	✓			
Review Study Eligibility	✓			
Medical History	✓			
Family History	✓			
Neuropsych Assessment		✓		
Computer Tasks		✓		
Vital Signs	✓		✓	✓
Urine Drug Screen/Pregnancy Test	✓	✓	✓	✓
Cheek Swabs	✓			
EKG	✓			
Study Drug or Placebo Administered			✓	✓
MRI Scans			✓	✓
Blood Draw	✓		✓	✓
Saliva Collection	✓		✓	✓
Questionnaires		✓	✓	✓
Total Time (hours)	**3**	**3**	**8**	**8**

Visit Schedule

Part 1: Visits 1 and 2:

Consent/Screening: Subjects will be consented and then screened for eligibility criteria. This will include medical history, vital signs, weighing, 12-lead electrocardiogram (EKG), and cheek swab for genotyping. Research staff with IRB-approved VA scope of work forms or the VA Portland Pathology Lab will collect urine, draw blood, and may collect oral fluid. Collection may happen in the Hoffman Lab or the Pathology Lab, both located at the VA. The urine drug screen (UDS) will confirm no use of drugs other than MA or nicotine and may be analyzed by either the research team or the VA lab. A screening blood draw will screen for HIV, Hepatitis C, complete blood cell count, chem 7 panel (glucose, creatinine, potassium, chloride, sodium, calcium, CO2), liver enzymes (aspartate aminotransferase, alanine aminotransferase and

gamma-glutamyl transferase) to ensure subjects meet criteria for inclusion in the study will be analyzed by the Portland, VA Pathology lab. An additional tube of blood will be drawn and given to the Janowsky lab to for DNA purification and then sent to the OHSU Core lab for sequencing of the htaar1 gene. Another additional tube of blood and/or oral fluid will also be collected to quantify MA levels. Subjects will also receive a neuropsych battery (NAB, WRAT4) and perform computer tasks (Iowa Gambling Task, Word/Color Stroop, Delay Discounting). Visit 1 and 2 may be combined or broken up into multiple visits to accommodate the participant's and the VA medical staff's schedules and will take place at VAPORHCS.

Part 2: Visits 3 and 4: Scan Days: All study procedures will happen at the Portland VA except for the MRI scans which will take place at the OHSU AIRC. MA administration and questionnaires may take place at either the VA or OHSU. Subjects are asked to abstain from MA for 72 h before the scan. A urinalysis will be performed to ensure that women are not pregnant and that no other drugs are present. Subjects will undergo a baseline MRI scan approximately 1 hour after the start of each visit followed by drug administration (placebo or MA) and a second scan 1.5 hours after that. Blood samples (3 mL) and/or oral fluid samples will be drawn before drug administration and after the second scan to quantify MA levels. At the Portland VA, during visit 2, up to 15 mL blood will be drawn and a cheek swab will be taken and both will be stored in the MARC biorepository located at the Portland VA. Blood may be stored as plasma or whole blood. Surveys and neurocognitive assessments will be performed before and after each scan at the Portland VA. Pulse, respiration, and pulse oximetry will be monitored throughout each scan. Each visit will last approximately 8 hours, and the subjects will be monitored (blood pressure, heart rate) closely throughout. The Systematic Assessment for Treatment Emergent Effects (SAFTEE) will be used to screen for adverse effects at the end of the day and the individual will be provided with discharge instructions in both verbal and paper form, which informs the subjects that these medications have the potential to impair driving and operation of heavy equipment. Subjects will be given a list of drugs that should be avoided for their interactive potential with MA and will be provided with a phone number to call Dr. Hoffman with questions. A break of at least two days will be required between visits to allow washout. Subjects will be required to take public transit or have a designated driver for each visit. Subjects may be offered a meal from OCTRI nutrition services, snacks or gift card to the VA canteen during each of these visits. Subjects may be asked to be a backup subject for Visits 3 or 4. Double-booking will help ensure the best use of time and resources. If both participants show up for the visit and we do not complete your visit, they will be paid $50 in prepaid debit cards for your time.

MA Administration and Randomization: For Part 2, subjects will randomly receive oral MA (0.25 -0.3 mg/kg; Desoxyn®, Lundbeck) on one visit and placebo on the other. Subjects with weight between 50-60 kg, will receive 15 mg oral dose; 60-80 kg, 20 mg; 80-100 kg, 25 mg; 100+ kg to max weight, 30 mg dose. The VA Portland Research pharmacy will provide MA and identical PBO in tablet form. The pharmacy will maintain a randomization schedule such that for each group of 6 subjects, three will receive MA on visit 2 and three will receive MA on visit 3. Study staff will be blinded to treatment.

