Functional genomics indicate that schizophrenia may be an adult vascular-ischemic disorder

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Table S1. Discovery sample based on TDT-studies

A list of genes extracted from the SZgene database[1] hosted by the Schizophrenia Research Forum (http://www.szgene.org) was used as discovery sample. Reproducibility of association was considered more important than a low *p* value. The criterion for inclusion in this sample was a *p*-value ≤ 0.05 obtained by at least two independent research groups in TDT studies. As of July 7, 2011, the SZgene database contained 33 genes that fulfilled this criterion. The TDT-based 33 candidate genes of schizophrenia are listed below.

(1) AKT1, (2) ARVCF, (3) BDNF, (4) CHRFAM7A, (5) CHRNA7, (6) CLDN5, (7) COMT, (8) DAOA, (9) DISC1, (10) DRD2, (11) DRD3, (12) DTNBP1, (13) GABRB2, (14) GAD1, (15) TRMT2A, (16) HTR2A, (17) IPO5, (18) MTHFR, (19) NOS1AP, (20) NOTCH4, (21) NRG1, (22) NTNG1, (23) PLA2G4A, (24) PPP3CC, (25) PRODH, (26) RBFOX2, (27) RGS4, (28) DAT1, (29) 5HTT, (30) SYN2, (31) TNF, (32) UFD1L, (33) ZDHHC8.

This sample was employed as discovery sample for the construction of the putative schizophrenia pathway depicted in Figs. 1 and 2. The TDT gene sample was updated as requested by an anonymous reviewer during the peer review process. The update increased the number of TDT genes from 33 to 41. The additional genes were (34) ACSL6, (35) DRD1, (36) ERBB4, (37) GABRB2, (38) NRG3, (39) PIP5K2A, (40) SNAP25, (41) ZNF804A. The last TDT sample of 41 candidate genes obtained in December 2014 from the SZ database was employed for the intersection analysis of the combined five samples (discovery sample and four replication sample). The results are shown in Table 1.

Table S2. Replication sample #1 based on case-control studies

Because of the higher rate of false positive findings in case-control studies[2], the requirement for replication was increased. The choice of three independent groups for inclusion was guided by the need to validate the findings by the highest possible number of replications and to obtain at the same time a sufficiently large number of genes for statistical analysis. On July 7, 2011, 58 candidate genes for schizophrenia were found in the SZgene database[1], which showed positive results in case-control studies by three independent groups. The case-control based candidate genes (CC genes) were

(1) ACSL6, (2) AHI1, (3) AKT1, (4) APOE, (5) BDNF, (6) CCKAR, (7) CFB, (8) CHGB, (9) CHI3L1, (10) CHRNA7, (11) COMT, (12) DAO, (13) DAOA, (14) DISC1, (15) DRD2, (16) DRD3, (17) DRD4, (18) DRD5, (19) DTNBP1, (20) EGF, (21) ERBB4, (22) GABRB2, (23) GC, (24) GCLM, (25) GNB1L, (26) GRIK3, (27) GRIN1, (28) GRIN2B, (29) GRM3, (30) GSTM1, (31) HP, (32) HTR2A, (33) IL10, (34) IL1B, (35) IL1RN, (36) KCNN3, (37) MTHFR, (38) NOS1, (39) NOTCH4, (40) NRG1, (41) NRG3, (42) NTF3, (43) NTNG1, (44) PCM1, (45) PDE4B, (46) PIK3C3, (47) PIP4K2A, (48) PLA2G4A, (49) RELN, (50) RGS4, (51) SLC18A1, (52) SLC6A3, DAT1, (53) SLC6A4, 5HTT, (54) SNAP25, (55) TH, (56) TNF, (57) TPH1, (58) UFD1L

The latest update of the SZgene database obtained in December 2014 did not change the number of genes from case-control studies.

Genome-wide association studies (GWAS)

Table S3. Replication sample #2 obtained from the NHGRI catalog

The second replication sample consisted of 164 genes from the NHGRI catalog of GWAS[3] (available at: www.genome.gov/gwastudies/ accessed March 3, 2015). These genes were indicated in the catalog as mapped to loci associated with schizophrenia at a *p*-value threshold of $p < 10E\text{-}08$ and were obtained from 45 GWAS of schizophrenia (PubMed IDs and first authors are given in the following Table S3 (see http://www.ncbi.nlm.nih.gov/pubmed). The dates of publication ranged from 2007 until 2014, but did not include the large-scale GWAS by the SWGPGC (2014).

PMID	First author	PMID	First author
24280982	Ruderfer 2014	21752600	Chen 2011
24043878	Wong 2014	21679298	Ma 2011
23358160	Borglum 2014	21674006	Yamada 2011
24253340	Lencz 2013	21107309	McClay 2011
24166486	Sleiman 2013	21057379	Curtis 2011
24086445	Wang 2013	20939080	Greenbaum 2010
24039173	McGrath 2013	20889312	Wang 2010
23974872	Ripke 2013	20713499	Huang 2010
23453885	Smoller 2013	20558996	Ott 2010
23894747	Aberg 2013	20185149	Athanasiu 2010
23142968	Betcheva 2013	19571811	Purcell 2009
23382809	Xu 2013	19571808	Stefansson 2009
23212062	Fanous 2012	19571809	Shi 2009
22885689	Levinson 2012	19197363	Need 2009
22883433	ISGC 2012	19023125	Potkin 2009
22688191	Bergen 2012	18677311	O'Donovan 2008
22648509	Wang 2012	18369103	Walsh 2008
22479419	Liou 2012	18347602	Sullivan 2008
21747397	Rietschel 2012	18332876	Kirov 2009
21682944	Alkelai 2012	18282107	Shifman 2008
22037555	Shi 2011	17522711	Lencz 2007
22037552	Yue 2011		
21926974	Ripke 2011		
21795503	Alkelai 2011		

Table S4. Replication sample #3 obtained from Ayalew et al. (2012)

An intersection analyses was also performed of the carefully selected set of 42 genes from GWAS described by Ayalew et al. (2012)[4]. This replication sample is characterised by high reproducibility and predictive ability in four independent cohorts of different ethnicities[4].

Table S5. Replication sample # 4 obtained from SWGPGC 2014

A fourth replication sample consisted of 111 genes assigned by proximity to the 108 genome-wide significant regions of the SWGPGC's recent large GWAS[5]. Genes were assigned to index-SNPs using a 50 kb window. If multiple genes were present within the 50 kb window, the hierachy described by Torkamani et al.[6] was employed: coding > intronic > 5'UTR > 3'UTR > 5' upstream > 3' upstream > nearest gene. Additionally, the entire list of 343 genes within range of genome-wide significant loci (as given by the SWGPGC in column 5 of their supplementary Table 3) was used to exclude the possibility of a bias by the gene assignment.

Functional gene sets

Table S6. Vascular and acute ischemia genes of the adult brain

A list of 2 866 ischemia or reperfusion-induced genes were obtained by literature mining from 61 sources including 75 genes from the Entrez Genes database of Homo sapiens (HS), which were extracted by use of the keywords hypoxia, ischemia, ischemic, erythropoietin or vascular. The remainder of the genes came mostly from gene-expression studies of the adult brain reported in the literature[7-65]. After removal of duplicate genes, a set of 1673 ischemia genes remained for statistical analysis.

The gene set for vascular genes consists of 3 500 genes involved in perivascular nerves[66-74] (N = 253), capillary endothelial cells[75] (N = 20), brain endothelial cells[76] (N = 301), capillary shear-stress[77-93] (N = 2 818), blood-brain barrier (BBB)[94] (N = 29) and vascular smooth muscle cells (VSMC)[95] (N = 79). After the removal of duplicates, 3 249 vascular genes remained.

Table S7. Neurodevelopmental genes

A list of 4 020 differentially expressed genes during neurodevelopment was extracted from 18 published studies[96-113]. The Entrez Genes database of HS[114] had no entries for the key words neurodevelopment or brain development. After removal of duplicates, a list of 3 211 neurodevelopmental genes remained for further analysis.

Table S8. Synaptic genes

A list of 2 988 synaptic genes was obtained from the Entrez Genes database of HS, from Bayés et al. ground-breaking study of human Postsynaptic Densities (hPSD)[115] and a list of 1 480 genes was compiled from two additional references[116,117]. The Entrez Genes database provided 50 genes, which were extracted by using the keywords synapse or synaptic. The hPSD study yielded 1 458 genes. Since 1 011 genes were found in several datasets, a gene set of 1 977 synaptic genes remained after removing duplicates.

Table S9. Post-ischemic repair genes

A list of 159 genes involved in post-ischemia repair was compiled from the literature[118-126]. They are designated as "R" in Tables and Figures. Since ND genes are involved in adult neurogenesis and post-ischemic repair[120,127], R and ND genes were combined and termed "Repair".

Figure S1. Venn diagrams

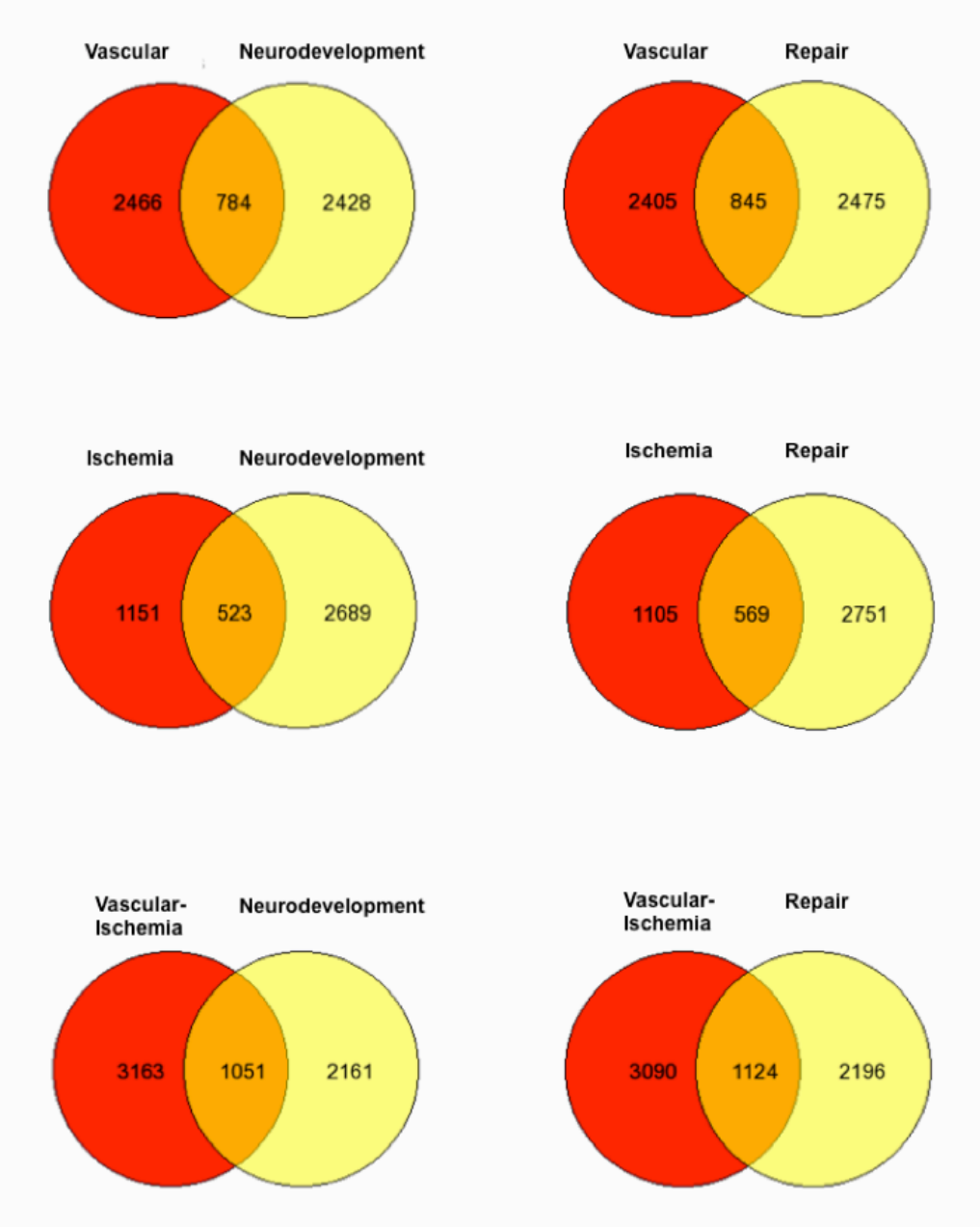


Figure S1. Venn diagram of vascular, ischemia, and vascular-ischemia genes overlapping with neurodevelopmental or repair genes. The diagram was produced by using GeneVenn (available at http://genevenn.sourceforge.net).

METHODS

Construction of schizophrenia pathway

Protein-protein interaction analysis using STRING

For protein-proteins interaction analysis, STRING (**S**earch **T**ool for the **R**etrieval of **In**teracting **G**enes/Proteins) version 8 at (http://string-db.org) was employed[128]. Supplementary Fig. S1 shows the protein-protein interactions of candidate genes for schizophrenia used in the present study.

