OPEN

Citation: Transl Psychiatry (2014) 4, e451; doi:10.1038/tp.2014.95

www.nature.com/tp

ORIGINAL ARTICLE

Genetic association of impulsivity in young adults: a multivariate study

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Impulsivity is a heritable, multifaceted construct with clinically relevant links to multiple psychopathologies. We assessed impulsivity in young adult ($N \sim 2100$) participants in a longitudinal study, using self-report questionnaires and computer-based behavioral tasks. Analysis was restricted to the subset ($N = 426$) who underwent genotyping. Multivariate association between impulsivity measures and single-nucleotide polymorphism data was implemented using parallel independent component analysis (Para-ICA). Pathways associated with multiple genes in components that correlated significantly with impulsivity phenotypes were then identified using a pathway enrichment analysis. Para-ICA revealed two significantly correlated genotype–phenotype component pairs. One impulsivity component included the reward responsiveness subscale and behavioral inhibition scale of the Behavioral-Inhibition System/Behavioral-Activation System scale, and the second impulsivity component included the non-planning subscale of the Barratt Impulsiveness Scale and the Experiential Discounting Task. Pathway analysis identified processes related to neurogenesis, nervous system signal generation/amplification, neurotransmission and immune response. We identified various genes and gene regulatory pathways associated with empirically derived impulsivity components. Our study suggests that gene networks implicated previously in brain development, neurotransmission and immune response are related to impulsive tendencies and behaviors.

Translational Psychiatry (2014) **4,** e451; doi:10.1038/tp.2014.95; published online 30 September 2014

INTRODUCTION

Impulsivity has been defined as 'a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others'.[1–4] Impulsivity is a complex, multidimensional construct related to responses to rewards/punishments, attention and other cognitive processes.[5] Impulsivity relates to multiple psychiatric disorders and abnormal behaviors, including attention-deficit hyperactivity disorder, suicide, aggression and addiction.[5] The Diagnostic and Statistical Manual of Mental disorders 5th edition (DSM V)[6] defines impulse-control features and/or impulsive symptoms as major factors in the diagnosis of bipolar, attention-deficit/hyperactivity, conduct and antisocial and borderline personality disorders, among others.[4,7] Impulsivity may predict suicidal behavior, psychopathy and conduct disorder, drug and alcohol problems.[8]

Impulsivity is genetically influenced and heritable.[5,9] Offspring of parents with substance-use disorders have increased impulsivity,[8] which may be transmitted as general risk factor for substance abuse.[10,11] Some putatively related genes related to impulsive behaviors have been identified.[12] Prior studies also report genetic associations in other impulsivity-associated pathological conditions including behavioral addictions and eating disorders, which may share similar neurobiological risk factors.[13–15] Quantifying precise genetic underpinnings of impulsivity hold promise for intervention development for multiple psychiatric conditions.

Similar to other complex, inherited, behavioral phenotypes analogous to complex medical disorders such as obesity[16] and psychological phenotypes such as extraversion are clearly influenced by multiple genes and also by environmental factors and their interactions. Various impulsivity-related single-nucleotide polymorphisms (SNPs) have been identified in previous genome-wide association studies, including those associated with dopaminergic and serotonergic genes.[17,18] Prior meta-analyses also link common variants in such genes to attention-deficit hyperactivity disorder and suicidal behaviors,[19,20] which are characteristically impulsive. Most genetic studies utilize a univariate (often genome-wide association studies) approach; however, this method is hindered by high statistical threshold owing to multiple testing corrections for SNP numbers and does not take into account the aggregate effects of genetic variants, such as those that might underlie epistasis and other types of interrelationships that likely underpin complex phenotypes. The role of any individual gene in impulsivity remains unclear, likely attributable to the common disease common variant model alluded above, for which univariate approaches are not optimal. Thus, alternate approaches that consider such genetic aggregates are important to pursue.

Multivariate analyses such as parallel independent component analysis (Para-ICA) provide a sensitive and powerful alternative to traditional univariate analyses using single SNPs and single phenotypes. Para-ICA is typically more powerful than univariate analyses because it examines clusters of related individual phenotypic measures in relation to clusters of related SNPs that

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Received 4 June 2014; revised 19 August 2014; accepted 21 August 2014

Table 1. Demographic Information

Demographic information								
	Caucasian		*African American*		*Hispanic*		*Mixed/other*	
	Male	Female	Male	Female	Male	Female	Male	Female
Subjects (*N*)	137	172	17	30	13	21	18	18
Age range (years)			17–24					
Mean age (years; s.d.)			18.31 (0.77)					

can be linked via annotation pathways to known molecular biological processes.[21] Para-ICA derives both these phenotypic and SNP clusters empirically from the data set, in a hypothesis-free manner, to reveal novel, biologically relevant associations that might otherwise not be detected.[22] Prior studies have shown that Para-ICA yields robust results with practical sample size of patients with various psychiatric disorders such as Alzheimer's disease and schizophrenia.[21,23] Consequently, in the current study, we used Para-ICA[22,24] to examine aggregate effects of common SNP variants underlying impulsivity-related constructs.

