Supplementary Information

**Genotyping:**

*National Institute on Alcohol Abuse and Alcoholism (NIAAA) Participants***:** Genomic DNAs were isolated from human whole blood using Maxwell® 16 DNA purification kit (Promega). The SNP of rs3796863 (T/G) was genotyped using the assay-on-demand (assay ID: C\_8950074\_1) from Applied Biosystems (Foster City, CA, USA). The assay contained a pair of primers and a pair of fluorescent quenched probes (one for allele T; one for allele G) designed by Applied Biosystems with no sequence information. Primers and probes were mixed with TaqMan® Universal PCR Master Mix (Applied Biosystems). 4.5 μl of genomic DNA (2.5 ng/μl) was transferred in triplicate to a 384-well plate, each well of which contained 5.5 µl PCR mixtures. The PCR reaction was performed following a protocol provided by ABI. The allele was discriminated by post-PCR plate read on an ABI PRISM® 7900HT Sequence Detector System (Applied Biosystems). Data were processed using SDS 2.1 software (Applied Biosystems). Participants were grouped into two genotypes for the rs3796863 polymorphism. T allele carriers (TT and TG) were pooled into one group (i.e., TX) and compared to GG homozygotes.

*Duke Neurogenetics Study (DNS) Participants***:** DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress or HumanOmniExpress-24 (1-4). Non-Hispanic European ancestry was determined by self-report and confirmed by ancestry informative principal components (no individuals were ± 6 SDs from the mean on the top 10 components).

**Intravenous Alcohol Self-Administration (IV-ASA) Study:** Individuals first pressed a button 4 times to receive 4 priming increments of IV-alcohol, designed to bring the breath alcohol concentration (BrAC) to 0.03 g/dL, and to provide participants with an opportunity to experience the effects of IV alcohol. After a 15-minute break, the Computerized Alcohol Infusion System (CAIS) system notified the participant of the start of the “free-access” phase of the IV-ASA session by displaying a prompt (“the bar is open”) on a computer screen. During this phase, for each button press, individuals would receive one infusion (increase of 0.075 g/dL). A participant could not receive an additional infusion if they were (a) currently receiving an infusion or (b) another infusion would put them above the 0.10 g/dL BrAC safety limit.

**Positron Emission Tomography (PET) Raclopride Study:** PET Analysis was based on a region of interest (ROI) methodology in the primary areas of post-synaptic dopamine release, namely the anterior ventral striatum, posterior ventral striatum, caudate, and putamen (5). The PET data from the placebo session was used as a measure of baseline [11C]-raclopride binding potential, using the simplified reference tissue model (6). Percent change in binding potential (%ΔBP) following alcohol was calculated as $\%ΔBP=(BPplacebo-BPalcohol)/(BPplacebo)$. Reduction in [11C]-raclopride binding is attributed to competition with dopamine endogenously released by the alcohol challenge, and the percent change in binding potential has been shown to be proportional to the magnitude of dopamine release (7). (For further details on analysis, see supplementary materials in (5)).

**Ventral Striatum (VS) Reactivity BOLD fMRI Study:**

***BOLD fMRI Paradigm:*** Participants completed a blocked-design, number-guessing paradigm, consisting of a pseudorandom presentation of three blocks each of predominantly positive (80% correct guess) or negative (20% correct guess) feedback, interleaved with three control blocks. There were five trials in three seconds to guess, via button press, whether the value of a visually presented card was lower or higher than five (index and middle finger, respectively). The numerical value of the card was then presented for 500 milliseconds and followed by appropriate feedback (green upward-facing arrow for positive feedback; red downward-facing arrow for negative feedback), for an additional 500 milliseconds. A crosshair was then presented for three seconds, for a total trial length of 7 seconds. During control blocks, participants were instructed to simply make button presses during the presentation of an "x" (3 seconds), which was followed by an asterisk (500 milliseconds) and a yellow circle (500 milliseconds). Each block was preceded by an instruction of "Guess Number" (positive or negative feedback blocks) or "Press Button" (control blocks) for 2 seconds, resulting in a total block length of 38 seconds and a total task length of 342 seconds. Participants were unaware of the fixed outcome probabilities associated with each block and were led to believe that their performance would determine a net monetary gain at the end of the scanning session. Instead, all participants received $10. We included one incongruent trial within each task block (e.g., one of five trials during positive feedback blocks was incorrect resulting in negative feedback), to prevent participants from anticipating the feedback for each trial and to maintain participants' engagement and motivation to perform well.