Figure S2. Results of interaction analysis by STRING

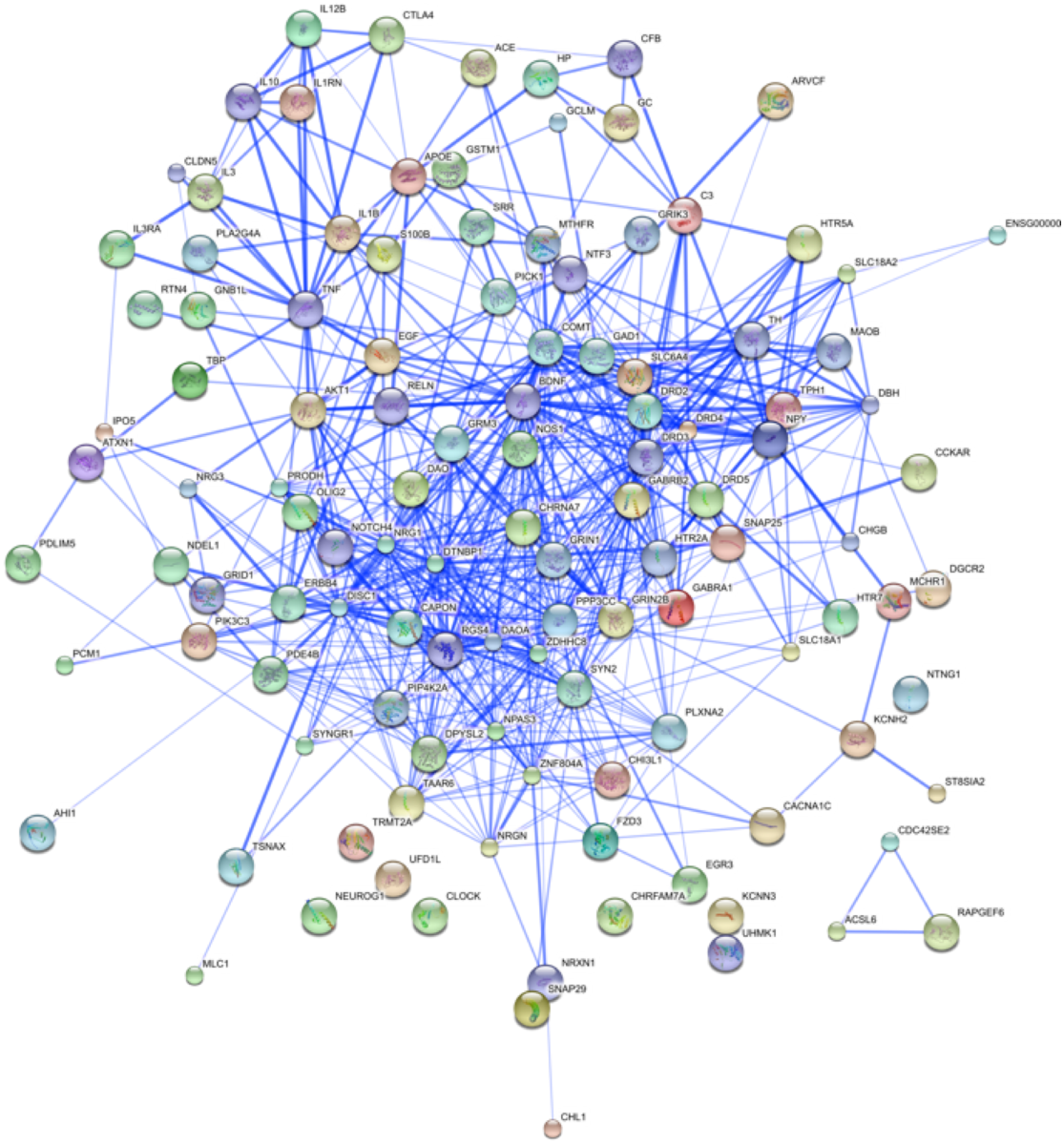


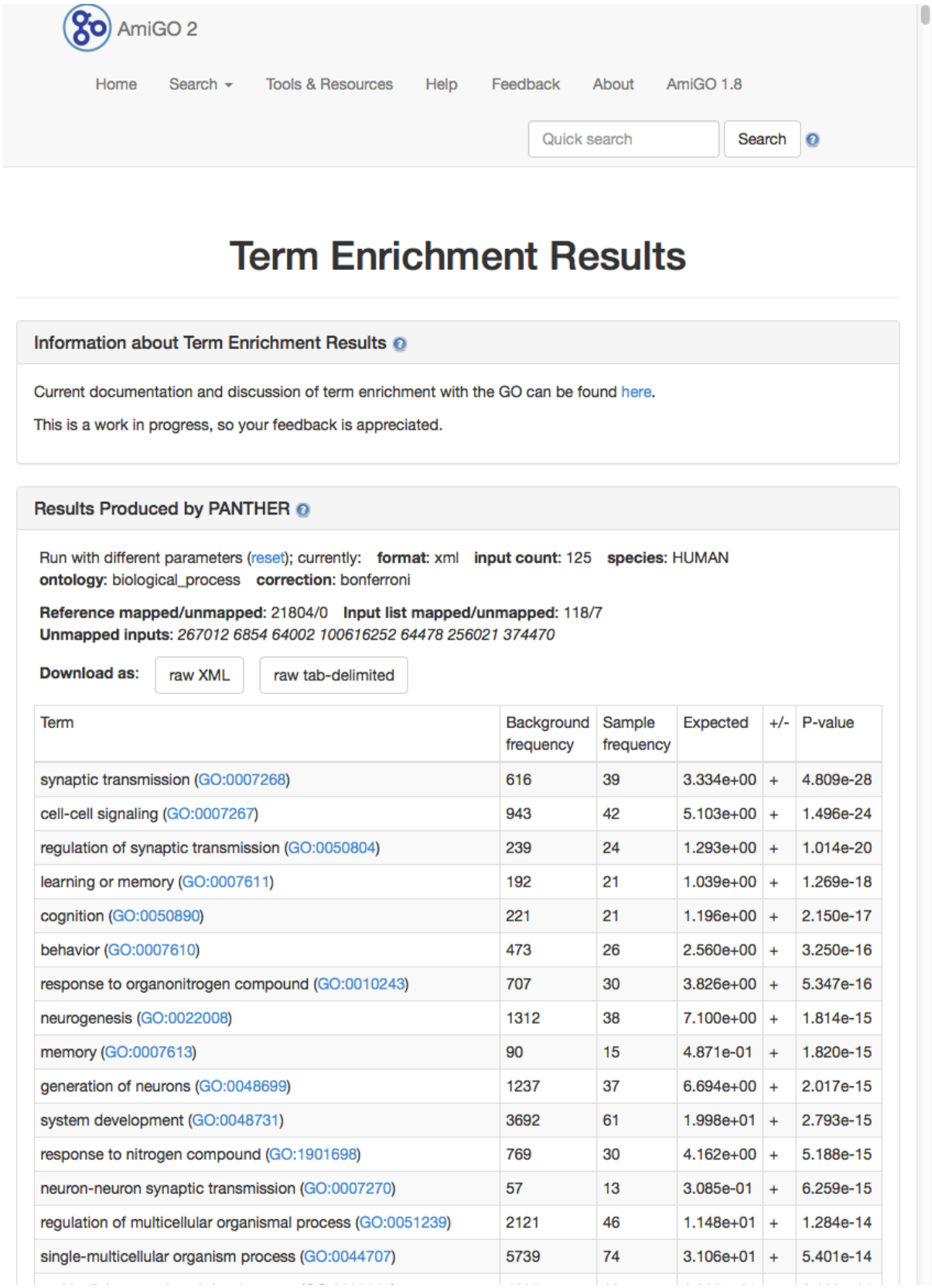
Figure S2. STRING's evidence view revealing protein-protein interactions of candidate genes for schizophrenia employed in the present study. Data from the STRING database were used for constructing the energy-supply pathway shown in Figs. 1 and 2.

Gene ontology analysis

The gene ontology (GO) database of the Gene Ontology Consortium[129] at (http://www.geneontology.org) was employed to search for overrepresentation of biological processes or cellular localisations among the genes of the discovery sample.

As requested by a reviewer, the results of such an analysis are shown in Supplementary Table S8. The 125 schizophrenia-associated genes of the combined four samples were employed for the GO term analysis. The GO analysis produced a long list of significant biological processes, which are difficult to interpret with regard to an unitary etiological factor. Only the first page is shown.

Table S10. GO terms enrichment



AmiGO 2

Home Search Tools & Resources Help Feedback About AmiGO 1.8

Quick search Search

Term Enrichment Results

Information about Term Enrichment Results

Current documentation and discussion of term enrichment with the GO can be found here.

This is a work in progress, so your feedback is appreciated.

Results Produced by PANTHER

Run with different parameters (reset); currently: **format**: xml **input count**: 125 **species**: HUMAN
ontology: biological_process **correction**: bonferroni

Reference mapped/unmapped: 21804/0 **Input list mapped/unmapped**: 118/7
Unmapped inputs: *267012 6854 64002 100616252 64478 256021 374470*

Download as: raw XML raw tab-delimited

Term	Background frequency	Sample frequency	Expected	+/-	P-value
synaptic transmission (GO:0007268)	616	39	3.334e+00	+	4.809e-28
cell-cell signaling (GO:0007267)	943	42	5.103e+00	+	1.496e-24
regulation of synaptic transmission (GO:0050804)	239	24	1.293e+00	+	1.014e-20
learning or memory (GO:0007611)	192	21	1.039e+00	+	1.269e-18
cognition (GO:0050890)	221	21	1.196e+00	+	2.150e-17
behavior (GO:0007610)	473	26	2.560e+00	+	3.250e-16
response to organonitrogen compound (GO:0010243)	707	30	3.826e+00	+	5.347e-16
neurogenesis (GO:0022008)	1312	38	7.100e+00	+	1.814e-15
memory (GO:0007613)	90	15	4.871e-01	+	1.820e-15
generation of neurons (GO:0048699)	1237	37	6.694e+00	+	2.017e-15
system development (GO:0048731)	3692	61	1.998e+01	+	2.793e-15
response to nitrogen compound (GO:1901698)	769	30	4.162e+00	+	5.188e-15
neuron-neuron synaptic transmission (GO:0007270)	57	13	3.085e-01	+	6.259e-15
regulation of multicellular organismal process (GO:0051239)	2121	46	1.148e+01	+	1.284e-14
single-multicellular organism process (GO:0044707)	5739	74	3.106e+01	+	5.401e-14

Table S11. References for candidate genes from TDT studies for Fig. 1 - 2.

Gene (Entrez Gene ID) functions and localizations
1. AKT1 (PKB) (207) is part of the PI3K-AKT-mTOR pathway (KEGG's pathway hsa04012+207) (see Fig. 2 in article), which regulates essential cellular functions such as glucose metabolism, growth, vascular homeostasis, angiogenesis, expression and activity of pro- and anti-angiogenic factors, activity of nitric oxide synthase (eNOS), NO production[130], contraction and relaxation of blood vessels induced by various agents[131]. Furthermore, it enhances vascular function[130,132,133], augments Hypoxia-Inducible Factor-1A (HIF1A) expression by increasing protein translation through a mammalian target of rapamycin (mTOR)[134], reduces ischemic damage[134,135] and is a vital cytoprotectant for vascular and neuronal cells[135].
2. ARVCF (421) The armadillo repeat gene deleted in velocardiofacial syndrome (ARVCF) associates with E-cadherin[136], which is part of the tight junctions between the endothelial cells of blood vessels. E-cadherin is important for the function of the blood–brain barrier (BBB). Short exposures to ischemia cause a decreased expression of E-cadherin and harm the BBB[137].
3. BDNF (627), brain-derived neurotrophic factor, attenuates microvascular permeability disturbances and axonal injury[138], prevents ischemia-induced neuronal cell death in the hippocampus[139] and plays a role in ischemic preconditioning[140].
4. CHRNA7 (1139), cholinergic receptor, nicotinic, alpha 7, is expressed in vascular smooth muscle cells[141] and induces cerebral vasodilatation[142]. Acetylcholine is known to induce dilation of intracortical microvessels and an increase in cortical perfusion[143].
5. CHRFAM7A (89832) CHRFAM7A, cholinergic receptor, nicotinic, alpha 7, exons 5-10, is a partially duplicated variant of CHRNA7. It is unknown but possible that CHRFAM7A is translated and that the gene product is able to interact with alpha 7 polypeptide since most of the contact regions are encoded in exons 5–10. Furthermore, CHRFAM7A has been found to be associated with four types of dementia, Alzheimer's disease, dementia with Lewy bodies, Pick's disease and vascular dementia[144].
6. CLDN5 (7122), claudin 5 is a major cell adhesion molecule of tight junctions in brain endothelial cells which function as blood-brain barrier (BBB). Hypoxia disrupts the BBB function through changes in the expression of claudin 5[145].
7. COMT (1312), catechol-O-methyltransferase, plays an important role in the metabolic degradation of the catecholamine neurotransmitters dopamine, adrenaline and noradrenaline. It is also involved in the vasoconstriction of cortical microvessels by dopamine[69].
8. DAOA (267012), D-amino acid oxidase, an enzyme that degrades D-serine, markedly inhibites neuronal damage by cortical ischemia and N-methyl-D-aspartate (NMDA)[29]. One isoform appears to play a role in mitochondrial function[146]. Furthermore, interaction of DAOA with COMT has been observed[147].

9. EGLN1, PHD2, disrupted in schizophrenia 1 (DISC1) (54583). The schizophrenia-associated Leu607Phe polymorphism hinders the axonal transport of mitochondria required for energy production in presynaptic terminals[148]. Furthermore, EGLN1 is part of the HIF-VHL-prolyl hydroxylase pathway[149], which functions as a cellular oxygen sensor and, under normoxic conditions, targets the hypoxia-inducible factor (HIF-1) alpha protein through hydroxylation for ubiquitination and proteasomal degradation via the von Hippel-Lindau (VHL) complex[150,151]. HIF-1 is a transcriptional complex that plays a central role in mammalian oxygen homeostasis and regulates, under hypoxic conditions, the transcription of numerous genes related to angiogenesis, cell survival, and glucose metabolism[152].

10. DRD2 (1813), dopamine receptor D2 is involved in peripheral vasoconstriction[153]. With regard to the brain, central dopaminergic neurones make close contacts with the basal lamina of arterioles and with astrocytic end-feet (reviewed in[154]). Microinjection of dopamine causes a pronounced constriction of cerebral microvessels[69]. Moreover, D2 receptor agonists produced negative changes in regional cerebral blood volume (rCBV). On the other hand, D1/D5 receptor agonists and DAT blockers induce positive hemodynamic changes[155].

11. DRD3 (1814). Similar to DRD2, D3 dopamine receptors are involved in peripheral vasoconstriction[153]. In the brain, D3 receptors are expressed by all astrocytes[156], by 75% of capillary endothelial cells, 25% of capillaries, and 40% of microvessels. D3 receptor agonists cause negative changes in rCBV[155].

12. DTNBP1 (84062), dystrobrevin binding protein 1. Dystrobrevin and probably its binding protein is localized in the astrocytic endfeet and endothelial cells of cerebral microvessels[157,158] and is part of the signal-transduction pathway for the α1D-adrenergic receptor (α1D-AR). The latter are ubiquitously expressed on vascular smooth muscle, cause vasoconstriction when activated by noradrenaline and adrenaline[159] and are responsible for increased blood pressure during exercise, injury, and stress (reviewed in[160]).

13. GABRB2 (2561), gamma-aminobutyric acid A (GABA-A) receptor beta 2. Cortical GABA interneurons provide a rich innervation to local microvessels and appear to act as local integrators for the tight coupling of neuronal activity and local perfusion, which is essential for normal brain function[161]. GABA-A receptors are present in cerebral microvessels[162,163] and respond by vasodilatation to GABA released from nerve terminals[163,164]. Muscimol, a GABA-A receptor agonist, elicites vasodilation in hippocampal microvessels[163]. Vasodilatation by cholinergic neurons is in part mediated by the local release of GABA from cholinoceptive cortical interneurons and through GABA-A receptors[165].

The transcription of GABRB2 itself is highly sensitive to hypoxia[166] and GABA-A receptors are involved in BBB disruption during cerebral ischemia[167]. With regard to cerebral ischemia, GABA exerts neuroprotective effects (reviewed in[168,169]) via GABA(A) and GABA(B) receptors[170]. And GABAergic interneurons survive ischemic injury for up to 30 days in all investigated brain regions[171]. Finally, the induction of ischemic tolerance by preconditioning depends on functional modifications of GABA synapses[172].

14. GAD1 (2571), glutamate decarboxylase 1 (brain, 67kDa) is responsible for catalyzing the production of gamma-aminobutyric acid (GABA) from L-glutamic acid. For GABA's

localisation and role in cortical microvessels, see GABRB2 above.

15. HTR2A (3356), 5-hydroxytryptamine (serotonin) receptor 2A mediates vasoconstrictive responses to 5-HT in many vascular smooth muscles and also potentiates the activity of growth factors (reviewed in[173]). Intracerebrally released serotonin cause a decrease of cerebral blood flow (CBF) in several brain regions such as the neocortex suggesting a major vasoconstrictor role[174]. In the CNS, 5-HT2A receptors are abundant in the cerebral cortex and the limbic system and are expressed in neurons as well as in astrocytes[175]. Astrocytes are involved in the regulation of cerebral blood flow (CBF) (reviewed in[176]). In addition, the HTR2A gene appears to be associated with ischemic stroke[177]. Antagonists of the 5-HT2A receptor such as ketanserin and ritanserin increase CBF in cortical areas and reduce ischemic damage (reviewed in[174]). Finally, atypical antipsychotic drugs (such as clozapine, aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone) produce extensive blockade of serotonin 5-HT2A receptors and stimulation of 5-HT1A receptors at clinically effective doses[178]. Both , i.e. 5-HT1A receptor agonists and 5-HT2 receptor antagonists, have a neuroprotective effect against ischemia-induced deficits[179].

16. IPO5 (3843) also known as imp5, RANBP5, IMB3, Pse1, and KPNB3 encodes the importin 5 protein, which is a member of the importin beta family, a cytoplasmic protein that binds to nuclear pore complexes (NPCs)[180], imports ribosomal proteins in the nucleolus where they are assembled into the eukaryotic ribosomal subunits required for protein synthesis[181] and mediates the nuclear import of H2A, H2B, H3 and H4 histones[182]. These four core histones - H2A such as Hist1H2AG, H2B such as Hist1H2BJ, H3 and H4 - are localized on chromosome 6p22, a region showing a strong association with schizophrenia[183]. The import of the four core histones is essential for the S-phase of the cell cycle during which DNA is replicated and newly synthesized histones are deposited onto the DNA in order to form the chromatin structure[182] (reviewed in[184]).

The S-phase of the cell cycle is important for the proliferation of vascular endothelial cells during angiogenesis (reviews[185-187]). Angiogenesis is a predictive marker of neurological outcome following hypoxia-ischemia[188,189]. Furthermore, histones H4[190], H3, and H2A are known to play a role in ischemia protection[190-194].

17. MTHFR (4524) methylene tetrahydrofolate reductase catalyzes the reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the predominant ciruclatory form of folate and carbon donor for the re-methylation of homocysteine to methionine. Two polymorphisms are known to cause mild enzyme deficiency. A common polymorphism in the MTHFR gene (C677T, Ala --> Val) is associated with a decreased activity of the enzyme due to thermolability. In case of homozygosity for the Val allele, a relative deficiency of the enzyme leads to a mild-to-moderate hyperhomocysteinaemia[195]. Hyperhomocysteinemia is a risk factor for cerebrovascular disease[196].