The main purpose of the current study was to uncover novel gene networks comprised of interacting SNPs associated with various impulsivity-related measures in a sample of healthy young adults. In addition, we aimed to identify the underlying molecular and biological mechanisms associated with these gene networks that might promote understanding the etiology of specific impulsivity-related behaviors and tendencies. Jupp and Dalley[25] recently reviewed various neurotransmission systems (dopaminergic, serotonergic, noradrenergic, glutamergic, GABAergic, opoidergic, cholinergic and cannabinoids) that have a putative role in impulsivity. The importance of these neurotransmission systems may differ with respect to different aspects of impulsive behavior.[25] In addition, brain organizational process during specific neurodevelopmental stages (such as adolescence) might impact the brain's motivation and inhibition substrates, influencing impulsive choice, risky behaviors and addiction risk.[26] We hypothesized that the biological processes identified by Para-ICA would contain genes identified previously as associated with brain development; impulsive traits and impulsivity-related behavioral problems such as externalizing behaviors, attention-deficit hyperactivity disorder, suicidal behavior and substance abuse; nervous system signal generation, amplification or transduction; and neurotransmitter function, for example, their associated receptors, reuptake sites and synthetic/degrading enzymes.

MATERIALS AND METHODS

Subjects

The study sample consisted of $N = 426$ young adult freshman students who participated in the National Institute of Alcohol Abuse and Alcoholism-funded Brain and Alcohol Research with College Students longitudinal study[11] consisting of the subset of participants from the larger sample ($N \sim 2100$) who provided genotyping data. Demographic information is shown in Table 1. All subjects provided written informed consent, approved by Hartford Hospital, Yale University, Trinity College and Central Connecticut State University. Exclusion criteria included current psychotic or bipolar disorder based on Mini International Neuropsychiatric Interview,[27] history of seizures, head injury with loss of consciousness >10 min, cerebral palsy, concussion in last 30 days, positive urine toxicological screens for common drugs of abuse and pregnancy. Although we did not collect classical intelligence quotient measures, we recorded Scholastic Assessment Test scores from all our participants. Prior studies have shown Scholastic Assessment Test scores to be a good predictor of intelligence quotient.[28] Thus, intelligence quotient estimates were calculated using Scholastic Assessment Test scores as recommended by Frey and Detterman.[28] Also, socio-economic status was calculated using the Hollingshead (1975) four factor index of social status.

Impulsivity-related measures

Five different self-report questionnaires and three behavioral tasks were used to measure impulsivity and related constructs. These measures were chosen to capture different facets of impulsivity and related constructs that had constituted separate factors in our prior research.[3] Self-report measures were as follows: (i) Barrat Impulsiveness Scale (BIS-11),[29] (ii) Behavioral-Inhibition System/Behavioral-Activation System scale (BIS/BAS),[30] (iii) Sensitivity to Punishment and Reward Questionnaire (SPSRQ),[31] (iv) Zuckerman Sensation Seeking Scale (SSS)[32] and (v) Padua Inventory (PI).[33] Computer-based behavioral tasks consisted of (i) two different versions of the Balloon Analog Risk Task (BART), the Java Neuropsychological Test (JANET) BART[34] and conventional BART,[35] and (ii) Experiential Discounting Task (EDT).[36] Subscales used in our analysis included attention, motor and non-planning from BIS-11; drive, fun-seeking and reward responsiveness subscales from BAS; reward and punishment scales from SPSRQ; thrill and adventure seeking (ZTAS), experience seeking (ZES), disinhibition (ZDIS) and boredom susceptibility (ZBS) from SSS; total score from PI; total balloon pumps and pops from JANET BART; average adjusted pumps from conventional BART; and area under the curve from the EDT, yielding 18 total impulsivity scores and subscores that were included in the analysis. Missing impulsivity-related values (10.5-14.1%) were imputed with mean substitution using SPSS v19.0 (www.ibm.com/software/analytics/spss/) and normalized.

SNP data collection and preprocessing

Genomic DNA was extracted with saliva collected from each subject using Oragene collection kits.[37] Genotyping was performed using Illumina (Illumina, San Diego, CA, USA) HumanOmni1-Quad v1.0 Beadchip (~1 million target SNPs) for 237 subjects and Illumina HumanOmni2.5-8v1 BeadChip (~2.5 million target SNPs) for 189 subjects. Both chips had identical allele coding. The SNP data from both chips were merged in PLINK software (http://pngu.mgh.harvard.edu/~purcell/plink/). SNPs common between two chips ($N = 582\,300$) were considered for further processing. We followed quality control steps of SNPs data using PLINK software as reported elsewhere.[38] Figure 1 is a conceptual illustration of the preprocessing steps in quality control of SNP data. To increase independence between markers, SNPs in high-linkage disequilibrium were removed (window size in SNPs = 50, number of SNPs to shift the window at each step = 5 and $r^2 > 0.5$). We performed principal component analysis using custom MATLAB scripts using algorithm similar to EIGENSTRAT.[39] In order to correct for stratification bias, data were corrected using top two eigenvectors. Stratification bias was verified using Q–Q plot based on the *P*-values from the association test. To further reduce the number of SNPs for optimal employment of Para-ICA,[22] we took processed SNPs and queried using Kyoto Encyclopedia of Genes and Genomes (KEGG) database (www.genome.jp/kegg). Finally, 26 142 SNPs that were part of pathways in KEGG database were considered for Para-ICA.

Genetic-impulsivity association

To identify associations between genetic and impulsivity-related data, Para-ICA from the Fusion ICA Toolbox (http://mialab.mrn.org/software/fit/) was used in MATLAB 7.7. Data were prepared for impulsivity analysis as (426 (subjects) × 18 (impulsivity-related measures)) and SNPs as (426 (subject) × 26142 (SNPs)), which were then input to Para-ICA.[22,24] The number of independent components for impulsivity-related and SNPs data was calculated using minimum description length criteria[40] and the number of components estimated was 6 for impulsivity-related measures and 17 for SNPs.

