REPLICATION IN IMAGING GENETICS:

THE CASE OF THREAT-RELATED AMYGDALA REACTIVITY

Supplementary Information

Supplementary Methods

Inclusion/Exclusion Criteria of Previous Studies. Because our genetic data is restricted to SNPs, we excluded 37 studies, which tested other types of polymorphisms (e.g., variable number tandem repeats). We also had to exclude 6 studies, which used tasks or contrasts that were not related to threat (e.g., gambling task or sad facial expressions) and were thus incomparable to our fMRI data. Two additional studies were excluded because they were based on clinical samples not well represented in our dataset (i.e., schizophrenia and posttraumatic stress disorder). One study did not find a significant association between 23 tagging-SNPs covering the oxytocin receptor gene and amygdala reactivity (1) and was therefore not included (2 of the 23 SNPs were represented by included studies). As several studies reported on the same SNPs, there were 37 unique associations we attempted to replicate (Table S1).

Inclusion/Exclusion Criteria of Participants. All participants were free of the following study exclusions: 1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Diagnosis of any current DSM-IV Axis I disorder or select Axis II disorders (antisocial personality disorder and borderline personality disorder), assessed with the electronic Mini International Neuropsychiatric Interview (2) and Structured Clinical Interview for the DSM-IV subtests (3), respectively, were not an exclusion criterion, as the Duke Neurogenetics Study seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. However, no

individuals, regardless of diagnosis, were taking any psychoactive medication during or at least 14 days prior to their participation. Of the 1117 participants used in our analyses, 236 individuals had at least one DSM-IV diagnosis, including 121 with alcohol use disorders, 43 with non-alcohol substance use disorders, 64 with major depressive disorders, 32 with bipolar disorders, 24 with panic disorder (no agoraphobia), 21 with panic disorder including agoraphobia, 11 with social anxiety disorder, 20 with generalized anxiety disorder, 13 with obsessive compulsive disorder, 10 with eating disorders, and 2 with posttraumatic stress disorder.

Genotype Imputation. Genotype imputation was performed on all DNS participants with genome-wide chip data using the prephasing/imputation stepwise approach implemented in SHAPEIT/IMPUTE2 (4, 5). Imputation was run separately for participants genotyped on the Illumina HumanOmniExpress (n = 685) and the Illumina HumanOmniExpress-24 (n = 432) arrays using biallelic SNPs only, the default value for effective size of the population (20,000), and chunk sizes of 3 Mb and 5 Mb for the respective arrays. Within each array batch, genotyped SNPs used for imputation were required to have missingness <.02, Hardy-Weinberg equilibrium p > 10-6, and minor allele frequency >.01. The imputation reference set consisted of 2504 phased haplotypes from the full 1000 Genomes Project Phase 3 data set (May 2013, >70 million variants, release "v5a"). Imputed SNPs were retained if they had high imputation quality (Info >.9), low missingness (<5%), and minor allele frequency >.01. A proxy was used if the target SNP was neither directly genotyped nor imputable. Proxy SNPs were found with the "LDproxy" tool in "https://analysistools.nci.nih.gov/LDlink/" based on the "Utah residents from north and west Europe" population. All proxies were in perfect linkage

disequilibrium with the target SNP (D'=1, R2=1), except for rs853180 (D'=.95, R2=.89). Details for the derivation of each target SNP are provided in Table S2. The alleles of six of the original SNPs were C/G or A/T, and therefore the target allele of the proxy was also matched based on frequency.

fMRI Task. The task version used in the DNS consisted of four blocks of a face-processing task interleaved with five blocks of a sensorimotor control task. During task blocks, participants viewed six trios of either fearful, angry, surprised, or neutral faces and matched one of two faces (bottom) identical to a target face (top). Each trial in the face-matching blocks lasted for 4 seconds with a variable interstimulus interval of 2–6 seconds (mean = 4 seconds). In the control blocks, each of six shape trios was presented for 4 seconds with a fixed interstimulus interval of 2 seconds. Each block began with a 2 second instruction screen (i.e., "Match Faces" or "Match Shapes") resulting in a total task time of 390 seconds.

BOLD fMRI Data Acquisition. Each participant was scanned using one of two identical research-dedicated GE MR750 3T 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=240mm; 3.75×3.75×4mm 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 T1-weighted structural images were obtained in 162 axial slices using a 3D Ax FSPGR BRAVO sequence (TR/TE/flip angle = 8.148 ms / 3.22 ms / 12°; voxel size=0.9375x0.9375x1mm; FOV=240mm; interslice skip=0; total scan time = 4 min and 13 s). In addition, high-resolution structural images were acquired in 34 axial slices coplanar with the functional scans and used for spatial registration for participants without Ax FSPGR BRAVO images (TR/TE/flip angle=7.7 s/3.0 ms/12; voxel size=0.9×0.9×4mm; FOV=240mm, interslice skip=0).

BOLD fMRI Data Pre-Processing. Anatomical images for each subject were skull-stripped, intensity-normalized, and nonlinearly warped to a study-specific average template in a standard stereotactic space (Montreal Neurological Institute template) using ANTs (6). BOLD time series for each subject were processed in AFNI (7). Images for each subject were despiked, slice-time-corrected, realigned to the first volume in the time series to correct for head motion, coregistered to the anatomical image using FSL's Boundary Based Registration (8), spatially normalized into MNI space using the non-linear warp from the anatomical image, resampled to 2mm 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. All transformations were concatenated so that a single interpolation was performed. Voxel-wise signal intensities were scaled to yield a time series mean of 100 for each voxel. Volumes exceeding 0.5mm frame-wise displacement or 2.5 standardized DVARS (9, 10) were censored from the GLM.

