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Genetic Sources of Sub-components of Event-Related Potential in the Dimension of Psychosis analyzed from the BSNIP Study

Balaji Narayanan, Ph.D.[1], **Lauren E. Ethridge, Ph.D.**[2], **Kasey O'Neil, B.S.**[1], **Sabra Dunn, B.S**[1], **Ian Mathew, B.S**[3], **Neeraj Tandon, B.S**[3], **Vince D. Calhoun, Ph.D**[4,5,9], **Gualberto Ruaño, M.D., Ph.D**[6,7], **Mohan Kocherla, M.S.**[6,7], **Andreas Windemuth, Ph.D.**[7], **Brett A. Clementz, Ph.D.**[8], **Carol A. Tamminga, M.D.**[2], **John A. Sweeney, Ph.D.**[2], **Matcheri S. Keshavan, M.D.**[3], and **Godfrey D. Pearlson, M.D.**[1,9]

[1]Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT-06106 [2]Department of Psychiatry, UT Southwestern Medical School, Dallas, TX-75390 [3]Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA-02215 and [4]Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM, 87131 [5]The Mind Research Network, Albuquerque, NM-87106 [6]Genetics Research Center, Hartford Hospital, Hartford, CT-06106 [7]Genomas Inc, Hartford, CT-06106 [8]Department of Psychology, University of Georgia, Athens, GA-30602; [9]Departments of Psychiatry & Neurobiology, Yale University School of Medicine, New Haven, CT-06520

Abstract

Objective—Biological risk factors underlying psychosis are poorly understood. Biological underpinnings of the dimension of psychosis can be derived using genetic associations with intermediate phenotypes such as sub-components of auditory event related potentials (ERPs). Various ERP sub-component abnormalities in schizophrenia (SZ) and bipolar disorder with psychosis (PBP) are heritable and expressed in unaffected relatives. Prior studies investigating genetic contributions to ERP abnormalities are limited. We used a novel parallel independent component analysis (Para-ICA) to determine which empirically-derived gene clusters are associated with data-driven ERP sub-components, assuming a complex etiology underlying psychosis.

Methods—We examined the multivariate polygenic association of ERP sub-components from 64-channel auditory oddball data in 144 SZ, 210 PBP probands and 95 healthy individuals from the multi-site BSNIP study. Data were reduced by principal component analysis to 2 target and 1 standard ERP waveforms. Multivariate association of compressed ERP waveforms with a set of 20,329 SNPs (reduced from a one million SNP array) was examined using Para-ICA. Genes associated with SNPs were further examined using pathway analysis tools.

Correspondence should be addressed to: Balaji Narayanan Ph.D, Olin Neuropsychiatry Research Center, Hartford Hospital (Institute of Living), Hartford, CT-06106 USA, Ph: 860-545-7779, balaji.narayanan@hhchealth.org.

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Results—Para-ICA identified 4 ERP components that were significantly correlated with 3 genetic components. Enrichment analysis revealed complement immune response pathway and multiple processes including synaptic cell adhesion, axon guidance and neurogenesis significantly mediating ERP abnormalities in psychosis.

Conclusions—We identified three genetic components comprising multiple genes mediating ERP sub-component abnormalities in SZ and PBP. Our data suggest a possible polygenic structure comprised of genes influencing key neurodevelopmental processes, neural circuitry, brain function mediating biological pathways plausibly associated with psychoses.

Keywords

Schizophrenia; Bipolar disorder; Psychosis; Single Nucleotide Polymorphism; gene; Pathway; Event-Related Potential

Introduction

The psychosis dimension contains complex, disabling mental illnesses including schizophrenia (SZ), schizoaffective (SZA) and psychotic bipolar disorder (PBP); evidence indicates significant overlap for clinical features (1), brain function and structure (2), pharmacological treatment (3) and genetic determinants (4). Psychotic disorders demonstrate high heritability; unaffected family members are at increased risk for all diseases. Recent studies implicate shared neurobiological mechanisms of psychosis including impaired calcium channel activity (5) and synaptic function (6). Although copy number variants account for a small proportion of cases (7), under polygenic models a single gene's contribution to disease liability is small but global effects arising from combination of gene subsets are significant because together they impact specific key neural systems at multiple points (8). Endophenotypes are heritable, state-independent phenotypes intermediate between the causative genes and clinical disease (9).

The auditory oddball event related potential (ERP) is a non-invasively measured electrical brain response elicited by an external auditory stimulus. The P300 is a major ERP subcomponent visible as endogenous positive voltage deflection ∼300 ms post stimulus presentation. P300 amplitude signifies attention allocation, cognitive information processing and context updating (10) and is highly heritable (11). Additionally, auditory ERPs comprise N1, N2 and P2 sub-components generated by auditory cortices and associated with stimulus characteristics. Multiple studies report P300 amplitude abnormalities (12, 13) in both SZ and PBP, suggesting general psychosis biomarker status. Auditory P300 amplitude is a frequently-employed SZ candidate endophenotype, because it is robustly reduced in SZ and their close relatives (14-16), highly heritable, stable across the course of illness, is relatively unaffected by illness exacerbations and is elicited by a straightforward task performed easily by psychotic patients. P300 amplitude abnormalities in PBP may be proband-specific (17). Deficits in ERP subcomponents N1, P2 and N2 are found in SZ patients (18, 19) and their relatives (20). Both N1 and P2 amplitude abnormalities (13) and their endophenotypic status are less studied in PBP.

The P300 amplitude response with a parietal maximum (P3b) has been related to norepinephrine (21) and dopamine neurotransmission (22). Recent studies examining genetic associations of P300 (23, 24) adopted traditional single nucleotide polymorphism (SNP)-based univariate approaches, such as genome wide association (GWA). One polygenic association study identified several interacting SNP loci including rs1045642 in the ABCB1 gene linked to P300 ERP in healthy individuals (25), plus genes related to dopaminergic, noradrenergic and signal transduction/amplification pathways. Prior studies (26-29) documented genetic associations of P300 amplitude deficits with known SZ risk genes including DISC1, NRG1 and COMT. One study (26) identified the above-mentioned SNP (rs1045642) as a SZ risk locus.