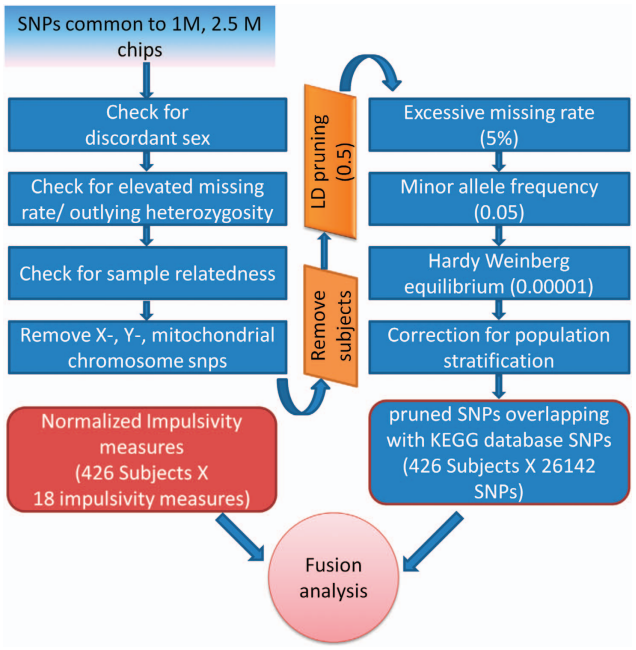

Figure 1. Illustration of quality control processing pipeline of single-nucleotide polymorphism (SNP) data. LD, linkage disequilibrium; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Correlations between modalities

Gene-impulsivity associations were established by examining correlations between loading coefficients between the SNP and impulsivity-related components. To account for confounding factors, partial correlation between loading coefficients of both modalities were computed controlling for calculated intelligence quotient scores, socio-economic status, age and sex using SPSS. Only those components surviving Bonferroni correction for multiple comparisons ($P < 0.05/(17\ (\text{SNP components}) \times 6\ (\text{impulsivity-related components}))$) were considered for further examination. *Post hoc* power calculation was performed on genotype–phenotype correlation pairs that survived multiple comparison corrected statistical threshold to ensure our sample adequately controlled the possibility of type II errors using G*Power software (http://www.gpower.hhu.de/).

Pathway analysis

Genes corresponding to dominant SNPs from the both (GC1 and GC2) genetic networks were selected using an arbitrary threshold $|z| > 2.5$. To correct for gene-size bias, gene-based trait association value was calculated using VEGAS software.[41] Genes with $P < 0.05$ values were input for enrichment analysis in Metacore-based annotation software GeneGo (https://portal.genego.com/) and ConsensusPathDB (http://cpdb.molgen.mpg.de/). Both ConsensusPathDB enrichment analysis and GeneGo allowed examination of pathway and/or gene ontology categories corresponding to gene sets in each component. The quantitative enrichment scores were calculated using a hyper-geometric approach to estimate the likelihood that significant genes were overrepresented in particular biological pathways. To correct for multiple comparisons, significance values were adjusted using false-discovery rate.[42]

RESULTS

Genetic-impulsivity associations

No significant inflation was noted in the association between loading coefficients and SNP data (see Figure 2 for Q–Q plot). Partial correlation controlling for calculated intelligent quotient, socio-economic status, age and sex revealed significant correlations between two independent impulsivity-related phenotypic components (IC1 and IC2) with two genetic components (GC1 and GC2). GC1 contained 618 SNPs from 304 genes and GC2 comprised 643 SNPs from 322 genes. The most significant impulsivity-related measures represented in IC1 were reward-sensitivity and Behavioral-Inhibition system scale scores of BIS/BAS scale.[30] The most significant impulsivity-related measures represented in IC2 were the non-planning subscale score of the BIS-11 (ref. 29) and the area under the curve score from the EDT.[36] IC1 correlated negatively with GC1 ($r = -0.19$, $P = 0.00008$) and IC2 correlated positively with GC2 ($r = 0.22$, $P = 0.000002$). Scatter plots of both component pairs are shown in Figure 3. The top 20 most significant genes from each of the genetic components GC1 and GC2 are listed in Tables 2 and 3, respectively. *Post hoc* power analysis revealed power attained from IC1–GC1 and IC2–GC2 correlation pairs were 99.6% and 98.1%, respectively.

Pathway analysis

Pathways associated with GC1 (associated with IC1) included calcium signaling, cell adhesion molecules (CAMs), cholinergic synapse, long-term depression (LTD), long-term potentiation and various immune response pathways. Similarly pathways associated with GC2 (associated with IC2) included focal adhesion, calcium signaling, LTD, long-term potentiation, glutamate regulation of dopamine D1A receptor signaling and various immune response pathways. Top 10 KEGG and GeneGo pathways associated with GC1 and GC2 along with their *P*-values and q-values are listed in Tables 4 and 5, respectively. Also, genes overlapping with gene clusters and top 10 significant pathways are listed in Supplementary Tables S1 and S2.

DISCUSSION

In this study, we used a multivariate technique, Para-ICA, to investigate the genetic associations of impulsivity traits in young adults. We hypothesized that the biological classes and processes identified by Para-ICA-derived gene components would contain a significant excess of genes identified previously with risk for impulsive traits and impulsivity-related behavioral problems, as well as pathways associated with brain development, nervous system signal generation, amplification or transduction and neurotransmission. The impulsivity measures included in the current analysis were based on our previous study.[3] Given that impulsivity construct validity and theoretical overlap remains a topic of active research, future studies could consider adding various other impulsivity assessments and explore their genetic associations in attempts to refine our understanding of impulsivity genotype–phenotype relationships.

