Impulsivity is a heritable, multifaceted construct with clinically relevant links to multiple psychopathologies. We assessed impulsivity in young adult (N = 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
can be linked via annotation pathways to known molecular biological processes.\textsuperscript{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.\textsuperscript{22,23} 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.\textsuperscript{21,23} Consequently, in the current study, we used Para-ICA\textsuperscript{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\textsuperscript{25} recently reviewed various neurotransmission systems (dopaminergic, serotonergic, noradrenergic, glutamergic, GABAergic, opiodergic, 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.\textsuperscript{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.\textsuperscript{26} We hypothesized that the biological processes identified by Para-ICA would contain genes identified previously as associated with brain development; impulsitive 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\textsuperscript{27} consisting of the subset of participants from the larger sample (\(N = 2100\)) 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,\textsuperscript{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.\textsuperscript{28} Thus, intelligence quotient estimates were calculated using Scholastic Assessment Test scores as recommended by Frey and Detterman.\textsuperscript{29} 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.\textsuperscript{1} Self-report measures were as follows: (i) Bariatt Impulsiveness Scale (BIS-11),\textsuperscript{29} (ii) Behavioral-Inhibition System/Behavioral-Activation System scale (BIS/BAS),\textsuperscript{30} (iii) Sensitivity to Punishment and Reward Questionnaire (SPSRQ),\textsuperscript{31} (iv) Zuckerman Sensation Seeking Scale (SSS)\textsuperscript{32} and (v) Padua Inventory (PI).\textsuperscript{33} Computer-based behavioral tasks consisted of (i) two different versions of the Balloon Analog Risk Task (BART), the Jive Neuropsychological Test (JANET) BART\textsuperscript{34} and conventional BART,\textsuperscript{35} and (ii) Experiential Discounting Task (EDT).\textsuperscript{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.\textsuperscript{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 (\(N = 582300\)) were considered for further processing. We followed quality control steps of SNPs data using PLINK software as reported elsewhere.\textsuperscript{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 SNP was ~ 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.\textsuperscript{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,\textsuperscript{22} we took processed SNPs and queried using Kyoto Encyclopedia of Genes and Genomes (KEGG) database (www.genome.jp/kegg). Finally, 26142 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://fusica.mrn.org/software/fitu/) was used in MATLAB 7.7. Data were prepared using PLINK and 18 (impulsivity-related measures) and SNPs as (426 subject) × 26142 (SNPs), which were then input to Para-ICA.\textsuperscript{22,24} The number of independent components for impulsivity-related and SNPs data was calculated using minimum description length criteria\textsuperscript{40} and the number of components estimated was 6 for impulsivity-related measures and 17 for SNPs.

---

**Table 1. Demographic Information**

| Demographic Information | Caucasian | African American | Hispanic | Mixed/other |
|-------------------------|-----------|------------------|----------|------------|
|                         | Male      | Female           | Male     | Female     | Male     | Female |
| Subjects (N)            | 137       | 172              | 17       | 30         | 13       | 21     |
| Age range (years)       |            |                  | 17–24    |            | 18       | 18     |
| Mean age (years; s.d.)  |            |                  | 18.31 (0.77) |            | 18.34 (0.87) |
impulsivity-related measures represented in IC1 were reward-sensitivity and Behavioral-Inhibition system scale scores of BIS/BAS scale. 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. 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 was 99.6% and 98.1%, respectively.

**Pathway analysis**

Pathways associated with GC1 (associated with IC1) included calcium signaling, cell adhesion molecules (CAMs), chololergic synapse, long-term depression (LTD), long-term potentiation and various immune response pathways. Similarly pathways associated with GC2 (associated with IC2) included focial 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. 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. The impulsivity-related constructs may vary depending upon the number and type of tests administered. The impulsivity-related components emerging from the current study differ from those we reported in a prior study. 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, 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,

---

**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

---

**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 both the 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. Genes with $P < 0.05$ values were input for enrichment analysis in Metacore-based annotation software GeneGo (https://portal.genego.com/) and ConsensusPathDB (http://crdb.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.