The univariate GWA approach relates single gene variants to a unitary phenotype. While straightforward it has two main drawbacks. First, the weak individual effect of common variants prevents most from reaching genome-wide significance, due to numerous multiple-comparisons, requiring extremely large samples to gain sufficient statistical power. Second, simultaneous coupling of multiple genes is ignored. To overcome these problems, multivariate association (30) based on parallel independent component analysis (Para-ICA) has been developed to model the polygenic architecture (combinatorial gene effects) of complex psychiatric illnesses. Prior Para-ICA studies revealed known and novel gene clusters implicated in Alzheimer's disease (31) and psychoses (32) based on structural and functional imaging data respectively.

The present study sought to: 1) identify risk genes collectively associated with ERP endophenotypes in psychosis; 2) determine whether the gene clusters mediate neurophysiological abnormalities in either or both disorders. We hypothesized that Para-ICA would identify novel interacting risk gene clusters (likely including known risk genes) mediating plausible physiological pathways disturbed in psychosis.

Material and Methods

Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP) Study

We assessed genotype–phenotype multivariate associations by combining genetic variants and ERP from SZ, SZA, PBP probands and healthy comparison subjects (HC) from the BSNIP study (www.b-snip.org), formed to investigate intermediate phenotypes from multiple modalities and their genetic underpinnings in psychosis.

Subject Recruitment

We examined a subset of 620 probands and HC selected from the overall ∼2600-person BSNIP (33) cohort who had undergone genotyping and participated in the BSNIP auditory oddball paradigm. These comprised 144 SZ, 210 PBP and 95 HC, aged 15-65 years (see Supplementary Table ST1 for demographic and clinical information). SZA depressive and mania subtype probands were classified as SZ and PBP respectively. SZ and PBP proband groups were unmatched on age, sex or ethnicity with HC. Probands' medication is listed in supplementary Table ST2. The study was explained to all subjects and institutional review board approved written informed consent obtained at respective participating sites.

Auditory Oddball Paradigm and Electroencephalogram (EEG) Data Acquisition

EEG was collected independently at each site from identical Neuroscan equipment equipped with 64 Ag/AgCl electrodes (Quik-Cap, Compumedrics, El Paso, Texas), while subjects were performing an auditory oddball task (see supplement text). Electrode positions were defined according to the International 10-10 EEG system (see Supplementary Figure SF1).

SNP Data Collection

Blood was collected from each subject and genomic DNA extracted. Genetic variants were obtained by genotyping for ∼one million (1,140,419) target SNPs across the whole genome using the Illumina Human Omni1-Quad chip and BeadArray™ platform at Genomas Inc, Hartford Hospital.

ERP Data Processing

EEG data were artifact rejected and averaged ERP data were reduced to 2 targets and 1 standard component (see Figure 1) using spatial principal component analysis (PCA) (13) (see details in supplementary text).

SNP Data Processing

SNP data were converted to discrete numbers and subjected to quality control process (Supplementary Figure SF2). Stratification bias was corrected using PCA (Supplementary Figure SF3). Data were reduced from million to 20,329 SNPs by selecting those significant at $p<0.05$ in the logistic regression (see supplementary text).

Para-ICA based SNP-ERP Association

Para-ICA is a multivariate association analysis that links linearly associated functional ERP activity with synergistic gene clusters by relating the hidden structures from both ERP and SNP data. Data were organized as a matrix of (i) subjects by SNPs (449 × 20329) and (ii) subjects by ERP component waveforms (449 × 294 (3×98 time points)) and were reduced to 11 and 8 components or factors respectively. ERP and SNP data were jointly processed by Para-ICA (25, 30) (see Supplementary Figure SF4 and supplementary text).

Correlation and Statistical Analysis

Bi-modal feature association using Para-ICA was assessed by correlations between SNP and ERP loading coefficients (LC). Significance levels were adjusted through partial-correlation by regressing effects of age, sex and site on LCs. Correlations for all component pair combinations (8×11=88) were evaluated and significance levels adjusted using Bonferroni multiple comparison correction number of combinations ($p<0.05/88$). ERP and SNP LCs of significant component pairs were examined for group differences using t-tests. Dominant SNPs and ERP features in the components contributing to the association were identified with a threshold of $|Z| = 2.5$ for both modalities. Supplementary analyses included correlation of ERP LCs with intelligence quotient (IQ) scores and chlorpromazine (CPZ) equivalents.

ERP-Structural Magnetic Resonance Imaging (sMRI) Association Analysis

Brain structures (see Supplementary methods for sMRI data collection) associated with the ERP components were identified by partial correlation (accounting for age, sex and site) of regional volumetric measures with ERP loading coefficients. P-values were corrected for multiple comparisons using false discovery rate.

Pathway Analysis

Genes corresponding to SNPs selected from the genetic component were entered into MetaCore annotation software GeneGo (Thompson Reuters, New York, NY) to determine the biological pathways associated with ERP abnormalities (see supplementary text).

Results

Gene-ERP Multivariate Linkage

Four (E1, E2, E3 and E6) of the 8 independent ERP components were significantly connected to 3 (G1, G4 and G9) of the 11 genetic/SNP components. ERP component E6 (frontal target P3a) was correlated negatively with G1 ($r=-0.23$, $N=449$, $p<0.0000007$) (Figure 2A); reflecting increased loading on G1 was related to diminished frontal target P3a. E1 was positively associated with G9 ($r=0.24$, $N=449$, $p<0.0000006$) (Figure 2C); indicating increased loading on G9 related to increased ERP features in E1 (frontal standard N1, P2, frontal and parietal target N1). Both E2 (parietal target N2) and E3 (parietal target P3b) components were negatively ($r=-0.21$, $N=449$, $p<0.000008$) and positively ($r=0.22$, $N=449$, $p<0.000002$) correlated (see Figure 2B) with the same gene component G4 respectively (see scatter plot in Figure 3). Although IQ differed between groups and was negatively correlated ($r= -0.166$, $N=446$, $p<0.0004$) with component E3, controlling its effects did not alter the ERP-SNP correlation. ERP component E2 positively correlated ($r= 0.179$, $N=215$, $p= 0.009$) with CPZ equivalents, reflecting higher CPZ dosage associated with increased abnormality. Post-hoc comparisons revealed significant differences in ERP and SNP LCs between HC and both SZ and PBP for all significantly correlated components (Figure 4). ERP component E6 (frontal target P3a) differed between SZ and PBP, while other ERP components failed to differentiate two proband groups. Reliability test by leave-one-out cross-validation revealed an average within modality correlation > 0.85, indicating stable ERP and SNP components.

