

The Genetics of Schizophrenia Converge Upon the NMDA Glutamate Receptor

By Stephen M. Stahl, MD, PhD

NEW TREND IN PSYCHOPHARMACOLOGY

Recent research shows that single genes do not cause schizophrenia, but that multiple “susceptibility” genes each provide a genetic “bias” towards schizophrenia. Each susceptibility gene codes for a subtle molecular abnormality that hypothetically causes inefficient information processing in brain circuits that mediate the symptoms of this disorder. It is therefore not surprising that many of the susceptibility genes that have been identified for schizophrenia are known to regulate neuronal connectivity, synaptogenesis, and *N*-methyl-D-aspartate (NMDA) glutamate receptor functions. This includes genes for brain-derived neurotrophic factor (BDNF), dysbindin, also known as dystrobrevin-binding protein 1, neuregulin, disrupted in schizophrenia-1 (DISC-1), D-amino acid oxidase activator (DAOA), and regulator of G-protein signaling (RGS4). Hypothetically, converging molecular abnormalities expressed by defective versions of these genes could cause dysregulation of NMDA receptors and NMDA synapses, leading to vulnerability for schizophrenia due to inefficient information processing at glutamate synapses.

NEURODEVELOPMENT AND SCHIZOPHRENIA

Schizophrenia is increasingly believed to be a disorder of abnormal neurodevelopment, linked to dysregulation of various genes that affect neuronal connectivity, synaptogenesis, and NMDA

glutamate receptors.¹⁻¹⁶ It is now recognized that single genes do not directly cause schizophrenia; rather, more than a dozen “susceptibility” genes code for subtle molecular abnormalities that hypothetically provide a genetic “bias” toward inefficient information processing in brain circuits that mediate the symptoms of schizophrenia (Table).² The coupling of sufficient genetic bias with stressful input from the environment is the modern formulation for how nature and nurture conspire to produce schizophrenia.^{2,16}

Four key genes that regulate neuronal connectivity and synaptogenesis in schizophrenia are shown in Figures 1–3. The genes for the four key proteins are BDNF, a known trophic factor^{2,14,16}; dysbindin, also known as dystrobrevin binding protein 1, involved in the formation of synaptic structures^{2,14,16}; neuregulin involved in neuronal migration and in the genesis of glial cells and subsequent myelination of neurons by these cells^{2,8-10,16}; and DISC-1, aptly named for a disrupted gene linked to schizophrenia that makes a protein involved in neurogenesis, neuronal migration, and dendritic organization.^{2,3,16}

It is not known exactly how these genes cause the hypothesized subtle molecular abnormalities that are thought to bias neuronal circuits toward schizophrenia, including not knowing whether these genes make abnormal proteins, or just do not turn on and off synthesis of their gene product protein when they should during neurodevelopment. The specific combinations of abnormal genes that are either necessary or

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sufficient for the development of schizophrenia are also not known. Nevertheless, the fact that several genes linked to schizophrenia are all involved in neurodevelopment strongly implicates that something has gone wrong with the connections between neurons in schizophrenia (Table, Figures 1–3).^{1,2,16}