Weight (kg)	MA Dose (mg)
50 - 60	15
60 – 80	20
80 – 100	25
100 +	30

Appointment Confirmation: Once subjects are consented, appointment confirmation with occur via phone or email. Appointment confirmation emails may be sent via Azure to subjects. Brief scheduling correspondence may also happen through Azure if the study team is not able to connect with the subject via phone. Subjects will be screened for COVID-19 symptoms during confirmation calls prior to study visits and again at the beginning of each in-person visit along with a temperature check. If any symptoms are revealed, the visit will be rescheduled for at least two weeks or until symptoms are resolved.

Subject Reimbursement: Participants will be paid in the form of Clincards for completing all or partial study procedures and will be paid at the end of the visit. For Clincard payments, subjects will be registered by name in the Clincard online system and issued a loaded debit card. Participants will be reimbursed $40 for the first and second visits, $100 for the third visit and $125 for the fourth visit (total = $305) in the form of prepaid debit cards. Participants who need to combine visits or break visits into multiple sessions will be prorated based on completion of tasks during the session. Subjects will also be offered Trimet day use tickets if they are using public transportation. If both subjects show-up to a double-booked appointment, the subject not undergoing imaging will receive a $50 prepaid gift card for the inconvenience and be rescheduled. Subjects may be asked to repeat procedures if data isn't usable. If an entire visit is repeated, then they'll be paid for the whole visit at the regular amount again. They will be paid at a pro-rate of $20/hr for any other repeated procedures or partial visits.

MA Metabolites: Blood/oral fluid drawn will be stored in a VAPORHCS freezer and then sent to the Center for Human Toxicology at the University of Utah to quantify the level of meth and meth metabolites present in the sample using Gas Chromatography/Mass Spectroscopy. Samples will be shipped via courier on dry ice (NIDA contract N01DA-19-8951). Samples will be recoded with a number (consecutive numbers, 1,2,3,etc) and will be labeled with this number prior to being shipped. No other information will be on the label or be provided to the University of Utah. These samples will be acquired once during V1 and twice each during V3 and V4 for individuals in the MUD group. Samples will be acquired only once during V3 and once during V4 for control subjects, after study drug is administered.

Biorepository Data/Specimen Use: A separate cohort of data/specimens will be pulled from the MARC biorepository and included in the analysis for this project. Data/specimens pulled will be nearly identical to the data used in this project and will include demographics (no identifiers), questionnaire data, information on drug/alcohol abuse, mental health diagnoses, computer task data, imaging data (MRI), coded lab results and saliva samples. Saliva samples will be sent out with the other saliva samples collected for this project and analyzed for methamphetamine metabolites at the University of Utah.

Data Acquisition and Processing

Rating scales: Subjective endpoints (MA-elicited craving, subjective high and intoxication), positive affect, will be measured using self-report surveys administered prior to scanning and again after the scan (Table 1).

MRI Acquisition: We will use a 3T Siemens Magnetom Prisma scanner and a 32-channel phased array head coil. RSFC (T_2*-weighted): One T_2*- weighted echo-planar imaging (EPI) functional run will be acquired. Each run will utilize real-time motion tracking, Framewise Integrated Real-time MRI Monitoring (FIRMM), to ensure at least 40 min of motion-free data per run is collected for analysis (Dosenbach et al., 2017). High-resolution anatomical (T_1-weighted [T_{1w}]): One magnetically prepared rapid acquisition gradient echo (MPRAGE) will be acquired for co-registration with functional images and statistical overlay. The collection of 40 min of high quality fcMRI data will ensure substantial increase in SNR of the connectivity signal and allow for the evaluation single subject changes (Laumann et al., 2015;Gordon et al., 2017).

Instrument	Measures
Visual Analog Scale for mood (VAS-today)	Methamphetamine effects
Visual Analog Scale for craving (VAS-crave)	Drug liking
Addiction Research Center Inventory (ARCI)	Drug effects
Global Rating of Stimulation (GRS)	Stimulation
Profile of Mood States (POMS)	Active mood states
Profile of Mood States-Bi Elevation (POMS-E)	Active mood states
Rapid Visual Information Processing Task (RVIPT)	Sustained attention
Digit Symbol Substitution Task (DSST)	Psychomotor speed; sustained attention
Controlled Oral Word Association Test (COWAT)	Verbal fluency

Table 1: Rating scales and instruments.

fMRI Standard Preprocessing: RSFC data will be corrected for B_0 inhomogeneity distortion, gradient nonlinearity distortion, head motion, and registration to pre-processed structural volumes. Gradient nonlinearity distortions will be corrected using scanner-specific field maps. Images will be preprocessed using FSL and software developed in-house by the Fair Laboratory. The motion censoring technique described recently by Power and colleagues, and used by Co-I Fair and colleagues, will greatly reduce the residual effect of head motion on observed time courses. fMRI time courses will be sampled to the cortical surface mesh, using the extent of overlap with the cortical ribbon as a weighting factor to account for partial volume effects to enable cortical surface-based analyses.