---

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

---

© 2014 Macmillan Publishers Limited

Translational Psychiatry (2014), 1 – 11

S Khadka et al
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.\textsuperscript{44} In addition, CAMs are associated with cognition\textsuperscript{45} and various neuropsychiatric disorders.\textsuperscript{46} Also, prior studies point to various CAM genes in addiction vulnerability.\textsuperscript{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.\textsuperscript{48} Focal adhesion pathways are responsible for cell motility, proliferation, differentiation, survival and regulation of gene expression,\textsuperscript{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.\textsuperscript{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.\textsuperscript{51} Mitogen-activated protein kinase and PI3K/Akt pathways influence focal adhesion kinases that are responsible for neurogenesis via integrin signaling.\textsuperscript{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.\textsuperscript{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.\textsuperscript{55,56} These proteins contribute importantly to neuronal differentiation, synapse formation, synaptic function, synaptic plasticity and activity-dependent refinement of synaptic connections,\textsuperscript{57} as well as in modulating behavior and stress reactivity, possibly through hypothalamic–pituitary–adrenal axis function.\textsuperscript{56} Immune-related genes are associated with genetic risk for alcoholism.\textsuperscript{58} MHC class II antigens are associated with obesity.\textsuperscript{59} In addition, association of immune-related genes in schizophrenia has received recent attention.\textsuperscript{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. As dopaminergic system is reportedly involved in neurodevelopment, learning, memory and life neurodegeneration.\textsuperscript{60} DCC (deleted in colorectal carcinoma) that has a critical role in brain development via axon and neuronal guidance,\textsuperscript{61} and in reorganizing dopamine circuitry,\textsuperscript{62} 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                  |
|--------------|---------------|-------------------------------|-----|-----|-----|--------------------------------------------------------------------------|------------------------------------------------------|
| rs2264926    | TNXB          | 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    | NDBP          | Negative elongation factor complex member B | 6p21.3 | 7.44  | 0.85 | Regulates elongation of transcription by RNA polymerase                  | Unknown                                              |
| rs2559639    | CHST1A        | Carbohydrate sulfate transferase 11 | 12q23.3 | 6.90  | 0.79 | Catalyzes transfer of sulfate                                            | Marijuana abuse                                      |
| rs9266231    | HLA-B         | MHC class I, B                | 6p21.3 | 6.79  | 0.78 | Immune system                                                            | MS, SZ, BP                                           |
| rs2249742    | HLA-C         | 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        | Notch4                        | 6p21.3 | 6.38  | 0.73 | Cognition, brain development.                                            | SZ, AD, BP                                           |
| rs6931646    | HLA-DRA       | 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       | 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           | 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- | 5.01  | 0.57 | Component of GPI transamidase complex                                     | Unknown                                              |
| rs1511179    | CTNNA2        | 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      | 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, cytotoxic, 2B, member 1 | 19q13.3 | 4.61  | 0.53 | Catalyzes sulfate conjugation of many hormones, neurotransmitters, drugs and xenobiotic compounds | PD                                                   |
| rs1152663    | CTPBP2        | C-terminal binding protein 2  | 10q26.13 | 4.60  | 0.53 | Targets diverse transcription regulators                                  | TBI                                                  |
| rs9664844    | PRKG1         | Protein kinase, cGMP dependent, type I | 10q11.2 | 4.48  | 0.51 | Nitric oxide/cGMP signaling pathway                                       | SZ, AD                                               |
| rs3117578    | CSNK2B        | 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          | 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 histocompatibility 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. *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.
| SNP     | Gene Name                        | CHR  | ZS   | RW  | Function                                                                 | Associated disease and/or behaviors                                  |