18. NOS1AP (9722) nitric oxide synthase 1 (neuronal) adaptor protein, alias CAPON, encodes a cytosolic adapter protein that activates neuronal nitric oxide synthase (nNOS/NOS1) and is involved in the synthesis of nitric oxide (NO)[197]. In humans, nNOS produces NO in nitric oxide interneurons and vascular smooth muscle cells regulating microvascular tone in humans[198-200]. In brain ischemia, nNOS stimulates the increase of NO from baseline nanomolar to micromolar levels NO (reviewed in[201]). However, the activation of nNOS alone has neurotoxic effects[202], whereas simultaneous activation of

eNOS appears to be neuroprotective (reviewed in[201,203]).

19. NOTCH4 (4855) alias INT3, encodes for the Notch-4 protein, an endothelial cell specific homologue of Notch. The expression of NOTCH4 is restricted to endothelial cells in the embryonic and adult brain[204]. The Notch-4 protein plays a crucial role in vasculogenesis, vascular repair of injury and angiogenesis[205,206]. The latter is a key response to cerebral ischemia[185-187] and predicts the neurological outcome[188,189]. During angiogenesis, Notch-4 induces microvessel differentiation of brain endothelial cells[207] and the formation of new blood vessels from existing vasculature. To allow for endothelial sprouting, the extracellular matrix around existing vasculature is degraded by matrix metalloproteases (MMPs)[208]. The MMPs is induced by VEGF signaling via VEGFR-2 and the PI3K/Akt pathway[209].

20. NRG1 (3084) neuregulin 1 alias glial growth factor 2 - also known as GGF; HGL; HRG; NDF; ARIA; GGF2; HRG1; HRGA; SMDF; MST131 – and two of its receptors (erbB2, erbB3) are expressed in brain microvascular endothelial cells[210], astrocytes and oligodendrocytes[211,212]. Neuregulin 1 activates the PI3K/AKT intracellular signaling pathway by binding to erbB receptors[211,213]. Cellular survival after ischemia depends in large extent on the activation of the PI3K/Akt pathway (reviewed in[214,215]). Like other growth factors, NRG1 activates the PI3K/Akt pathway and subsequently the mTOR-dependent protein synthesis[210,213,216,217] required for ischemia protection and repair. NRG1 has been shown to be a powerful neuroprotective factor in ischemia[119,218-220] and to play a role in repair[119]. Following vessel hypoxia and injury, the expression of of NRG1 and erbB is upregulated whereas in uninjured vessels it is low[218,221,222] .

21. NTNG1 (22854) Netrin G1 belongs to a conserved family of proteins that act as axon guidance cues during vertebrate nervous system development[114,223].

Another member of this family Netrin-1, has the ability to attract blood vessels as well as axons, and is capable of functioning as a vascular growth factor[224]. In addition, netrin-1 stimulates NO production in mature endothelial cells[225] and has been shown to protect the cerebral cortex from the effect of ischemia[226].

Little is known about a possible vascular function of netrin G1. However, the fact that the trajectories of nerves and blood vessels are often shared, led to the hypothesis that tissues may use identical or similar factors to guide innervation and vascularization[227]. Human NTNG1 is localized at the chromosomal position 1p13.3. This region is syntenic with mouse chromosome 3, where a modifier locus for renal vascular disease lesions has been identified[228].

22. PLA2G4A (5321) (alias cPLA2-alpha). The gene product, cytosolic, calcium – dependent phospholipase A2 (cPLA2), is expressed in astrocytes[229], mediates agonist-induced release of AA[230,231], responds to stress, inflammation, G protein-coupled receptors, adrenoreceptor-mediated vasoconstriction[232] and ischemia[233]. AA is further metabolized into prostaglandin molecules by cyclooxygenase-2 (COX-2) causing relaxation of vascular smooth muscles and subsequent vasodilatation. This mechanism is also activated by the skin flush induced by niacin (nicotinic acid)[231,234-239]. AA are metabolized by cytochrome P450 (CYP) epoxygenase to form epoxyeicosatrienoic acids (EETs) which are known key astrocyte- and endothelium-derived regulators of cerebrovascular function[240]. EETs have been shown to protect astrocytes and neurons against ischemia and to be key regulators of

cortical angiogenesis, which is important for recovery from ischemia[241] (reviewed in[240]).

23. PPP3CC (5533) PPP3CC (aliases CNA3; CALNA3; PP2Bgamma) codes for calcineurin A gamma subunit[114]. Calcineurin is a serine/threonine phosphatase that is activated by calcium and calmodulin[242]. It promotes the expression of Hypoxia-inducible Factor 1 alpha (HIF-1α) via the receptor for activated C kinase 1 (RACK1)[242]. Highly localized in the brain, especially in those parts which are vulnerable to hypoxia/ischemia, it has protective as well as toxic effects and the balance may be important for the outcome of ischemia[243].

24. PRODH (5625) encodes proline oxidase (POX), a mitochondrial inner-membrane enzyme that metabolizes l-proline. Most of the alleles associated with schizophrenia result in severely reducted POX activity and hyperprolinemia[244]. The latter impairs the activity of cytochrome c oxidase, an enzyme of the respiratory electron transport chain of mitochondria[245]. In the cerebral cortex, proline causes mitochondrial dysfunction, oxidative stress and impaired energy metabolism[246].

25. RBFOX2 (23543) alias Rbm9, RNA binding protein, fox-1 homolog. The mammalian Fox genes are complex transcription units that specifically recognize the RNA element UGCAUG and generate transcripts from multiple promoters[247]. Fox-1/2 are preferentially expressed in brain, heart and muscle tissues. They target genes involved in muscle contraction and vascular regulation, such as potassium ion transport, myosin, dystrophin, calmodulin binding[92].

Potassium (K+) channels play an important role in neurovascular coupling (reviewed in[248]), cerebral ischemia (reviewed in[249]) and endothelial dysfunction (reviewed in[250]). Myosin is expressed in vascular smooth muscle and pericytes[251] suggesting a role in vasoconstriction. Dystrophin is involved in flow (shear stress)-induced endothelium-dependent dilation and its absence in mice reduces NO-dependent vascular function[252]. Calmodulin and calcium activate calcineurin, which promotes the expression of hypoxia-inducible Factor 1 alpha (HIF-1α)[242].

26. RGS4 (5999), regulator of G-protein signaling 4, is selectively enriched in the heart and brain (reviewed in[253]). RGS proteins modulate hormone and neurotransmitter signaling[254]. With regard to the former, insulin release from pancreatic beta-cells is negatively regulated by RGS4[255]. Insulin activates the PI3K/Akt pathway, which is important for ischemia protection and repair from ischemia injury by angiogenesis. The latter is inhibited by RGS4[256]. Concerning neurotransmitter signaling, RGS proteins modulate and inhibit signal transduction by G-protein-coupled receptors (GPCRs) (reviewed in[253,257,258]). Mice deficient for RGS4 show increased concentration of serum catecholamines[259]. In addition, RGS4 is linked to regulation of cholinergic and serotonergic signaling in the brain and is expressed in most cortical layers (reviewed in[253]). GPCRs are widely associated with the regulation of vascular smooth muscle cell contractility[260] and RGS proteins are known to play a role in the regulation of vascular tone[261,262].

27. SLC6A3, DAT1 (6531), solute carrier family 6 (neurotransmitter transporter, dopamine) member 3, is situated in the plasma membrane of the dopaminergic neurons where it mediates the re-uptake of dopamine from the synaptic cleft into the presynaptic neuron[263,264]. Dopaminergic signaling in the brain is primarily modulated by dopamine

transporters (DATs) (reviewed in[265]). In rats, DAT blockers induce positive hemodynamic changes via D1/D5 dopamine receptors and smaller negative changes through D2/D3 receptors on microvessels and astrocytes[155]. In humans, the DAT blocker cocaine caused dose-dependent cerebral vasoconstriction as revealed by magnetic resonance angiography[266]. Cocaine abuse and dependence is associated with increased incidence of stroke and myocardial ischemia[267,268]. The latter has been shown to be a consequence of vascular spasms[268].

28. SLC6A4, 5HTT (6532), solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 - also known as HTT; 5HTT; OCD1; SERT; 5-HTT; SERT1; hSERT; 5-HTTLPR - encodes a membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons. It terminates the action of serotonin and recycles it[114]. Serotonergic perivascular nerves are involved in the regulation of cerebrovascular tone[68]. Intracerebrally released serotonin (5-HT) has a major vasoconstrictor effect resulting in a decrease of cerebral blood flow (CBF) in several brain regions including the neocortex (reviewed in[174]). A serotoninergic pathway originating in the raphe nucleus projects to cortical microvessels endowed with several 5-HT receptors including 5-HT1B receptors that mediate their contraction (reviewed in[68,174]). Consistent with serotonin's vasoconstrictor effect, 5-HT2 receptor antagonists such as ketanserin and ritanserin, have been shown to increase CBF in cortical areas and to exert a protective effect in ischemia[174].

29. SYN2 (6854), synapsin II - is a member of the synapsin family and encodes a neuron-specific phosphoprotein that selectively binds to small synaptic vesicles in the nerve terminal[114]. Synapsin proteins have important functions in maintaining the integrity and stability of synaptic vesicles[269] and are regulators of neurotransmitter release from presynaptic nerve terminals (reviewed in[270,271]).

SNYN2 is a negative regulator of catecholamine release. SYN2 knock-out mice showed an increase of catecholamine release[272]. Furthermore, double knock-out mice, with deletions of SYN1 and SYN2, display higher concentrations of acetylcholine in the cortex[269]. SYN2 knock-out mice also had an increase of glutamatergic and GABAergic synaptic transmission in the spinal cord after nerve injury[273]. Catecholamines and acetylcholine play a role in neurovascular regulation (reviewed in[68]). Glutamate release following ischemia is thought to cause neuronal injury (reviewed in[274]).

30. TRMT2A (27037), HpaII tiny fragments locus 9c protein, HTF9C, TRM2 tRNA methyltransferase 2 homolog A is a protein expressed in proliferating cells. It is overexpressed in breast cancer[275] suggesting a role for TRMT2A in angiogenesis and in protection and recovery from ischemia. Angiogenesis is predictive of neurological outcome following hypoxia-ischemia[188,189].

The transcription of TRMT2A is repressed in quiescent tissues and growth-arrested cells, activated at the G1/S transition of the cell cycle, and peaks in S phase[276,277]. The G1/S transition is the first brake-point through which the cell must pass before it can enter cell division. During S-phase of the cell cycle, DNA is replicated and de novo chromatin assembly takes place[278].

A key response to tissue hypoxia is angiogenesis, which requires the proliferation of vascular endothelial cells (reviewed in[185-187]). Prevention of endothelial cells to enter G1 phase of the cell cycle results in reduced angiogenesis[279,280] and hence in protection and

recovery from ischemia.
31. TNF (7124), tumor necrosis factor, is a multifunctional proinflammatory cytokine[114] which is induced within 1 hour in brain ischemia, It has oligodendrocyte cytotoxic as well as neuroprotective effects (reviewed in[281,282]). The activation of the Akt pathway has protective effects on TNF-mediated oligodendrocyte cytotoxicity[283]. Concerning neuroprotection, TNF activates also the mammalian target of rapamycin (mTOR) which has an influence on mitochondrial energy metabolism, protein synthesis and adaptation to ischemia[284]. Moreover, TNF activates cPLA2 (reviewed in[285]), which regulates cerebrovascular function via arachidonic acid (AA) and epoxyeicosatrienoic acids (EETs) (reviewed in[240,286]). Finally, TNF improves ischemia repair by upregulating the erythropoietin receptor (EPOR) thereby sensitizing cerebral endothelial cells for erythropoietin-induced angiogenesis[287].
32. UFD1L (7353), ubiquitin fusion degradation 1 like. The protein encoded by this gene forms a complex with two other proteins, nuclear protein localisation-4 and valosin-containing protein. This complex is necessary for the degradation of ubiquitinated proteins[114]. Ubiquitination of proteins is the first step in the degradation of proteins by the proteasome system. The ubiquitin-proteasome system degrades hypoxia-inducible factor 1alpha (HIF-1alpha) protein under normoxic conditions, while it is stabilized and accumulated rapidly following exposure to low oxygen tensions[288,289]. HIF-1 is a master regulator of response to hypoxia by activating the transcription of many genes, including those involved in blood flow, cell survival, glucose transport, energy metabolism, i.e. genes whose protein products increase oxygen delivery or facilitate adaptation to hypoxia[114]. Ubiquitin fusion degradation protein 1 (UFD1) is a blood marker for the early diagnosis of ischemic stroke[290].
33. ZDHHC8 (29801), zinc finger, DHHC-type containing 8 (DHCC8), is localised in mitochondria and presynaptic processes, mostly glutmatergic and to a lesser extent GABAergic processes. It interacts interacts with mitochondrial Complex III. ZDHHC8 dosage change is able to disrupt mitochondrial function and to influence cell survival and death[291].

Pathway analyses

Preliminary pathway analyses

KEGG pathway analysis

The Kyoto Encyclopedia of Genes and Genomes (KEGG)[292] at (http://www.kegg.jp) was used for pathway analysis and as guide for the construction of the candidate schizophrenia pathway depicted in Figs. 1 and 2.

As requested by one of the reviewers, results of these analyses are shown as Supplementary Information. The KEGG pathway analyses produced a five pages long list of pathways, which are difficult to interpret with regard to the etiology of schizophrenia. Table S12 lists the top results on the first page of output from KEGG. Figs. S3S5 are

shown to exemplify the help provided by KEGG pathways for constructing the candidate pathway for schizophrenia depicted in Figs. 1 and 2.

The first page of the results from the KEGG pathway analysis is shown in Table S12. Five genes from our list of candidate genes for schizophrenia were not found in the KEGG database. Yellow highlights pathways related to vascular regulation or the energy-delivering pathway depicted in Figs. 1 and 2.