ERP-Structural Volume Associations

ERP component E1 (frontal standard N1, P2, frontal and parietal target N1) was associated with volume reduction in gray matter regions including pars opercularis**,** posterior cingulate, insula, caudal middle frontal, middle temporal and supramarginal gyrus (see Table 1). E3 (P3b) was associated with volume reduction in left entorhinal and hippocampal regions.

Pathway Analysis

Prominent process networks associated (see Supplementary Table ST3) with G1 (related to ERP component E6) included (but not limited to) neurogenesis-axon guidance and cell adhesion (cadherins, synaptic contact). Major metabolic components included Lyso-

phosphatidylserine and sphingomyelin pathways. Functional properties for the top 20 genes from all the three genetic components are summarized in Table 2.

Process networks (collection of coordinated genes controlling a biological processes) associated with G4 were cell adhesion (synaptic contact, cadherins and amyloid proteins) and development neurogenesis (synaptogenesis). Several metabolic networks enriched for genes in G4 included (but were not limited to) N-acyl-sphingosine phosphate, Lyso-phosphatidylserine, phosphatidic acid and ceramide pathways. Gene component G9 (related to ERP component E1) was significantly (after false discovery rate correction) enriched with immune response genes (classical, alternative and lectin-induced complements) and G-protein signaling (RhoA regulation). Primary process networks related to G9 were cell adhesion (synaptic contact, cadherins) and the inflammation-complement system. Pathways, known diseases and major human brain regions from Allen Brain Atlas (www.brain-map.org) (assessed based on expression Z-scores) associated with the top 20 genes are listed in supplementary Table ST4.

Discussion

Etiological mechanisms for SZ and PBP are complex, but one approach to gain insight is to examine biological measures such as ERP that are putatively close to the genetic variation. Currently, the neural substrates or genetic basis for eliciting ERP components are unknown. Various ERP sub-components demonstrate significant heritability, suggesting strong genetic influences. As a preliminary step, we investigated polygenic sources underlying abnormal ERP sub-components in the psychosis dimension from a large multi-site dataset including all probands, based on multivariate association. Additionally we compared SZ and PBP probands against HC based on DSM criteria.

ERP Components

ERP component E1 (a linear combination of standard N1, P2, frontal and parietal target N1) showed overall increased loadings (less change from baseline) in SZ and PBP compared to controls reflecting deficits in early sensory processing, consistent with prior SZ (18, 20, 34) and PBP (13) studies. The primary source of N1 and P2 is the auditory cortex (35, 36) (Heschl's gyrus); we identified reduction in gray matter regions surrounding this structure. Parietal target N2 in E2 was significantly increased (reduced change from baseline) in probands indexing abnormal stimulus classification (37). Psychosis probands exhibited decreased frontal target P3a in E6 and parietal target P3b in E3, consistent with prior psychosis literature (12). The role of hippocampus in P3b generation is debated (38); however, our finding of P3b amplitude reduction associated with lesser hippocampus volume is consistent with prior evidence (39).

Gene Components

Para-ICA identified gene groups comprising interacting genes with a weight associated to each linkage-contributing gene. We discuss here the genetic underpinnings of ERP abnormalities based on the functionality of top ranking and frequently appearing genes in each component and biological properties associated with the gene clusters. Of all unique

genes pooled across the 3 genetic components found in this study (N=376), 76 have previously been identified as risk genes for SZ, PBP or both, while we report 300 new genes associated with ERP alterations in psychosis

G1

Top Genes and Those Identified Repeatedly

The highest-ranking gene in G1 was DCC, encoding a netrin-1 (40) receptor and a novel SZ candidate risk gene (41). Multiple (27 occurrences in the top 50) intronic SNPs within DCC were associated with frontal target P3a in E6. The dominant SNP loading was negative with a negative correlation between G1 and E6, indicating decreased minor allele frequency associated with increased frontal target P3a. DCC plays a critical role in neuronal circuitry modulating synaptic connectivity by mediating brain development via axon guidance and dendrite growth (42) with roles in functional reorganization of mesocortical dopamine circuitry (43). DCC is also involved in development of human brain lateralization (44), abnormal in SZ (45).

Several intronic SNPs within the BOC gene were found in G1. BOC is the receptor for the molecule Sonic Hedgehog, whose critical role in spatial specificity of synapse formation (46) guide the formation of cortical microcircuits (47) and dorsoventral axon patterning (48). Multiple SNPs within PDLIM5 encoding the LIM domain protein were detected in G1. PDLIM5 is a candidate risk gene for SZ, PBP and major depression and interacts with brain neuronal N-type calcium channel and protein kinase-C (49). Postsynaptic density proteins containing PDZ domain, interact with glutamate receptors to regulate synaptic plasticity (50, 51). The HDAC9 gene encoding the histone deacetylase 9 enzyme involved in transcriptional regulation and cell cycle progression is a known SZ risk gene (52), pivotal in neocortical neuron development through transcription regulation via histone modification and regulates dendritic growth in developing cortical neurons (53). HDAC inhibitors modulate cell lineage differentiation during brain development (52) and are direct targets of valproic acid, a mood stabilizer used to treat PBP (54); and may impact antipsychotic response (55). Several SNPs within DISC1, a known SZ risk gene were found in G1 but not ranked in the top 20.

Pathways, Process and Metabolic Networks

Neurogenesis (in particular axon guidance) and cell adhesion (cadherins and synaptic contact) were the enriched functional processes associated with gene clusters in G1 engaged in modulating frontal target P3a abnormality common to psychosis, indicating that these processes are general psychosis risk mediators. Adult neurogenesis likely plays essential roles in both brain function (56) and pathophysiology of psychiatric illnesses (57, 58). The primary neurogenesis-axon guidance associated genes are PCSK5, CACNA1C, DCC, SLIT3, UNC5C, SLIT1, DISC1, NCAM1, NTRK3, ROBO2, GDA and PLCB1: of these several are implicated in psychosis risk.

Another key process identified was cell-adhesion mediated by cadherins and synaptic contact. Cadherins depend on calcium ion function to facilitate cell adhesion involved in intracellular signaling, memory-formation, neuronal migration, synapse-formation and

maturation (59), associated with neuropsychiatric disorders. Genes associated with cadherin-based cell adhesion were CTNND2, PTPRJ, PCDH15, PDZK3, CTNNA2, CDH12, VAV2, CDH13 and WNT5B. Several of these are implicated in multiple psychiatric disorders; in particular CDH12 is associated psychosis. Synaptic cell adhesion molecules mediate neural connections and synapse development. Such genes were SYT9, NRXN3, CTNND2, GRIN2B, CTNNA2, NCAM1 and OBCAM, of which NRXN3 is implicated in SZ, NCAM1 and GRIN2B in both SZ and PBP. Sphingomyelin is a signal transduction system, impacting neural tissue and neuronal membrane integrity, suggesting that sphingolipid metabolism may play a key role in pathogenesis of neuropsychiatric disorders (60).