|---------|----------------------------------|------|------|-----|--------------------------------------------------------------------------|----------------------------------------------------------------------|
| rs1008805 | CYP19A1                         | 15q21.1 | -5.05 | 1.00 | Regulates aromatase activity in catalyzing estrogen biosynthesis from androgens | Obesity, impulsivity                                               |
| rs6467802 | ATP6V0A4                        | 7q34  | -4.82 | 0.95 | Neurotransmitter release                                                 | Unknown                                                              |
| rs6952633 | PDE1C                           | 7p14.3 | 4.79  | 0.94 | Neuronal plasticity. Hydrolyzes cAMP and cGMP                            | Male mating problems in melagaster                                  |
| rs1224391 | PRKGI                           | -     | 4.76  | 0.94 | —                                                                         | —                                                                   |
| rs8028974 | RYR3                            | 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                  |
| rs1277566 | CTNNB3                          | 10q22.2 | -4.57 | 0.90 | Cell–cell adhesion                                                      | AD                                                                   |
| rs9050418 | PPP29R2A                        | 8p21.2 | 4.53  | 0.89 | —                                                                         | Height                                                               |
| rs1313762 | ABCG2                           | 4q22  | 4.52  | 0.89 | Brain development.                                                       | AD, drug abuse                                                      |
| rs8080721 | PRKCA                           | 17q22-q23.2 | 4.51 | 0.89 | Emotional memory formation                                               | PTSD, SZ, alcoholism, obesity                                      |
| rs1709417 | CHST11                          | —     | 4.44  | 0.87 | —                                                                         | —                                                                   |
| rs924138  | ABCI                            | 16p13.1 | 4.41  | 0.87 | Brain development. Drug transport across CNS                             | AD, neurodevelopment disorders                                      |
| rs198241  | RYR2                            | 1q43  | -4.39 | 0.86 | Role in CBF and pathological responses in brain. Neuronal plasticity     | SZ                                                                   |
| rs4416750 | MGAM                            | 7q34  | -4.38 | 0.86 | Cell proliferation, migration, apoptosis. Sensitive to environmental stimuli, for example, pH, glucose | Unknown                                                              |
| rs751933  | KCNK5                           | 6p21  | 4.36  | 0.86 | Brain maturation                                                         | MS                                                                   |
| rs362794  | RELN                            | 7q22  | -4.32 | 0.85 | Synaptic plasticity, brain development. Functional and behavioral development in juvenile prefrontal circuits | ASD, SZ, BP, MDD, AD, impulsivity                                  |
| rs16531   | CAONB1                          | 17q21-q22 | 4.23 | 0.83 | Sypaptic transmission                                                   | Unknown                                                              |
| rs1709834 | PRKCH                           | 14q23.1 | -4.21 | 0.83 | NRG1 Interactor in neurite formation                                      | SZ, MDD                                                             |
| rs1460756 | MAPK10                          | 4q22.1-q23 | 4.21 | 0.83 | Neuronal proliferation, differentiation, migration                       | Anxiety                                                              |
| rs16948648 | ITGA3                           | 17q21.33 | 4.17 | 0.82 | Transmembrane glycoprotein connecting extracellular matrix to cytoskeleton | Neural tube defects, SZ                                            |
| rs7811880 | WBSCR17                         | 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. *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.
linked to impulsivity, association of DCC and impulsivity seems plausible. Also, increased DCC expression was found in brain of people who committed suicide. 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. Ryynodine receptor genes (RYR2 and RYR3), among the top 20 genes in GC2, mediate calcium signaling and are important for neuronal plasticity. Prior studies reported RYRs to have roles in impulsivity, which suggests a role of RYRs in impulsivity. Also, RYRs are involved in the regulation of calcium channels and are important for neuronal plasticity.