The AFNI program 3dREMLfit (7) was used to fit a general linear model for first-level fMRI data analyses. Following preprocessing, linear contrasts employing canonical

hemodynamic response functions were used to estimate expression specific effects (e.g., angry expression blocks > control blocks) as well as a general threat effect (i.e., anger and fear expression blocks > control blocks) for each individual. These Individual contrast images were then used in second-level random effects models in SPM12 (http://www.fil.ion.ucl.ac.uk/spm) accounting for scan-to-scan and participant-to-participant variability to determine mean condition-specific regional responses using one-sample t-tests. A statistical threshold of $p<0.05$, family-wise error corrected across our anatomical amygdala regions of interest (defined using a high-resolution templated generated from 168 Human Connectome Project datasets 11) was applied to the contrasts. Specific region of interest (ROI) analyses for the combined Central and Medial Nuclei of the amygdala were also conducted as two of the studies (12, 13) reported associations for this amygdala subregion only.

fMRI Quality Assurance Criteria. Quality control criteria for inclusion of a participant's imaging data were: >5 volumes for each condition of interest retained after censoring for FD and DVARS and sufficient temporal SNR within the bilateral amygdala, defined as greater than 3 standard deviations below the mean of this value across subjects. The amygdala was defined using a high-resolution templated generated from 168 Human Connectome Project datasets (11). Additionally, data were only included in further analyses if the participant demonstrated sufficient engagement with the task, defined as achieving at least 75% accuracy during the face matching condition.

Table S1. Studies reporting on an association between a genetic variation and threat-related amygdala reactivity.

Included/Excluded	Reason for exclusion	Gene	Study
Excluded	Not a SNP	5HTTLPR	Oathes et al., 2015 (14)
Excluded	Not a SNP	5HTTLPR	Shneck et al., 2016 (15)
Excluded	Not a SNP	5HTTLPR	Stoeckel et al., 2015 (16)
Excluded	Not a SNP	5HTTLPR	Bastiaansen et al., 2014 (17)
Excluded	Not a SNP	5HTTLPR	Klumpp et al., 2014 (18)
Excluded	Not a SNP	5HTTLPR	Costafreda et al., 2013 (19)
Excluded	Not a SNP	5HTTLPR	Klucken et al., 2013 (20)
Excluded	Not a SNP	5HTTLPR	O'Nions et al., 2011 (21)
Excluded	Not a SNP	5HTTLPR	Morey et al., 2011 (22)
Excluded	Not a SNP	5HTTLPR	Lonsdorf et al., 2011 (23)
Excluded	Not a SNP	5HTTLPR	Lemogne et al., 2011 (24)
Excluded	Not a SNP	5HTTLPR	Kobiella et al., 2011 (25)
Excluded	Not a SNP	5HTTLPR	Furman et al., 2010 (26)
Excluded	Not a SNP	5HTTLPR	Dannlowski et al., 2010 (27)
Excluded	Not a SNP	5HTTLPR	Gillihan et al., 2011 (28)
Excluded	Not a SNP	5HTTLPR	Lau et al., 2009 (29)
Excluded	Not a SNP	5HTTLPR	Rao et al., 2007 (30)
Excluded	Not a SNP	5HTTLPR	Dannlowski et al., 2008 (31)
Excluded	Not a SNP	5HTTLPR	Heinz et al., 2007 (32)
Excluded	Not a SNP	5HTTLPR	Bertolino et al., 2005 (33)
Excluded	Not a SNP	5HTTLPR	Hariri et al., 2005 (34)
Excluded	Not a SNP	5HTTLPR	Hariri et al., 2002 (35)
Excluded	Not a SNP	5HTTLPR	Lee and Ham 2008 (36)
Excluded	Not a SNP	5HTTLPR	Smolka et al., 2007 (37)
Excluded	Not a SNP	MAOA	Lee & Ham 2008 (38)
Excluded	Not a SNP	NOS1	Kuhn et al., 2016 (39)
Excluded	Not a SNP	MAOA	Meyer-Lindenberg et al., 2006 (40)
Excluded	Not a SNP	MAOA	Denson et al., 2014 (41)
Excluded	Not a SNP	DAT1/SLC6A3	Wetherill et al., 2014 (42)
Excluded	Not a SNP	DAT1/SLC6A3	Bergman et al., 2014 (43)
Excluded	Not a SNP	AR	Manuck et al., 2010 (44)
Excluded	Not a SNP	ADRA2B	Rasch et al. 2009 (45)