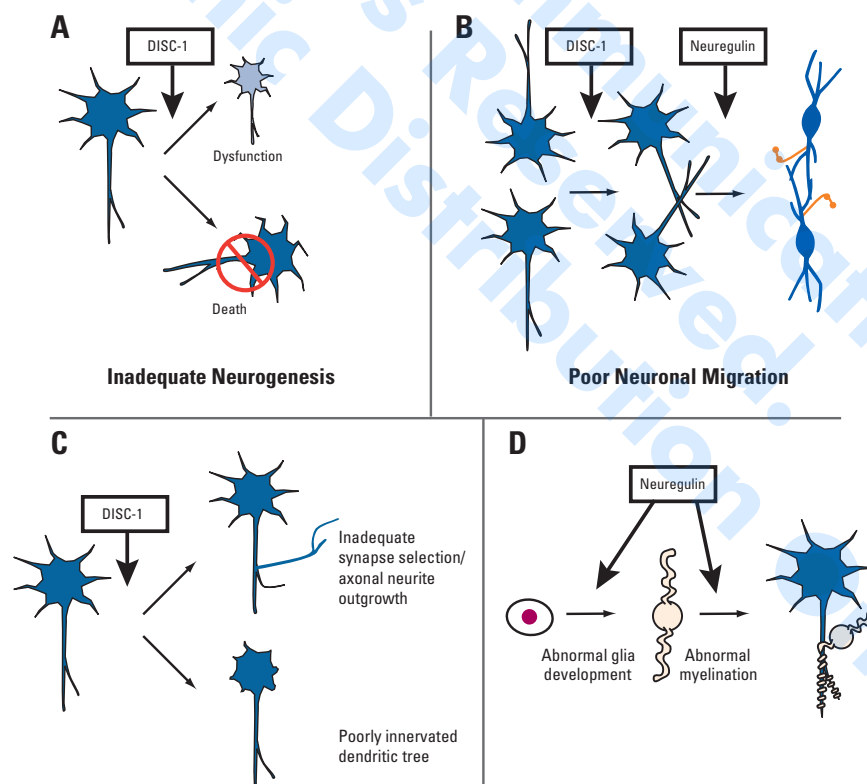
DISCONNECTIVITY

The results of abnormal genetic programming during critical periods of neurodevelopment could include selecting the wrong neurons to survive in the fetal brain (Figure 1A); having neurons migrate to the wrong places (Figure 1B); having neurons innervate the wrong targets, perhaps from getting the nurturing signals mixed up so that what innervates these neurons is also mixed up (Figure

1C); or having abnormal development of the glial cells so that they are unable to myelinate neurons properly (Figure 1D).^{1,16}

To the extent that something is wrong with major susceptibility genes for schizophrenia during the formation of the brain before birth, DISC-1 could affect early neurogenesis (Figure 1A), neuronal migration (Figure 1B) and dendritic organization (Figure 1C),^{1,4-6,16} whereas neuregulin could affect neuronal migration, especially of γ -aminobutyric acid-ergic interneurons (Figure 1B) as well as myelination of neurons once they have migrated into place in the forming brain (Figure 1D).^{1,8-10,16} These neurodevelopmental processes are absolutely critical for normal brain development, occur over large distances, and impact the functioning of the brain for an entire lifetime.

FIGURE 1. Neurodevelopmental hypothesis of schizophrenia: subtle genetic abnormalities in DISC-1 or neuregulin causing disconnectivity¹⁶



DISC-1=disrupted in schizophrenia.

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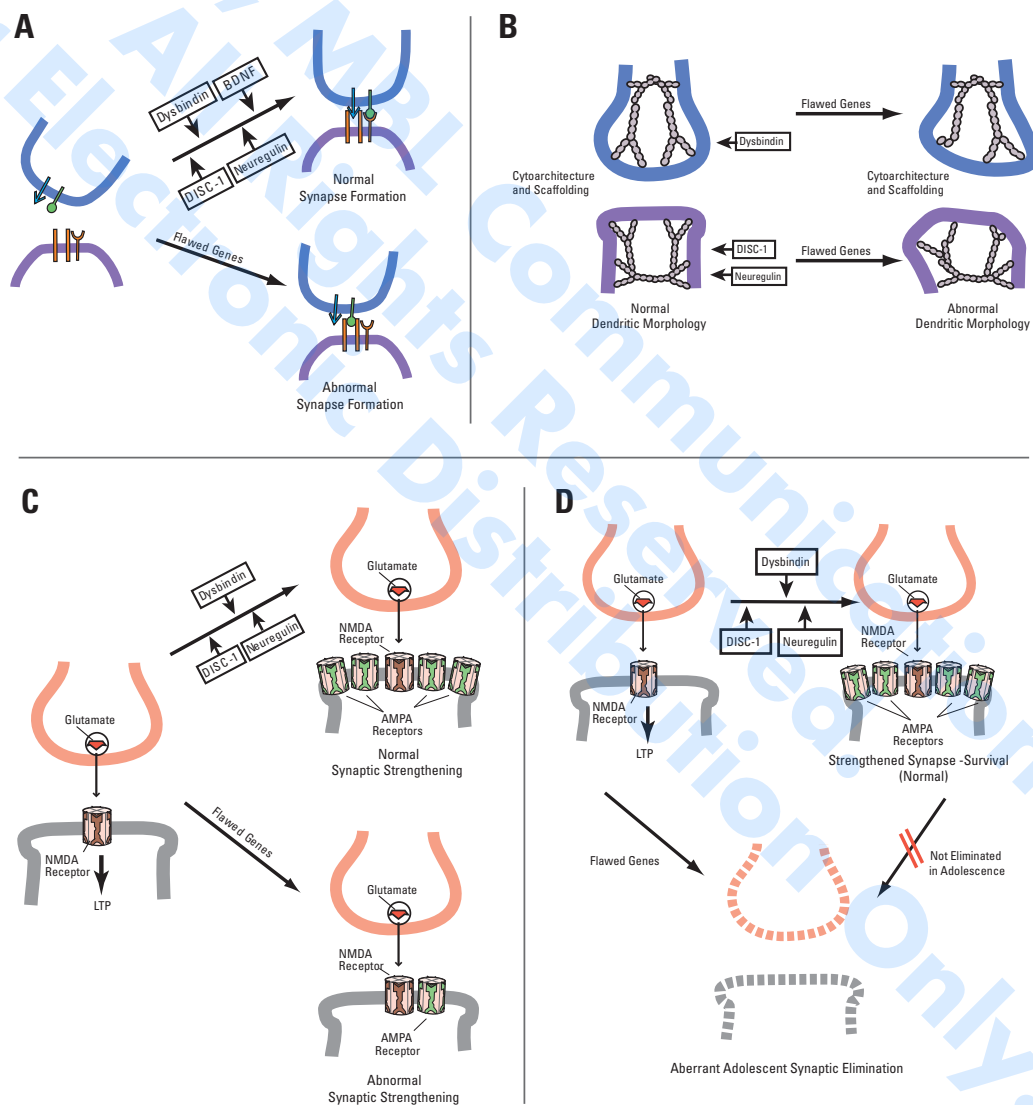
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ABNORMAL SYNAPTOGENESIS