### Table 4. List of top 10 significant pathways for GC1

| Pathways                                      | P-value | q-value |
|-----------------------------------------------|---------|---------|
| Calcium signaling                             | 2.18 x 10^{-15} | 4.14 x 10^{-14} |
| Arrhythmogenic right ventricular cardiomyopathy | 1.90 x 10^{-14} | 1.80 x 10^{-13} |
| Long-term depression                          | 1.75 x 10^{-11} | 1.11 x 10^{-10} |
| Circadian entrainment                         | 2.97 x 10^{-11} | 1.41 x 10^{-10} |
| Cell adhesion molecules                       | 7.24 x 10^{-11} | 2.75 x 10^{-10} |
| Hypertrophic cardiomyopathy                   | 2.49 x 10^{-10} | 7.18 x 10^{-10} |
| Pathways in cancer                            | 2.64 x 10^{-10} | 7.18 x 10^{-10} |
| Cholinergic synapse                           | 4.27 x 10^{-10} | 9.61 x 10^{-10} |
| MAPK signaling pathway                        | 4.55 x 10^{-10} | 9.61 x 10^{-10} |
| Retrograde endocannabinoid signaling          | 7.37 x 10^{-10} | 1.40 x 10^{-08} |

**GeneGo pathways**

| Pathways                                      | P-value | q-value |
|-----------------------------------------------|---------|---------|
| Neurophysiological process_ACM regulation of nerve impulse | 7.05 x 10^{-09} | 4.12 x 10^{-06} |
| Immune response_NFAT in immune response       | 2.51 x 10^{-08} | 6.20 x 10^{-06} |
| Signal transduction_Activation of PKC via G-protein-coupled receptor | 3.18 x 10^{-08} | 6.20 x 10^{-06} |
| Immune response_BCR                          | 5.01 x 10^{-08} | 7.32 x 10^{-06} |
| Neurophysiological process_NMWD-dependent postsynaptic long-term potentiation in CA1 hippocampal neurons | 9.51 x 10^{-08} | 1.11 x 10^{-05} |
| Development_Gastrin in differentiation of the gastric mucosa | 1.20 x 10^{-07} | 1.17 x 10^{-05} |
| Immune response_IL-22 signaling              | 4.97 x 10^{-07} | 4.15 x 10^{-05} |
| Immune response_Fc epsilon RI                 | 5.74 x 10^{-07} | 4.19 x 10^{-05} |
| Immune response_CCR5 signaling in macrophages and T lymphocytes | 1.01 x 10^{-06} | 6.05 x 10^{-05} |
| Transport_Alpha-2 adrenergic receptor regulation of ion channels | 1.04 x 10^{-06} | 6.05 x 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; NMWD, 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 |
|-----------------------------------------------|---------|---------|
| Calcium signaling                             | 1.2 x 10^{-23} | 2.3 x 10^{-21} |
| Pathways in cancer                            | 2.2 x 10^{-19} | 2.2 x 10^{-17} |
| Focal adhesion                                | 4.2 x 10^{-19} | 2.7 x 10^{-17} |
| Dilated cardiomyopathy                        | 6.1 x 10^{-17} | 6.9 x 10^{-16} |
| MAPK signaling                                | 1.7 x 10^{-17} | 6.9 x 10^{-16} |
| Hypertrophic cardiomyopathy                   | 3.1 x 10^{-17} | 1.0 x 10^{-15} |
| Calcium signaling                             | 4.3 x 10^{-17} | 1.2 x 10^{-15} |
| PI3K-Akt signaling                            | 2.7 x 10^{-17} | 6.8 x 10^{-17} |
| Vascular smooth muscle contraction             | 1.5 x 10^{-11} | 8.4 x 10^{-10} |
| Long-term depression                          | 5.8 x 10^{-11} | 1.1 x 10^{-09} |