Included/Excluded	Reason for exclusion	Gene	Study
Excluded	Not a SNP	ADRA2B	Cousijn et al., 2010 (46)
Excluded	Not a SNP	ADRA2B	Urner et al., 2011 (47)
Excluded	Not a SNP	ADRA2B	Li et al., 2015 (48)
Excluded	Not a SNP	AVPR1A	Meyer-Lindenberg et al., 2009 (49)
Excluded	Not a SNP	FMR1	Hessl et al., 2007 (50)
Excluded	Language task	GWAS bipolar disorder score	Whalley et al., 2012 (51)
Excluded	Monetary task	ODZ4	Heinrich et al., 2013 (52)
Excluded	Alcohol related task	GATA4	Jorde et al., 2014 (53)
Excluded	Sad > Neutral faces	HTR2A	Lee & Ham., 2008 (36)
Excluded	Sad > Neutral faces	TPH1	Lee et al., 2009 (54)
Excluded	Gambling videos	DBH	Yang et al. 2016 (55)
Excluded	Only significant in SCZ	OXTR	Haram et al., 2016 (56)
Excluded	Null finding	OXTR	Loth et al., 2014 (1)
Excluded	PTSD risk sample	ADCYAP1R1	Stevens et al., 2014 (57)
Included		PCDH17	Chang et al., 2017 (58)
Excluded	Fakra et al., 2009 (59) used as target study	HTR1A	Domschke et al., 2006 (60) Panic disorder patients.
Excluded	Fakra et al., 2009 (59) used as target study	HTR1A	Straube et al., 2014 (61) A clinical sample of panic disorder patients with agoraphobia.
Included		HTR1A	Fakra et al., 2009 (59)
Included		NPSR1	Dannlowski et al., 2011 (27)
Included		RGS2	Smoller et al., 2008 (62)
Included		ASIC1/ACCN2	Smoller et al., 2014 (63)
Excluded	Hariri et al., 2009 (64) used as target study	FAAH	Gunduz-Cinar et al., 2013 (65)
Included		FAAH	Hariri et al., 2009 (64)
Included		NR3C2	Bogdan et al., 2012 (66)
Included		PET-1	Wellman et al., 2013 (67)
Included		CHT1	Neumann et al., 2006 (68)
Included		FKBP5	Holz et al., 2015 (69)
Included		OXTR	Tost et al., 2010 (70)
Included		IFN-ɣ	Redlich et al., 2015 (71)
Included		ADCY7	Joeyen-Waldorf et al., 2012 (72)

Included/Excluded	Reason for exclusion	Gene	Study
Included		GTF2I	Swartz et al., 2015 (73)
Included		VMAT1	Lohoff et al., 2014 (74)
Included		FREM3	Nikolova et al., 2015 (75)
Included		FREM3	Nikolova et al., 2015 (75)
Included		CACNA1C	Tesli et al., 2013 (76)
Excluded	Tesli et al., 2013 (76) used as target study	CACNA1C	Sumner et al., 2015 (77) 58 adolescents and young adults viewing negative > neutral images, AA higher activation.
Excluded	Tesli et al., 2013 (76) used as target study	CACNA1C	Jogia et al., 2011 (78) 116 healthy and BD patients; A carriers higher activation; fearful > neutral.
Excluded	Tesli et al., 2013 (76) used as target study	CACNA1C	Wessa et al., 2010 (79) Reward task, 64 participants, A allele associated with higher activation in right amygdala.
Included		19 SNPs related to GR	Arloth et al., 2015 (12)
Included		PHOX2B	Ousdal et al., 2012 (80)
Included		OXTR	Waller et al., 2016 (81)
Included		CNIH3	Nelson et al., 2016 (82)
Included		IL-18	Swartz et al., 2016 (13)
Included		COMT	Domschke et al., 2012 (83)
Excluded	Domschke et al., 2012 used as target study	COMT	Lonsdorf et al., 2011 (23) 54 participants, 29 females, age 24, passively viewing two white male angry faces, white fixation cross, angry > control, left amygdala, Met/Met higher.
Excluded	Domschke et al., 2012 used as target study	COMT	Kempton et al., 2009 (84) 34 females, sample of 74, 1.5T, fear facial expression changing intensity, extracted values, higher in left amygdala with Val/Val.
Excluded	Domschke et al., 2012 used as target study	COMT	Smolka et al., 2005 (85) 35 subjects, 26 males, age 41, 1.5T, Caucasians, affectively unpleasant, pleasant, and neutral pictures, unpleasant > neutral, right amygdala, Met carriers.
Excluded	Domschke et al., 2012 used as target study	COMT	Drabant et al., 2006 (86) 101 subjects, 50 females, age 30, 3T, face matching task, fearful and angry, did not find link.
Excluded	Domschke et al., 2012 used as target study	COMT	Klucken et al., 2015 (87) 80 subjects, appetitive conditioning, erotic pictures as UCS, 1.5T, CS+ > CS-, left amygdala, Val/Val.
Excluded	Domschke et al., 2012 used as target study	COMT	Lelli-Chiesa et al., 2011 (88) sample of 40 BD, 25 healthy relatives, 22 relatives with MDD or anxiety, and 50 healthy controls, 1.5T, extracted values, sad face intensity and neutral, sad > neutral, Val carriers, no effect of group.
Excluded	Domschke et al., 2012 used as target study	COMT	Rasch et al., 2010 (89) 56 subjects, 15 males, age 24, positive, negative, and neutral pictures, 3T, unpleasant > neutral, Met higher in right amygdala.