Phenotypic component IC1 (BAS-Reward and BIS) represented an impulsivity construct describing self-reported tendencies relating to propensities to seek out rewarding situations and the regulation of aversive motivations, and IC2 (BIS-11 non-planning and EDT) represented an impulsivity construct relating to propensities of focusing on present rather than future events and the favoring of immediate rewards over longer-term consequences. Prior studies suggest a multidimensional nature of impulsivity; however, how best to parse impulsivity-related domains remains debated.[5] Impulsivity-related constructs may vary depending upon the number and types of tests administered.[3,43] The impulsivity-related components emerging from the current study differ from those we reported in a prior study.[3] Components extracted in this study (Supplementary Table S3) were based on ICA, which differs conceptually and empirically from the principal component analysis used previously. Para-ICA constrains both genotype and phenotype components to maximize their cross-correlation,[22] which likely explains differences in component structure. Additional differences may relate to the sample and the impulsivity measures used in the study. In the current study, the JANET BART was included along with four submeasures (thrill and adventure seeking, experience seeking,

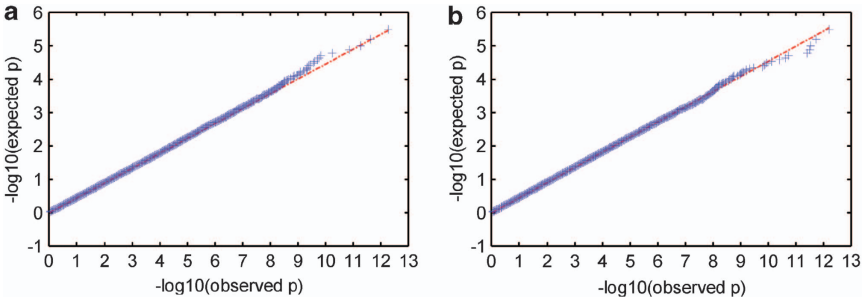

Figure 2. Quantile-Quantile (Q–Q) plot of *P*-values for (**a**) IC1 and (**b**) IC2.

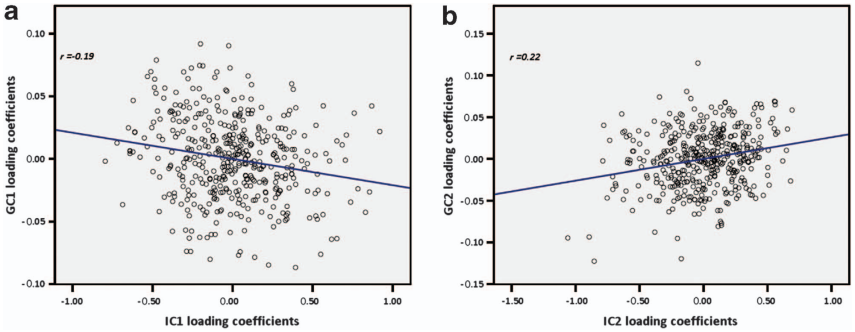

Figure 3. (**a**) Scatter plots of loading coefficients of gene cluster GC1 and impulsivity component IC1; and (**b**) scatter plots of loading coefficients of gene cluster GC2 and impulsivity component IC2.

disinhibition and boredom susceptibility) from the SSS instead of the SSS total score used in our prior study.

Pathway analysis revealed various pathways related to neural development (for example, CAMs in GC1 and focal adhesion in GC2). The association of these pathways seems plausible and suggests neurodevelopmental effects on impulsive behavior. CAM pathways have a vital role in neurogenesis, immune response, interneuronal signaling for learning and memory, and brain development.[44] In addition, CAMs are associated with cognition[45] and various neuropsychiatric disorders.[46] Also, prior studies point to various CAM genes in addiction vulnerability.[47] Neuronal CAM gene, implicated in the CAM pathway (Supplementary Table S1) is involved in neuron–neuron adhesion and promotes directional signaling during axonal cone growth. Neuronal CAM has been associated with drug abuse and personality characteristics such as novelty seeking and reward dependence.[48] Focal adhesion pathways are responsible for cell motility, proliferation, differentiation, survival and regulation of gene expression,[49] and have a major role in central nervous system development. The mitogen-activated protein kinase signaling pathway significantly associated with GC1 and GC2 is involved in cellular proliferation, differentiation and migration. Mitogen-activated protein kinases have a role in various neurodegenerative diseases.[50] The PI3K-Akt signaling pathway associated with GC2 have key role in controlling cellular processes by phosphorylating substrates involved in apoptosis, protein synthesis, metabolism and the cell cycle. Also, PI3K/Akt signaling promotes neural development in hippocampus and has been associated with cognition.[51] Mitogen-activated protein kinase and PI3K/Akt pathways influence focal adhesion kinases that are responsible for neurogenesis via integrin signaling.[52,53] Integrin complex genes overlap between GC2 and both focal adhesion and PI3K/Akt signaling pathways (Supplementary Tables S1 and S2). In addition, abnormality in hippocampal neurogenesis has been linked to impairment of hippocampal-related learning and memory and addiction vulnerability.[54]

Unexpectedly, we found that the first gene component GC1 contained multiple examples of genes related to the major histocompatibility complexes (MHC) classes I and II, and to complement components that are primarily known for immune-related functions. Eight such gene SNPs occurred among the 20 most significantly ranked within GC1, with multiple occurrences of different SNPs from the same genes reoccurring in the same component. In recent years, much attention has been given to the role of MHC proteins, particularly MHC class I, in brain development and plasticity.[55,56] These proteins contribute importantly to neuronal differentiation, synapse formation, synaptic function, synaptic plasticity and activity-dependent refinement of synaptic connections,[55] as well as in modulating behavior and stress reactivity, possibly through hypothalamic–pituitary–adrenal axis function.[56] Immune-related genes are associated with genetic risk for alcoholism.[57] MHC class II antigens are associated with obesity.[58] In addition, association of immune-related genes in schizophrenia has received recent attention.[59] The MHC and complement genes, together with other top-ranked SNP members of GC1, are all located on 6p21.3 (Table 2). Tenascin XB, a MHC class II gene, was the top-ranked gene in GC1. Tenascin XB mediates interactions between cell and extracellular matrix, and has been reported to be associated with schizophrenia,[59] a disorder in which impulsivity has been identified as major problem.[60]