***MRI Data Acquisition:*** Each participant was scanned using a research-dedicated GE MR750 3 T scanner equipped with high-power, high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1MHz at the Duke-UNC Brain Imaging and Analysis Center. A semi-automated, high-order shimming program was used to ensure global field homogeneity. A series of 34 interleaved axial functional slices aligned with the anterior commissure-posterior commissure plane were acquired for full-brain coverage using an inverse-spiral pulse sequence to reduce susceptibility artifacts (TR/TE/flip angle = 2000 ms/30 ms/60°; FOV = 240 mm; 3.75×3.75×4 mm voxels; interslice skip = 0). Four initial radiofrequency excitations were performed (and discarded) to achieve steady-state equilibrium. To allow for spatial registration of each participant's data to a standard coordinate system, high-resolution three-dimensional structural images were acquired in 34 axial slices coplanar with the functional scans (TR/TE/flip angle = 7.7 s/3.0 ms/12°; voxel size =0 .9×0.9×4 mm; FOV = 240 mm, interslice skip = 0).

***BOLD fMRI Data Pre-Processing****:* Pre-processing was conducted using SPM12 (www.fil.ion.ucl.ac.uk/spm). Images for each subject were realigned to the first volume in the time series to correct for head motion, spatially normalized into a standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model (final resolution of functional images = 2 mm isotropic voxels), and smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter, set at 6 mm full-width at half-maximum. Voxel-wise signal intensities were ratio normalized to the whole-brain global mean. Variability in single-subject whole-brain functional volumes was determined using the Artifact Recognition Toolbox (http://www.nitrc.org/projects/artifact\_detect). Individual whole-brain BOLD fMRI volumes meeting at least one of two criteria were assigned a lower weight in determination of task-specific effects: (1) significant mean-volume signal intensity variation (i.e., within volume mean signal greater or less than 4 SD of mean signal of all volumes in time series) and (2) individual volumes where scan-to-scan movement exceeded 2 mm translation or 2° rotation in any direction.

***fMRI Quality Assurance Criteria:*** Quality control criteria for inclusion of a participant's imaging data were: < 5% volumes exceed artifact detection criteria for motion or signal intensity outliers and ≥ 90% coverage of signal within 5 mm bilateral ventral striatum spheres centered at (± 12, 10, -10). Additionally, data were only included in further analyses if the participant demonstrated sufficient engagement with the task, defined as responding to and receiving positive or negative feedback on at least 60% of trials within win and loss blocks, respectively. See **Table S2**. These data were coded as missing and included in FIML analyses, but excluded from listwise deletion analyses.

***BOLD fMRI Data Analysis:*** The general linear model of Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm) was used to conduct fMRI data analyses. Following pre-processing, linear contrasts employing canonical hemodynamic response functions were used to estimate differential effects of feedback (i.e., reward) from the contrast of Positive Feedback > Negative Feedback and Positive Feedback > Control for each individual (p<0.05 family-wise error rate (FWE); Ke=10) within a bilateral ROI based on prior studies (MNI coordinates: ±12 12 -10) (3, 8, 9). Individual contrast images were then used in second-level random effects models to conduct group-level analyses. Parameter estimates were extracted from lusters, corresponding to the left and right VS for each contrast (Positive Feedback > Negative Feedback: Left: cluster size = 289, max voxel MNI coordinates: -12 8 -8; Right: cluster size = 289, max voxel MNI coordinates: -12 8 -8; Positive Feedback > Control: Left: cluster size = 223, max voxel MNI coordinates: -12 -12 0; Right: cluster size = 186, max voxel MNI coordinates: 14 14 -2, all ps < 0.05 FWE) which were averaged for each contrast and then used for all statistical analyses. Extracting parameter estimates, rather than voxels correlated with the primary variables of interest, minimizes the possibility of regression coefficient inflation which results from capitalizing on the same data twice (5). A recent neurogenetics study reported that the most powerful technique to reliably detect group differences is to utilize values from the top most activated voxels within an ROI (6). This technique has been extensively used previously (7,8).