Included/Excluded	Reason for exclusion	Gene	Study
Excluded	Domschke et al., 2012 used as target study	COMT	Domschke et al., 2008 (90) 20 patients with panic disorder, 3T, tested with various facial expression, found with fear > grey rectangle - the control stimulus, right amygdala Val carriers.
Excluded	Domschke et al., 2012 used as target study	COMT	Opmeer et al., 2014 (91) 125 participants, 28 healthy and rest MDD, mostly females, age 38, gender judgment task on various emotional faces, scrambled face and button press as control, 3T, positive expressions > control, left amygdala, Met carriers, but most of it was the hippocampus.
Excluded	Domschke et al., 2012 used as target study	COMT	Williams et al., 2010 (92) 46 participants, 21 females. Masked and unmasked fear, happy, and neutral, 1.5T, fear > neutral unmasked, met carriers, bilateral.
Excluded	Domschke et al., 2012 used as target study	COMT	Smolka et al., 2007 (37) 48 subjects all males, age 41, Caucasians, 1.5T, unpleasant, pleasant, and neutral pictures, unpleasant > neutral, Met carriers.
Excluded	Kilpatrick et al., 2011 (93) used as target study	HTR3A	Iidaka et al., 2005 (94) Japanese sample; 26 people.
Included		HTR3A	Kilpatrick et al., 2011 (93)
Included		DRD2/ANKK1	Lee et al., 2011 (95)
Excluded	Canli et al., 2005(96)used as target study	TPH2	Brown et al., 2005 (97)
Included		TPH2	Canli et al., 2005 (96)
Included		DRD2	Blasi et al., 2009 (98)
Included		PCLO	Woudstra et al., 2012 (99)
Included		IL1B	Baune et al.,2010 (100)
Included		DOK5	Liu et al., 2010 (101)
Included		NPY	Zhou et al., 2008 (102)
Included		NPY	Domschke et al., 2010 (103)
Included		BDNF	Soliman et al., 2010 (104)
Excluded	Soliman et al., 2010 (104) used as target study	BDNF	Montag et al., 2008 (105) Sample of 37 women; mean age 23; viewing emotional pictures.
Excluded	Soliman et al., 2010 (104) used as target study	BDNF	Lau et al., 2010 (106) Greater response only in MDD and anxiety adolescent patients.
Excluded	Soliman et al., 2010 (104) used as target study	BDNF	Gasic et al., 2009 (107) Val/Val 29 Caucasians.
Included		NR3C1	Ridder et al., 2012 (108)
Included		NR3C1	Ridder et al., 2012 (108)
Included		NR3C1	Ridder et al., 2012 (108)

Included/Excluded	Reason for exclusion	Gene	Study
Included		CRHR1	Weber et al., 2016 (109)
Included		OXTR	Marusak et al., 2015 (110)

Table S2. Summary of 37 candidate gene association studies of threat-related amygdala reactivity

Target Study	Demographics	Ethnicity	Gene	Gene product	Polymorphism	Functionality
Chang et al., 2017 (58)	N=297 (163 females), age: 33.5	European descent	PCDH17	Cadherin protein, associated with cell to cell interactions in the brain.	rs9537793	G allele associated with higher mRNA levels (58)
Fakra et al., 2009 (111)	N=89 (44 females), age: 45.74	Caucasian	HTR1A	Serotonin receptor 1A	rs6295 (used proxy rs358527)	G allele leads to higher expression levels of the 5-HT1A autoreceptor (112)
Dannlowski et al., 2011 (27)	N=72 (41 females), age: 36.77	European	NPSR1	Neuropeptide S receptor 1. Has an anxiolytic effect. Possibly affects the neurotransmission of serotonin, dopamine, and noradrenaline	rs324981 (used proxy rs324987)	the T-allele (Ile) leads to increased NPSR expression (113, 114)
Smoller et al., 2008 (62)	N=55 (41 females), age: 19.52	Missing (but controlled for ancestry based on informative marker clusters)	RGS2	Regulator of G protein signaling 2. Accelerates deactivation of G proteins to reduce G protein–coupled receptor signaling. Related to anxiety.	rs4606 (used proxy rs3767488)	G allele is associated with low RGS2 expression and increased G-protein-coupled signaling (115)
Smoller et al., 2014 (63)	N=103 (54 females), age: 20.37	Caucasians	ACCN2	Amiloride-sensitive cation channel 2. A sodium/calcium exchanger, expressed in the brain and kidney, antihypertensive drug Amiloride binds to it in the kidney.	rs10875995	Unknown
Hariri et al., 2009 (64)	N=82 (39 females), age: 44.85	Caucasian	FAAH	Fatty acid amide hydrolase. A key enzyme in regulating endocannabinoid (eCB) signaling.	rs324420	A allele associated with reduced expression of FAAH and elevations in circulating levels of the eCB anandamide (65)
Bogdan et al., 2012 (66)	N=279 (140 females), age: 13.59	Caucasian, Hispanic, and other	NR3C2	Nuclear Receptor Subfamily 3 Group C Member 2. A receptor with equal affinity to mineralocorticoids and glucocorticoids. Involved in the negative feedback loop of the HPA axis.	rs5522	The G allele has been associated with lower efficiency in using cortisol as ligand (116, 117)
Neumann et al., 2006 (68)	N=32 (14 females), age: 41.13	European	CHT1	Human choline transporter gene. Carries choline into acetylcholine-synthesizing neurons.	rs333229 (imputed)	Unknown
Holz et al., 2015 (69)	N=153 (87 females), age: 25	European	FKBP5	FK506 binding protein 5. Higher levels of the protein coded by this	rs1360780	T allele associated with higher FKBP5 expression and impaired