G4

Top Genes and Those Identified Repeatedly

The most significant G4 candidate gene (associated with parietal target N2 and P3b) was MSRA, a gene that shields against oxidative stress and is associated with SZ susceptibility (61-63). Oxidative stress is important in SZ pathophysiology (64), associated with hypoactive N-methyl-D-aspartate glutamate receptors (65). The chromosome region 8p23.1, in particular SNP D8S542 within MSRA is strongly associated with both SZ and PBP (66, 67).

Pathways, Process and Metabolic Networks

Developmental neurogenesis, synaptogenesis and cell adhesion was the significant process network mediating psychosis risk through parietal P3b and N2 abnormalities. Metabolic processes including Lyso-phosphatidylserine, phosphatidic acid and ceramide networks regulated P3b and N2 abnormalities in SZ and PBP. Phospholipids constitute cell membranes regulating signal transduction and acting as key secondary messengers. Abnormal phospholipid distribution occurs in SZ prefrontal cortex (68). Both calcium independent and dependent Phospholipase A2 enzymes are abnormal in SZ (69, 70). Ceramides are lipid signaling molecules guiding cellular differentiation, proliferation and apoptosis altered in both first-episode schizophrenia (71) and depression.

G9

Top Genes and Those Identified Repeatedly

Multiple SNPs were identified in the ME1 gene encoding the cytosolic, NADP-dependent malic enzyme involved in metabolic pathways. No direct evidence from prior studies suggests ME1's role in SZ and PBP, except for increased postmortem expression in unmedicated bipolar brain (72) and, linkage signals in SZ in the vicinity of ME1 (73). The PEMT gene encodes for an enzyme synthesizing membrane phospholipids associated with SZ (74). This gene helps mediate Arachidonic acid signaling, neuronal differentiation and neurite growth (75). The GPC6 gene belongs to the glypicans that promote glutamate receptor clustering, receptivity and induce postsynaptic synapse formation (76). SNAP91 encodes for clathrin coat assembly protein 180, enriched in presynaptic neuronal terminals (77). SNAP91 is involved in intracellular signaling (78) associated with the WNT pathway (79) and is implicated in PBP (80).

Pathways, Process and Metabolic Networks

Multiple immune response pathways were associated with psychosis risk mediated by frontal, parietal target N1 and standard N1 and P2 ERP abnormalities in probands, suggesting immune system's role in psychosis pathogenesis (81), consistent with prior SZ studies (82, 83). The classical complement pathway acts on synapse remodeling, pruning, neuronal plasticity and neurodevelopmental processes via immune system cells and molecules (C3) (84) and implicated in the pathophysiology of neurodegenerative disorders (85, 86). This study implicated immune system CR2 and C3 genes; the latter is a SZ risk gene (87). C3 is involved in synapse development and regulates neuronal connectivity (88). Gene component G9 was associated with cell adhesion regulated by cadherins and synaptic contact, relevant to SZ and PBP risk.

Replication analyses were not conducted to validate the current findings; however several candidate genes and processes found in this study are previously implicated in SZ and PBP, supporting the neurodevelopmental hypothesis of SZ (89) and affective disorders (90). Findings from the current study point to converging evidence from pathway-based studies that identified similar biological mechanisms including axon guidance (91-93), cell adhesion (94, 95), inflammation and immune system (96) associated with SZ risk. A recent BSNIP resting fMRI-genetic study (32) using Para-ICA identified similar processes including developmental neurogenesis, axon guidance, synaptic and cadherin cell adhesion, immune response, nervous system development, ceramide and sphingosine pathways mediating aberrant default mode activity in psychosis. These data help confirm the current findings and validate the approach undertaken to merge functional and genetic data to dissect the complex mechanisms mediating biological phenotypes in these disorders. A complete overlap in pathways and processes across diverse phenotypes is unlikely as they probably probe different domains of neurophysiology in these disorders.

Strengths and Limitations

Advantages of the present study include our use of high density spatial ERP data in a large multi-site psychosis sample. Limitations included unmatched age, sex and sample sizes between groups, adjusted for by controlling their effects through partial correlation between the SNP and ERP LCs: multi-site effects were accounted for by regressing data collection site. Examined ERP phenotypes may be medication-influenced; it was not straightforward to control for medication effects because probands were on numerous medications, combined with varying chronicity, severity and illness duration. The current findings could not be validated due to lack of replication sample. Para-ICA was optimized by selecting nominally disease-associated SNPs from univariate analysis. Thus, other genetic netrowks that may be weakly associated with the ERP sub-components were overlooked.

Conclusions

As hypothesized, we derived both novel interacting candidate genes and known SZ and PBP risk genes mediating ERP abnormalities in psychosis. In general, our data suggests a strong multifactorial genetic component comprised of brain-relevant genes playing a key role in neural functions, specifically those controlling neuronal circuits and neurodevelopmental processes. We identified one genetic cluster enriched with genes for neurogenesis related