Although it is possible that schizophrenia susceptibility genes may impact brain development once and forever in a type of fetal “hit and run” damage that is complete by the time the brain is formed, it is also possible that an abnormal neurodevelopmental process continues in the schizophrenic brain throughout a

lifetime. Most neurons are formed, selected, migrate, differentiate, and myelinate before birth, but the process of neurogenesis continues for a lifetime in selected brain areas.^{1,16} Perhaps more importantly, synaptogenesis, synaptic “strengthening,” elimination, and reorganization continue over a lifetime. Thus, to the extent that schizophrenia susceptibility genes affect

FIGURE 2. Neurodevelopmental hypothesis of schizophrenia: key susceptibility genes causing abnormal synaptogenesis¹⁶



BDNF=brain-derived neurotrophic factor; DISC-1=disrupted in schizophrenia-1; NMDA=N-methyl-D-aspartate; AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; LTP=long-term potentiation.

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synapse formation, they have the potential to affect ongoing brain function for a lifetime.

Many of the known susceptibility genes for schizophrenia have profound impact upon synaptogenesis (Figure 2A and 2B). Dysbindin, BDNF, DISC-1, and neuregulin all affect normal synapse formation and thus some combination of abnormalities in these molecules could lead to abnormal synapse formation in schizophrenia (Figure 2A).^{1-7,14,16} For example, abnormal genetic programming of dysbindin could affect synaptic cytoarchitecture and scaffolding in schizophrenia,^{1,2,7,16} whereas abnormal programming of DISC-1 and neuregulin could affect dendritic morphology, and together lead to structurally abnormal synapses in schizophrenia (Figure 2B).^{1-6,8-10,16}

NMDA RECEPTORS, AMPA RECEPTORS AND SYNAPTOGENESIS

Earlier columns have reviewed and illustrated the NMDA receptor hypofunction hypothesis of schizophrenia,^{16,17} and shown how novel therapeutics are now targeting glycine modulation of this receptor.^{16,18} Here, it is shown that the functions of the proteins coded by the specific

genes linked to susceptibility for schizophrenia support the NMDA receptor hypofunction hypothesis¹⁷ and provide a rationale for target-

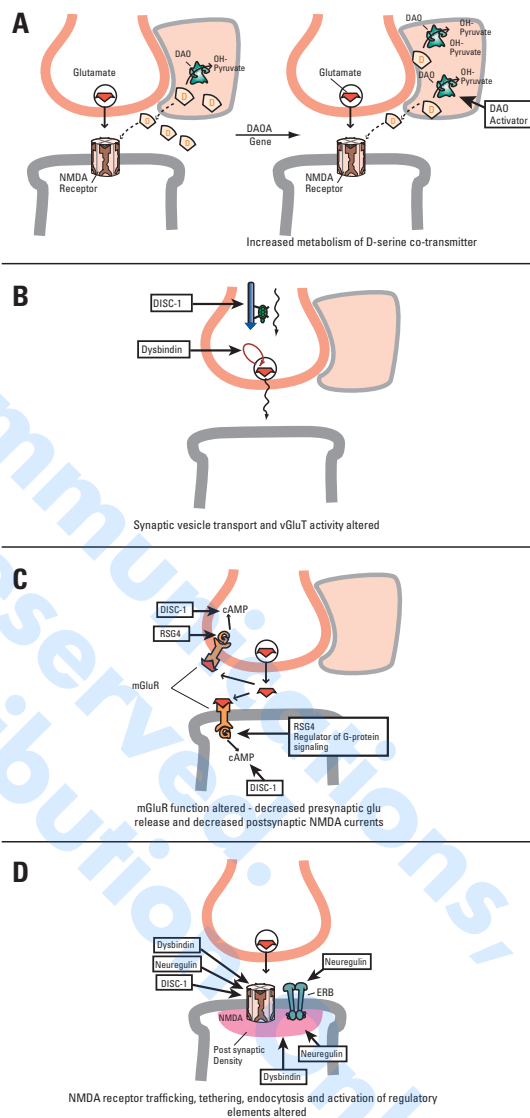
TABLE.
Susceptibility Genes for Schizophrenia