RSFC time courses will also be normalized and detrended, and signals correlated with motion, mean white matter, mean ventricle and mean brain, along with their temporal derivatives, will be removed through linear regression. Motion regression will include 6 parameter displacement time courses plus their derivatives and squares; only frames where displacement is below standard cutoffs will be included in the regression. Post-regression time courses will be band-pass filtered between 0.009 and 0.08 Hz. Signal from ventricular regions and from white matter will be removed from the data through linear regression estimations.

Specific Outcome Measures and Hypotheses: We will use a mixed effects model with one between-subjects variable (genotype) to investigate outcome variables. Precision brain mapping (Gordon et al., 2017) allows these analyses to occur between subjects with excellent power. **SA 1** and **Hy 1** predicts a significant effect of genotype on baseline intrastriatal connectivity and craving. Subsequent analyses can be conducted in several ways based on these data. We will use both a hypothesis driven seed region approach based on *a priori* region of interests (ROIs) of the VS, midbrain, dorsolateral prefrontal cortex, and ventromedial prefrontal cortex and a data driven approach based on a fcMRI correlation matrix. Bivariate correlations between the average BOLD signals from these regions will provide connectivity estimates. In addition to our planned seed-based comparisons, we will secondarily investigate whole brain connectivity with pair-wise correlations between each ROI within the several sets of functionally-defined parcellations and subcortical ROIs, forming correlation matrices. We use ROIs from the highly cited and utilized Gordon Parcellation (Schaefer et al., 2017;Gordon et al., 2016), a set of 333 ROIs supplemented by a set of 19 subcortical regions defined by FreeSurfer (Fischl, 2012) during pre-processing. Correlations will be Fisher's Z transformed to correct for non-normality and to allow averaging across groups. Sub-matrices will be derived using InfoMap and sub-graphs identified with known cerebral networks (Fortunato and Hric, 2016;Rosvall and Bergstrom, 2008). Correlation matrices will provide access to specific circuits within individuals and will be utilized to describe and provide specific pre-defined network strengths and characteristics (e.g. default-mode, fronto-parietal, dorsal attention and salience attribution), as well as topological properties for each individual and genotype group. Statistical analysis for these effects are modeled after Feczko et al. (2017) and Eggebrecht et al. (2017) and are detailed in *4.4 Statistical Design and Power*. Such an approach allows us to consider individual differences in the functional neuroanatomy, as well as investigate genotype-MA interactions. Topological measures include: connection density and strength, network segregation, global efficiency, rich club coefficients, and global segregation; "hub" measurements will include hub degree, strength, within module z-score, and participation coefficient. **SA 2** and **Hy 2** predicts a significant genotype x acute drug administration interaction, specifically that acute MA administration will have a blunted effect in the CV group. For **Hy 2** and **Hy 3** our primary analytic model

will again be a linear mixed effects analysis, with two within-subjects factors (scan day and drug) with either RSFC or behavioral measures included as dependent variables and main effects of genotype and their interaction as primary predictors. Post-hoc analyses will be used as necessary to examine effects for individual outcomes and to estimate allelic frequency associations as well as sex by genotype interactions. **HY 3** would be confirmed by finding a blunted effect of MA administration on reports of euphoria and craving and on effects on attention and cognitive control in the CV group.
Interpretation of Results: Higher RSFC in CV vs. WT would be consistent with our hypothesis that neuroadaptations to *chronic* MA use interact with genotype to differentially alter striatal connectivity. A blunted effect of *acute* MA on RSFC in CV vs. WT groups would be consistent with our hypothesis that the CV, v288v, is associated with increased TAAR1 signaling that diminishes the corticostriatal effects of MA. The lack of group differences would suggest that genotype does not moderate the MA effects and opposing results may indicate compensatory mechanisms in those with the *htaar1* variant.

Risks to Subjects
All study data derived from subject procedures (including tasks, rating scales, screening interview questionnaires and MRI scan) are obtained specifically for research purposes and not for treatment. Urine and blood specimens will be analyzed by the VA lab and destroyed according to protocol. UAs will be obtained and analyzed by the research team or the VA lab and will be destroyed according to protocol. Two cheek swabs will be taken, the first will be analyzed for genotype and then destroyed. The second will be taken during Visit 2 and banked for future research. MRI scans are obtained at the Advanced Imaging Research Center at OHSU and stored on a disk partition specific to this study and only accessible by study staff. The imaging data are downloaded to image analysis workstations located in the Hoffman Lab at the VA and raw images are archived on a dedicated server at the OHSU Advanced Computing Center (ACC). Coded data may be processed temporarily on additional OHSU servers in the future.

Risks of Questionnaires, Computer Tasks and Cognitive/Neuropsychological Testing: Participants may become upset or frustrated while answering personal questions during the interview or during administration of the neuropsychological tests

Risks of MRI: Subjects who are claustrophobic may become frightened in the MRI machine. Subjects with metal fragments, wire sutures, staples, implanted pacemakers or defibrillators or metal fragments from welding or shrapnel from combat are at risk from damage due to movement or heating of metal fragments in the 3T magnetic field. Participants will be systematically assessed for ferromagnetic metallic foreign bodies and excluded if there is any doubt. Rarely, subjects experience vertigo, a metallic taste or muscle stimulation. Although none are currently known, there may be unknown risks to fetuses in from the MRI procedure and so pregnant women are excluded.