The top-ranked gene in GC2, cytochrome p450, family 19, subfamily A, polypeptide 1 (CYP19A1), regulates aromatase activity in catalyzing estrogen biosynthesis from androgens. Androgens are involved in the regulation of aggression, cognition, emotion and personality,[61] with aromatase activity associated with aggression, including impulsive aggression, in humans and animals.[62]

Among the top 20 most significant genes in our gene networks, we identified many associated with neurogenesis, brain development and several previously reported to be associated with impulsive behaviors. Notch4, among the top 20 genes in GC1, is reportedly involved in neurodevelopment, learning, memory and late-life neurodegeneration.[63] DCC (deleted in colorectal carcinoma) that has a critical role in brain development via axon and neuronal guidance,[64] and in reorganizing dopamine circuitry,[65] was among the top genes in GC1. As dopaminergic system is

Table 2. List of the top 20 genes in GC1

SNP	*Gene*	*Name*	*CHR*	*ZS*	*RW*	*Function*	*Associated disease and/or behavior*
rs2269426	*TNXB*[a]	Tenascin XB	6p21.3	−8.66	1.00	Mediates interactions between cells and extracellular matrix.	SZ
rs2734335	*C2*	Complement component 2	6p21.3	7.60	0.87	Part of complement system	Autoimmune disease, obesity
rs2072633	*RDBP*	Negative elongation factor complex member B	6p21.3	7.44	0.85	Regulates elongation of transcription by RNA polymerase	Unknown
rs2559639	*CHST11*[a]	Carbohydrate sulfotransferase 11	12q23.3	6.90	0.79	Catalyzes transfer of sulfate	Marijuana abuse
rs9266231	*HLA-B*[a]	MHC class I, B	6p21.3	6.79	0.78	Immune system	MS, SZ, BP
rs2249742	*HLA-C*[a]	MHC class I, C	6p21.3	−6.54	0.75	Immune system	Psoriasis, SZ, BP
rs4151657	*CFB*	Complement factor B	6p21.3	−6.54	0.75	Part of complement system.	SZ
rs3134798	*NOTCH4*[a]	Notch4	6p21.3	6.38	0.73	Cognition, brain development.	SZ, AD, BP
rs6931646	*HLA-DRA*[a]	MHC class II, DR alpha	6p21.3	6.12	0.70	Immune system	AD, BP, PD, obesity
rs2844519	*MICA*	MHC class I polypeptide-related sequence A	6p21.33	5.43	0.62	Antigen presentation.	AD
rs151719	*HLA-DMB*[a]	MHC class II, DM beta	6p21.3	5.27	0.60	Peptide loading of MHC class II molecules by helping release the CLIP.	SZ, MS, obesity
rs1787729	*DCC*[a]	Deleted in colorectal carcinoma	18q21.3	5.20	0.60	Axon and neuronal guidance.	SZ, depression
rs2741566	*PIGT*	Phosphatidylinositol glycan anchor biosynthesis, class T	20q12–q13.12	5.01	0.57	Component of GPI transamidase complex	Unknown
rs1511179	*CTNNA2*[a]	Catenin, alpha 2	2p12-p11.1	−4.66	0.53	Cell–cell adhesion and differentiation in nervous system	Excitement seeking/risk taking, AD, ADHD
rs2213565	*HLA-DQA2*[a]	MHC class II, DQ alpha 2	6p21.3	4.62	0.53	Peptide loading of MHC class II beta chain.	Obesity, BP, SZ
rs2544800	*SULT2B1*	Sulfotransferase family, cytosolic, 2B, member 1	19q13.3	4.61	0.53	Catalyzes sulfate conjugation of many hormones, neurotransmitters, drugs and xenobiotic compounds	PD
rs1152663	*CTBP2*[a]	C-terminal binding protein 2	10q26.13	4.60	0.53	Targets diverse transcription regulators	TBI
rs9664844	*PRKG1*[a]	Protein kinase, cGMP dependent, type I	10q11.2	4.48	0.51	Nitric oxide/cGMP signaling pathway	SZ, AD
rs3117578	*CSNK2B*[a]	Casein kinase 2, beta polypeptide	6p21.3	4.46	0.51	Wnt signaling pathway. Regulates basal catalytic activity of the alpha subunit	Unknown
rs7176717	*RORA*[a]	RAR-related orphan receptor A	15q22.2	−4.43	0.51	DA/GLU signaling, circadian rhythms, learning	Autism, PTSD, Depression, BP, MDD

Abbreviations: AD, Alzheimer's disease; ADHD, attention-deficit hyperactivity disorder; BP, bipolar; CHR, chromosome; CLIP, class II-associated invariant chain peptide; MDD, major depressive disorder; MHC, major histocompatibilty complex; MS, multiple sclerosis; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; RW, rank weights; SNP, single-nucleotide polymorphism; SZ, schizophrenia; TBI, traumatic brain injury; ZS, *Z*-score. [a]Multiple SNP occurrence (>2) in gene network. Information provided was gathered from PubMed, genecards and gene associated databases. Refer to Supplementary Table S4 for detailed references.