axon guidance mediating psychosis risk via frontal target P3a abnormalities in probands. The second genetic component was enriched with genes involved in developmental neurogenesis-synaptogenesis, ceramide and phospholipid networks, influencing P3b abnormalities in psychosis. The third genetic component comprised genes coding for the complement immune response pathway associated with SZ and PBP risk through standard N1, P2, frontal and parietal target N1 abnormalities. All three genetic components mediated ERP abnormalities across the psychosis dimension. Cell adhesion mediated by synaptic contact and cadherins was the prominent network process driving all the ERP abnormalities in psychoses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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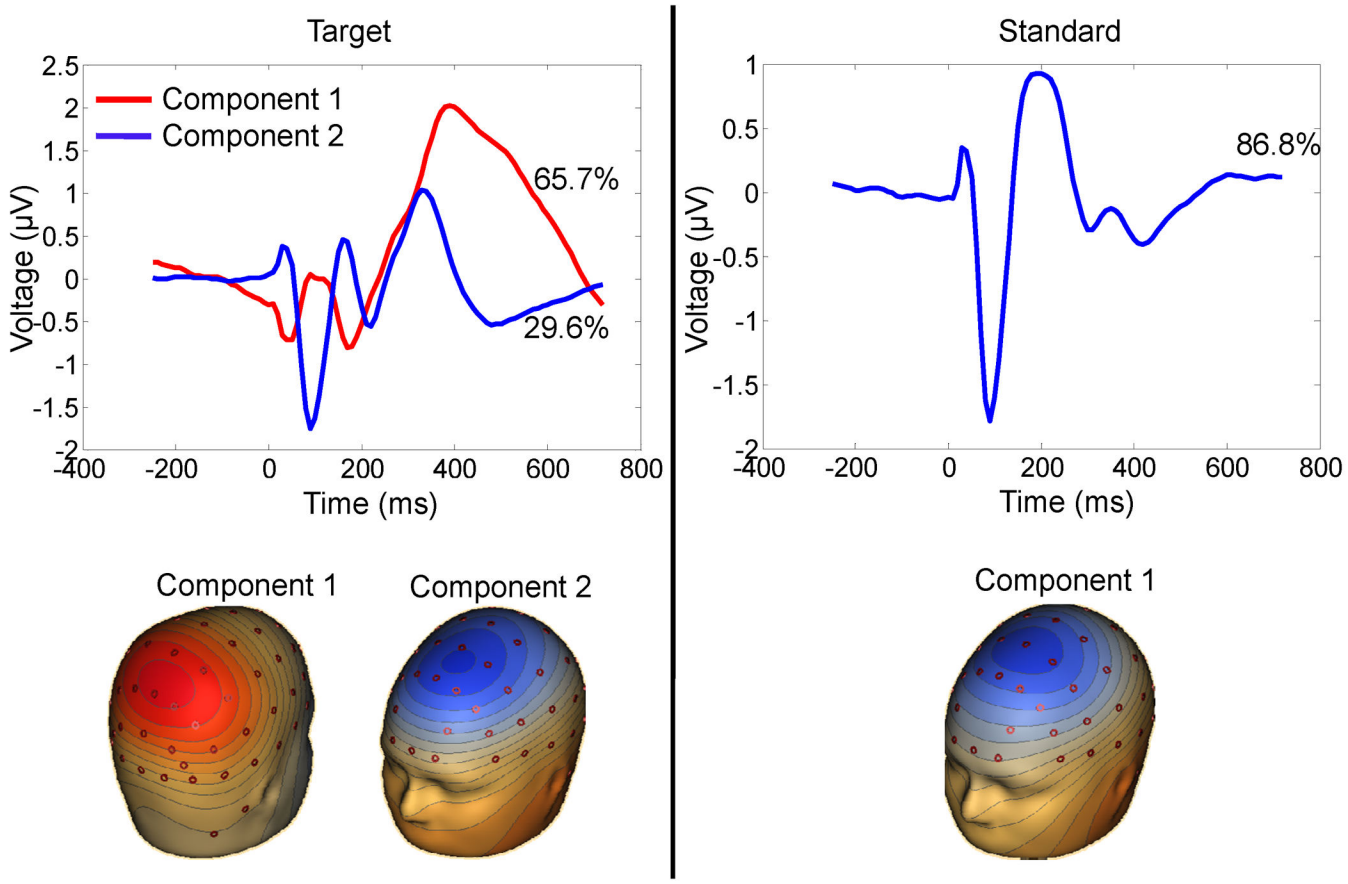

Figure 1.

Spatial topography associated with principal components for target and standard stimulus conditions. Two targets (parietal and frontal topography) and one standard component (frontal) was derived from principal component analysis of grand average 64 channel data. The time window for each component is between 250 msec before to 720 msec after stimulus onset.

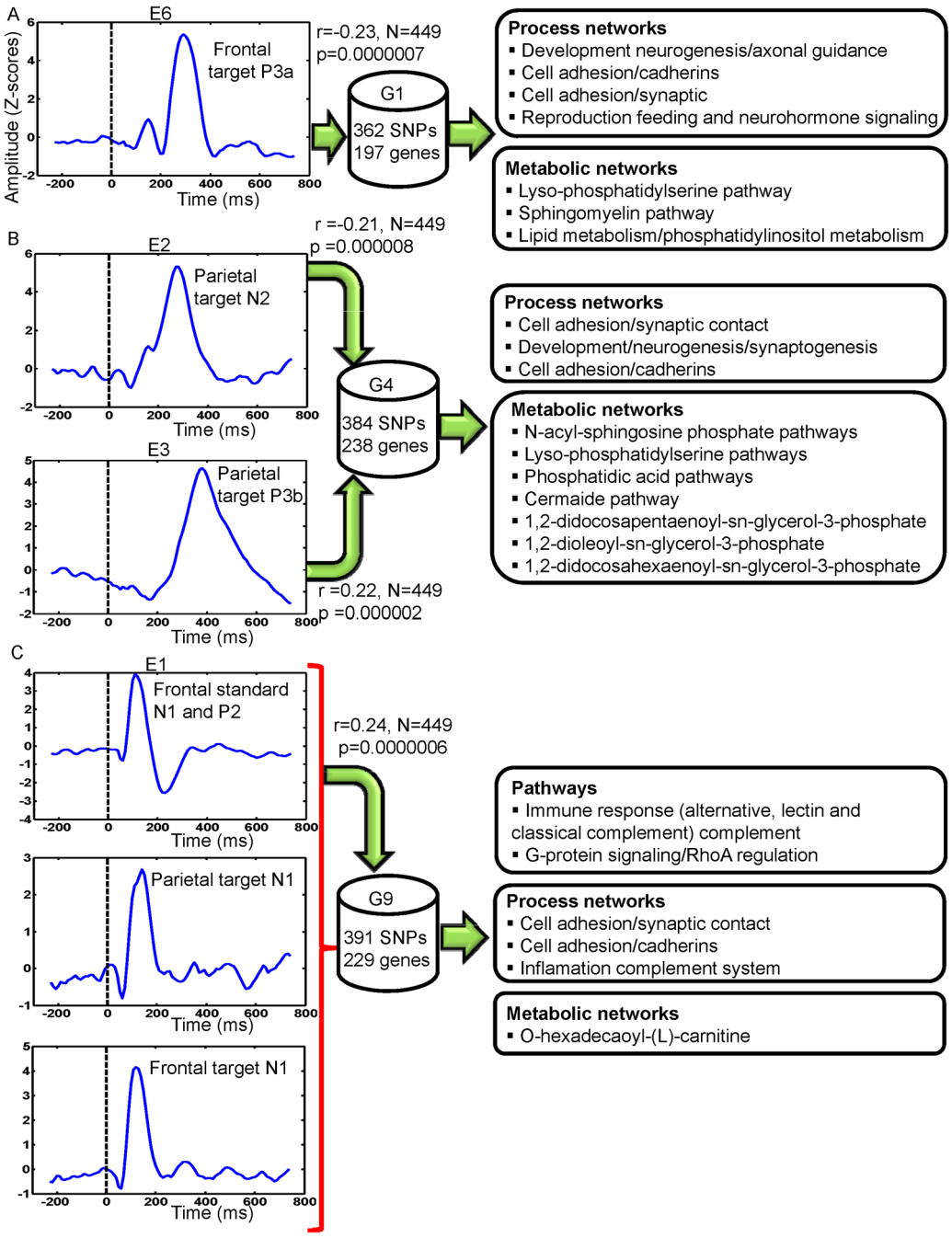

Figure 2.