Risks of Methamphetamine Administration: MA has a high potential for abuse and dependence with continual use. Hypersensitivity reactions are known and include angioedema and anaphylactic reactions. Sudden death, stroke, and heart attack have been reported with use of high doses of methamphetamine and other stimulants. According to FDA-approved Desoxyn® labeling, adverse events include: elevation of blood pressure, tachycardia and palpitation, psychotic episodes, dizziness, dysphoria, overstimulation, euphoria, insomnia, tremor, restlessness, headache, exacerbation of motor and phonic tics and Tourette's syndrome, diarrhea, constipation, dry mouth, unpleasant taste, gastrointestinal disturbances, urticarial, impotence and changes in libido, frequent or prolonged erections, rhabdomyolysis, suppression of growth in children, and alopecia. Stimulants can cause teratogenic and embryocidal effects during pregnancy and amphetamines can be excreted in human milk. Our subjects typically self-administer much higher doses of MA than are used in this study.

NIDA guidelines for administering abusable substances to individuals currently addicted to drugs:
1) A serious and concerted effort be made to link these individuals to drug abuse treatment. We will engage participants (all of whom will be current MA users and meet criteria for MUD) in education about MA addiction and we will offer referral to VA or community treatment at each visit.
2) Inclusion of medical examination and screening to assure the absence of any medical or mental condition for which further drug exposure would be contraindicated. This examination will be performed at the initial visit and subjects will be excluded for co-morbid medical or psychiatric conditions that contraindicate low doses of MA.
3) A thorough assessment of the risks entailed if participants are to be exposed to higher doses, rate of

administration, and/or new route of administration than they would normally encounter by their own choice in their usual circumstance. Subjects recruited for this study typically self-administer up to 500 mg MA orally, intravenously, by smoking or insufflation. The low oral dose of MA used in this study is considerably less than subjects routinely self-administer.

Risks to Confidentiality: There are risks to confidentiality, particularly sensitive information about genetics, medical history and drug use. Breaches in confidentiality may result in loss of privacy and could result in monetary loss due to identity theft. It could also carry other risks, such as embarrassment or affect current or future job status, relations with your family, immigration status, parental right or responsibilities or status in the community. Banking specimens and data in a biorepository and sharing data with the University of Minnesota slightly increases the risk of a breach of confidentiality.

Risks of X-Ray: If there is a chance that subjects have metal fragments lodged in their eyes or face, we will perform an orbital x-ray to check. Risks include exposure to radiation of about 40 mrems. No increased risk has been scientifically demonstrated from this level of exposure, though a very small increase in cancer risk may exist.

Risks of Specimen Collection: Blood drawing may cause pain or bruising at the site and carries a small risk of infection. There is also a risk of fainting during or after a blood draw.

Adequacy of Protection against Risks

A clinician will be available to consult with any participants who experience discomfort for any reason during the study visit. Subjects will be asked to remain in laboratory either until the problem has been resolved or immediate referral to appropriate treatment is accomplished. Subjects not in need of emergent treatment will be offered referral to counseling or other support resources as appropriate. The subject may request termination of the assessments at any time. Subjects may refuse any single non-critical procedure in the study if it makes them uncomfortable without disqualification from the rest of the study.

Protection of Risks of Questionnaires, Computer Tasks and Cognitive Testing: Subjects or study staff will terminate questioning or task performance at any time that the subject becomes upset or overly frustrated and does not wish to continue.

Protection of Risks of MRI: Subjects are interviewed extensively to screen for any contraindication to MRI, e.g., surgical aneurysm clips, pacemaker, prosthetic heart valve, neuro-stimulator, implanted pumps, cochlear implants, metal rods, plates or screws, previous surgery, hearing aids, history of welding, metal shrapnel or tattoos with ferro-magnetic particles. If there is any doubt, the subject will be excluded. The research team will obtain orbital x-rays if subjects have any history of welding, grinding or other exposure to metallic particles that could lodge in the eye. Pregnant women (negative urine pregnancy test required before the scan), because of the unknown risk to the fetus, will also be excluded. Participants will be taken to a mock MRI prior to the procedure if they are concerned about claustrophobia. If a subject becomes frightened during the procedure it can be terminated immediately.

Protection of Risks of Methamphetamine Administration: The study team will thoroughly screen potential participants for medications and conditions which would contraindicate use of stimulants. This will include a medical history, family medical history and a brief physical performed by a study physician. Women will be screened for pregnancy at the beginning of each visit and will be removed from the study if found to be pregnant. After the administration of MA, subjects will be continuously monitored for blood pressure and heart rate changes by research staff and during the MRI. Participants will complete a safety questionnaire before they can leave the lab after MA administration and will not be allowed to drive on study visits where MA may be administered.