Table S12. Results of pathway analysis by KEGG

Pathway Search Result

Following object(s) was/were not found ncbi-geneid:54806 ncbi-geneid:421 ncbi-geneid:89832 ncbi-geneid:267012 ncbi-geneid:27185 ncbi-geneid:84062 ncbi-geneid:3843 ncbi-geneid:5999 ncbi-geneid:6854 ncbi-geneid:27037 ncbi-geneid:29801 ncbi-geneid:91752

Sort by the pathway list

Show all objects

- hsa04080 Neuroactive ligand-receptor interaction - Homo sapiens (human) (7)
- hsa04728 Dopaminergic synapse - Homo sapiens (human) (7)
- hsa01100 Metabolic pathways - Homo sapiens (human) (6)
- hsa04010 MAPK signaling pathway - Homo sapiens (human) (5)
- hsa04020 Calcium signaling pathway - Homo sapiens (human) (5)
- hsa04012 ErbB signaling pathway - Homo sapiens (human) (4)
- hsa04726 Serotonergic synapse - Homo sapiens (human) (4)
- hsa05034 Alcoholism - Homo sapiens (human) (4)
- hsa04024 cAMP signaling pathway - Homo sapiens (human) (4)
- hsa05030 Cocaine addiction - Homo sapiens (human) (4)
- hsa04370 VEGF signaling pathway - Homo sapiens (human) (3)
- hsa04664 Fc epsilon RI signaling pathw sapiens (human) (3)
- hsa04540 Gap junction - Homo sapiens (human) (3)
- hsa05031 Amphetamine addiction - Homo sapiens (human) (3)
- hsa04380 Osteoclast differentiation - Homo sapiens (human) (3)
- hsa05166 HTLV-I infection - Homo sapiens (human) (3)
- hsa05205 Proteoglycans in cancer - Homo sapiens (human) (3)
- hsa05012 Parkinson's disease - Homo sapiens (human) (3)
- hsa05033 Nicotine addiction - Homo sapiens (human) (3)
- hsa04210 Apoptosis - Homo sapiens (human) (3)
- hsa04727 GABAergic synapse - Homo sapiens (human) (3)
- hsa05032 Morphine addiction - Homo sapiens (human) (3)
- hsa04660 T cell receptor signaling pathway - Homo sapiens (human) (3)
- hsa05152 Tuberculosis - Homo sapiens (human) (3)
- hsa04920 Adipocytokine signaling pathway - Homo sapiens (human) (3)
- hsa05160 Hepatitis C - Homo sapiens (human) (3)
- hsa04150 mTOR signaling pathway - Homo sapiens (human) (2)
- hsa04921 Oxytocin signaling pathway - Homo sapiens (human) (2)

Figure S3. KEGG's mTOR pathway

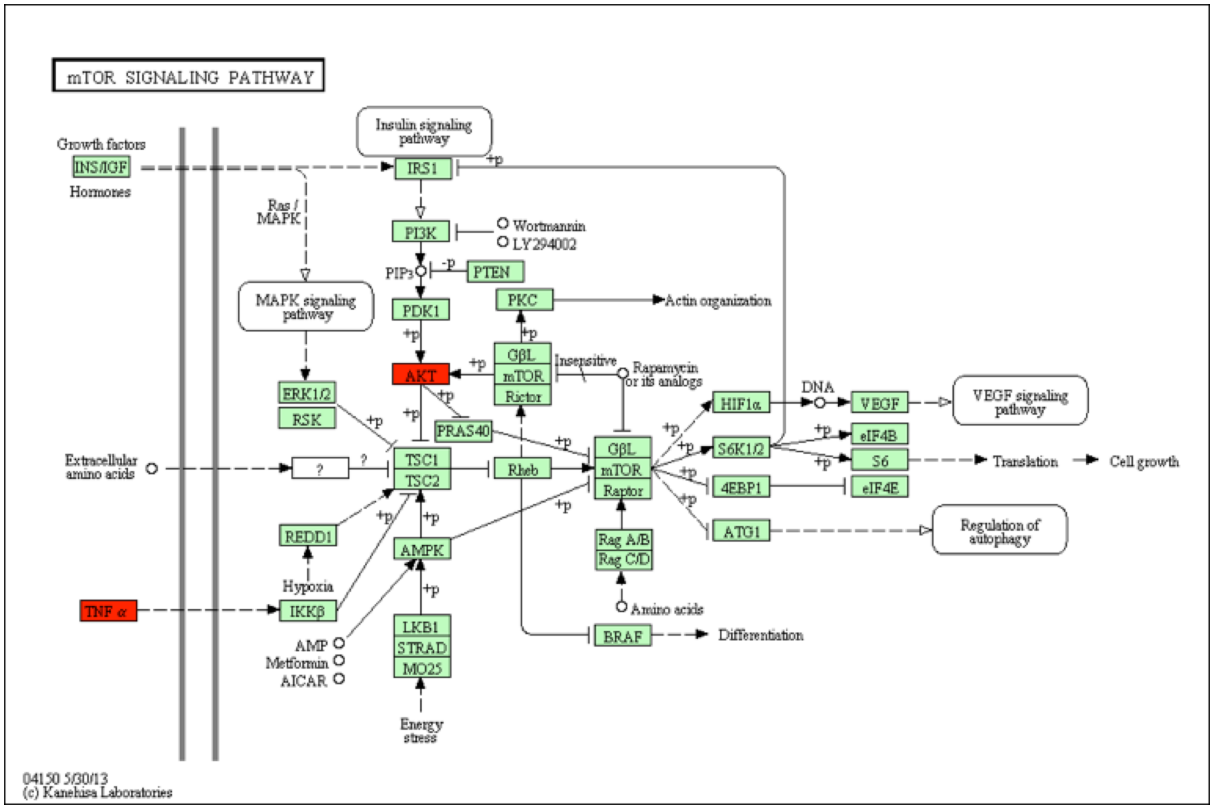


Figure S3. Two candidate genes for schizophrenia from the TDT sample (in red) mapped by KEGG to the mTOR signaling pathway are shown as an example of the data from KEGG employed for constructing the energy-delivering pathway (see Figs. 1 and 2).

Figure S4. KEGG's Hypoxia-Inducible Factor (HIF) pathway

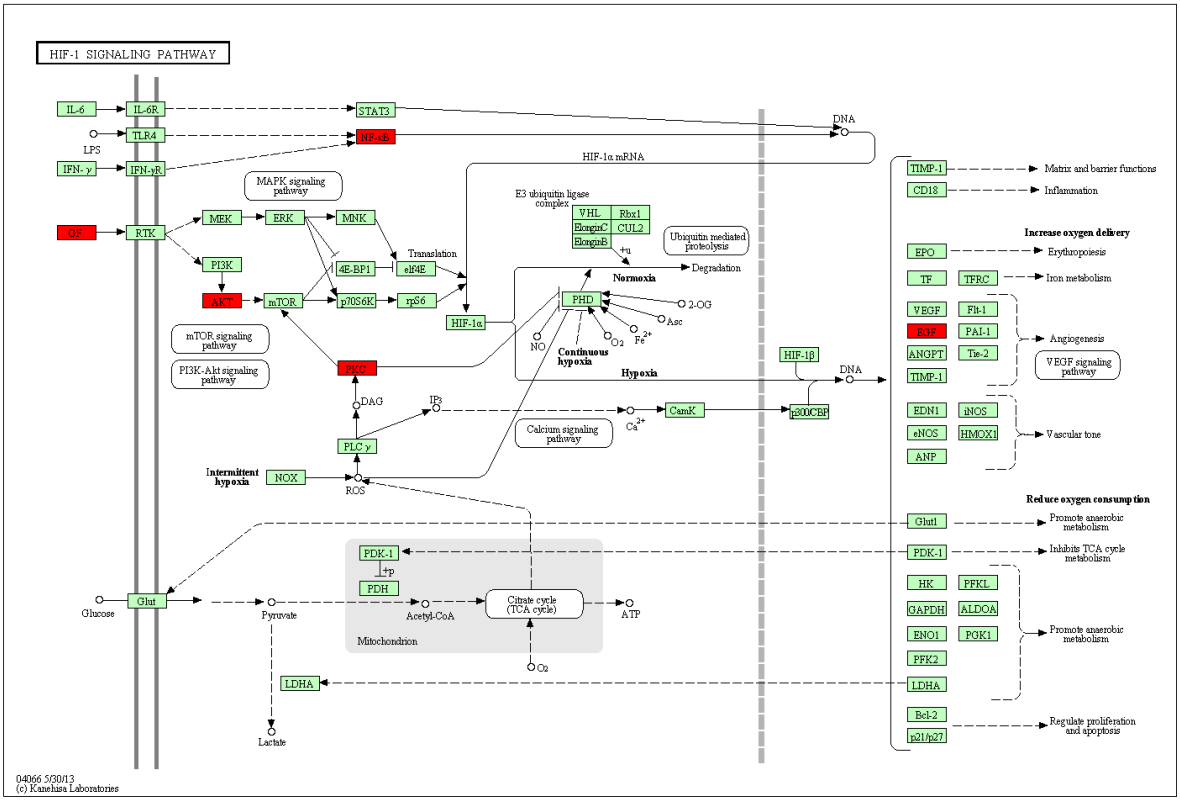


Figure S4. Five schizophrenia-associated genes mapped by KEGG to the Hypoxia-Inducible Factor (HIF) signaling pathway. The combined sample of 345 schizophrenia-associated genes was used to obtain this figure from KEGG.

Figure S5. KEGG's Vascular Smooth Muscle Contraction (VSMC) pathway

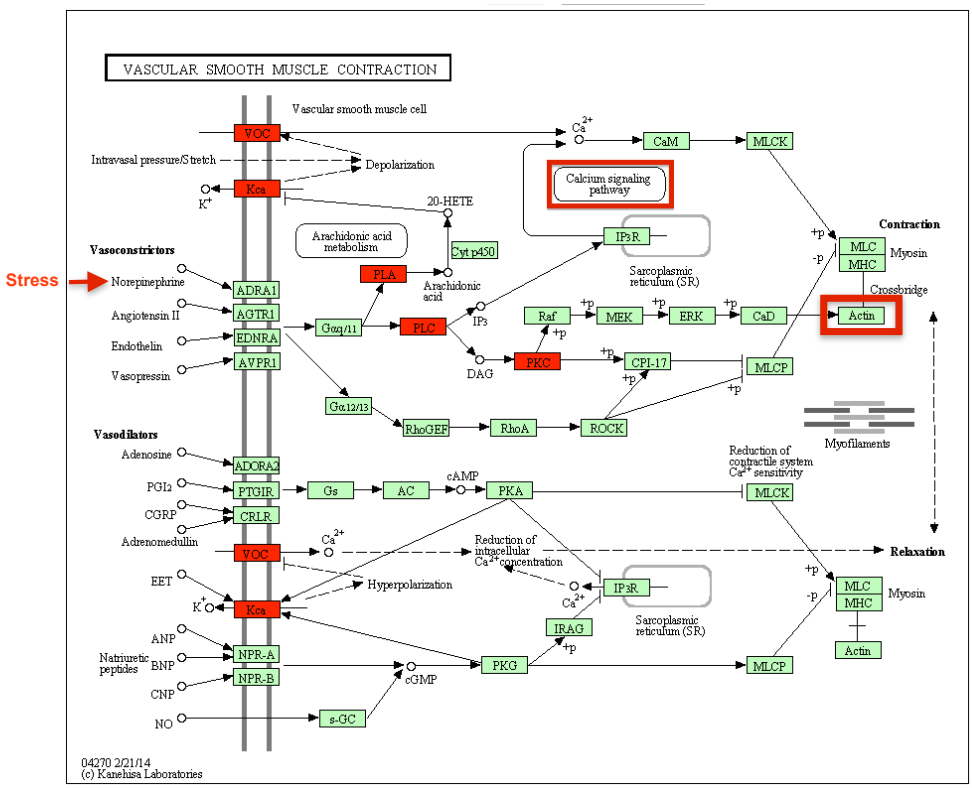


Figure S5. Five schizophrenia-associated genes were mapped by KEGG to the VSMC pathway. The combined sample was used for this Figure. In addition, actin was marked, because Fromer et al. (2014) and Zhao et al. (2014) found evidence for the involvement of actin in schizophrenia[293,294]. Furthermore, the polymerisation status of the submembranous actin web in vascular endothelium determines the activity of eNOS and the release of NO[295] (see also Fig. 1–2). In addition, a role for calcium signaling genes in schizophrenia was reported in the 2014 GWAS by the SWGPGC[5] and has recently been emphasized by Tansey et al. (2015)[296].

PANTHER pathway analysis

The PANTHER (**P**rotein **AN**alysis **TH**rough **E**volutionary **R**elationships) Classification System[297] at (http://www.pantherdb.org) was employed for pathway analysis of the discovery and the combined sample. The results of the latter are shown in Table S13. They involved the dopamine receptor mediated signaling pathway, adrenaline and noradrenaline biosynthesis, EGF receptor signaling pathway, 5HT2 type receptor mediated signaling pathway, nicotinic acetylcholine receptor signaling pathway. P values are Bonferroni corrected for multiple testing.

Table S13. Results of pathway analysis by PANTHER

Displaying only results with P<0.05; click here to display all results

	Homo sapiens (REF)	Client Text Box Input				
PANTHER Pathways	#	#	expected	Fold Enrichment	+/-	Δ P value
Unclassified	19446	16	33.89	.47	-	0.00E00
Dopamine receptor mediated signaling pathway	57	6	.10	> 5	+	1.26E-07
Adrenaline and noradrenaline biosynthesis	28	3	.05	> 5	+	2.66E-03
EGF receptor signaling pathway	123	4	.21	> 5	+	9.88E-03
5HT2 type receptor mediated signaling pathway	50	3	.09	> 5	+	1.48E-02
Nicotinic acetylcholine receptor signaling pathway	74	3	.13	> 5	+	4.65E-02

Genetic disease association analysis by DAVID

The discovery and the combined gene samples described in this article were also analysed genetic disease associations by the **D**atabase for **A**nnotation, **V**isualization and **I**ntegrated **D**iscovery (DAVID)[298] at (http://david.abcc.ncifcrf.gov/). Table S14 shows some of the results.

Table S14. DAVID's genetic associations with diseases

Rerun Using Options | Create Sublist

22 chart records | Download File

Sublist	Category	Term	RT	Genes	Count	%	P-Value	Bonferroni	Fisher Exact
	GENETIC_ASSOCIATION_DB_DISEASE	schizophrenia	RT		37	92,5	7,0E-37	6,8E-34	6,1E-38
	GENETIC_ASSOCIATION_DB_DISEASE	bipolar disorder	RT		14	35,0	1,1E-10	1,1E-7	9,6E-12
	GENETIC_ASSOCIATION_DB_DISEASE	cognitive function	RT		10	25,0	4,9E-11	4,8E-8	1,4E-12
	GENETIC_ASSOCIATION_DB_DISEASE	alcohol abuse	RT		10	25,0	7,2E-10	7,0E-7	3,0E-11
	GENETIC_ASSOCIATION_DB_DISEASE	Parkinson's disease	RT		10	25,0	2,2E-5	2,1E-2	3,4E-6
	GENETIC_ASSOCIATION_DB_DISEASE	smoking behavior	RT		9	22,5	6,7E-9	6,5E-6	2,7E-10
	GENETIC_ASSOCIATION_DB_DISEASE	depression	RT		9	22,5	1,0E-8	1,0E-5	4,6E-10
	GENETIC_ASSOCIATION_DB_DISEASE	alcoholism	RT		9	22,5	8,3E-8	8,1E-5	4,9E-9
	GENETIC_ASSOCIATION_DB_DISEASE	attention deficit disorder conduct disorder oppositional defiant disorder	RT		9	22,5	2,8E-7	2,7E-4	1,9E-8
	GENETIC_ASSOCIATION_DB_DISEASE	methamphetamine abuse	RT		8	20,0	2,4E-10	2,3E-7	3,4E-12
	GENETIC_ASSOCIATION_DB_DISEASE	heroin abuse	RT		8	20,0	4,0E-10	3,9E-7	6,3E-12
	GENETIC_ASSOCIATION_DB_DISEASE	attention deficit hyperactivity disorder	RT		8	20,0	3,1E-7	3,0E-4	1,6E-8
	GENETIC_ASSOCIATION_DB_DISEASE	Alzheimer's Disease	RT		8	20,0	2,3E-2	1,0E0	8,2E-3
	GENETIC_ASSOCIATION_DB_DISEASE	Tourette syndrome	RT		7	17,5	1,6E-8	1,6E-5	2,9E-10
	GENETIC_ASSOCIATION_DB_DISEASE	tardive dyskinesia	RT		7	17,5	3,3E-7	3,2E-4	1,1E-8
	GENETIC_ASSOCIATION_DB_DISEASE	personality traits	RT		7	17,5	4,2E-7	4,1E-4	1,5E-8
	GENETIC_ASSOCIATION_DB_DISEASE	migraine	RT		7	17,5	3,9E-6	3,8E-3	2,2E-7
	GENETIC_ASSOCIATION_DB_DISEASE	depressive disorder, major	RT		7	17,5	1,4E-5	1,4E-2	1,0E-6
	GENETIC_ASSOCIATION_DB_DISEASE	obsessive compulsive disorder	RT		6	15,0	5,7E-7	5,5E-4	1,2E-8
	GENETIC_ASSOCIATION_DB_DISEASE	Anorexia Nervosa	RT		6	15,0	1,6E-6	1,5E-3	4,3E-8
	GENETIC_ASSOCIATION_DB_DISEASE	schizophrenia; bipolar disorder	RT		6	15,0	2,8E-6	2,7E-3	8,8E-8
	GENETIC_ASSOCIATION_DB_DISEASE	bipolar disorder schizophrenia	RT		6	15,0	3,6E-6	3,5E-3	1,2E-7

2 gene(s) from your list are not in the output.

Legend for Table S14. Functional annotation of the discovery sample by DAVID's genetic association database. Interestingly, seven of the candidate genes for schizophrenia are also involved in migraine (see above).

Gene set analysis

All genes from other species were transformed into human orthologous genes and identified by Entrez Gene IDs. The association between schizophrenia-associated genes and functional gene sets were computed by using the intersect function of the programming language R (version 3.0.2, platform: x86_64-apple-darwin10.8.0, 64-bit)[299].

Supplementary statistics information

Genome resampling test

Homo sapiens' complete list of genes was downloaded on April 8, 2011 from the Entrez Gene database maintained by the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/gene). It had 45 386 entries.