Target Study	Demographics	Ethnicity	Gene	Gene product	Polymorphism	Functionality
				gene lead to impaired HPA axis negative feedback.		recovery of cortisol levels in response to stress (118, 119)
Tost et al., 2010 (70)	N=228 (126 females), age=31.9	Caucasian	OXTR	Oxytocin receptor	rs53576	Unknown
Redlich et al., 2015 (71)	N=337 (218 females), age:36.46	Caucasian	IFN-ɣ	Interferon ɣ. A cytokine that is critical for innate and adaptive immune response	rs1861494	C allele introduces a new CpG dinucleotide sequence that serves as an epigenetic target for DNA methylation, leading to reduced gene expression (120)
Joeyen-Waldorf et al., 2012 (72)	Sample 1: N=82 (46 females), age: 44.76; Sample 2: N=98 (40 females), age: 40.53	Caucasian	ADCY7	Adenylate cyclase 7. A membrane-bound adenylyl cyclase that catalyses the formation of cyclic AMP from ATP.	rs1064448	Unknown
Tesli et al., 2013 (76)	N=250 (66 BD, 61 SZ, 114 females), age:34.4	Northern European	CACNA1C	a1c subunit of the L-type voltage-gated calcium channel. Implicated in synaptic plasticity and neuronal survival.	rs1006737	Unknown
Ousdal et al., 2012 (80)^^	N=224 (51 SZ, 64 BD, and 12 with 'other psychosis', 109 females), age: 32.1	Missing (but mention that individuals with a calculated ancestry different from the majority of the TOP sample were removed)	PHOX2B	Paired-like homeobox 2b. A homeodomain transcription factor. Regulates the expression of enzymes necessary for the synthesis of several monoamines and is essential for the development of the autonomic nervous system	rs10014254 (imputed)	Unknown
Blasi et al., 2009 (98)	N=134 (84 females), age: 26.4	Caucasians	DRD2	Dopamine receptor D2	rs1076560	GG genotype associated with relatively greater expression of DRD2 short (autoreceptor) mRNA in prefrontal cortex and in striatum (121)
Kilpatrick et al., 2011 (93)	N=55 (26 IBS, all females), age: 32.54	Missing	HTR3A	Serotonin receptor 3A	rs1062613	T allele leads to increased HTR3A expression (122)
Lee et al., 2011 (95)	N=45 (all females), age: 23.15	Asian	DRD2/ANKK1	Ankyrin repeat and kinase domain containing 1. While the SNP is located in the ANKK1 gene it is thought to affect DRD2 expression	rs1800497	A1 (T) allele predicts lower availability of DRD2 in the striatum (123), but in Zhang et al. (121) a direct effect of this variant was not found and it was postulated that previous found

Target Study	Demographics	Ethnicity	Gene	Gene product	Polymorphism	Functionality
						effects were due to an LD with rs1076560
Canli et al., 2005 (96)	N=29 (18 females), age: 22.8	Missing (but mention that ethnicity did not differ according to genotype)	TPH2	Iisoenzyme of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin	rs4570625	Unknown
Woudstra et al., 2012 (99)	N=126 (96 MDD, 78 females), age:38.1	Western European	PCLO	Piccolo Presynaptic Cytomatrix Protein. Involved in monoamine neurotransmission. Part of the presynaptic cytoskeletal matrix, which is involved in establishing active synaptic zones and in synaptic vesicle trafficking.	rs2522833	Unknown
Zhou et al., 2008 (102)	N=71 (40 females), age: 44.4	91% Caucasians	NPY	neuropeptide Y. Involved in anxiety and stress. Has anxiolytic effects.	Haplotypes of 6 SNPs (rs3037354, rs17149106, rs16147, rs16139, rs5573, rs5574)	The various haplotypes are associated with mRNA expression and plasma levels(102)
Domschke et al., 2010 (103)	N=35 (all MDDs, 24 females), age: 37.3	Northern European	NPY		rs16147	C allele associated with decreased expression (102)
Baune et al.,2010 (100)	N=32 (all MDDs, 22 females), age:37.8	Caucasian	IL-1β	Interleukin 1β. Proinflammatory cytokine.	rs16944	Mixed findings regarding which allele is associated with higher expression. May be functional in a haplotype (124)
^Wellman et al., 2013(67)	N=89 (50 females), age: 19.55	Asians	PET-1	Pheochromocytoma 12 ETS factor-1; FEV-1. A transcription factor essential for differentiation and forebrain targeting of serotonin neurons	rs860573	Unknown
^Nelson et al., 2016 (82)	N=312 (161 females), age: 19.71	European American	CNIH3	Cornichon family AMPA receptor auxiliary protein 3. Regulates the trafficking and gating properties of AMPA-selective glutamate receptors	rs10799590	Unknown
^Waller et al., 2016 (81)	N=312 (213 females), age: 19.71	Non Hispanic Caucasians	OXTR	Oxytocin receptor	rs1042778	Unknown
^Swartz et al., 2015 (73)	N=808 (454 females), age: 19.71	Caucasian, African	GTF2I	General transcription factor IIi. This locus, along with several other neighboring genes, is deleted in	rs13227433 (imputed)	Unknown