Protection of Risks to Confidentiality: Study data will be coded and kept separately from any HIPAA Identifiers. Paperwork will be kept in locked cabinets in a locked office at the Portland VA. Digital data, including the spreadsheet linking the subject ID to personally identifiable information, will be kept behind password protected applications and spreadsheets. Data and specimens in the biorepository will not be linked to any personally identifiable data and the code linking spreadsheet will be encrypted once the original study is completed.

Protection of Risks of X-Ray: Only subjects suspected of having a foreign body in their eyes or face will

undergo this procedure. The images will be obtained at the VA clinical imaging center and will be performed by clinical x-ray staff and read by a radiologist.

Protection of Risks of Specimen Collection: Blood will be collected by trained VA phlebotomists to ensure the highest level of safety for subjects.

Potential Benefits of the Proposed Research to Research Participants and Others
This project is not intended to benefit individual subjects but results may help us understand the neurobiology of methamphetamine addiction and potentially help us evaluate future pharmacological treatment approaches for addicted individuals in the future.

Importance of the Knowledge to be Gained
The results of this project will be valuable for understanding genotypic modulation of how addicted individuals respond to MA and informing our understanding of by establishing biomarkers useful in predicting and evaluating treatment response. A predictive model will help individualize relapse risk through a better understanding of neurobiological factors that influence addiction, craving and cognition.

Participation of Non-Veterans
This is an ambitious study and requires recruitment of subjects who are currently experiencing methamphetamine addiction. There are also significant gender effects which necessitate have a gender balanced sample. We will, therefore, need to recruit non-veterans to meet our ambitious recruitment goals and to recruit sufficient numbers of women. Non-veterans may be recruited using flyers posted at OHSU, the Portland VA, local retailers, college campuses, and businesses where social service assistance is provided. Additionally, advertisement will occur on OHSU's Study Participation Opportunities web page, and Craigslist. The Craigslist ad will include a phone number for potential subjects to call and the email response option will be turned off during the generation of the ad. VHA Notice of Privacy Practices (NOPP) us provided to non-veterans and an NOPP acknowledgement is signed.

Data and Safety Monitoring Plans
Data Security and Privacy: Data will be stored in a manner intended to preserve patient confidentiality. Hard-copy PHI will be stored in locked cabinets in the PIs VA office and laboratory space. Electronic PHI will be stored only on servers behind the VA firewall accessed by password-protected VA computers. Any email contact with subjects will occur through Azure secure email. Each subject is given a unique identifier (UI) based on a random number and study identifier. Only coded or de-identified data, not PHI, are used for analysis. The file linking the UI to the patient's name will be stored in a separate password-protected file on a secure server behind the VA firewall. Once the study has ended, the link will be stored by the VA R&D office (or destroyed if regulations change). We expect this study to be funded by the National Institute of Drug Abuse (NIDA). This funding will provide the study with an automatic certificate of confidentiality. Basic information about participation in the study, study procedures and x-ray results will be entered into the subject's VHA medical record.

The primary repository for de-identified data and neuroimages will be stored on a password-protected network drive at the OHSU Advanced Computing Center, to which only the research team has access. Coded data will also be stored on OHSU's REDCap application, a highly secure and robust web-based research data collection and management system. No identifiable information will be entered into this application at any time. The statisticians will not have access to the code or PHI at any time. The spreadsheet linking the code to the subject will remain behind the VA firewall at VAPORHCS.

Data being sent to Minnesota will be sent and returned via secure Box folder accessible only to approved study staff or by encrypted VA email. Data will be stored at the University of Minnesota (UMN) via the Minnesota Supercomputing Institute (MSI)'s high performance storage, "Tier 1" system. Tier 1 storage is connected to two HPC servers only accessible through UMN's private network. Data will be stored and only accessible on Dr. Anita Randolph's personal share and only users granted permission by Dr. Randolph will be able to access the data. Data access is further restricted through the UMN's campus; permitted users would need to login to the UMN network in order to access the data. Permitted users outside the UMN campus may be able to access the data by logging into UMN's virtual private network (VPN). Both forms of access require a) a login and password, and b) two-factor authentication via Duo. Data will be returned to the Portland VA and OHSU after it is analyzed at UMN.

Clincard (by greenphire) will be used to pay subjects for each study visit which may require inputting subject's name, address, SSN, and DOB. This a secure website that is approved by OHSU/VA as a form of

payment.

MRI images are collected at the Advanced Imaging Research Center (AIRC) at OHSU. No PHI is used to identify subjects and only the subject's coded ID is entered at the time of the scan. Images are archived on a separate partition on the AIRC PACS server to which only Hoffman Lab research computers and the AIRC IT specialist have access. The raw data for each MRI scan is downloaded to Hoffman Lab Linux workstations at the VA. These workstations are, by necessity, hooked up to the OHSU network, but can be accessed only by Hoffman Lab personnel. Image analysis takes place on these workstations in VA space.