To improve the power (i.e. the chances of obtaining an intersection of randomly drawn genes from the database with functional gene sets), the list was curated by deleting all genes with unknown function from the Entrez Gene database. Using the Unix stream editor SED, genes with the following key words were removed: pseudogene, hypothetical LOC, hypothetical protein, pseudo, miscRNA, readthrough, read-through, open reading frame, deletion syndrome, duplication syndrome, triplication syndrome, unknown, uncharacterised protein, putative uncharacterised protein and repeat sequence. Next, all candidate genes for schizophrenia and functional gene sets were added and duplicates removed to ensure that all genes under investigation are represented equally among the constructed representation of the Human Genome and have a chance of being drawn during genomic resampling. The final modified list of Entrez Genes was comprised of 21 012 human genes mostly of known function.

The number of intersections between schizophrenia-associated genes and functional gene sets was determined by the intersect function implemented in R[299]. A genomic resampling procedure was employed to obtain estimates of the expected numbers of intersecting genes by drawing the same number of genes as the candidate genes 1 million times at random (with replacement) from the representation of the Human Genome described above and determining the intersection of the random genes with the functional gene set. The resampling method has the avantage of being independent of the distribution assumption, but due to computational restrictions significance can only be computed up to a threshold of $p \geq$ 10E-6. Within this limit imposed by computational restriction, the empiciral *p*-values were identical to the nominal *p*-values from Fisher's Exact Test.

RESULTS

Putative schizophrenia pathway

The stress-induced increase of cortisol and desoxycorticosterone (DOC)[300] has an inhibitory influence on the expression of glucose transporters[301], brain metabolism[302], and serotonin uptake[303]. Furthermore, stress induces the release of adrenaline into the circulation and of noradrenaline and dopamine in the prefrontal cortex (reviewed in[304]); these are neurotransmitters known for their vasoconstrictive effects[69,303] (reviewed in[305]). Magnitude and duration of the signals of these neurotransmitters is primarily influenced by their plasma membrane transporters (e.g., DAT1, NAT1 and 5-HTT) (reviewed in[306]). The expression of these transporters at the cell surface depends on the activity of the PI3K/Akt pathway and its stimulation by insulin and insulin-like growth factor 1 (IGF-1)[307].

Numerous studies have shown that growth factors, cytokines and hormones (such as insulin, IGF-1, EGF, prolactin, estrogens and erythropoietin) have a positive effect on Akt, thereby probably reducing the vasoconstrictive impact of stress via Akt's positive influence on DAT1[264], NAT1[308] and eNOS[309]. At low concentrations, testosterone exerts an activating effect on Akt, but an inhibitory effect at high concentrations[310]. In addition, prolactin activates Akt[311] suggesting that the hyperprolactinemia caused by typical antipsychotics is likely to have vasodilatatory and ischemia-protective effects (Fig. 2).

In summary, cerebral blood flow and energy supply depend on growth factors, hormones and genes involved in the PI3K–Akt–mTOR pathway. Activation of this pathway also protects tissue from ischemia by influencing the protein synthesis of the hypoxia-inducing factor (HIF)[312], which subsequently induces the translation of more than 70 proteins in order to increase blood flow, cellular survival and alternative energy production from lactate.

Discovery sample

Table S15. Intersection between functional gene sets and candidate genes for schizophrenia obtained from TDT studies.

Functions	*N*	SZ *N*	E (N)	O (N)	E (%)	O (%)	RF	CI	Nominal $p \leq$	Bonferroni corrected $p \leq$
VIRND	6409	41	13	28	30.4	68.3	2.3	22–41	6.8E-07	1.3e-05 **
VI	4213	41	8	25	20.1	61.0	3.0	19–41	1.2E-08	2.3e-07 ***
V	3249	41	6	20	15.4	48.8	3.2	14–41	5.9E-07	1.1e-05 **
PV	253	41	1	11	1.2	26.8	22.3	6–41	1.7E-12	3.2e-11 ***
I	1673	41	3	15	8.0	36.6	4.6	1041	2.8E-07	5.3e-06 **
R	159	41	0	11	0.7	26.8	35.5	6–41	8.5E-15	1.6e-13 ***
Repair	3319	41	6	23	15.8	56.1	3.6	17-41	3.7E-09	7.0e-08 ***
ND	3211	41	6	16	15.3	39.0	2.6	11–41	1.9E-04	3.6e-03 *
SY	1977	41	4	19	9.4	46.3	4.9	13–41	9.9E-10	1.9e-08 ***
VI x ND	1051	41	2	13	5.0	31.7	6.3	8–41	5.4E-08	1.0e-06 ***
VI x Repair	1124	41	2	20	5.3	48.8	9.1	14–41	2.8E-15	5.3e-14 ***
V x ND	784	41	2	11	3.7	26.8	7.2	6–41	2.0E-07	3.8e-06 **
V x Repair	845	41	2	18	4.1	43.9	10.9	13–41	5.3E-15	1.0e-13 ***
I x ND	523	41	1	8	2.5	19.5	7.9	4–41	6.4E-06	1.2e-04 **
I x Repair	569	41	1	12	2.7	29.3	10.8	7–41	5.2E-10	9.9e-09 ***
VI -ND	3163	41	6	12	15.1	29.3	1.9	7–41	0.02 n.s.	0.38 n.s.
VI -SY	3273	41	6	9	15.5	22.0	1.4	5–41	0.18 n.s	1.0 n.s.
ND -VI	2161	41	4	3	10.3	7.3	0.7	1–41	0.81 n.s	1.0 n.s.
SY -VI	1037	41	2	3	4.9	7.3	1.5	1–41	0.33 n.s	1.0 n.s.

Legend for Table S15. CI, 95 percent confidence intervals expressed as number of identical genes; E, Expected number and percentage of intersecting genes by chance; I, ischemia genes; Minus sign (-), overlapping genes removed; ND, neurodevelopmental genes; O, Observed number or percentage of intersecting genes; PV, perivascular nerve genes; R, post-ischemic repair genes; Repair, R and ND genes combined because ND

genes are involved in post-ischemic repair[120,127]; RF, representation factor, i.e., the number of intersecting genes divided by the expected number of intersecting genes drawn from two independent groups. RF > 1 indicates an overrepresentation of genes; SY, synaptic genes; SZ, schizophrenia-associated genes; x, indicate interacting genes; VI, vascular and ischemia genes of the brain combined. VIRND, all genes involved in ischemia combined, i.e., V, I, R and ND genes. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq p \leq$ 1.0E-06.

Replication sample #1

Table S16. Intersection between functional gene sets and candidate genes for schizophrenia obtained from case-control studies (CC).

Functions	*N*	**SZ** *N*	**E** **(N)**	**O** **(N)**	**E** **(%)**	**O** **(%)**	**RF**	**CI**	**Nominal** $p \leq$	**Bonferroni corrected** $p \leq$
VIRND	6409	58	18	47	30.6	81.0	2.7	41–58	2.4E-15	5.0e-14 ***
VI	4213	58	12	43	20.1	74.1	3.7	36-58	2.2E-16	4.6e-15 ***
V	3249	58	9	36	15.4	62.1	4.0	29-58	9.0E-16	1.9e-14 ***
PV	253	58	1	19	1.2	32.7	27.2	13-58	2.2E-16	4.6e-15 ***
I	1673	58	5	28	8.0	48.3	6.1	21-58	4.5E-16	9.5e-15 ***
R	159	58	0	19	0.7	32.8	43.3	13–58	2.2E-16	4.6e-15 ***
Repair	3319	58	9	29	15.8	50.0	3.2	22–58	1.3E-09	2.7e-08 ***
ND	3211	58	9	16	15.3	27.6	1.8	10-58	0.01 n.s.	2.1e-01 n.s.
SY	1977	58	6	23	9.4	39.7	4.2	16-58	8.0E-10	1.7e-08 ***
VI x ND	1051	58	3	13	5.0	22.4	4.5	8–58	4.4E-06	9.2e-05 **
VI x Repair	1124	58	3	25	5.3	43.1	8.1	19–58	2.2E-16	4.6e-15 ***
V x ND	784	58	2	12	3.7	20.7	5.6	7–58	1.2E-06	2.5e-05 **
V x Repair	845	58	2	24	4.0	41.4	10.3	18–58	2.2E-16	4.6e-15 ***
I x ND	523	58	1	8	2.5	13.8	5.6	4–58	8.8E-05	1.8e-03 *
I x Repair	569	58	2	16	2.7	27.6	10.2	11–58	1.9E-12	4.0e-11 ***
VI -ND	3163	58	8	30	15.0	51.7	3.4	23-58	7.6E-11	1.6e-09 ***
VI -SY	3273	58	9	21	15.5	36.2	2.3	15-58	1.0E-04	2.1e-03 *
I -ND	1151	58	3	20	5.5	34.5	6.3	14-58	1.4E-11	2.9e-10 ***
I -SY	1180	58	3	15	5.6	25.9	4.6	10-58	5.1E-07	1.1e-05 **
ND -VI	2161	58	6	3	10.2	5.2	0.5	1–58	0.96 n.s.	1.0 n.s.
SY -VI	1037	58	3	1	4.9	1.7	0.3	1–58	0.95 n.s.	1.0 n.s.

Legend for Table S16. Abbreviations are explained at Table S15. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq p \leq$ 1.0E-06.

Replication sample #2

Table S17. Intersection of the schizophrenia gene set obtained from the NHGRI catalog with functional gene sets.

Functions	*N*	SZ *N*	E (N)	O (N)	E (%)	O (%)	RF	CI	Nominal $p \leq$	Bonferroni corrected $p \leq$
VIRND	6409	164	50	76	30.5	46.3	1.5	65–164	6.0E-06	1.1e-04 **
VI	4213	164	33	44	20.0	26.8	1.3	35–164	0.02	0.38 n.s.
V	3249	164	25	37	15.5	22.6	1.5	28–164	0.01	0.19 n.s.
PV	253	164	2	7	1.2	4.3	3.5	3–164	0.004	7.6e-02 n.s.
I	1673	164	13	16	7.9	9.8	1.2	10–164	0.23	1.0 n.s.
R	159	164	1	6	0.7	3.7	4.8	3–164	0.001	1.9e-02 n.s.
Repair	3319	164	26	50	15.8	30.5	1.9	40–164	9.2E-07	1.7e-05 **
ND	3211	164	25	46	15.3	28.0	1.8	37–164	2.1E-05	4.0e-04 **
SY	1977	164	15	31	9.4	18.9	2.0	23–164	1.4E-04	2.7e-03 *
VI x ND	1051	164	8	15	5.0	9.1	1.8	9–164	0.02	0.38 n.s.
VI x Repair	1124	164	9	18	5.3	11.0	2.1	12–164	0.003	5.7e-02 n.s.
V x ND	784	164	6	13	3.7	7.9	2.1	8–164	0.007	0.13 n.s.
V x Repair	845	164	7	15	4.0	9.1	2.3	9–164	0.003	5.7e-02
I x ND	523	164	4	8	2.5	4.9	2.0	4–164	0.05	0.95 n.s.
I x Repair	569	164	4	10	2.7	6.1	2.3	5–164	0.01	0.19 n.s.
VI -ND	3163	164	25	29	15.1	17.7	1.2	21–164	0.20	1.0 n.s.
VI -SY	3273	164	25	29	15.6	17.7	1.1	21–164	0.26	1.0 n.s.
ND -VI	2161	164	17	31	10.2	18.9	3.7	23–164	6.4E-04	1.2e-02 n.s.
SY -VI	1037	164	8	16	4.9	9.8	2.0	10–164	8.0E-03	0.15 n.s.

Legend for Table S17. Abbreviations are explained at Table S15. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq$ $p \leq$ 1.0E-06.

Replication sample #3

Table S18. Intersection of the schizophrenia gene set developed by Ayalew et al.[4] with functional gene sets.

Functions	*N*	SZ *N*	E (N)	O (N)	E (%)	O (%)	RF	CI	Nominal $p \leq$	Bonferroni corrected $p \leq$
VIRND	6409	42	13	36	30.5	85.7	2.8	31–42	1.6E-13	3.0e-12 ***
VI	4213	42	8.5	31	20.2	73.8	3.7	25–42	1.2E-13	2.3e-12 ***
V	3249	42	6	24	15.5	57.1	3.7	18–42	6.9E-10	1.3e-08 ***
PV	253	42	1	12	1.2	28.6	23.7	1-42	7.4E-14	1.4e-12 ***
I	1673	42	3.4	22	8.0	52.4	6.6	16–42	8.4E-14	1.6e-12 ***
R	159	42	0	11	0.7	26.2	34.6	6–42	1.2E-14	2.3e-13 ***
Repair	3319	42	7	29	15.8	69.0	4.4	23–42	1.6E-14	3.0e-13 ***
ND	3211	42	6.5	26	15.4	61.9	4.1	20–42	9.9E-12	1.9e-10 ***
SY	1977	42	4.0	29	9.5	69.0	7.3	23–42	2.2E-16	4.2e-15 ***
VI x ND	1051	42	2	21	5.0	50.0	10.0	15–42	2.2E-16	4.2e-15 ***
VI x Repair	1124	42	2	24	5.3	57.1	10.7	18–42	2.2E-16	4.2e-15 ***
V x ND	784	42	2	16	3.8	38.1	10.2	11–42	8.0E-13	1.5e-11 ***
V x Repair	845	42	2	19	4.1	45.2	11.3	14–42	5.6E-16	1.1e-14 ***
I x ND	523	42	1	14	2.4	33.3	13.4	9–42	8.0E-13	1.5e-11 ***
I x Repair	569	42	1	17	2.7	40.5	15.0	12–42	2.4E-16	4.6e-15 ***
VI -ND	3163	42	6.4	10	15.2	23.8	1.6	5–42	0.09 n	1.0 n.s.
VI -SY	3273	42	6.6	7	15.7	16.7	1.1	3–42	0.50	1.0 n.s.
ND -VI	2161	42	4.4	5	10.4	11.9	1.2	2–42	0.44	1.0 n.s.
SY -VI	1037	42	2.1	5	5.0	11.9	2.4	2–42	0.06	1.0 n.s.

Abbreviations are explained at Table S15. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq p \leq$ 1.0E-06.

Replication sample #4 (all genes within range)

Table S19. Intersection of all the 343 genes within range of 108 genome-wide significant loci reported in 2014 by the SWGPGC in the largest GWAS of schizophrenia to date.

Functions	*N*	**SZ** *N*	**E (N)**	**O (N)**	**E (%)**	**O (%)**	**RF**	**CI**	**Nominal** $p \leq$	**Bonferroni corrected** $p \leq$
VIRND	6409	343	105	154	30.5	44.9	1.5	139–343	5.2E-09	9.9e-08 ***
VI	4213	343	69	97	20.1	28.3	1.4	83–343	1.7E-04	3.2e-03 *
V	3249	343	53	76	15.5	22.2	3.5	63–343	6.8E-04	1.3e-02 n.s.
PV	253	343	4	12	1.2	3.5	2.9	7–343	0.001	1.9e-02 n.s.
I	1673	343	27	46	8.0	13.4	1.7	36–343	3.8E-04	7.2e-03 *
R	159	343	3	7	0.8	2.0	2.7	3–343	0.01	0.19 n.s.
Repair	3319	343	54	95	15.8	27.7	1.8	81–343	7.4E-09	1.4e-07 ***
ND	3211	343	52	91	15.2	26.5	1.7	78–343	5.9E-08	1.1e-06 ***
SY	1977	343	32	49	9.4	14.3	1.5	39–343	0.002	3.8e-02 n.s.
VI x ND	1051	343	17	35	5.0	10.2	2.0	26–343	4.4E-05	8.4e-04 **
VI x Repair	1124	343	18	38	5..3	11.1	2.1	29–343	1.5E-05	2.8e-04 **
V x ND	784	343	13	28	3.7	8.2	2.2	20–343	8.1E-05	1.5e-03 *
V x Repair	845	343	14	31	4.0	9.0	2.3	23–343	2.0E-05	3.8e-04 **
I x ND	523	343	9	22	2.5	6.4	2.6	15–343	4.6E-05	8.7e-04 **
I x Repair	569	343	9	23	2.7	6.7	2.5	16–343	5.8E-05	1.1e-03 *
VI -ND	3163	343	52	62	15.0	18.1	1.2	50–343	0.07	1.0 n.s.
VI -SY	3273	343	53	67	15.6	19.5	1.3	55–343	0.03	0.57 n.s.
ND -VI	2161	343	35	56	10.3	16.3	1.6	45–343	3.7E-04	7.0e-03 *
SY -VI	1037	343	17	19	4.9	5.5	1.1	12–343	0.34	1.0 n.s.