**GeneGo pathways**

| Pathways                                      | P-value | q-value |
|-----------------------------------------------|---------|---------|
| Signal transduction_Activation of PKC via G-protein-coupled receptor | 1.0 x 10^{-09} | 6.3 x 10^{-07} |
| Immune response_Fc epsilon RI                 | 2.5 x 10^{-08} | 6.1 x 10^{-06} |
| Immune response_CCR5 signaling in macrophages and T lymphocytes | 3.1 x 10^{-08} | 6.1 x 10^{-06} |
| Neurophysiological process_Long-term depression in cerebellum | 4.8 x 10^{-08} | 7.0 x 10^{-06} |
| Immune response_NFAT in immune response       | 7.2 x 10^{-08} | 8.4 x 10^{-06} |
| Immune response_T cell receptor signaling     | 1.1 x 10^{-07} | 1.0 x 10^{-05} |
| Neurophysiological process_NMWD-dependent postsynaptic long-term potentiation in CA1 hippocampal neurons | 2.6 x 10^{-07} | 7.19 x 10^{-05} |
| Glutamate regulation of dopamine D1A receptor signaling | 3.1 x 10^{-07} | 2.0 x 10^{-05} |
| Ca(2+)-dependent NF-AT signaling in cardiac hypertrophy | 3.7 x 10^{-07} | 2.1 x 10^{-05} |

**Abbreviations:** KEGG, Kyoto Encyclopedia of Genes and Genomes; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NMWD, 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.

© 2014 Macmillan Publishers Limited
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 ability73 and mood disorder personality trait in neuroticism.74 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 impairment77 and predisposition to strong emotional memory.76 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, muscarinic (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 function85 and has been associated with drug addiction and acute stress.86 ACM participates 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 plasticity90 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.17,99 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 CTNNB1, RYRs and PRKCA (also among the top 20 genes in GC1 and GC2) are associated with impulsivity 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

MHP has received financial support or compensation for the following: MHP has consulted for Ironwood and Lundbeck; has received research support from Mohegan Sun Casino, the National Center for Responsible Gaming and Psyadon pharmacueticals; 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 & AA119036 to Dr GD Pearlson.