Event-related potential (ERP) sub-components and associated gene components derived from the multivariate parallel independent component analysis. A E6-G1 component pair, B E2-G4 and E3-G4 component pairs, C E1-G9 component pair E6 comprised frontal target P3a sub-component. E2 and E3 comprised parietal target N2 and P3b subcomponents respectively. E1 comprised standard N1 and P2, parietal target N1 and frontal target N1 subcomponents. Peak amplitude within predefined time periods post-stimulus was used to identify the ERP component. The polarity of the ERP waveforms for N1, N2 and P2

subcomponents is reversed by independent component analysis. Biological pathways and process networks associated with each gene component from enrichment analysis are also displayed.

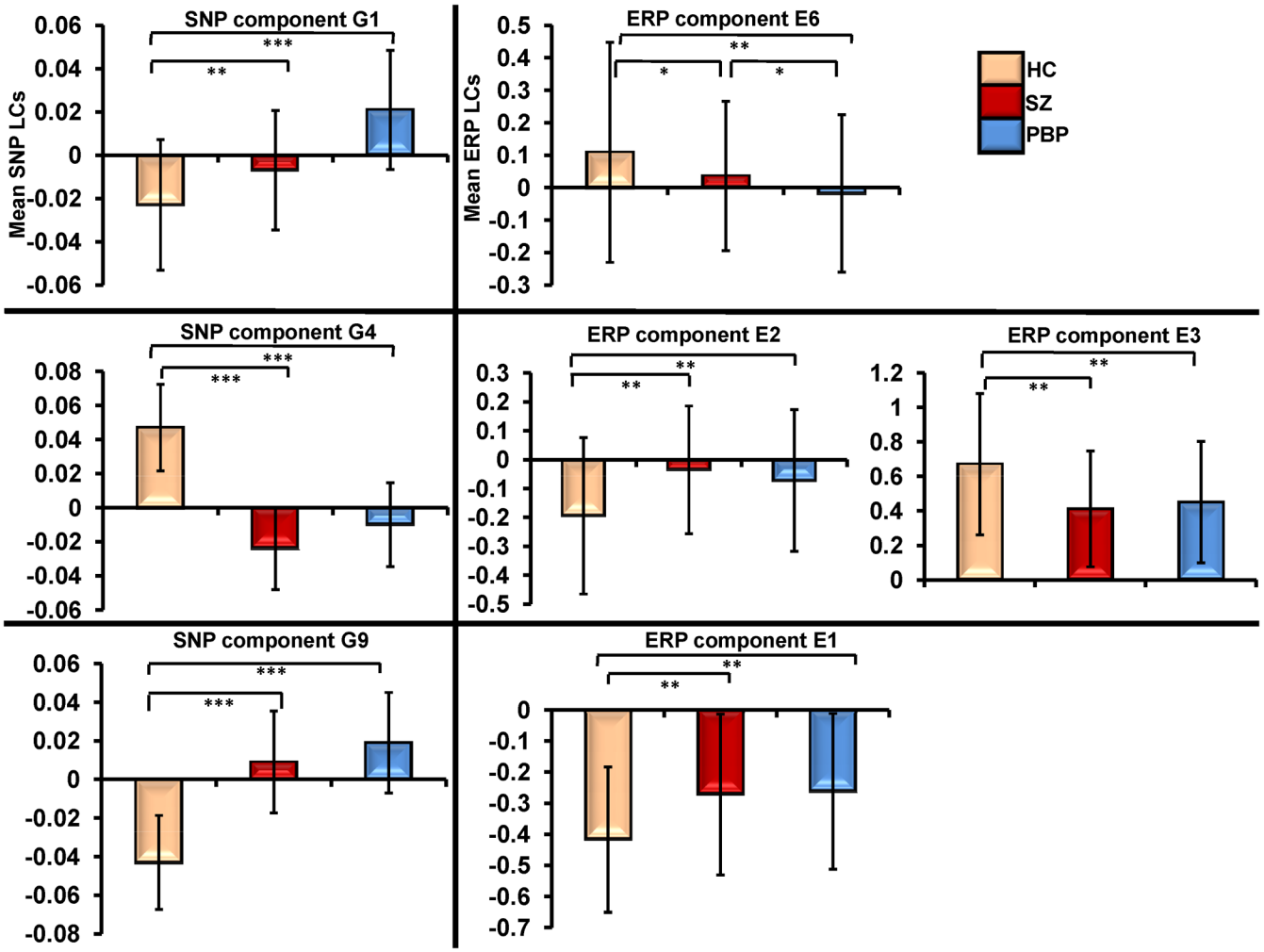

Figure 3.