Table 3. List of the top 20 genes in GC2

SNP	*Gene*	*Name*	*CHR*	*ZS*	*RW*	*Function*	*Associated disease and/or behaviors*
rs1008805	*CYP19A1*[a]	Cytochrome p450, family 19, subfamily A, polypeptide 1	15q21.1	−5.05	1.00	Regulates aromatase activity in catalyzing estrogen biosynthesis from androgens	Obesity, impulsivity
rs6467802	*ATP6V0A4*[a]	ATPase, H+ transporting, lysosomal V0 subunit a4	7q34	−4.82	0.95	Neurotransmitter release	Unknown
rs6952633	*PDE1C*	Phosphodiesterase 1C	7p14.3	4.79	0.94	Neuronal plasticity. Hydrolyzes cAMP and cGMP	Male mating problems in melanogaster
rs1224391	*PRKG1*[a]	Refer to Table 4	—	4.76	0.94	—	—
rs8028974	*RYR3*[a]	Ryanodine receptor 3	15q14–q15	4.60	0.91	Relases calcium from intracellular storage. Neuronal plasticity. Role in CBF and pathological brain response	Social contact, pain sensitivity, fear conditioning
rs12777566	*CTNNA3*	Catenin alpha 3	10q22.2	−4.57	0.90	Cell–cell adhesion	AD
rs9650418	*PPP2R2A*	Protein phosphatase 2, regulatory subunit B, alpha	8p21.2	4.53	0.89	Unknown	Height
rs1313762	*ABCG2*[a]	ATP-binding cassette, subfamily G, member 2	4q22	4.52	0.89	Brain development.	AD, drug abuse
rs8080721	*PRKCA*[a]	Protein kinase C, alpha	17q22–q23.2	4.51	0.89	Emotional memory formation	PTSD, SZ, alcoholism, obesity
rs1704917	*CHST11*	Refer to Table 4	—	4.44	0.87	—	—
rs924138	*ABCC1*	ATP-binding cassette, subfamily C, member 1	16p13.1	4.41	0.87	Brain development. Drug transport across CNS	AD, neurodevelopment disorders
rs918241	*RYR2*	Ryanodine receptor 2	1q43	−4.39	0.86	Role in CBF and pathological responses in brain. Neuronal plasticity	SZ
rs4416750	*MGAM*	Maltase–glucoamylase	7q34	−4.38	0.86	Brain maturation	Unknown
rs751933	*KCNK5*	Potassium channel, subfamily K, member 5	6p21	4.36	0.86	Cell proliferation, migration, apoptosis. Sensitive to environmental stimuli, for example, pH, glucose	MS
rs362794	*RELN*[a]	Reelin	7q22	−4.32	0.85	Synaptic plasticity, brain development. Functional and behavioral development in juvenile prefrontal circuits	ASD, SZ, BP, MDD, AD, impulsivity
rs16531	*CACNB1*	Calcium channel, voltage-dependent, beta 1	17q21–q22	4.23	0.83	Synaptic transmission	Unknown
rs1709834	*PRKCH*	Protein kinase C, Eta	14q23.1	−4.21	0.83	NRG1 interactor in neurite formation	SZ, MDD
rs1460756	*MAPK10*	Mitogen-activated protein kinase 10	4q22.1–q23	4.21	0.83	Neuronal proliferation, differentiation, migration	Anxiety
rs16948648	*ITGA3*	Integrin alpha 3	17q21.33	4.17	0.82	Transmembrane glycoprotein connecting extracellular matrix to cytoskeleton	Neural tube defects, SZ
rs7811880	*WBSCR17*[a]	Williams–Beuren syndrome chromosome region 17	7q11.23	4.13	0.81	Lamellipodium formation, O-glycosylation, macropinocytosis	Williams–Beuren syndrome

Abbreviations: AD, Alzheimer's disease; ASD, autism spectrum disorder; BP, bipolar; CBF, cerebral blood flow; CHR, chromosome; CNS, central nervous system; MDD, major depressive disorder; MS, multiple sclerosis; SNP, single-nucleotide polymorphism; PTSD, post-traumatic stress disorder; RW, rank weights; SZ, schizophrenia; ZS, *Z*-score. [a]Multiple SNP occurrence (>2) in gene network. Information provided was gathered from PubMed, genecards and gene associated databases. Refer to Supplementary Information Table S5 for detailed references.

Table 4. List of top 10 significant pathways for GC1

Pathways	P-*value*	q-*value*
KEGG pathways		
Calcium signaling	2.18×10^{-15}	4.14×10^{-13}
Arrhythmogenic right ventricular cardiomyopathy	1.90×10^{-14}	1.80×10^{-12}
Long-term depression	1.75×10^{-11}	1.11×10^{-09}
Circadian entrainment	2.97×10^{-11}	1.41×10^{-09}
Cell adhesion molecules	7.24×10^{-11}	2.75×10^{-09}
Hypertrophic cardiomyopathy	2.49×10^{-10}	7.18×10^{-09}
Pathways in cancer	2.64×10^{-10}	7.18×10^{-09}
Cholinergic synapse	4.27×10^{-10}	9.61×10^{-09}
MAPK signaling pathway	4.55×10^{-10}	9.61×10^{-09}
Retrograde endocannabinoid signaling	7.37×10^{-10}	1.40×10^{-08}
GeneGo pathways		
Neurophysiological process_ACM regulation of nerve impulse	7.05×10^{-09}	4.12×10^{-06}
Immune response_NFAT in immune response	2.51×10^{-08}	6.20×10^{-06}
Signal transduction_Activation of PKC via G-protein-coupled receptor	3.18×10^{-08}	6.20×10^{-06}
Immune response_BCR	5.01×10^{-08}	7.32×10^{-06}
Neurophysiological process_NMDA-dependent postsynaptic long-term potentiation in CA1 hippocampal neurons	9.51×10^{-08}	1.11×10^{-05}
Development_Gastrin in differentiation of the gastric mucosa	1.20×10^{-07}	1.17×10^{-05}
Immune response_IL-22 signaling	4.97×10^{-07}	4.15×10^{-05}
Immune response_Fc epsilon RI	5.74×10^{-07}	4.19×10^{-05}
Immune response_CCR5 signaling in macrophages and T lymphocytes	1.01×10^{-06}	6.05×10^{-05}
Transport_Alpha-2 adrenergic receptor regulation of ion channels	1.04×10^{-06}	6.05×10^{-05}