REFERENCES

1 Canli T, Congdon E, Todd Constable R, Lesch KP. Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on neural correlates of affective processing. Biol Psychology 2008; 79: 118–125.
2 Congdon E, Lesch KP, Canli T. Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. Am J Med Genet B Neuropsychiatr Genet 2008; 147B: 27–32.
3 Meda SA, Stevens MC, Potenza MN, Pittman B, Gueorguieva R, Andrews MM et al. Investigating the behavioral and self-report constructs of impulsivity domains using principal component analysis. Behav Pharmacol 2009; 20: 390–399.
4 Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry 2001; 158: 1783–1793.
5 Fineberg NA, Chamberlain SR, Goudriaan AE, Stein DJ, Vanderschuren LJ, Gillan CM et al. New developments in human neurocognition: clinical, genetic, and brain imaging correlates of impulsivity and compulsivity. CNS Spect 2014; 19: 69–89.
6 First MB. Diagnostic and statistical manual of mental disorders, 5th edition, and clinical. J Nerv Ment Dis 2013; 201: 727–729.
7 Chamberlain SR, Sahakian BJ. The neuropyschiatry of impulsivity. Curr Opin Psychiatry 2007; 20: 255–261.
8 Verdejo-Garcia A, Lawrence AJ, Clark L. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk, problem gamblers and genetic association studies. Neurosci Biobehav Rev 2008; 32: 777–810.
9 Balestri M, Calati R, Serretti A, De Ronchi D. Genetic modulation of personality traits: a systematic review of the literature. Int Clin Psychopharmacol 2013; 29: 1–15.
10 Cervenka A, Nagel BJ. Risky decision-making: an FMRI study of youth at high risk for alcoholism. Alcohol Clin Exp Res 2012; 36: 604–615.
11 Dager AD, Anderson BM, Stevens MC, Pulido C, Rosen R, Jaintonio-Kelly RE et al. Influence of alcohol use and family history of alcoholism on neural response to alcohol cues in college drinkers. Alcohol Clin Exp Res 2013; 37: E161–E171.
12 Terracciano A, Eiko T, Sutin AR, de Moor MH, Meirelles O, Zhu G et al. Meta-analysis of genome-wide association studies identifies common variants in CTNNA2 associated with excitement-seeking. J Hum Genet 2012; 57: 428–434.
13 Volkow ND, Wang GJ, Tomasi D, Baler RD. Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Indiv Diff 2001; 31: 837–862.
14 Zuckerman M, Neeb M. Sensation seeking and psychopathology. Psychiatry Res 1979; 1: 255–264.
15 Sternberger LG, Burns GL. Obsessions and compulsions: psychometric properties of the Padua Inventory with an American college population. Behav Res Ther 1990; 28: 341–345.
16 Chekli S, Satish S, Mathew SS, Dinesh N, Kumar CT, Lombardo LE et al. Cross-cultural standardization of the South Texas Assessment of Neurocognition in Indian. J Med Res 2012; 136: 280–288.
17 Hunt MK, Hopko DR, Bare R, Lejuez CW, Robinson EV. Construct validity of the Balloon Analog Risk Task (BART): associations with psychopathy and impulsivity. Assessment 2005; 12: 416–428.
18 Reynolds B, Schiffrauer R. Rating state changes in human delayed discounting: an experimental discounting task. Behav Process 2004; 67: 343–356.
19 Nunes AP, Oliveira IO, Santos BR, Millech C, Silva LP, Gonzalez DA et al. Quality of DNA extracted from saliva samples collected with the Oragene DNA self-collection kit. BMC Med Res Methodol 2012; 12: 65.
20 Anderson CA, Pettersson FH, Clarke GM, Cardon LR, Morris AP, Zondervan KT. Data quality control in genetic case-control association studies. Nat Protoc 2010; 5: 1564–1573.
21 Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis correctly assesses for stratification in genome-wide association studies. Nat Genet 2006; 38: 904–909.
22 Calhoun VD, Adali T, Pearlson GD, Pekar JI. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 2001; 14: 140–151.
23 Liu JZ, McElroy AE, Nyholm DR, Medland SE, Wray NR, Brown KM et al. A versatile gene-based test for genome-wide association studies. Am J Hum Genet 2010; 87: 139–145.
24 Reiner-Benaim A. FDR control by the BH procedure for two-sided correlated tests. Psychol Methods 2009; 14: 1–15.
25 Dick DM, Smith G, Olausson P, Mitchell SH, Leeman RF, O'Malley SS et al. Understanding the construct of impulsivity and its relationship to alcohol use disorders. Addict Biol 2010; 15: 217–226.
26 Benson DL, Schnapp LM, Shapiro L, Huntley GW. Making memories stick: cell-adhesion molecules in synaptic plasticity. Trends Cell Biol 2000; 10: 473–482.
27 Gallistel CR, Tucci V, Nolan PM, Schachner M, Jakovlevski I, Kheifets A et al. Cognitive assessment of mice strains heterozygous for cell-adhesion genes reveals strain-specific alterations in timing. Philos Trans R Soc Lond Biol Sci 2014; 369: 20464.
for posttraumatic stress disorder in genocide survivors. Proc Natl Acad Sci USA 2010; 107: 8746–8751.

57 Rood ZA, Kimpel MW, Edenberg HJ, Bell RL, Strother WN, McLintick JN et al. Differential gene expression in the nucleus accumbens with ethanol self-administration in inbred alcohol-prefering rats. Pharmacol Biochem Behav 2008; 89: 481–498.

58 Melen E, Himes BE, Brehm JM, Boutaoui N, Klandereman BJ, Sylvia JS et al. Analyses of shared genetic factors between asthma and obesity in children. J Allergy Clin Immunol 2010; 126: 631–e1-8.

59 Jablensky A, Morar B, Wiltshire S, Carter K, Dragovic M, Baddock JC et al. Poly-morphisms associated with normal memory variation also affect memory impairment in schizophrenia. Genes Brain Behav 2011; 10: 410–417.

60 Feloum TD, Fatiemi SH. The involvement of Reelin in neurodevelopmental disorders. Neuropharmacology 2013; 68: 122–135.