Scatter plots of loading coefficients (LC) for the three groups including schizophrenia (SZ), psychotic bipolar disorder (PBP) probands and healthy comparison subjects (HC). The overall association between the LCs across three groups is displayed as the linear fit. ERP=event-related potential; SNP=single nucleotide polymorphism

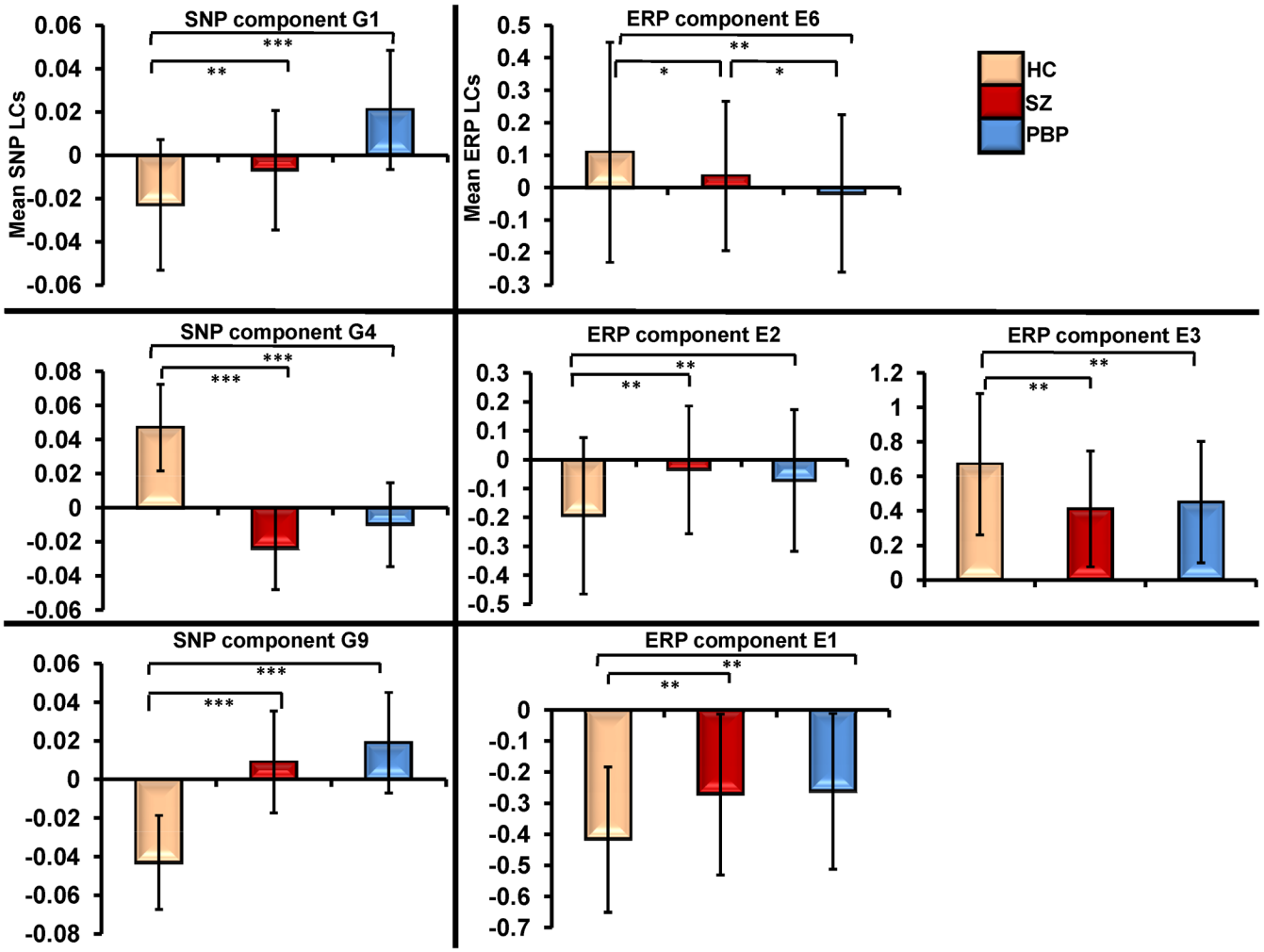

Figure 4.

Mean loading coefficients (LC) for significantly associated event-related potential (ERP) and gene components for schizophrenia (SZ) (N=144), psychotic bipolar probands (PBP) (N=210) and healthy comparison subjects (HC) (N=95). Error bars represent standard deviation. Post-hoc comparisons included pairwise t-tests between HCs and SZ and PBP probands. *** $P \ll 0.000000001$ ** $p<0.0001$ * $p<0.05$ SNP=single nucleotide polymorphism

Table 1

Association of event-related potential (ERP) with cortical and subcortical structural volumes. 82 brain volumes were extracted for N=369 subjects out of the 449 who had ERP data using Freesurfer. The association was evaluated using partial correlation adjusting for age, sex and data collection site. ERP component E1 was correlated with six regional volumes (after false discovery rate correction (FDR)), while E3 was related to 2 regional volumes. ERP components E2 and E6 did not yield significant correlations after FDR correction.

Brain Regions (volume)	**E1**	
	R	**P**
L. caudal middle frontal	-0.158	0.00238
L. pars opercularis	-0.173	0.00086
L. posterior cingulate	-0.153	0.00324
L. insula	-0.158	0.00236
R. middle temporal	-0.152	0.00351
R. supramarginal	-0.148	0.00433
	E3	
L. entorhinal	0.171	0.00098
L. Hippocampus	0.167	0.00125

L, Left; R, Right

Table 2

Functional attributes and gene-specific information for top 20 unique genes in genetic components G1, G4 and G9 from multivariate association analysis. Only the single nucleotide polymorphism (SNP) with maximal loading within each gene is listed in the table, (most genes were represented by several SNPs). Relative weights indicate normalized Z-scores (ZS) (absolute Z-score divided by the maximum absolute SNP weight). SNP locations are based on GRCh37/hg19 assembly.

Gene networks						
Gene (G1)	**SNP**	**Chromosome**	**Position**	**Z-score**	**Relative weights**	**Functional Attribute**
DCC*	rs16956411[I]	18q21.2	50775428	-9.93	1	Axon guidance, neuronal migration
BOC*	rs775228[I]	3q13.2	112997554	-4.84	0.487	CA and synaptic development
SEC14L2*	rs4820845[I]	22q12.2	30800338	-4.5	0.461	Lipid binding
PDLIM5*	rs13121500[I]	4q22.3	95577290	4.41	0.444	Regulates protein kinase C activity; synapse & dendritic spine morphogenesis
HDAC9*	rs12699994[I]	7p21.1	18895297	-4.31	0.434	Neocortical neuron development by transcriptional regulation
MAML3*	rs7678266[I]	4q31.1	140668374	-4.23	0.426	Unknown
B3GNTL1*	rs1001865[I]	17q25.3	80914988	4.1	0.417	Unknown
TBCD*	rs3785520[I]	17q25.3	80895745	-4.00	0.402	Captures & stabilizes beta-tubulin
SNAP91*	rs1546977[I]	6q14.2	84314423	-3.96	0.399	Formation of clathrin coated vesicles at presynaptic membranes
LY9	rs574610[Utr-3]	1q23.3	160797684	-3.91	0.384	Unknown
CD244	rs485618[Utr-3]	1q23.3	160800480	-3.86	0.389	Mediates non-major HC restricted killing and modulates natural killer-cell cytolysis
CDKAL1*	rs7758129[I]	6p22.3	20609241	3.85	0.388	Unknown
ESRRG*	rs3929399[I]	1q41	216718378	3.84	0.387	CP
MCTP2*	rs1655455[I]	15q26.2	94858686	-3.83	0.386	Ca^{2+} ion binding; intracellular signal transduction
PIP4K2A	rs7071450[I]	10p12.2	22867451	3.79	0.381	CPD
TMEFF2*	rs10185068[I]	2q32.3	192924987	-3.78	0.381	Unknown
ZC3H18*	rs12445653[I]	16q24.2	88677230	-3.75	0.378	Unknown
VWA3B*	rs10211067[Utr-5]	2q11.2	98703659	-3.73	0.376	Unknown
RASGRP3	rs11687777[I]	2p22.3	33764709	-3.66	0.368	Signal transduction
ANKIB1	rs721015[I]	7q21.2	91925256	-3.59	0.361	Unknown