Legend for Table S19. Abbreviations are explained at Table S15. SZ, all the genes within range of the 108 genome-wide significant loci listed in column 5 of supplementary Table 3 of the large GWAS of schizophrenia by the SWGPGC 2014[5]. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq p \leq$ 1.0E-06.

Replication sample #4 (genes assigned by proximity)

Table S20. Intersection between functional gene sets and 111 genes assigned by proximity to 108 genome-wide significant loci from the largest GWAS of schizophrenia to date.

Functions	*N*	SZ *N*	E (N)	O (N)	E (%)	O (%)	RF	CI	Nominal $p \leq$	Bonferroni corrected $p \leq$
VIRND	6409	111	34	58	30.5	52.3	1.7	49–111	1.4E-06	2.7e-05 **
VI	4213	111	22	40	20.0	36.0	1.8	32–111	6.7E-05	1.3e-03 *
V	3249	111	17	33	15.4	29.7	1.9	25–111	1.0E-04	1.9e-03 *
PV	253	111	1	8	1.2	7.2	6.0	4–111	6.5E-05	1.2e-03 *
I	1673	111	9	19	8.0	17.1	2.1	13–111	0.001	1.9e-02 n.s.
R	159	111	1	6	0.8	5.4	7.1	3–111	2.0E-04	3.8e-03 *
Repair	3319	111	18	40	15.8	36.0	2.3	32–111	1.5E-07	2.8e-06 **
ND	3211	111	17	37	15.3	33.3	2.2	29–111	1.8E-06	3.4e-05 **
SY	1977	111	10	18	9.4	16.2	1.7	12–111	0.02	0.38 n.s.
VI x ND	1051	111	6	19	5.0	17.1	3.4	13–111	2.4E-06	4.6e-05 **
VI x Repair	1124	111	6	22	5.3	19.8	3.7	15–111	8.4E-08	1.6e-06 **
V x ND	784	111	4	15	3.7	13.5	3.6	9–111	1.6E-05	3.0e-04 *
V x Repair	845	111	4	18	4.0	16.2	4.0	12–111	4.4E-07	8.4e-06 **
I x ND	523	111	3	13	2.5	11.7	4.7	8–111	3.9E-06	7.4e-05 **
I x Repair	569	111	3	14	2.7	12.6	4.7	9–111	1.8E-06	3.4e-05 **
VI -ND	3163	111	17	21	15.1	18.9	1.2	15–111	0.16	1.0 n.s.
VI -SY	3273	111	17	27	17.3	24.3	1.6	20–111	0.01	0.19 n.s.
ND -VI	2161	111	11	18	10.3	16.2	1.6	12–111	0.04	0.76 n.s.
SY -VI	1037	111	5	5	4.9	4.5	0.9	2–111	0.65	1.0 n.s.

Abbreviations are explained at Table S15. Levels of significance (Bonferroni corrected): * indicates $p \leq$ 1.0E-02; ** indicates $p \leq$ 1.0E-03; *** indicates $p \leq p \leq$ 1.0E-06.

Postmortem studies of schizophrenia

Table S21. Intersection of functional gene sets with genes differentially expressed in postmortem brains of schizophrenic patients.

Functional Gene Set		Genes Differentially Expressed in Postmortem Brains of Schizophrenic Patients								
		SZ All			SZ Up			SZ Down		
	N	*N*	RF	Bonferroni corrected $p \leq$	*N*	RF	Bonferroni corrected $p \leq$	*N*	RF	Bonferroni corrected $p \leq$
VIRND	6409	113	1.3	0.03 *	31	1.6	0.02*	82	1.2	1.0 n.s.
VI	4213	113	1.2	0.95 n.s.	31	1.7	0.13 n.s.	82	1.1	1.0 n.s.
V	3249	113	1.1	1.0 n.s.	31	1.6	1.0 n.s.	82	1.0	1.0 n.s.
I	1673	113	1.4	1.0 n.s.	31	1.8	1.0 n.s.	82	1.2	1.0 n.s.
R	159	113	0.7	1.0 n.s.	31	2.7	1.0 n.s.	82	0.0	1.0 n.s.
Repair	3319	113	1.7	3.4e-04 **	31	1.7	0.57 n.s.	82	1.7	3.2e-03 **
ND	3211	113	1.8	1.3e-04 **	31	1.7	0.38 n.s.	82	1.8	1.5e-03 **
SY	1977	113	1.7	0.08 n.s.	31	0.6	1.0 n.s.	82	2.0	5.3e-03 **
VI x ND	1051	113	2.6	4.6e-04 ***	31	2.4	0.57 n.s.	82	2.6	4.0e-03 **
VI x Repair	1124	113	2.4	1.3e-03 **	31	2.3	0.76 n.s.	82	2.4	8.7e-03 **
V x ND	784	113	2.2	0.06 n.s.	31	1.6	1.0 n.s.	82	2.5	0.06 n.s.
V x Repair	845	113	2.1	0.11 n.s.	31	1.5	1.0 n.s.	82	2.3	0.11 n.s.
I x ND	523	113	2.5	0.10 n.s.	31	2.4	1.0 n.s.	82	2.5	0.38 n.s.
I x Repair	569	113	2.3	0.17 n.s.	31	2.2	1.0 n.s.	82	2.3	0.57 n.s.
VI -ND	3163	113	0.8	1.0 n.s.	31	1.5	1.0 n.s.	82	0.6	0.19 n.s.
VI -SY	3273	113	1.2	1.0 n.s.	31	2.1	0.02 *	82	0.8	1.0 n.s.
ND -VI	2161	113	1.4	0.76 n.s.	31	1.4	1.0 n.s.	82	1.4	1.0 n.s.
ND -I	2689	113	1.7	5.9e-03 **	31	1.6	1.0 n.s.	82	1.7	0.06 n.s.
SY -VI	1037	113	1.8	0.19 n.s.	31	0.8	1.0 n.s.	82	2.2	0.10 n.s.

Abbreviations are explained at Table S15. The differentially expressed gene samples were obtained from the large combined cohort by Mistry et al.[313]. Because of the small sample

sizes, the p-value for significance was increased to 0.05 (Bonferroni corrected): * indicates $p \leq 0.05$; ** indicates $p \leq 0.01$; *** indicates $p \leq p \leq 1.0e-03$

Overview of significant findings

Table S22. Overview of significant findings.

Sample	VIRND	VI x ND	VI x Repair	VI	I	R	Repair	ND	SY	ND -VI	VI - ND	VI - SY
Candidate-gene association studies												
Discovery	**	***	***	***	**	***	***	*	***			
Replication #1	***	**	***	***	***	***	***		***		***	*
GWA studies												
Replication #2	**						**	**	*			
Replication #3	***	***	***	***	***	***	***	***	***			
Replication #4												
(Proximity)	**	**	**	*		*	**	**				
(Within range)	***	**	**	*	*		***	***		*		
All combined	***	***	***	***	***	***	***	***	***		**	
Postmortem gene expression studies of prefrontal cortex												
All DE genes	*	***	**				**	**				
Up-regulated	*											*
Down-regulated		**	**				**	**	**			

Legend for Table S22. Significant findings from Tables S15–S21 and Table 1 are shown. The number of asterisks refers to Bonferroni corrected *p*-values as given in these Tables.

- minus sign, overlapping genes removed;
DE, differentially expressed genes;
I, genes induced by cerebral ischemia;
ND, neurodevelopmental genes;
proximity, genes assigned by proximity to index SNP;
R, post-ischemic repair genes;
Repair, R and ND genes combined, because ND genes are involved in post-ischemic repair[120,127];
SY, synaptic genes;
VI, vascular-ischemia genes;
VIRND, all genes involved in ischemia, i.e., V, I, R and ND genes;
within range, all genes within range of index SNP;
x, overlapping, i.e., interacting genes.

Quasi experimental study

Figure S6. Quasi-experimental impairment of components of the candidate pathway

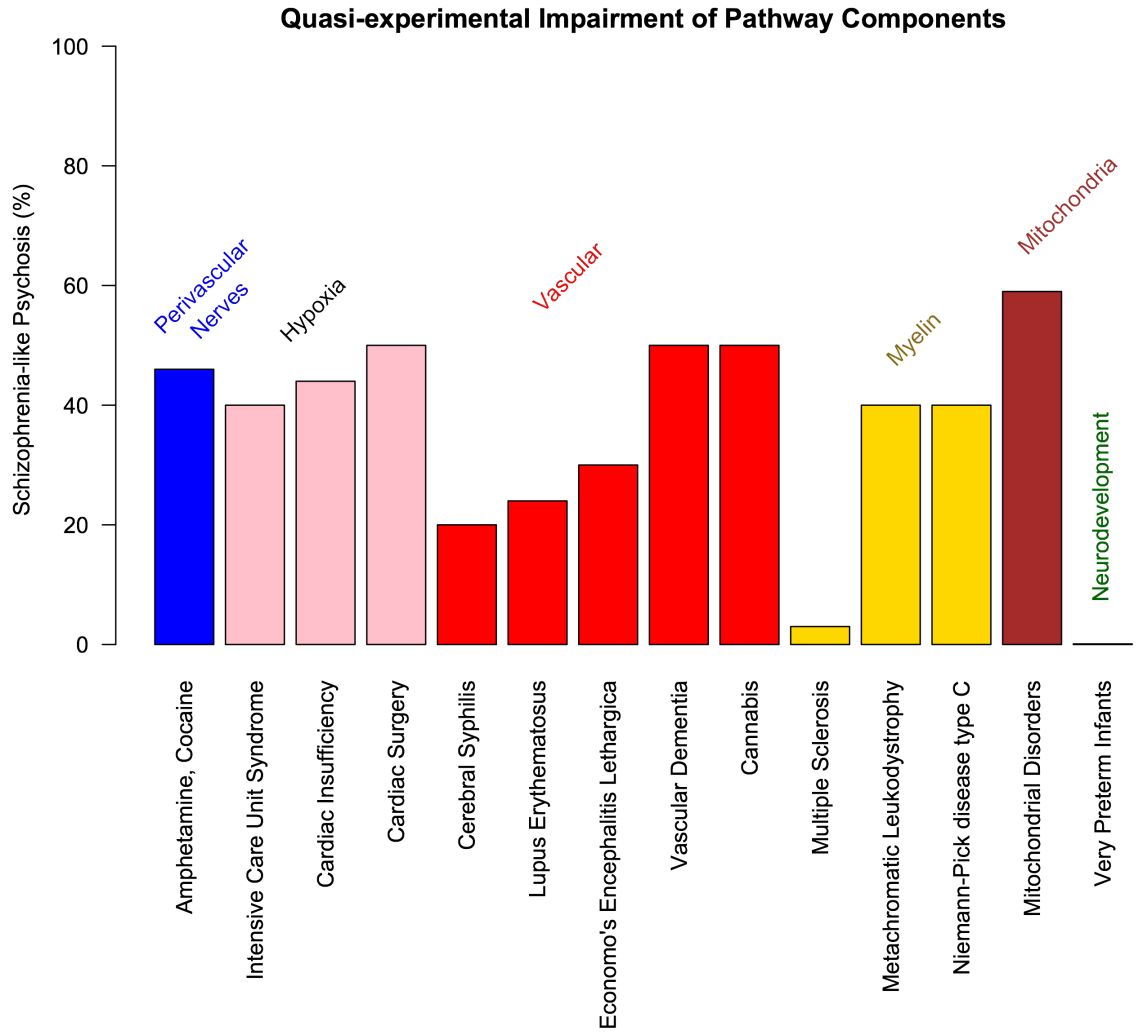


Figure S6. Results of quasi-experimental impairment of components of the postulated schizophrenia pathway. Disturbances of all components of the energy-supply pathway, i.e. perivascular nerves, oxygen, microvessels, oligodendrocytes, and mitochondria (see Fig. 1 in article), appear to produce a high percentage of schizophrenia-like symptoms. Multiple sclerosis (MS) is the exception, which might be due to the localized damage of myelin in MS. Very preterm birth seems to impair neurodevelopment independent of an increase in risk for ischemic disorders[314,315]. It causes high rates of neurodevelopmental disabilities from 25% to 50% such as cerebral palsy (5% to 15%)[316], but only 0.05 % (495 of 1 022 431) of term births compared to 0.1 % (6 of 5125) of very preterm births (gestational age < 32 weeks) developed later a non-affective psychosis[317]. For more data and references, see also supplementary Table S23–S24.

Table S23. Quasi-experimental disturbance of candidate schizophrenia pathway

as independent variables and the production of schizophrenia-like symptoms.

Putative schizophrenia pathway	Evidence for mild ischemia	Schizophrenia-like symptoms§	Max. Rate
Hypoxia			
Cardiac Insufficiency	Insufficient tissue oxygenation, mild ischemia	Cardiac psychosis, paranoid-hallucinatory syndromes in 44% of acute cardiogenic psychosis[318].	44%
Cardiac Surgery	Measures of hypoxia and cerebral hypoperfusion predict postoperative neuropsychiatric disorders[319,320]	Paranoid-hallucinatory syndromes[321,322], psychoses, delirium, and cognitive dysfunction are common following a lucid postoperative interval[323]. Neuropsychological dysfunction occurs frequently in 40% to 50%, up to 79% of patients[323].	50%
Intensive Care Unit Syndrome (ICUS)	ICU syndrome/delirium is associated with decreased anemia and extended times on the ventilator[324].	Hallucinations and delusions usually as part of delirium[325].	40%
Perivascular nerves			
Amphetamine (AMPH) and Cocaine	AMPH and cocaine cause a decrease in CBF[326], cerebral vasospasms[327,328] and ischemic as well as hemorrhagic strokes[267,329-331], probably via their action on DAT1, NAT1 and 5-HTT resulting in an increase of dopamine, noradrenaline and serotonin[332,333].	Paranoid state with auditory and visual hallucinations in chronic users[334,335] resembling schizophrenia[336-338]. Drug-induced psychosis has been reported in 8–46% of regular users of amphetamines[339].	46%
Anticholin-ergics	Reduced cortical perfusion, mainly in the frontal cortex[340].	Paranoid-hallucinatory psychosis[341,342], worsening of positive symptoms in schizophrenia[343].	
Traumatic Brain Injury (TBI)	TBI consistently damages cerebral perivascular nerves and impairs autoregulation of CBF[344].	Higher frequency of prior TBI in schizophrenia compared to other psychiatric disorders[345].	
Vascular component			

Vascular Dementia (VaD)	VaD results from ischemic injury or sustained mild ischemia[346,347].	In mild VaD, 37% of patients had hallucinations and 50% paranoid symptoms[348]. In VaD, 8.1% heard voices and 8.6% talked to people who were not there[349].	50%
Neuro-psychiatric Systemic Lupus Erythematosus (NPSLE)	Vasculitis is rare but vascular hyalinization, endothelial proliferation and perivascular gliosis are common[350]. Furthermore, small lesions in white matter (WM) (100%), diffuse WM abnormalities (43%) and cerebral infarction (29%)[351]. Cerebral hypoperfusion measured by SPECT is related to neuropsychiatric symptoms in NPSLE[352].	Psychosis has been reported in 5% of NPSLE[353] including schizophrenia-like psychosis[354-356]. In consultation psychiatry, 24% of NPSLE had schizophrenia or unclassified psychosis[354].	24%
Cerebral syphilis	Treponema pallidum invades - through the intercellular junctions of endothelial cells[357] into perivascular areas[358] causing perivasculitis, adhesion of leukocytes, endothelial cell abnormalities[359] and ischemic stroke as primary symptom in about 14% of neurosyphilis patients[360].	Schizophrenia-like psychoses have been reported in patients with general paresis from 3.5% up to 20% (reviewed in[361])	20%
Economo's Encephalitis Lethargica (EL)	Perivascular inflammation and infiltrates of lymphocytes within the Virchow-Robin spaces of small vessels in acute EL[362]. In 45% of cases, the cortex is affected[363].	Postencephalitic schizophrenia-like psychoses[364] in 15-30% of EL cases[365].	30%
Cannabis	Increase of CBF in acute cannabis use, but decrease of CBF in frontal cortex of chronic users[366].	Cannabis-induced psychosis shares genetic predisposition and many common symptoms with schizophrenia[367,368]. The maximum proportion of psychosis attributable to cannabis in psychosis-free subjects is higher than 50 percent[369].	50%
Oligodendro-cyte & myelin component			
Metachromatic	Bilateral fronto-temporal white	Adult onset psychosis in 25-	40%

leukodystrophy	matter is affected (reviewed in[370]).	40% (reviewed in[370]).	
Niemann–Pick disease type C	Callosal and periventricular white matter is affected (reviewed in[370]).	Adult-onset psychosis or dementia in 25-40% (reviewed in[370]).	40%
Multiple sclerosis (MS)	MS is an inflammatory-mediated demyelinating disease of the human brain (reviewed in[371]).	In 2% - 3% of MS patients, a psychosis develops (reviewed in[372]).	3%
Mitochondrial component			
Mitochondrial disorders	Symptoms of mitochondrial disorders can appear either in infancy or adulthood. Various organs can be affected including the brain with stroke-like episodes in MELAS (Mitochondrial encephalo-myopathy, lactic acidosis, stroke-like episodes) (reviewed in[373]).	Psychosis or psychotic features combined with mood disorders were diagnosed in 35 of 59 cases (59%) with a mitochondrial disorder (reviewed in[374]).	59%
Neuro-development			
Preterm infants	Very preterm infants (< 32 weeks of gestational age), have shown in follow-up studies high rates of neurodevelopmental disability with 5% to 15% having cerebral palsy, severe neurosensory impairment, and 25% to 50% having cognitive, behavioral, and social difficulties that impede progress in school[316].	Increased rate of psychiatric hospitalization for non-affective psychoses (i.e. schizophrenia and schizoaffective psychosis) from 0.05% (495 of 1022431 cases) for term birth to 0.1% (6 of 5125 cases) for very preterm infants (< 32 weeks of gestational age)[317].	0.1%

§ defined as hallucinations and/or delusions with or without disorientation

Experienced clinical psychiatrist will have observed, that the former, i.e., hallucinations and/or delusions with disorientation, correspond to the diagnosis of delirium and might demand an explanation for the lumping together of schizophrenia with delirium.