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes; BCR, B-cell antigen receptor; IL, interleukin; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NMDA, N-methyl-D-aspartate; PKC, protein kinase C. Uncorrected and false-discovery rate corrected *P*-values are reported in the table.

Table 5. List of top 10 significant pathways for GC2

Pathways	P-*value*	q-*value*
KEGG pathways		
Arrhythmogenic right ventricular cardiomyopathy	1.2×10^{-23}	2.3×10^{-21}
Pathways in cancer	2.2×10^{-19}	2.2×10^{-17}
Focal adhesion	4.2×10^{-19}	2.7×10^{-17}
Dilated cardiomyopathy	1.6×10^{-17}	6.9×10^{-16}
MAPK signaling	1.7×10^{-17}	6.9×10^{-16}
Hypertrophic cardiomyopathy	3.1×10^{-17}	1.0×10^{-15}
Calcium signaling	4.3×10^{-17}	1.2×10^{-15}
PI3K-Akt signaling	2.7×10^{-13}	6.8×10^{-12}
Vascular smooth muscle contraction	1.5×10^{-11}	3.4×10^{-10}
Long-term depression	5.8×10^{-11}	1.1×10^{-09}
GeneGo pathways		
Signal transduction_Activation of PKC via G-protein-coupled receptor	1.0×10^{-09}	6.3×10^{-07}
Immune response_Fc epsilon RI	2.5×10^{-08}	6.1×10^{-06}
Immune response_CD28 signaling	3.1×10^{-08}	6.1×10^{-06}
Immune response_CCR5 signaling in macrophages and T lymphocytes	4.8×10^{-08}	7.0×10^{-06}
Neurophysiological process_Long-term depression in cerebellum	7.2×10^{-08}	8.4×10^{-06}
Immune response_NFAT in immune response	1.1×10^{-07}	1.0×10^{-05}
Immune response_T cell receptor signaling	1.7×10^{-07}	1.4×10^{-05}
Neurophysiological process_NMDA-dependent postsynaptic long-term potentiation in CA1 hippocampal neurons	2.6×10^{-07}	1.9×10^{-05}
Glutamate regulation of dopamine D1A receptor signaling Glutamate regulation of Dopamine D1A receptor signaling	3.1×10^{-07}	2.0×10^{-05}
Ca(2+)-dependent NF-AT signaling in cardiac hypertrophy	3.7×10^{-07}	2.1×10^{-05}

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NMDA, N-methyl-D-aspartate; PKC, protein kinase C. Uncorrected and false-discovery rate corrected *P*-values are reported in the table. KEGG: Kyoto Encyclopedia of Genes and Genomes.

linked to impulsivity,[17] association of DCC and impulsivity seems plausible. Also, increased DCC expression was found in brain of people who committed suicide.[66] CAMs, including catenin (CTNNA2 and CTNNA3) were among the top 20 genes in gene clusters GC1 and GC2. Catenin alpha 2 (CTNNA2) is expressed in prefrontal, temporal and cingulate cortex, hypothalamus and amygdala; brain regions associated with executive function, learning and emotion. In addition, CTNNA2 was previously identified as a gene associated with excitement seeking/risk taking.[12] Ryanodine receptor genes (RYR2 and RYR3), among the top 20 genes in GC2, mediate calcium signaling and are important for neuronal plasticity.[67] Prior studies reported RYRs to have roles in cerebral blood flow and brain responses.[68] Also, RYRs expression is regulated by dopamine D1 receptor signaling system.[69] Dopaminergic system has been associated with impulsivity,[17,25] which suggest role of RYRs in impulsivity. Also,

maltase-glucoamylase, which was among the top 20 genes in GC2, has role in brain maturation.[70]

The RAR-related orphan receptor (RORA), a nuclear hormone receptor gene, has an important role in maintaining circadian rhythms and immune system,[71] and was among the top 20 genes in GC1. Prior mouse studies show the RORA gene to be expressed strongly in the cerebellum and thalamus.[72] In addition, RORA has been associated with learning ability[73] and mood disorder personality trait in neuroticism.[71] Top 20 ranked genes in GC2 included protein kinase C, protein kinase C-alpha (PRKCA) and Reelin. PRKCA is involved in cell proliferation and cell growth arrest by positive and negative regulation of cell cycle, and has an important role in learning and memory.[74] PRKCA has been associated with alcoholism,[75] obesity,[76] memory impairment[77] and predisposition to strong emotional memory.[74] Reelin, whose main function is layering of neurons in cerebellum cortex and cerebellum has an important role in neural plasticity and development,[78] and also has been associated with executive function.[79] Also, interaction of brain dopaminergic, serotonergic and opioid systems with Reelin have role in anxiety and impulsivity.[80]