Gene networks						
Gene (G1)	**SNP**	**Chromosome**	**Position**	**Z-score**	**Relative weights**	**Functional Attribute**
(G4)						
MSRA*	rs7459532[I]	8p23.1	10261068	-7.96	1	Enzymatic reduction of methionine sulfoxide & repairs oxidative damage
XKR6*	rs2409691[I]	8p23.1	10943276	-7.3	0.917	Unknown
RP1L1	rs7386213[I]	8p23.1	10503525	-6.47	0.813	Binds to microtubules; regulates microtubule polymerization
BLK	rs2618451[I]	8p23.1	11376266	-6.32	0.794	CPD
TNKS*	rs7840706[I]	8p23.1	9535056	-5.39	0.677	Unknown
TPO*	rs2276702[I]	2p25.3	1426621	-5.06	0.635	Iodination of tyrosine residues in thyroglobulin
IL1F10*	rs6761276[M]	2q13	113832312	-5.04	0.632	Regulates innate immune responses
MFHAS1*	rs4841044[I]	8p23.1	8664940	5.00	0.628	Unknown
ADAMTS16*	rs270178[I]	5p15.32	5165415	4.65	0.584	Unknown
DOCK8*	rs10967788[I]	9p24.3	282180	- 4.62	0.58	Interacts with Rho GTPases, intracellular signaling networks
TAF8	rs6917299[I]	6p21.1	42025058	-4.04	0.508	Involved in transcription factors
GSG1L*	rs1645362[I]	16p12.1	27891473	-4.04	0.508	Unknown
ODZ3*	rs957053[I]	4q35.1	183248389	-4.04	0.508	Unknown
VAT1L*	rs9933953[I]	16q23.1	77909692	4.02	0.507	Unknown
USH2A*	rs17025267[I]	1q41	215903907	3.97	0.495	Development & homeostasis of inner ear
COL2A1*	rs1793923[I]	12q13.11	48384122	3.95	0.498	Unknown
INPP5K*	rs1109303[I]	17p13.3	1403477	3.92	0.496	Regulates actin cytoskeleton
NRXN3*	rs10782463[I]	14q24.3	78978482	- 3.92	0.492	Receptors and synaptic CAM in CNS
PNPLA1*	rs12197079[M]	6p21.31	36274153	3.85	0.483	Lipid metabolism, (lipolytic & acyltransferase)
PKP3	rs7105848[I]	11p15.5	396546	3.83	0.481	Links cadherins to intermediate cytoskeleton filaments
(G9)						
ME1*	rs1170348[I]	6q14.2	84020324	-6.90	1	Fatty acid biosynthesis and brain Co_2 fixation
PEMT*	rs11078389[I]	17p11.2	17478352	5.60	0.812	Synthesizes membrane phospholipids:affects choline levels
GPC6*	rs4369513[I]	13q31.3	94958719	5.42	0.786	Cell growth, cell division & CNS synapse formation

Gene networks						
Gene (G1)	**SNP**	**Chromosome**	**Position**	**Z-score**	**Relative weights**	**Functional Attribute**
SNAP91*	rs217291[I]	6q14.2	84393942	5.38	0.78	Refer to table G1
DLGAP1*	rs1465947[I]	18p11.31	3973509	4.76	0.69	Molecular organization of synapses & neuronal cell signaling
PRSS35	rs592911[I]	6q14.2	84223563	-4.47	0.648	Unknown
PCSK5*	rs2842467[I]	9q21.13	78938628	-4.32	0.626	Mediates posttranslational endoproteolytic processing for several integrin alpha subunits
FRK*	rs12662901[I]	6q22.1	116305637	4.24	0.615	Tyrosine kinase role in cell cycle & growth suppression
KCTD8*	rs2020159[I]	4p13	44330067	4.23	0.613	Unknown
PDLIM1*	rs11593722[I]	10q24.1	97006105	-4.13	0.599	Regulates actin cytoskeleton dynamics & neutrite growth
CYP2C19*	rs10786172[I]	10q23.33	96581094	4.08	0.591	
ANO2*	rs1035066[I]	12p13.31	5756592	-4.08	0.591	Unknown
SRRM4	rs1405050[I]	12q24.23	119443713	-4.05	0.586	Unknown
YSK4*	rs4953941[I]	2q21.3	135727531	-4.03	0.584	Unknown
CNTNAP2*	rs700281[I]	7q35	146192877	4.03	0.584	CNS Cell to cell interaction
PRDM16*	rs1798246[I]	16q24.2	3080855	-4.02	0.583	Unknown
TNNI1	rs3767548[I]	1p36.32	201388148	-3.98	0.577	Regulate Ca^{2+} sensitivity of muscle myofibril contractile apparatus
GLT1D1*	rs516034[I]	12q24.33	129459959	3.98	0.576	Unknown
ESRRG*	rs1833036[I]	1q41	216707012	-3.86	0.359	Refer to table for G1
ZNF385B*	rs10432487[I]	2q31.2	180512804	3.85	0.558	Unknown

* indicates multiple SNP occurrences (>2) of the gene within the genetic network.

CA, cell adhesion; CA^{2+}, Calcium ion, CAM, cell adhesion molecule, CNS; Central nervous system; CO_2, carbon dioxide; CP, cell proliferation; CPD, cell proliferation and differentiation; HC, histocompatibility complex; I, Intronic; M, missense; Utr-3, three prime untranslated region; Utr-5, five prime untranslated region