Dysbindin	Erb-B4
Neuregulin	FEZ1
DISC-1	MUTED
DAOA	MRDS1
DAAO	BDNF
RGS4	Nur77
COMT	MAO-A
CHRNA7	Spinophylin
GAD1	Calcyon
GRM3	Tyrosine hydroxylase
PPP3CC	Dopamine ₂ receptor
PRODH2	Dopamine ₃ receptor
AKT1	

DISC-1=disrupted in schizophrenia-1; DAOA=D-amino acid oxidase activator (G72/G30); DAAO=D-amino acid oxidase; RGS4=regulator of G-protein signalling 4; COMT=catechol O methyl transferase; CHRNA7=α-7 nicotinic cholinergic receptor; GAD1=glutamic acid decarboxylase 1; GRM3=glutamate receptor, metabotropic 3; BDNF=brain derived neurotrophic factor; MAO-A=monoamine oxidase A.

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FIGURE 3.
NMDA receptor hypofunction hypothesis of schizophrenia: role of multiple susceptibility genes¹⁶



NMDA=*N*-methyl-D-aspartate; OH-Pyruvate=3-hydroxy-2-oxo-propanoic acid; DAO=D-amino acid oxidase; DAOA=D-amino acid oxidase activator; DISC-1=disrupted in schizophrenia-1; vGluT=vesicular glutamate transporter; cAMP=cyclic adenosine monophosphate; RGS4=regulator of G-protein signalling 4; mGluR=metabotropic glutamate receptor.

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ing glycine modulation of this receptor.¹⁸ That is, several of the known susceptibility genes for schizophrenia impact the NMDA receptor (Figure 2C, 2D and Figure 3A, 3B, 3C, and 3D). Dysbindin, DISC-1, and neuregulin are all involved in the normal “strengthening” of glutamate synapses (Figure 2C).^{1-10,16} Normally, when glutamate synapses are active, their NMDA receptors trigger an electrical phenomenon known as long-term potentiation (LTP). With the help of dysbindin, DISC-1, and neuregulin, LTP leads to structural and functional changes of the synapse that make neurotransmission more efficient.¹⁶ This includes increasing the number of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Figure 2C).

AMPA receptors are important for mediating excitatory neurotransmission and depolarization at glutamate synapses. Thus, more AMPA receptors can mean a “strengthened” synapse (Figure 2C). If something is wrong with the genes that regulate synaptic strengthening, it is possible that this causes NMDA receptors to be hypoactive, leading to ineffective LTP and fewer AMPA receptors trafficking into the postsynaptic neuron. Such a synapse would be “weak,” theoretically causing inefficient information processing in its circuit and thus symptoms of schizophrenia (Figure 2C).¹⁶

Furthermore, the “strength” of a synapse is likely to determine whether it is eliminated or maintained (Figure 2D). Specifically, “strong” synapses with efficient NMDA neurotransmission and many AMPA receptors survive whereas “weak” synapses with few AMPA receptors may be targets for elimination (Figure 2D). This normally shapes the brain’s circuits so that the most critical synapses are not only strengthened, but also survive the selection process, keeping the most efficient and most frequently utilized synapses, while eliminating inefficient and rarely utilized synapses. However, if critical synapses are not adequately strengthened in schizophrenia, it could lead to their elimination, disrupting information flow from circuits now deprived of synaptic connections where communication needs to be efficient (Figure 2D).¹⁶

Competitive elimination of “weak” but critical synapses during adolescence could even explain why schizophrenia has onset at this time. Normally, almost half of the brain’s synapses are eliminated in adolescence. If abnormalities in genes for dysbindin, neuregulin and/or DISC-1 lead to the lack of critical synapses being strengthened, these criti-

cal synapses may be mistakenly eliminated during adolescence with disastrous consequences, namely the onset of symptoms of schizophrenia.