First, lumping and splitting of diagnostic categories are widely used in psychosis research (see Kraepelin's lumping of paranoia, hebephrenia and catatonia and his splitting of major psychoses into schizophrenia and manic depression or the current debate about the lumping of bipolar disorder and schizophrenia based on genomic findings[375,376].

Second, similarities between schizophrenia and neurodevelopmental disorders, such

as cerebral palsy, epilepsy, and mental retardation, have frequently been used to support the neurodevelopmental hypothesis[377,378]. See, e.g., page 401 of Weinberger's and Harrison's recent, excellent book on schizophrenia[379]: "In a sense, schizophrenia appears to be on a developmental continuum with other behavioral disorders that appear in childhood, including autism, intellectual disability, and epilepsy, arising perhaps from overlapping biological risk factors that may each have distinct covariants, but schizophrenia reflects the relatively least noise burden of this group of developmental disturbances[378]".

Third, the same reasoning may be applied to ischemia, with stroke on one end of the continuum, delirium and schizophrenia in the middle, hyperperfusion on the other end (see Fig. 4), and cerebral localization as covariant. Differences in severity or cerebral localization of ischemia might account for differences in disorientation. Consequently, an acute ischemic psychosis of known etiology would be diagnosed as delirium and an ischemic psychoses of unknown cause without disorientation as schizophrenia. For this discussion of hallucinations/delusions with disorientation, it is important to note that disorientation has also been found in some acute[380], as well as in chronic schizophrenic patients[381-384]. In regard to cerebral localization, isolated time orientation has been observed in 4 percent of patients with thalamic ischemia[385].

Table S24. Quasi-experimental neurodevelopmental disturbance

as independent variable and the production of schizophrenia-like symptoms.

Etiology of neurodevelop-mental disturbance	**Evidence for neurodevelopmental disturbance**	**Schizophrenia-like symptoms§**	**Max. Rate**
Obstetric complications (OBC)	After intrauterine and neonatal insults, the most common long-term outcome were developmental delay (59%), cognition and learning difficulties or cerebral palsy (21%), hearing impairment (20%) and visual impairment (18%) (meta-analysis[386]).	Since OBC is associated with the development of cardiovascular disorders[387,388] and stroke in adulthood[314,315,389,390] (reviewed in[391,392]), OBC cannot be considered here as proving that schizophrenia-like symptoms are caused by neurodevelopmental disturbance.	
Perinatal brain damage	A 1966 North Finland Birth Cohort revealed that 29.9% of the children surviving perinatal brain damage developed cerebral palsy, epilepsy or mental retardation (IQ less than 71)[393].	In the 1966 North Finland Birth Cohort, six of the 125 survivors (4.8%) of severe perinatal brain damage developed later schizophrenia[394]. However, these data cannot exclude perinatal brain damage due to OBC, which is associated with coronary heart disease and stroke (see row above).	
Preterm infants	Since length of gestation and preterm birth is not associated with coronary heart disease[314] or stroke[315], the effect of neurodevelop-mental disturbances independent of vascular factors can only be investigated in preterm infants. Very preterm infants (< 32 weeks of gestational age), have shown high rates of neurodevelop-mental disability in follow-up studies with 5% to 15% having cerebral palsy, severe neurosensory impairment and 25% to 50% having	Increased rate of psychiatric hospitalization for non-affective psychoses (i.e. schizophrenia and schizoaffective psychosis) from 0.05% (495 of 1022431 cases) for term birth to 0.1% (6 of 5125 cases) for very preterm infants (< 32 weeks of gestational age)[317].	0.1%

	cognitive, behavioral, and social difficulties that impede progress in school[316].		

§ defined as hallucinations and/or delusions with or without disorientation

DISCUSSION

Evidence for ischemia during schizophrenic psychosis

Table S25. Supplementary references for Figure 4

CBF (ml/100 g/min)	**Consequence**	**Similar findings in schizophrenia**
100	Hyperperfusion in man[395]. Focal hyperperfusion after ischemia[396]	Regional cerebral hyperperfusion and hypoperfusion in unmedicated patients[397-399]
60	Normal CBF depending on species[400-402]	
50	Mean human CBF[403]	
40	Mild hypoperfusion (oligemia)[395,403]	Reduced CBF and CBV mostly frontal (review[404])
35	Onset of decrease in oxidative phosphorylation and increased generation of reactive oxygen species (ROS) causing mitochondrial damage[405]. Mild ischemia may be much more damaging than total ischemia because the availability of sufficient oxygen for producing ROS[405].	Evidence for increased oxidative damage[406-408], mitochondrial dysfunction[409-411] (reviews[412,413], and impaired energy metabolism (review[414]) have been found in the post-mortem brains of schizophrenic patients.
30[§]	Depression of protein synthesis at approximately 60 - 40 % of mean CBF[415,416]. After 7 hrs, onset of loss of dendritic structure and spines at 64% of perfusion in some animals[417].	Only 1 rather preliminary study measured protein metabolism in 4 schizophrenic patients and found focal suppression of protein metabolism in the parietal cortex of 1 patient[418]. Reduced dendritic spine density and arborization[419-421].
25[§]	Beginning of decrease in phosphocreatine (high energy phosphate) and increase in lactate[422] (review[423]).	Decrease of phosphocreatine and ATP in the frontal cortex of neuroleptic-free schizophrenic patients[424], but not in medicated or chronic patients[425]. Increase of lactate was found in the blood[426], post-mortem brain tissue[409], and CSF[427] of schizophrenic patients.

22	Increase in cortical conduction time[428] and reduction in the amplitude of evoked potentials (EP)[403,429].	Increase in latency and reduction in the amplitude of EP (ERP, event-related potentials) is one of the most replicable biological marker in schizophrenia[430](meta-analysis[431]). The same changes have been reported for gamma oscillations[432,433].
20	Functional threshold (mild paresis), penumbra threshold[395].	Disturbed voluntary motor activity in schizophrenic patients[434]. Increased frequency of frontal release signs (primitive reflexes, i.e. soft neurological signs) in transient ischemic attacks[435] and schizophrenia[436,437].
18	Disturbance of energy metabolism: anaerobic glycolysis at ca. 33 % of mean CBF, corresponding to 17 ml/100g/min in humans[401,416].	Reduction of glycolysis was found in brain tissue of schizophrenic patients obtained during prefrontal leukotomies[438] or post-mortem[409,439,440].
18	Threshold for synaptic transmission failure (range 20 – 8)[400,416,429].	
18§	Evoked potentials abolished (range 22 – 6)[401,441].	
18	Nerve cells cease spontaneous activity[401].	
15§	Drop in ATP (range 15 - 8 depending on species[416,422].	
15	Terminal depolarization and potassium efflux[401]	
12	Critical threshold[395]	
10	Membrane failure[401]	
8	Irreversible damage, infarction[395]	Nine of 10 post-mortem studies reported focal infarctions in the brain of schizophrenic patients[442] (review[443]).

Legend for Table S25: § Values from animal studies were converted to approximate CBF values for humans by using the percentage of reductions from mean CBF. However, this approach cannot take into account the physiological and biochemical differences among species.

Table S26. Signs of cerebral ischemia in adult schizophrenic patients

Consequences of cerebral hypoxia/ischemia	Presence in schizophrenic patients
Biochemical signs	
Mitochondrial dysfunction follows incomplete cerebral ischemia despite reperfusion[444-446].	Reduced oxygen uptake in brain tissue from schizophrenic patients[447], impaired energy metabolism (review[414]), mitochondrial dysfunction[313,409-411] (reviewed in[412,413]).
Lactate formation is increased during hypoxia-ischemia (reviews[423,448]).	Increase of lactate in schizophrenic patients has been reported for blood[426], post-mortem brain tissue[409], and CSF[427].
Oxidative stress: Incomplete ischemia generates reactive oxygen species (ROS), which attack mitochondrial lipids, proteins, and DNA[444-446].	Evidence for increased oxidative damage[406-408]
ROS initiate lipid peroxidation[449]	Increased lipide peroxides[450-453]
Inflammation is activated in response to focal cerebral ischemia[454,455].	Inflammatory signs in schizophrenia (reviewed in[456]), increased hsCRP levels (meta-analysis[457]).
Increased Endothelin 1 (ET-1)[458]	ET-1 has a very long-lasting constrictive effect on cerebral vasculature[459]. ET-1 blood values are elevated in cerebral ischemia[458] and schizophrenia[460].
Increased S100B serum level[461]	Increased serum S100B[462,463]
High skeletal muscle creatine kinase (CK) in serum after stroke[464]	High skeletal muscle creatine kinase in serum during acute schizophrenic psychosis[465-467]
Impaired Blood-Brain Barrier (BBB)[145]	Evidence for increased BBB permeability in 5% - 20% of schizophrenic patients[468-470]
Cellular signs	
Hypoxia/ischemia and chronic cerebral hypoperfusion lead to slight degeneration of astrocytic end-feet processes and BBB disruption[471,472].	Signs of ultrastructural damage to capillaries of the neocortex in schizophrenic patients that resemble those observed in chronic hypoperfusion, oxidative stress, damaged blood brain-barrier, or cerebral ischemia[473].
Mitochondrial damage[474]	Reduced density of mitochondria as well as deformed, hypoplastic and small mitochondria (review[406])
Oligodendrocyte are selectively vulnerable to ischemia{Lyons	Neuropathological, transcriptomic, proteomic and brain imaging studies show

1998) (reviewed in[475]).	damage of oligodendrocytes and myelin (reviewed in[476-479]).
Loss of spine and dendrite structure[417]	Lower density of dendritic spines, reduced dendritic arborizations[480], and decreased presynaptic protein markers (reviewed in[481,482]).
Electroencephalographic signs	
Slowing of EEG[400,483], increased latency of evoked potentials (EPs, ERPs)[403]	Delayed latency of P300 (meta-analyses[484,485])
Reduced amplitude in ERPs[400,403]	Reduced amplitude of P300 (meta-analysis[484] decreasing with symptom exacerbations and increasing with improvements[486] (reviewed in[430]).
Gamma-oscillations are highly vulnerable to hypoxia[487,488].	Delayed latency and decreased magnitude of gamma-oscillations[432,433]
Brain imaging evidence	
Hypoperfusion[395]	Hypoperfusion in frontal cortex (hypofrontality), parietal cortex and medial cingulate gyri) (meta-analyses[489,490]; review[404]). Hypoperfusion correlates with negative symptoms[397,398]. Amelioration of regional cerebral blood flow is associated with clinical improvement[491].
Focal hyperperfusion after ischemia[396].	Regional cerebral hyperperfusion and hypoperfusion in unmedicated patients[397-399,404]. Positive symptoms correlated with either cerebral hyper- or hypoperfusion. This correlation disappeared after reduction of positive symptoms[398].
Clinical signs of hypoxia	
Inappropriate affect and facial expression, silly laugther during experimental hypoxia[492]	Inappropriate affect[493,494], elation[494], inappropriate laughter[495], and silly emotions[496].
Perseveration during experimental hypoxia[492]	Perseveration[494]
Cognitive impairment during experimental hypoxia[492]	Cognitive impairment is the core of the disorder[493] and begins between the premorbid phase and first episode[497]

The foundation of the neurodevelopmental hypothesis can also be explained by adult vascular disorders

The left column of Table S27 lists the evidence interpreted as support for the neurodevelopmental hypothesis according to reviews by Harrison[498], Moises et al.[499], Marenco et al.[377], and Weinberger[378]. The right column shows findings of a literature search in PUBMED and Google SCHOLAR using the key words of the left column and "cardiovascular" or "cerebrovascular".

Summing up, the foundation of the neurodevelopmental hypothesis is not only associated with schizophrenia, but also with adult vascular disorders (depicted in supplementary Fig. S7). In conclusion, schizophrenia as adult vascular disorder is an alternative explanation for the available evidence previously interpreted as support for the neurodevelopmental hypothesis.

Table S27. The foundation of the neurodevelopmental hypothesis and adult vascular disorder as alternative explanation.