**Resting State Functional Connectivity fMRI Study:**

***MRI Data Acquisition:*** Whole-brain anatomical images and five minutes of closed-eye, resting state fMRI were collected using 3T General Electric and 3T Siemens MRI scanners. High resolution T1-weighted, 3-D structural scans were acquired for each subject using an MPRAGE sequence (128 axial slices, TR = 1,200 ms TE = 30 ms, 256 × 256 matrix). Resting-state fMRI datasets were collected using a single-shot gradient echo planar imaging pulse sequence with 36 axial slices acquired parallel to the anterior/posterior commissural line (TR = 2,000 ms, TE = 30 ms, flip angle = 90°, 3.75 mm × 3.75 mm × 3.8 mm voxels).

***Resting State Data Pre-Processing:*** Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) was used to pre-process the resting state data. For each participant, the first three time points were removed to account for the pre-steady state BOLD signal. Next, spikes in the voxel-time series were truncated and the time-series was interpolated to correct for non-simultaneous slice acquisition (using sinc interpolation). The data were then corrected for head-motion and spatially smoothed with a Gaussian kernel (FWHM = 4 mm). To further correct for motion, 3D motion data and its derivatives were regressed out of the time series. We then applied band-pass temporal filtering (0.01-0.10 Hz) on the residual time signals. Finally, we used ANATICOR(AFNI) to regress out signal from locally averaged white matter. Pre-processed time series data were then prepared for functional connectivity analysis using 3dSetupGroupInCorr.

**Voltammetry Studies with *Cd38*KO Mice Study:**

***In Vitro Voltammetry Recording:*** Mouse brains were sliced using a vibratome (Leica) in an ice cold cutting solution containing (in mM) 225 sucrose, 13.9 NaCl, 26.2 NaHCO3, 1 NaH2PO4, 1.25 glucose, 2.5 KCl, 0.1 CaCl2, 4.9 MgCl2, and 3 kynurenic acid. Sagittal slices (240 μm) were recovered in artificial cerebral spinal fluid (ACSF; containing, in mM: 124 NaCl, 1 NaH2PO4, 2.5 KCl, 1.3 MgCl2, 2.5 CaCl2, 20 glucose, 26.2 NaHCO3, and 0.4 ascorbic acid) for 20 min at 33°C and maintained in the dark at room temperature before recordings. During recordings, slices were superfused (2 mL/min) with ACSF at 32°C, using an in-line heater (Harvard Apparatus). The nicotinic acetylcholine receptor (nAChR) antagonists, Dihydro-β-erythroidine (DHβE; 1 μM), was also used in the experiments.

***Drugs:*** DHβE was purchased from Tocris and all other chemicals were purchased from Sigma.

***Statistical Analysis:*** Statistical analysis was performed with Prism (GraphPad), using 2-way RM ANOVA. All data were expressed as mean and standard error of the mean (SEM).

# Table S1: DSM-IV-TR Diagnoses in the Duke Neurogenetics Study

|  |  |
| --- | --- |
| DSM-IV Axis I Current or Past Diagnosis | *N* |
| Agoraphobia without history of Panic Disorder | 8 |
| Alcohol Abuse | 35 |
| Alcohol Dependence  | 29 |
| Bipolar I or II | 3 |
| Bipolar NOS (hypomania but no depression) | 13 |
| Bulimia Nervosa | 3 |
| Generalized Anxiety Disorder | 9 |
| Major Depressive Disorder | 24 |
| OCD | 3 |
| Panic Disorder (with or without agoraphobia) | 14 |
| Social Anxiety Disorder | 5 |
| Substance abuse (cannabis)  | 10 |
| Substance dependence (cannabis) | 6 |
| Any Axis-I Psychopathology | 118 |

*Note.* Includes comorbid disorders, whereby some individuals received more than one diagnosis.

NOS = Not otherwise specified, OCD = Obessive Compulsive Disorder

**Table S2: Reasons for Participant Exclusion: Duke Neurogenetics Study**

|  |  |
| --- | --- |
| Reason | *N* |
| Movement outliers in fMRI data | 27 |
| Scanner/equipment malfunction | 4 |
| Inadequate behavioral feedback schedule | 3 |
| Incidental finding | 2 |
| Subjects falling asleep | 1 |
| Missing rs76760690 | 3 |
| Total | 40 |

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