Target Study	Demographics	Ethnicity	Gene	Gene product	Polymorphism	Functionality
		American, and Asian		Williams-Beuren syndrome, which is characterized by hypersociability and increased approach to strangers.		
^Swartz et al., 2016 (13)	N=448 (261 females), age: 19.71	Non Hispanic Caucasians	IL-18	Interleukin 18. Proinflammatory cytokine	rs187238 (used proxy rs795467) and rs1946518	Haplotype comprising the major C risk allele of rs187238 and the major G risk allele of rs1946518 associated with increased expression of IL-18 mRNA (125) and plasma IL-18 (126).
^Lohoff et al., 2014 (74)	N=298 (173 females), age: 19.63	Caucasian, Asian, African American, Latino, other	VMAT1	Vesicular monoamine transporter 1. Embedded in synaptic vesicles and serves to transfer monoamines, such as norepinephrine, epinephrine, dopamine, and serotonin, between the cytosol and synaptic vesicles.	rs1390938 (imputed)	A allele leads to increased monoamine transport into presynaptic vesicles (74)
^Nikolova et al., 2015 (75)	N=365 (192 females), age: 19.71	Non Hispanic Caucasians	FREM3	FRAS1-related extracellular matrix protein 3. Extracellular matrix protein which may play a role in cell adhesion.	rs7676614	A allele may lead to reduced FREM3 gene expression (a trend in (75))
^Nikolova et al., 2015 (75)	N=365 (192 females), age: 19.71	Non Hispanic Caucasians	FREM3		rs1391187 (imputed)	G allele associated with reduced FREM3 gene expression (75)
^Arloth et al., 2015 (12)	N=647 (362 females), age: 16.65	Caucasian, African American, Latino, Asian, and other	19 SNPs*	SNPs that are associated with the genetic regulation of GR stimulated gene expression		
Marusak et al., 2015 (110)	N=55 (34 females), age: 11.7	Caucasian, African American, Hispanic, Mixed	OXTR	Oxytocin receptor	rs2254298	Unknown
Liu et al., 2010 (101)	N=68 (29 BD, 42 females), age=14	Mostly Caucasian (6 African American and 5 unknown)	DOK5	Docking protein 5. Plays an important role in neurotrophin signaling pathways, neuronal development,and differentiation.	rs2023454 (used proxy rs16999924)	Unknown
Domschke et al., 2012 (83)	N=85 (51 females) age=37.37	European	COMT	Catechol-O-methyltransferase. Degrades catecholamines such as	rs4680	A (Met) allele alters the structure of COMT and leads to a reduction in its activity (127)

Target Study	Demographics	Ethnicity	Gene	Gene product	Polymorphism	Functionality
				dopamine, epinephrine, and norepinephrine		
Ridder et al., 2012 (108)	Sample 1: N=60 (22 females), age=21.25; Sample 2: N=52 (20 females), age: 22.27	Missing	NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1. Glucocorticoid receptor. Involved in the negative feedback loop of the HPA axis.	Carriers of 3 or more minor alleles vs all others: rs33389, rs41423247 (used proxy rs853180), rs4986593.	Unknown
Soliman et al., 2010 (104)	N=72 (33 females), age=25.64	Mixed (Caucasian, Asian, Hispanic, African American)	BDNF	Brain-derived neurotrophic factor. A member of the nerve-growth-factor family. Plays an important role in neuronal survival and development.	Val66Met (rs6265)	Met allele leads to impairments in intracellular trafficking and activity-dependent secretion (128, 129).
Weber et al., 2016 (109)	N=48 (Panic disorder, 33 females), age=36.06	Caucasian	CRHR1	Corticotropin-releasing hormone/factor receptor 1. Involved in the initiation of the stress response.	rs17689966 (imputed)	G allele associated with reduced mRNA expression in the amygdala and forebrain (109)

^ Study is based on a subsample of our replication sample. ^^ In the original study a replication was attempted with a subsample of our replication sample that included 99 participants. The replication was not successful. * rs11588837, rs8106959, rs10002500, rs1894823, rs2281677, rs12611262, rs10229363, rs9858280, rs4838884, rs2072443, rs2269799 (used proxy rs2285625), rs2395891, rs2422008, rs2956993, rs7534993, rs12901022, rs921320, rs7194275, rs7252014.

Table S3. Studies that were excluded from the replication analyses.