Evidence supporting the ND hypothesis	**Alternative explanation**
Prenatal evidence	
Broadly defined **obstetric complications** (OC)[377,378,498] are associated with an increased risk for schizophrenia (meta-analysis[500]). However, overall effect of OC on the occurrence of schizophrenia is small[377]. 93% of schizophrenic patients did not experience such OC (see Table S28).	**Obstetric complications** (OC) are frequently a sign of placental inefficiency[388,501], which causes fetal undernutrition, intrauterine growth restriction (IUGR), OBC, insulin-resistance, type 2 diabetes and increased risk for cardiovascular disorders[387,388], and stroke in adulthood[314,315,389,390] (reviewed in[391,392]).
Preeclampsia[377]: The only OC study able to adjust for mother's psychotic illness during her adult life found only preeclampsia to be significantly associated with an increased risk for schizophrenia[502].	**Preeclampsia** has a strong genetic component (reviewed in[503]) associated with an increased risk of cardiovascular or cerebrovascular disease (meta-analysis[504]).
Birth weight[377] is inversely related to schizophrenia[505].	**Birth weight** is inversely related to systolic blood pressure, ischemic heart disease, and stroke[506].
Maternal influenza[377,378,498]	**Maternal influenza** is associated with an 20% increase in cardiovascular disease[507].
Prenatal famine[377,378,498] results in a 2-fold increase of risk for schizophrenia[508-510].	**Prenatal famine** causes increase of hypertension, raised glucose levels, increased blood pressure response to stress,

	and a 2-fold increase of risk for coronary heart disease (reviewed in[510]).
Blood group incompatibilities[378,511]	Thickening of the amniotic epithelium[512] and the trophoblast basement membrane[513] suggests reduced diffusion and availability of nutrients mimicking prenatal famine.
Winter birth[498]. The effect correlates with the latitude[514] (colder winter temperatures) and is not detectable in the Southern Hemisphere[515] (relatively warm winters).	Cold outdoor temperature at birth is associated with increased coronary heart disease and insulin resistance[516].
Maternal homocysteine level elevated[378]	Elevated homocysteine concentrations at pregnancy are associated with increased risk of cardiovascular disease, angina, and stroke (reviewed in[517]).
Paternal age at conception[378]	Paternal age results in reduced telomere length in his offspring[518]. Reduced telomere length is associated with premature myocardial infarction[519].
Maternal severe stress during pregnancy[378]	Maternal stress, anxiety, and glucocorticoids reduce fetal growth and birth weight, and predispose the offspring to adult cardiovascular disorder and stroke[520,521].
Structural cerebral abnormalities (ventricular enlargement, reduced cortical volume)[498]	Progressive changes in ventricular and gray matter volume challenge the neurodevelopmental hypothesis (meta-analyses[522,523])
Neuropathology[498]: Reported cytoarchitectural abnormalities related to intrauterine development have not been replicated and are not unequivocally established[443].	In comparison, the undisputed cytoarchitectural findings, such as alterations in neuronal size, and synaptic and dendritic organization, could well originate much later[443].
Postnatal evidence	
Delays in motor and speech development[378,498], poor motor coordination[377]. The delays are very modest and do not cause concern to physicians or parents. Furthermore, most individuals with such a delay do not develop	Maturational delay, i.e., slow growth in fetal life, infancy, and during childhood is associated with adult cerebrovascular disorder[524]. Furthermore, delays in motor development are associated with the personality dimension of neuroticism (trait anxiety) in adulthood[525]. Neuroticism seems to predispose to schizophrenia[526].

schizophrenia[378].	
Behavioural abnormalities as infants[498] such as hyperactivity, poor verbal abilities, nervous, withdrawn, or disruptive, aggressive, and antisocial behavior in school[377].	These behavioural abnormalities are characteristic for the two personality dimensions frequently observed in schizophrenic patients: introversion / neuroticism (trait anxiety)[527] and impulsive/antisocial/psychopathic personality[528-530]. Social introversion and psychoticism/psychopathy (type A behaviour pattern) are associated with an increased risk for myocardial infarction[531,532]
Soft neurological signs have been observed in up to 60% of schizophrenic patients and are interpreted as evidence for premorbid brain damage in schizophrenia[436,437] (meta-analysis[533]).	These signs are present in up to 40.6% of normal individuals (meta-analysis[533]). Transient ischemia increases the frequency of these signs[435]. In schizophrenic patients, soft neurological signs decrease in parallel with the remission of acute psychosis (meta-analysis[534]).
Enuresis in childhood[378,535]	Enuresis is associated with anxiety/ withdrawal[536], extraversion[537], conduct problems, attention deficit behaviors, and anxious/withdrawn[536] or antisocial/ psychopathic personality[538]. The latter predisposes to schizophrenia[528-530]
Lower premorbid IQ of about 0.5 standard deviations (SD)[378] (meta-analysis[539]).	The superior premorbid high intelligence (IQ) of a considerable number of patients{ [540-542] is not compatible with a premorbid fronto-cortical brain damage. However, a premorbid high IQ is not at variance with the adult ischemia hypothesis. .

Figure S7. Foundation of neurodevelopmental hypothesis and adult vascular disorder as alternative explanation.

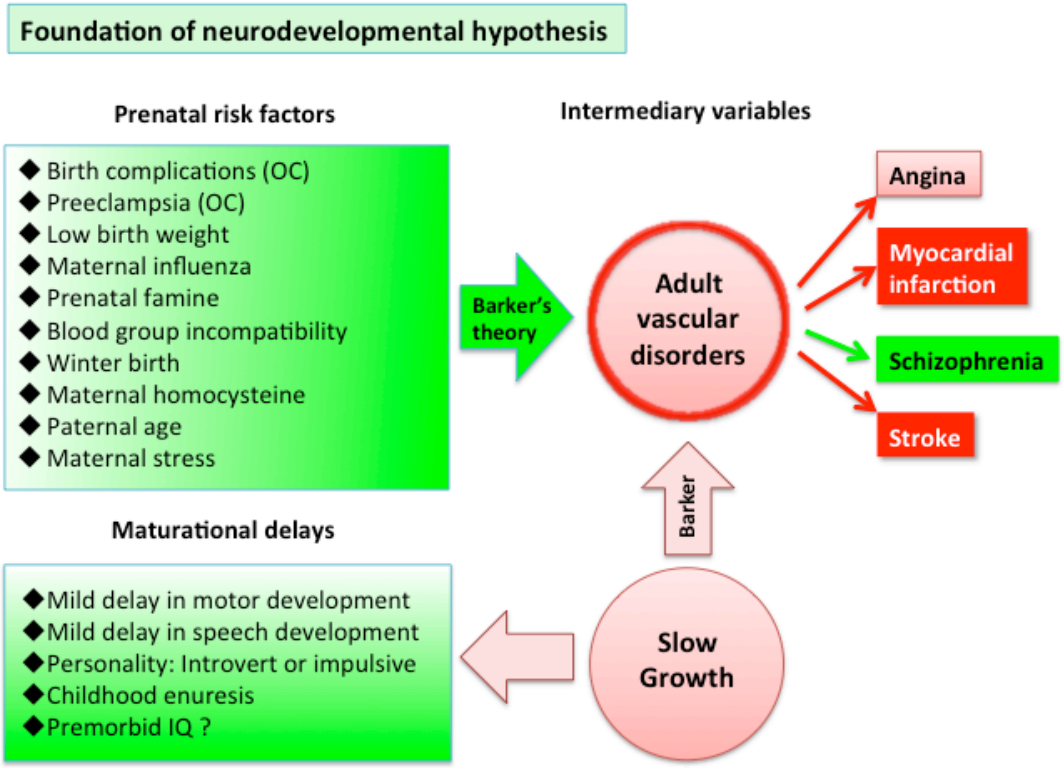


Figure S7. The foundation of the neurodevelopmental hypothesis of schizophrenia consists of epidemiological studies showing that prenatal factors and delayed growth are associated with an increased risk for schizophrenia (in green, for reviews[377,378,498,499]). The same factors increase the risk for adult cardiovascular and cerebrovascular disorders (in red, references in supplementary Table S27), also known as Barker's theory[391,392,524]. Adult vascular disorder as intermediary variable between broadly defined birth complications (OC) and schizophrenia has been ignored suggesting that OC are a proxy variable for the predisposition to adult cerebrovascular disorders, and that the Barker theory might be a well-founded substitute for the neurodevelopmental hypothesis to explain prenatal risk factors and maturational delays in schizophrenia. IQ, intelligence quotient; OC, obstetric complications.

Normal or superior intelligence in schizophrenia

The average premorbid IQ of schizophrenic patients is on average only 0.5 SD below the population average[539], which might be explained by their higher trait anxiety (neuroticism)[526] and not necessarily an indication of a neurodevelopmental brain damage. Trait anxiety is known to correlate positively with test anxiety and negatively with IQ test results (reviewed in[543])

The Danish draft-board study by Ufer-Parnas et al. found a premorbid uni-modal normal distribution (mean 94.38, SD 16.24) in schizophrenia[541]. Superior intelligence or the cognitive abilities of genius are often defined as an IQ ≥ 120 or IQ ≥ 130, respectively. The percentage and number of schizophrenic patients exceeding that level can be calculated from the normal distribution of IQ scores, 0.4% for global lifetime prevalence[544], and an estimated global population of 7 billion for 2015.

The results show that 36.5%, 10.2%, 5.7%, and 1.4% of schizophrenic patients are expected to premorbidly have an IQs of ≥ 100, ≥ 115, ≥ 120, ≥ 130 corresponding globally to 10.2 millions of schizophrenic patients with a normal IQ ≥ 100, 2.8 millions with IQ ≥ 115, 1.6 millions with IQ ≥ 120, and 0.4 millions with IQ ≥ 130. Such a large number of individuals with normal or superior intelligence contradicts the postulated neurodevelopmentally caused premorbid brain defect.

Birth complications in only 7% of schizophrenic patients

Data for calculating the percentage of obstetric complications in schizophrenic patients were obtained from Table 2 of the meta-analysis of prospective population-based studies by Cannon et al. (2002)[500].

In 93% of schizophrenic patients and in 94.6% of normal controls, no evidence of (broadly defined) birth complications were found (see Table S28). In conclusion, the overall majority of schizophrenic patients were not exposed to birth complications that might have caused a defect of brain development.

Table S28. Percentage of schizophrenic patients with broadly defined birth complications

Obstetric complications	Schizophrenic patients	Exposed	Controls	Exposed
Diabetes in pregnancy	237	3	1909	3
Placental abruption	308	3	508352	1643
Birth weight <2000 g	504	6	10926	78
Emergency Cesarean section	818	20	507863	1595
Congenital malformations	737	10	508781	6144
Uterine atony	659	27	507703	16913
Rhesus variables	759	18	17537	2911
Threatened premature delivery	308	8	508352	6498
Asphyxia	1109	60	2297	119
Bleeding in pregnancy	1223	34	524972	9367
Birth weight <2500 g	1294	60	536045	19343
Head circumference <32 cm	758	53	508315	15388
Smoking in pregnancy	105	26	17886	5752
Preeclampsia	1712	75	510275	18286
Anemia in pregnancy	522	20	1526	96
Gestational age <37 weeks	1290	67	536051	21710
Small for gestational age	1272	86	519229	23485
Induction of labor	689	186	2361	232
Apgar score <7 at 1 minute after birth	390	18	507434	22771
Gestational age >42 weeks	1187	34	508747	16065
Child stayed in hospital after mother discharged	973	110	1488	99
Forceps delivery or vacuum extraction	1724	124	527058	29753
Birth length <49 cm	761	130	51320	105205
Cephalopelvic disproportion	662	10	2338	42
Cord around neck	893	171	1345	333
Cesarean section	1214	63	526045	42947
Birth weight <2500 g and premature	954	41	11376	215
Nonvertex presentation	1667	74	510208	61130
Breech delivery	464	11	508508	13580
Urinary tract infection in pregnancy	690	20	507730	7115
Nonspontaneous delivery	331	46	17108	1554
Total	23208	1614	7300987	391603

Percentage with complications	**7,0%**	**5,4%**
Percentage without complications	**93,0%**	**94,6%**
Difference	**1.6%**	

Data from[500].

Schizophrenia treatments improve CBF and ischemia protection

All treatments found to improve schizophrenia also improve cerebral perfusion and/or protect against ischemia or its harmful consequences such as inflammation (see Table S29).

Table S29. Effects of treatments for schizophrenia on cerebral perfusion and ischemia.

Treatment in schizophrenia	Effects
Acetylsalicylic acid[545]	prevents cerebral ischemia[546]
Atypical antipsychotics[547,548]	enhance CBF[397,491,549]. Clinical improvement correlates with CBF[491]. A recent meta-analysis provides a more variable picture with increased as well as decreased areas of rCBF following antipsychotic treatment[550].
Celecoxib[551-553], nonsteroidal anti-inflammatory drugs (NSAID)[554]	Celecoxib is an non-steroidal anti-inflammatory drug with potent neuroprotective effect against ischemia-induced inflammatory reaction[555]
Electroconvulsive therapy (ECT)[556]	Epileptic seizures are accompanied by an increase in focal CBF[557,558]. ECT improves CBF and catatonia[559]
Erythropoietin (EPO)[560]	EPO enhances cerebral vasodilatation[561], activates the PI3K/Akt pathway[562] and improves the consequences of cerebral ischemia[563]
Exercise[564]	increases cerebral vasodilatation, BDNF[565], and cerebral blood volume in the hippocampus[566]
Ginkgo Biloba Extract[567,568]	increases CBF[569,570], and protects against cerebral ischemia[571]
Glucose[572,573]	Glucose, the obligatory energy substrate for the brain[574], is lacking in ischemia.
Insulin Coma Therapy (ICT)[575,576]	Insulin causes cerebral vasodilatation[577], and activates the PI3K/Akt pathway in neurons following brain ischemia[578]. Furthermore, insulin-induced hypoglycemia leads to a marked increase in CBF[579].
Nicotine (alpha-7 nicotinic agonists)[580,581]	enhances cholinergic vasodilation in the cerebral cortex[582]
Reserpine[583]	depletes dopamine and noradrenaline from the brain[584]. Its use as antihypertensive drug suggests a vascular effect[585].
Transcranial Magnetic Stimulation (rTMS)[586,587]	increases CBF in some areas of the brain[588-590].
Typical neuroleptics[591]	Dopamine causes a dose-dependent vasoconstriction in about 50% of cortical microvessels[69].

	Antipsychotic drugs block D2/3 receptors[592] and increase CBF[397,491,549,593], mainly in paranoid patients[550]. But see also evidence for a decrease of CBF[490,550]. Clinical improvement was found in one study to correlate with CBF[491].

Table S30. Evidence for repair mechanisms in schizophrenia.

	Evidence
1	Adult neurogenesis and synaptic plasticity are involved in postischemic repair and in schizophrenia (reviewed in[594,595]).
2	Adult neurogenesis and synaptic plasticity have been implicated in schizophrenia by previous pathway analyses (see supplementary information).
3	Motor endplate alterations in schizophrenic patients resemble axonal destruction followed by regeneration[596].
4	Erythropoietin, a stimulator of adult neurogenesis, improves cognitive functions in chronic schizophrenic patients[560].
5	Neuroleptics appear to stimulate adult neurogenesis either directly or indirectly via prolactin[597,598].
6	Drug responding patients show signs of myelin repair in brain imaging[599].
7	Physical exercise increases BDNF, adult neurogenesis, hippocampal volume, and improves negative symptoms in schizophrenic patients[564,565,600,601].
8	The PI3K/Akt pathway mediates not only the effects of stress, growth factors, and hormones on metabolism, vasoconstriction, and vasodilatation, but also on synaptic plasticity and adult neurogenesis, i.e., repair[602,603] (see Fig. 2).
9	Neural stem cell proliferation required for adult neurogenesis is reduced in schizophrenia, but not in major depression[604].

The AVIH seems to offer a better explanation for the evidence compared to the NDH

Theory choice is a search for the best explanation of the evidence. The three main criteria for the evaluation of a hypothesis are consilience, simplicity, and analogy[605]. The adult vascular-ischemia hypothesis better fulfills the criteria of consilience, simplicity, and analogy than the neurodevelopmental hypothesis. For consilience, see Table S31.

Table S31. Consilience of the NDH and the AVIH with the evidence

Evidence/facts		Explanation by ND hypothesis	Explanation by AVI hypothesis
Genetic			
1	Overrepresentation of VI[606], ND, and repair genes (Table S22, Fig. 3a)	**Yes**	**Yes**
Prenatal			
2	Evidence supporting the ND hypothesis (Table S27 and Fig. S7)	**Yes**	**Yes**
3	Absence of birth complications in 93% of schizophrenic patients, difference to normal population only 1.6% (meta-analysis[500]) (see Table S28)	No	**Yes**
4	Absence of minor physical signs in 65% of patients[607] (reviewed in[608])	No	**Yes**
5	Absence of neuropathological evidence for neurodevelopmental brain defect[443,482]	No	**Yes**
Premorbid			
6	High premorbid intelligence (IQ)[540-542,609-612] (supplementary info above)	No	**Yes**
Schizophrenic psychosis			
7	Late-onset schizophrenia (reviewed in[613])	No	**Yes**
8	Signs of cerebral ischemia during acute psychosis (Fig. 4, Table S26)	No	**Yes**
9	Progressive brain tissue loss[614] (meta-analysis[523])	No	**Yes**
10	Improvement by blockade of dopamine D2/D3 and 5-HT2A receptor (review[178]) (see Fig. 1)	No	**Yes**
11	Soft neurological signs decrease in parallel with the remission of acute psychosis (meta-analysis[534]) (see also refs. in Table 27).	No	**Yes**
12	Course: remissions, relapses, and progressions[615]	No	**Yes**
13	Treatment-dependent outcome (review[608])	No	**Yes**

Legend for Table S31. AVI, adult vascular-ischemia; ND, neurodevelopmental; VI, vascular-ischemia.

The criterion of simplicity is met by requiring less auxiliary hypotheses, e.g., for evidence # 3–13 in Table S31 above. Finally, disorders disturbing the cerebral energy-supply (Table 23, Fig. S6) and adult vascular disorders (Fig. 7) provide useful analogies for better understanding the pathogenesis of schizophrenia, whereas the analogy of the NDH with neurodevelopmental disturbances in very preterm infants is surprisingly unconvincing (see supplementary Fig. S7, Tables S23–S24).

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