It is possible that “the die is cast” much earlier, due to aberrant neuronal selection, migration, and connections that remain silent until adolescence. However, in the late teens to 20s, abnormal synaptic restructuring due to elimination of necessary synapses that are not adequately strengthened could unmask the neurodevelopmental problems that were previously hidden. To add insult to injury, ongoing problems in synaptic strengthening throughout adulthood in a schizophrenic patient may lead to perpetual elimination of critical synapses, causing new symptom formation or exacerbation of ongoing symptoms due to circuits with progressively and unremittingly aberrant synaptogenesis.

CONVERGENCE OF SUSCEPTIBILITY GENES FOR SCHIZOPHRENIA UPON GLUTAMATE SYNAPSES

Many of the known susceptibility genes for schizophrenia (Table) not only regulate synaptogenesis at glutamate synapses, but also many other functions linked to glutamate neurotransmission, such as the NMDA receptor. For example, the gene for DAOA codes for a protein that activates the enzyme D-amino acid oxidase (Figure 3A).^{2,11-13,16} We have previously discussed how DAO degrades the co-transmitter D-serine that acts at glutamate synapses and at NMDA receptors.¹⁸ DAOA activates this enzyme (Figure 3A), so abnormalities in the gene for DAOA would be expected to alter the metabolism of D-serine.^{11-13,16} This in turn would alter glutamate neurotransmission at NMDA receptors (Figure 3A).

Dysbindin regulates the activity of the vesicular transporter for glutamate, vGluT (Figure 3B).^{7,16} DISC-1 affects the transport of synaptic vesicles into presynaptic glutamate nerve terminals (Figure 3B), and also regulates cyclic adenosine monophosphate signaling, which would affect the functions of glutamate neurotransmission mediated by metabotropic glutamate receptors (Figure 3C).^{1-6,16} Another schizophrenia susceptibility gene is RGS4 (Table), and this gene product also impacts metabotropic glutamate receptor signaling through the G-protein coupled signal transduction system (Figure 3C).^{2,15,16}

Finally, numerous susceptibility genes regulate various elements of NMDA receptor mediated signaling (Figure 3D). Dysbindin, neuregulin, and

DISC-1 all affect NMDA receptor number by altering NMDA receptor trafficking to the postsynaptic membrane, NMDA receptor tethering within that membrane, and NMDA receptor endocytosis that cycles receptors out of the postsynaptic membrane to remove them (Figure 3D).^{1-10,16} Both dysbindin and neuregulin impact the formation and function of the postsynaptic density, a set of proteins that interacts with the postsynaptic membrane to provide structural and functional regulatory elements for neurotransmission and for NMDA receptors (Figure 3D). Neuregulin also activates an Erb signaling system that is co-localized with NMDA receptors (Figure 3D). This Erb signaling system is a member of the receptor tyrosine kinase and neurotrophin signal transduction system. These Erb receptors also interact with the postsynaptic density, and may be involved in mediating the neuroplasticity triggered by NMDA receptors (Figure 3D).¹⁶

Thus, there is a powerful convergence of the known susceptibility genes for schizophrenia upon connectivity, synaptogenesis, and neurotransmission at glutamate synapses and specifically at NMDA receptors (Figures 2C, 2D, and 3A, 3B, 3C, and 3D).² These observations strongly support the NMDA receptor hypofunction hypothesis as a plausible theory for schizophrenia.¹⁷ Genes that code for any number of subtle molecular abnormalities linked to NMDA receptor function in specific brain circuits theoretically create inefficient information processing at glutamate synapses that can produce the symptoms of schizophrenia. If enough of these genetically mediated abnormalities occur simultaneously in a permissive environment, the syndrome of schizophrenia could be the result.

CONCLUSION

Genetics studies in schizophrenia have identified a number of susceptibility genes that increase risk for schizophrenia but do not cause schizophrenia. Since the best understood and most replicated of these genes are involved in neurodevelopment, neuronal connectivity and synaptogenesis, most scientists now believe that schizophrenia is caused

by various possible combinations of many different genes plus stressors from the environment conspiring to cause abnormal neurodevelopment. Genetic and pharmacologic evidence in schizophrenia also points to abnormal neurotransmission at glutamate synapses, possibly involving hypofunctional NMDA receptors.^{16,17} Several new therapies that target NMDA receptors are thus being tested for schizophrenia.^{16,18} **CNS**

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