At the end of the study, the AIRC will scrub the partition containing archives and remove the partition, so that the data are permanently erased from the AIRC. The Hoffman Lab will archive the raw image files in the already established MARC server and bank imaging in the MARC biorepository.

Records will be maintained according to the VA research retention schedule.

Blood and Data Banking

Serum, leukocytes (from whole blood samples) and a buccal swab will be obtained (via separate permission on the HIPAA and ICF), linked to study data for coded storage in the MARC Translational Service Core Biorepository (Jennifer Loftis, PhD, Administrator). No PHI will be stored in the data repository.

Banked contact information

Subjects will be asked to have the following information collected for a contact repository: contact information, date of birth, gender, Veteran status, smoking status, substance use information, mental health status and previous participation in a Hoffman lab research study. This will be used to contact subjects who may be eligible for future studies with the Hoffman lab. Subjects will sign an addendum to the VA ICF if they consent to having their information stored for future contact, which is optional. Information will be contributed to the Hoffman Lab Contact Information Data Repository (mIRB 4512, William Hoffman, MD, PhD Administrator).

Oversight

IRB-approved study staff will ensure that any protocol deviations or adverse event will be reported immediately to the PI, who will examine the patient and determine if any additional evaluation or treatment is needed. The PI will ensure that significant adverse events are properly reported to the IRB (within 5 days to comply with VA policy). The Hoffman Lab will examine all cumulative adverse events semi-annually to determine if there are any systematic problems. OHSU's IRB3 will oversee the study and will be the sole source for study documentation and approval.

Inclusion/Vulnerable Populations

Women and Minorities: Given that gender effects may be prominent in this population, it is important that the ratio of male/female subjects approach 50/50. We will recruit outside of the VA SATP to ensure that women are represented equally with men, in alcohol detox and treatment centers in the Portland area. Minority subjects will be recruited to be a representative cross section of the Portland, Oregon population. That population is primarily Caucasian 82.4%, with 7% African-American, 7%, Asian, 1.8% Native Hawaiian or Other Pacific Islander, and 1.8% Native American. Additionally, the population will be primarily non-Hispanic 93%, with 7% Hispanic.

Children: Children will be excluded from this study.

Prisoners: No prisoners will be included. If subjects are incarcerated during their enrollment, they will be dropped from the study. Potential subjects will not be in any formal treatment program.

Decisionally-Impaired: Methamphetamine-addicted individuals do not typically exhibit cognitive deficits that interfere with capacity. Acute intoxication or psychosis could potentially impair decision making. Subjects will not be recruited if they are acutely intoxicated. Symptoms of psychosis are common in MUD, but do not per se interfere with decision making. Subjects who score high on the MINI psychosis scale will be evaluated by Dr. Hoffman or Dr. Huckans to ensure that they can explain the purpose of the study, the risks and benefits to others after having the study explained. The MARC has recruited actively using MUD subjects in the past and did not exclude any for lack of capacity. Note that the dose of MA administered (max 30 mg) is much less that active users typically take (100 to over 500 mg per day) and is not expected to cause significant intoxication.

Economically Disadvantaged: Study compensation is in line with that used in previous investigations recruiting active users and the amount should not be coercive to individuals experiencing economic hardship. Compensation will be provided in the form of prepaid debit cards instead of cash both to minimize possible coercion and to discourage immediate use of the stipend to obtain illicit drugs.

Determining VA from Non-VA Research

This study will take place both at the Portland VA and at OHSU. VA Research will include consent, screening, questionnaires, blood draws, EKG, urinalyses, x-rays, computer task training, cheek swabs, medication dispensing and administration, and data analysis. Non-VA Research will be the MRI scans acquired at OHSU's AIRC, advertising, and data analysis.

Preliminary Studies

PS1: MUD group with TAAR1 CV Report Increased Craving: Individuals were enrolled into one of five groups: 1) CS group (n = 31): no lifetime history of dependence on any substance other than nicotine or caffeine; 2) MA-active (MA-ACT) group (n = 13): actively using MA and meeting criteria for MA dependence; 3) MA-remission (MA-REM) group (n = 19): early remission from MUD (≥ 1 month and ≤ 6 months); 4) Active polysubstance dependence (POLY-ACT) group (n = 11): actively using MA and meeting criteria for MA dependence and using at least one other substance (other than caffeine or nicotine); and 5) polysubstance remission (POLY-REM) group (n = 32): early remission from MUD (abstinence ≥ 1 month and ≤ 6 months) and at least one other substance (other than caffeine or nicotine).