Study	Sample	Ethnicity	Type of scanner	Gene	Gene product description	Polymorphism functionality	Higher activation	Contrast
Numerous studies				SLC6A4 (5-HTTLPR, insertion/deletion)	Solute carrier family 6 member 4. Serotonin transporter	Short allele is associated with reduced transcription and expression of the transporter (Lesch et al., 1996)	Inconsistent	
Lee & Ham, 2008	N=54 (all females), mean age: 23.2	Asian	1.5T	HTR2A (rs6311, A-1438G)	Serotonin receptor 2A	G allele leads to higher levels of methylation and higher levels of expression (Polesskaya et al., 2005)	T allele	Sad > neutral (not in angry > neutral)
Lee et al., 2009	N=26 (all females), mean age=50.3	Asian	1.5T	TPH1 (rs1800532, A218C)	Iisoenzyme of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of serotonin	Unknown	A allele	sad > neutral, but not in angry > neutral.
Meyer-Lindenberg et al., 2006	N=142 (72 females), mean age: 29.64	Caucasians	3T	MAOA (VNTR)	Monoamine oxidase A. Oxidative deamination of amins, serotonin, dopamine, norepinephrine	3.5 and 4 repeats are associated with higher transcription levels (Sabol et al., 1996)	Low expression variants (2,3, or 5 repeats)	angry and fearful > shapes
Yang et al. 2016	N=18 pathological gamblers (5 females) and 25 controls (10 females), mean age: 32.76	European American	3T	DBH (rs1611115, C-1021T)	Dopamine beta-hydroxylase. Mostly converts dopamine to norepinephrine	T allele predicts low DBH plasma activity (Zabetian et al., 2001)	CC genotype	Higher activation to videos > the baseline before and after viewing the scenarios
Bergman et al., 2014	N=85 (44 females), mean age: 45.2	Caucasians	3T	DAT1/SLC6A3 (VNTR)	Dopamine active transporter 1	Mixed. 9-repeat associated with higher levels of DAT in the striatum (van Dyck et al., 2005; van de Giessen et al., 2009). Conversely, 9-repeat was associated with lower expression in the putamen (Heinz et al., 2000) and lower expression in vitro (Fuke et al., 2001; VanNess et al., 2005). However, another study did not find a difference between the variants in vitro (Mill et al., 2005).	9-repeat	angry and fearful > shapes

Study	Sample	Ethnicity	Type of scanner	Gene	Gene product description	Polymorphism functionality	Higher activation	Contrast
Meyer-Lindenberg et al,. 2009	N=121 other details not provided for fMRI subsample	European Caucasians	3T	AVPR1A (RS3)	Vasopressin receptor 1A	Long alleles (>325) associated with higher mRNA in the hippocampus (Knafo et al., 2008) and shorter alleles have been associated with decreased promoter activity (Tansey et al., 2011)	334 allele	angry and fearful > shapes
Haram et al., 2016	N=104 schizophrenia patients (41 females), 100 affective disorder patients (57 females), and 142 controls (58 females). Only significant in SCZ. Mean age:31.5	Caucasians	1.5T	OXTR (rs237902)	Oxytocin receptor	Unknown	AA genotype	angry + fearful > shapes
Jorde et al., 2014	N=81 abstinent, alcohol-dependent patients (24 females). Mean age: 45.59	Missing (German sample)	3T	GATA4 (rs13273672)	GATA binding protein 4. A transcription factor regulating the transcription of the atrial natriuretic peptide (ANP). Binding of ANP to natriuretic peptide receptors has been found to inhibit noradrenergic and dopaminergic neurotransmission. In addition, natriuretic peptides reduce the release of corticotrophin-releasing hormone (CRH) receptors	Reduced variability of ANP in carriers of at least one G allele. (Keifer et al., 2011)	AA genotype	alcohol > neutral cues
Kuhn et al., 2016	N=49 (25 females), mean age: 25		3T	NOS1 (exon 1f - VNTR)	Nitric oxide synthase 1	Long alleles are associated with higher gene expression levels (Kuhn et al., 2016)	Short allele	unpredictable context > safe context

Study	Sample	Ethnicity	Type of scanner	Gene	Gene product description	Polymorphism functionality	Higher activation	Contrast
Heinrich et al., 2013	N=485 (248 females), mean age: 14.26	Missing	3T	ODZ4 (rs12576775)	The protein encoded by this gene plays a role in establishing proper neuronal connectivity during development.	unknown	G allele	No effect on face task. Higher activation during reward sensitivity and reward expectation.
Rasch et al. 2009;	N=57 (41 females), mean age: 24.1	Caucasians	3T	ADRA2B (deletion)	Presynaptic noradrenergic α2B receptor	Deletion shows both agonistic and antagonistic effects (Small et al., 2001), and needs to be clarified	deletion	negative > neutral and positive > neutral
Stevens et al., 2014	N=49 PTSD risk females, mean age: 38.7.	African American	3T	ADCYAP1R1 (rs2267735)	Adenylate cyclase activating polypeptide 1 receptor type 1. The pituitary adenylate cyclase-activating polypeptide (PACAP) receptor.	Females with the CC genotype express significantly less ADCYAP1R1 mRNA than males, or than females who are G carriers. (Ressler et al., 2011)	CC genotype	fearful > neutral
Hessl et al., 2007	N=21 males (11 with the FMR1 premutation), mean age: 42.9	Caucasians, Hispanic, East Indian	1.5T	FMR1 (CGG repeat)	Fragile X mental retardation 1. Codes for fragile X mental retardation protein which is involved in RNA binding and translation of proteins. May be involved in synaptic plasticity.	higher repeats in premutation alleles associated with higher mRNA levels (Tassone et al., 2000)		fearful > scrambled (lower activity in premutation carriers) neutral > scrambled (higher activity in premutation carriers)
Whalley et al., 2012	N=73 bipolar disorder risk and 52 controls. No details are given for the fMRI subsample	Missing	1.5T	A polygenic risk score for BD based on GWAS				sentence completion > baseline