61 Baune BT, Konrad C, Suslow T, Domschke K, Birosova E, Sehlmeyer C et al. The Reelin (RELN) gene is associated with executive function in healthy individuals. Neurobiol Learn Mem 2010; 94: 446–451.

62 Laviola G, Ognibene E, Romano E, Adriani W, Keller F. Gene-environment interaction during early development in the heterogeneous reeler mouse: clues for modelling of major neurobehavioral syndromes. Neurosci Biobehav Rev 2009; 33: 560–572.

63 Hasbi A, Fan T, Aljianaram M, Nguyen T, Perreault ML, O'Dowd BF et al. Calcium signaling cascade links dopamine D1-D2 receptor heteromer to striatal BDNF production and neuronal growth. Proc Natl Acad Sci USA 2009; 106: 21377–21382.

64 Geelen J, Kranzler HR, Sherva R, Koesterer R, Almasy L, Zhao H et al. Genome-wide association study of opioid dependence: multiple associations mapped to calcium and potassium pathways. Biol Psychiatry 2013; 76: 66–74.

65 Marambaud P, Drees-Werringloer U, Vingtdeux V. Calcium signaling in neurodegeneration. Mol Neurodegener 2009; 4: 20.

66 Massesy PV, Bashir ZI. Long-term depression: multiple forms and implications for brain function. Trends Neurosci 2007; 30: 176–184.

67 Seelam LD. A role for synaptic plasticity in the adolescent development of executive function. Transl Psychiatry 2013; 3: e238.

68 Collingridge GL, Peineau S, Howland JG, Wang YT. Long-term depression in the CNS. Nat Rev Neurosci 2010; 11: 459–473.

69 Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993; 361: 31–39.

70 Birnbaum SG, Yuan PX, Wang M, Vijayaraghavan S, Bloom AK, Davis DJ et al. Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. Science 2004; 306: 882–884.

71 Pattij T, Vanderschuren LJ. The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci 2008; 29: 192–199.

72 Lucas-Meunier E, Fossier P, Baux G, Amar M. Cholinergic modulation of the cortico-striatal cholinergic system. Behav Brain Res 2011; 221: 367–378.

73 Tsutsui-Kimura I, Ohumura Y, Izuimi T, Yamaguchi T, Yoshida T, Yoshio M. Endogenous acetylcholine modulates impulsive action via alpha4beta2 nicotinic acetylcholine receptors in rats. Eur J Pharmacol 2010; 641: 148–153.

74 Gao Y, Vasilyev DV, Goncalves MB, Howland PV, Hobbs C, Reisenberg M et al. Loss of retrograde endocannabinoid signaling and reduced adult neurogenesis in dyscycloperid lipase knock-out mice. J Neurosci 2010; 30: 2017–2024.

75 Wiskerke J, Stoop N, Schetters D, Schoffelmeer AN. Pattij T. Cannabinoid CB1 receptor activation mediates the opposing effects of amphetamine on impulsive action and impulsive choice. PLoS One 2011; 6: e25856.

76 Navarrete F, Perez-Ortiz JM, Manzano J. Cannabinoid CB1 receptor-mediated regulation of impulsive-like behaviour in DAB2A mice. Br J Pharmacol 2012; 165: 260–273.

77 Dinu IR, Popa S, Bicu M, Mota E, Mota M. The implication of CNR1 gene’s polymorphisms in the modulation of endocannabinoid system effects. Rom J Intern Med 2009; 47: 9–18.

78 Ridell LC, Metrik J, Mcgeary J, Palmer RH, Francazio S, Knopik VS. Impulsivity, cadian systems: nature and nurture in rhythms and blues. Neuroscience 2011; 197: 8–16.

79 Groth RD, Weick JP, Bradley KC, Luoma J, Aravamudan B, Klug JR et al. D1 dopamine receptor activation of NFAT-mediated striatal gene expression. Eur J Neurosci 2008; 27: 31–42.
Genetic association of impulsivity in young adults
S Khadka et al

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