Subjects were rated on the PHQ9 (depression), GAD7 (anxiety), FSS (fatigue), BPI severity and intensity (pain), PRMQ (memory), a sleep disturbance scale (P57) and three visual analog scales (VAS) of craving for MA, alcohol or any other drug. Four components from a principal components analysis, which accounted for 80% of the variance, were varimax rotated (**Error! Reference source not found.**). A general linear model (GLM) was calculated with the factor scores as dependent variables and diagnostic group, TAAR1 (WT, at least one CV), a genotype by group interaction term and age, education and sex as covariates. The overall GLM had a significant F with largest effect for Craving. For PC3 (craving response), there was a significant [X^2(4df) = 15.82, p = 0.003] interaction involving TAAR1 and study group. CS showed no association between PC3 and TAAR1 (fold change = 0.99, p = 0.94), while the adjusted mean PC3 for MA-ACT and MA-REM groups, with at least one copy of the CV, was estimated to be, 1.55 (95% CI: 1.03 - 2.35; p = 0.036) and 1.77 (95% CI: 0.95 - 3.27; p = 0.071) times the mean response, respectively, for those without the CV. The POLY-REM group evidenced a similar, but non-significant trend; the adjusted mean PC3 for the CV group was estimated to be 1.34 (95% CI: 0.90 - 2.01; p = 0.152) times the adjusted mean response for the WT group. In the POLY-ACT group, the direction reversed, such that the adjusted mean response for the CV group was lower than that of the WT group (95% CI: 0.41 - 0.91; p = 0.016); however, the POLY-ACT group was limited to only three participants without the CV (Figure 2,**Error! Reference source not found.**).

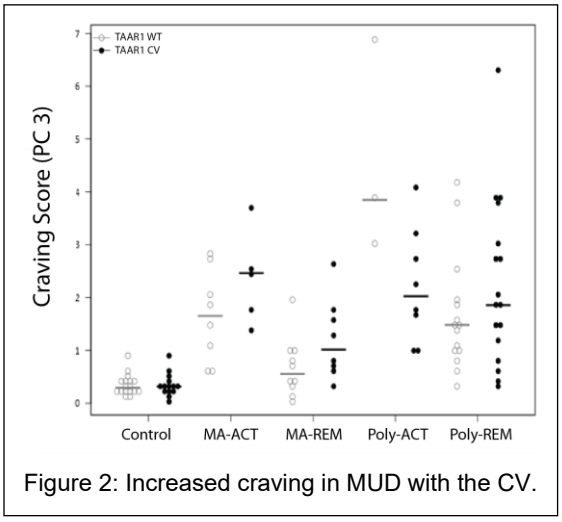

Figure 2: Increased craving in MUD with the CV.

Further analysis revealed that the TAAR1 genotype effects in the MA-ACT and MA-REM groups (i.e., 1.55- and 1.77-fold increases) did not differ significantly [X^2 (1df) = 0.11, p = 0.75], implying a shared underlying effect on craving for those with MUD. Having at least one copy of the TAAR1 CV SNP was associated with a 1.68 (95% CI: 1.14 - 2.47, p = 0.009) fold increase in the adjusted mean craving response as characterized by PC3. Thus, MUD participants with the CV reported higher craving than WT participants.

PS2: TAAR1 genotype modulates RSFC in CS and MUD: Samples from the MARC Data Repository were examined under an IRB approved protocol. The *htaar1* gene was sequenced in 24 CS (15 WT and 9 CV) and 26 MUD subjects in remission (13 WT and 13 CV) by the Core Laboratory at OHSU. The reported allelic frequency of the synonymous v288v SNP in the general population is 22% (Lek et al., 2016) and, in our sample, 24%. There was no difference in the distribution of v288v genotypes between MUD and CS. Homozygotes for the CV (n=4) were combined with heterozygotes for comparison to the WT group.

RSFC scans were processed with FSL (Smith et al., 2004) using a variation on the methods in Kohno et al. (2017). We hypothesized that effects of TAAR1 genotype would be most robust in striatum. Thus, we examined RSFC between a ventral striatum (VS) seed and dorsal striatum (DS), midbrain, insula, anterior cingulate and dorsolateral prefrontal cortex and found a significant main effect of group ($p = 0.018$) and a group by genotype interaction ($p < 0.005$) with the regions in Figure 3.

PS3: Effect of CV v288v SNP on expression of TAAR1 receptor *in vitro*: Chinese Hamster Ovary cells in culture were transfected with equal doses of either WT or CV cDNA tagged with Venus (a yellow fluorescing variant of green fluorescent protein). Figure 5 indicate more *protein* expression for the CV by the Venus light intensity. The Venus tag is part of the protein molecule and co-expressed with the TAAR1 receptor. Note that at all post transfection time points, the CV protein was expressed at higher levels than the WT protein. Finally, cAMP production (Figure 5D) was higher in the CV transfected cells compared to WT transfected cells in response to beta phenethylamine, but EC50s were similar. So, it is likely that expression but not protein structure was altered by the polymorphism. The Janowsky lab used TAAR1 specific antibodies to further confirm protein expression, but available antibodies lack sensitivity and specificity. Whether the CV genotype has any effect on expression in the brain is not known. It is possible, however, that the CV, through effects on mRNA splicing, structure or rate of translation, results in altered levels of the TAAR1 receptor *in vivo* (Sauna and Kimchi-Sarfaty, 2011;Hunt et al., 2014). *We assume, in our predictive model* (Figure 1*) that the CV genotype is associated with increased TAAR1 expression in the human brain.* This assumption leads to testable **Hypotheses (Hy) 1-3.**