Table S4. Hardy Weinberg equilibrium of all included SNPs

				HWE original p values				
CHR	**SNP**	**A1**	**A2**	**Caucasians**	**Latino**	**African American**	**Asians 1**	**Asians 2**
1	rs324420	A	C	0.8913	1	0.4122	0.6796	0.808
1	rs4838884	G	A	0.7754	1	1	0.4984	1
1	rs11588837	G	A	1	1	1	1	1
1	rs3767488	G	A	0.4243	1	0.3615	0.7615	0.5721
1	rs7534993	A	G	0.702	0.6117	0.2098	0.44	0.3857
1	rs10799590	A	G	0.2873	0.2596	0.6457	0.6308	1
2	rs921320	A	C	0.1928	0.6483	0.7865	1	0.7696
2	rs2422008	A	C	0.6602	0.1106	0.03496	0.6258	1
2	rs12620091	C	T	0.8519	1	0.03139	0.2965	1
2	rs333229	T	G	0.4853	0.1212	0.09176	1	0.7981
2	rs16944	A	G	0.9225	0.4816	0.4747	0.6308	0.5027
2	rs860573	A	G	N/A	N/A	N/A	0.07888	1
3	rs1042778	T	G	1	0.8114	0.855	0.2244	1
3	rs2254298	A	G	0.03175	0.6899	0.01863	0.3463	0.8781
3	rs53576	A	G	0.7645	0.5613	0.7967	0.6076	0.7543
3	rs9858280	C	T	0.7067	0.7879	1	0.7289	1
4	rs10014254	T	C	1	1	1	1	1
4	rs10002500	T	C	0.6689	0.6811	0.2192	0.3527	0.649
4	rs1391187	A	G	0.1147	0.253	0.3678	0.05897	0.5447
4	rs7676614	G	A	0.1893	1	1	0.7963	1
4	rs5522	C	T	0.3768	1	1	1	1
5	rs358527	T	C	0.6003	0.4909	0.08443	0.8105	1
5	rs853180	G	A	0.05168	0.2491	0.5924	0.03044	0.005043
5	rs4986593	G	A	0.7165	1	1	0.04808	0.04186
5	rs33389	T	C	0.5842	0.1056	0.3648	1	0.2045
6	rs1360780	T	C	0.9188	0.608	1	1	0.0691

				HWE original p values				
CHR	**SNP**	**A1**	**A2**	**Caucasians**	**Latino**	**African American**	**Asians 1**	**Asians 2**
7	rs10254767	G	A	0.3065	0.4979	1	0.7835	1
7	rs17149106	T	G	1	1	1	0.3507	1
7	rs16147	T	C	0.1617	0.2497	0.5775	0.3338	1
7	rs16139	C	T	1	1	1	0.2396	1
7	rs5573	G	A	0.1896	0.2357	0.573	0.4687	1
7	rs5574	T	C	0.2573	0.02153	0.7007	0.7609	0.4722
7	rs324987	C	T	0.9303	0.05445	1	0.2375	0.5891
7	rs10229363	G	A	0.4091	1	0.4282	1	1
7	rs13227433	G	T	0.521	0.7638	1	0.53	0.6101
7	rs2522833	C	A	0.3275	0.82	1	1	0.4433
7	rs2072443	T	C	0.9286	1	0.5647	0.3467	0.4214
8	rs1390938	A	G	0.3693	0.1755	0.5998	0.5968	0.5263
11	rs6265	T	C	0.8919	1	1	0.1052	0.1801
11	rs2956993	G	T	0.221	0.4472	0.2394	0.4942	1
11	rs795467	A	G	0.2624	0.5988	1	1	0.7467
11	rs1946518	T	G	0.592	0.03973	0.5709	1	0.8934
11	rs1800497	A	G	0.4092	0.3347	0.8399	0.2339	0.2153
11	rs1076560	A	C	0.5042	0.4491	0.09248	0.3602	0.3393
11	rs1062613	T	C	0.897	1	0.376	0.3527	1
12	rs1006737	A	G	0.229	0.8042	1	1	0.3596
12	rs1894823	T	C	0.05853	0.2041	0.614	1	0.109
12	rs10875995	C	T	0.6934	1	0.03916	0.7969	1
12	rs1861494	C	T	0.06035	0.5184	1	0.6177	0.3084
12	rs4570625	T	G	0.152	0.7512	1	0.6051	0.2166
13	rs9537793	G	A	0.4816	1	0.3768	0.3312	0.7853
14	rs2281677	A	G	0.9262	0.6117	0.7222	0.6341	0.2728
15	rs12901022	T	C	0.4873	0.361	0.0825	0.6276	0.7477
15	rs2285625	C	T	0.1323	1	1	0.2742	0.595

				HWE original p values				
CHR	**SNP**	**A1**	**A2**	**Caucasians**	**Latino**	**African American**	**Asians 1**	**Asians 2**
16	rs7194275	C	T	0.4723	1	0.4754	1	0.1647
16	rs1064448	G	T	0.9305	0.4929	0.7816	0.4238	1
17	rs17689966	G	A	0.9274	1	1	0.3826	0.2682
19	rs2395891	T	G	0.334	0.7874	0.1497	0.007006	1
19	rs12611262	T	C	0.168	0.8147	0.3212	0.3376	0.5516
19	rs7252014	A	G	0.4345	1	0.2968	0.6308	0.25
19	rs8106959	G	A	0.2571	1	0.614	0.2791	1
20	rs16999924	A	G	0.3832	1	1	1	1
22	rs4680	G	A	0.09833	0.1714	1	1	0.4995

Note. All p values were higher than the lowest FDR corrected p value of ~0.00016. CHR=chromosome number.

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