We identified various pathways related to nervous system signal generation, amplification or transduction (calcium signaling, LTD, activation of protein kinase C via G-protein-coupled receptor, N-methyl-D-aspartate-dependent long-term potentiation in hippocampal CA1 neurons in both GC1 and GC2, and cholinergic receptor, muscarinin (ACM) regulation of nerve impulse in GC1). Calcium signaling was the top-most significant pathways in GC1, and is important in neuronal synaptic transmission, signal transduction and cell signaling.[81] Association of this pathway seems plausible because calcium signaling has also been linked with dopamine receptors that have a significant role in impulsivity-associated behaviors.[17,81] Also, calcium signaling pathway is associated with opioid dependence.[82] Calcium signaling is also important in neural plasticity and has been linked with neurodegenerative diseases.[83] Thus, our finding suggests that altered calcium signaling might relate to impulsivity-related behaviors. LTD has an important role in learning and memory and is altered in various pathological conditions.[84] In addition, LTD is involved in adolescent cognitive and executive function[85] and has been associated with drug addiction and acute stress.[86] ACM participate in many physiological processes through regulation of calcium ion transport (for example, regulation of neuronal neurotransmitter release). Long-term potentiation is responsible for learning and memory.[87] Prior study reported abnormal protein kinase C signaling in prefrontal cortex to be associated with impulsivity, distraction and impaired judgment.[88]

Pathways related to neurotransmission (cholinergic synapse, retrograde endocannabinoid signaling, alpha 2 adrenergic receptor regulation of ion channels in GC1 and glutamate regulation of dopamine D1A receptor signaling in GC2) were significantly associated with our gene clusters. Implication of these pathways in our study supports prevailing hypothesis that impulsive behaviors are modulated by neurotransmitters and their receptors.[89] The cholinergic signaling pathway modulates neural differentiation, neurogenesis, involved in synaptic plasticity[90] and neural development.[91] Also, acetylcholine function is associated with impulsive action.[92] The retrograde endocannabinoid signaling pathway regulates axonal growth and guidance during development and adult neurogenesis.[93] The associated cannabinoid receptor (CB1) is expressed in hippocampus, basal ganglia and cerebellum;[94] rodent studies suggest that CB1 and CB2 receptors has a role in regulation of impulsive behaviors.[94,95] The endocannabinoid system also has been associated with substance abuse, addiction and other psychiatric disorders.[96] The type-1 cannabinoid receptor may also moderate the relationship between trait impulsivity and marijuana-related behavioral problems.[97] Identification of glutamate regulation of dopamine D1A receptor signaling pathways was consistent with prior studies reporting glutamate and dopamine involvement in impulsivity.[17,20]

Circadian entrainment pathway was associated with GC1. Prior study has shown association of sleep duration and impulsivity in men.[98] Serotonin, a key neurotransmitter is associated with both impulsivity and sleep/wake cycle.[17,98] Serotonin and circadian systems of brain are linked both anatomically and genetically through various signaling molecules.[99] Thus, implication of circadian pathways suggests that abnormal circadian rhythm might induce impulsive behavior. Other significant pathways were related to cardiovascular diseases including various cardiomyopathy-associated pathways. Most of the genes overlapping with gene cluster and pathways were calcium signaling, integrin and CAMs (Supplementary Tables S1 and S2). Also, these genes are most likely expressed in brain as well as heart. Nuclear factor of activated T cells in immune response and Ca(2+)-dependent nuclear factor of activated T cells signaling in cardiac hypertrophy were among significant pathways. Members of the nuclear factor of activated T cells family of transcription factors are implicated in shaping neuronal function throughout the nervous system. Also, stimulation of D1 dopamine receptors induces nuclear factor of activated T cells-dependent transcription through activation of L-type calcium channels.[100] To our surprise, pathways in cancer was associated with both GC1 and GC2. However, genes overlapping between gene clusters and pathways were associated with neurogenesis (AKT2, AKT3, integrin molecules and CAMs), calcium signaling (RYRs and PRKCA), regulation of neurotransmitters (AKT2, AKT3 and BCL2; Supplementary Tables S1 and S2). Also, overlapping genes CTNNA2, RYRs and PRKCA (also among the top 20 genes in GC1 and GC2) are associated with impulsive behavior and disorders associated with impulsivity (Supplementary Tables S4 and S5).

Limitations and future directions

Owing to limitation of Para-ICA, we were only able to include a subset of SNP data in the analysis. Thus, it is possible that we overlooked other genetic components that potentially might be associated with impulsivity. Current study was limited with sample from young adults (age 18–24 years). Also, current study does not take into account the current medications, substance abuse that might have confounding effects on their impulsive behaviors. There are multiple other impulsivity measures that were not included in the current study. Impulsivity measures in our study were based on those used in our prior studies and limited by the number of test batteries that could be practically completed in a single test session without risking participant fatigue and disengagement. Future studies should consider other impulsivity assessments to further investigate their genetic and biological associations.

CONCLUSION

In the current study, we used the multivariate technique Para-ICA to identify genetic associations with impulsivity-related measures and identified various genetic pathways and genes associated with impulsivity and related constructs. Many of the genetic pathways identified contribute to brain development, nervous system signal generation, amplification or transduction, neurotransmitter regulation, calcium signaling and immune response. This study suggests that these pathways and associated genes contribute to impulsive behaviors in young adults. Furthermore, pathways identified in current study might be potential target sites for medication development and a future research area for various psychiatric conditions characterized by elevated impulsivity.

CONFLICT OF INTEREST

MNP has received financial support or compensation for the following: MNP has consulted for Ironwood and Lundbeck; has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming and Psyadon pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for law offices and gambling entities on issues related to impulse-control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the National Institutes of Health and other agencies; has edited journals or journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The remaining authors declare no conflict of interest.

ACKNOWLEDGMENTS

This study is funded by National Institute of Alcohol Abuse and Alcoholism Grants AA016599 & AA19036 to Dr GD Pearlson.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)