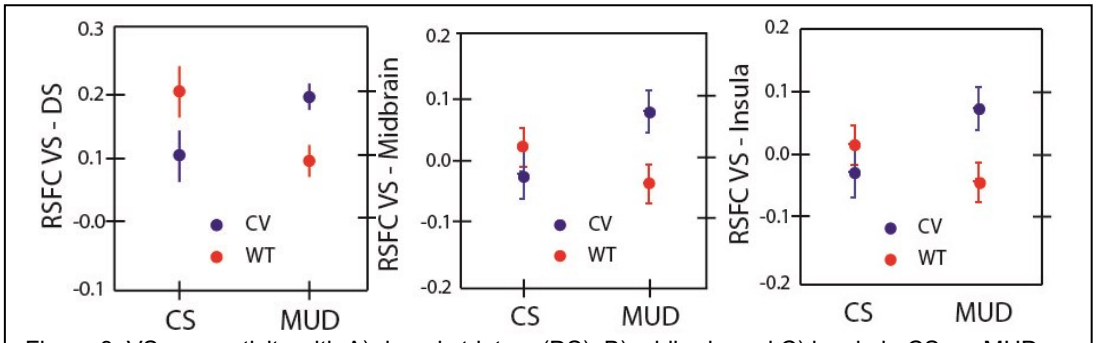

Figure 3: VS connectivity with A) dorsal striatum (DS), B) midbrain and C) insula in CS vs. MUD.

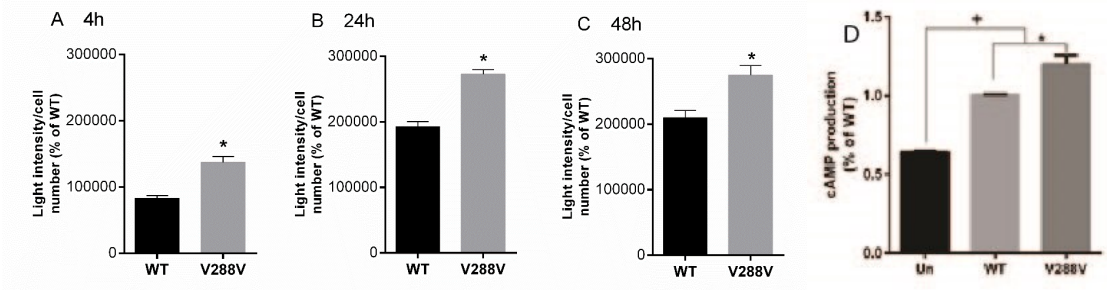

Figure 5: Fluorescent VENUS tagged- WT or -v288v hTAAR1 were transiently transfected into cells. Cells were collected and counted at 4, 24 and 48 hours post transfection. Fluorescence intensity was measured using a PerkinElmer Victor X light fluorescence plate reader. Light intensity was normalized to cell number of each condition (expressed as % WT) to correct for cell growth at different time points. Bar heights are mean ±SEM, * *P<0.01*. Shi and Janowsky (2017), private communication.

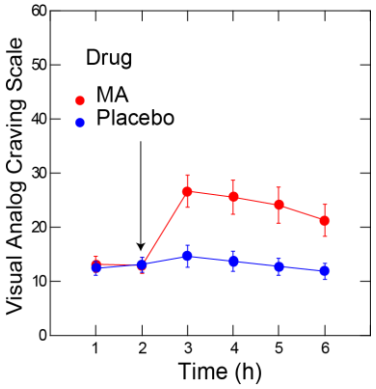

Figure 4: Normal CS respond with robust reports of craving over a several hour time window when given MA compared to placebo.

PS4: Administration of oral MA: We performed this study to develop methods for safely administering MA and monitoring behavioral responses. Twelve healthy CS (8 women and 4 men; mean age 31 y), who had previous experience with stimulants but did not regularly use stimulants recreationally or by prescription were enrolled. None met criteria for any substance use disorder, including nicotine use disorder. The subjects were familiarized with the procedure, given a test dose of 20 mg oral S-methamphetamine (Desoxyn®, Lundbeck) and monitored for 6 hours after the dose. They returned on four more occasions when they were given either MA or a placebo 2 hours after baseline self-report and cognitive testing. All subjects tolerated the procedure without subjective or objective (pulse, heart rate) measures of distress. We show results from the VAS for craving, a self-report inventory (Figure 4). This protocol showed that MA can be safely administered in a controlled setting. The time for peak subjective effects is

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