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Review

Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia

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ABSTRACT

Schizophrenia is a severe mental illness that afflicts nearly 1% of the world's population. One of the cardinal pathological features of schizophrenia is perturbation in synaptic connectivity. Although the etiology of schizophrenia is unknown, it appears to be a developmental disorder involving the interaction of a potentially large number of risk genes, with no one gene producing a strong effect except rare, highly penetrant copy number variants. The purpose of this review is to detail how putative schizophrenia risk genes (DISC-1, neuregulin/ErbB4, dysbindin, Akt1, BDNF, and the NMDA receptor) are involved in regulating neuroplasticity and how alterations in their expression may contribute to the disconnectivity observed in schizophrenia. Moreover, this review highlights how many of these risk genes converge to regulate common neurotransmitter systems and signaling pathways. Future studies aimed at elucidating the functions of these risk genes will provide new insights into the pathophysiology of schizophrenia and will likely lead to the nomination of novel therapeutic targets for restoring proper synaptic connectivity in the brain in schizophrenia and related disorders.

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1. Introduction

Schizophrenia is a disabling mental disorder that affects nearly 1% of the population (Perala et al., 2007). It is characterized clinically by positive symptoms (psychosis, hallucinations), negative symptoms (social withdrawal, flat affect, anhedonia), and cognitive deficits. One of the over-arching pathologies of this disorder is impaired synaptic connectivity, which has been observed across numerous human *post mortem*, as well as functional and structural brain imaging studies (Selemon and Goldman-Rakic, 1999). The abnormalities in neural connectivity are present in multiple brain regions that are important for regulating cognitive function, sensory processing, and affect.

One of the most consistent structural abnormalities found in schizophrenia is the volumetric reduction of the medial temporal lobe (hippocampal formation, subiculum, parahippocampal gyrus) and of the neocortex (Ross et al., 2006). In schizophrenia, there is decreased cortical volume (Rasser et al., 2009) and widespread reduction in cortical thickness, which is most pronounced in the temporal cortex and frontal lobe (Goldman et al., 2009). Since these volumetric reductions are associated with increased cell packing density, but not changes in neuronal number, they are likely due to decreased amounts of cortical neuropil (the axon terminals, dendrites and dendritic spines, and glial processes that occupy the inter-neuronal spaces) (Selemon and Goldman-Rakic, 1999). Several lines of evidence support this notion. *Post mortem* studies have found changes in cortical molecular markers that suggest that both neuronal and/or axonal integrity are compromised (Bertolino et al., 1996; Buckley et al., 1994), and that the number of synapses (Stanley et al., 1995) is reduced in schizophrenia. In addition, the complexity of dendritic branching, total dendritic length, and dendritic spine density of pyramidal neurons is reduced in the prefrontal cortex (PFC) of patients with schizophrenia (Garey et al., 1998; Glantz and Lewis, 2000; Kalus et al., 2000; Rajkowska et al., 1998). The number of puncta immunoreactive for spinophilin, a marker of dendritic spines, is reduced in the primary auditory cortex in schizophrenia (Sweet et al., 2008). As dendritic spines are the principal structural targets of excitatory neurotransmission, these findings suggest that the disruptions in dendritic morphology alter the cortical and/or thalamic circuitry in schizophrenia, which in turn might be the neurobiological substrate underlying the cognitive and sensory dysfunctions observed in patients (Lewis and Gonzalez-Burgos, 2008).

Neuroimaging studies have also provided evidence for impaired connectivity in schizophrenia. Functional magnetic resonance imaging (fMRI) has shown abnormalities in the activation of the dorsolateral prefrontal cortex (DLPFC), medial temporal lobe, hippocampus, anterior cingulate, striatum, and thalamus (Niznikiewicz et al., 2003), which are associated with impaired working memory (Potkin et al., 2009). Diffusion tensor imaging (DTI), a technique that exploits the directionality of water diffusion, can evaluate the organization and coherence of white matter fiber tracts. These tracts serve as anatomical connections between proximal and distant brain regions, thereby creating functional networks. Deficits in white matter tracts appear to be present in the early stages of schizophrenia, even in neuroleptic-naive patients (Kyriakopoulos and Frangou, 2009). Although the pattern of abnormalities is not totally consistent across studies, white matter tracts are most affected in frontotemporal, frontoparietal, and temporooccipital connections (Kyriakopoulos and Frangou, 2009). These imaging results provide further evidence for the presence of structural disconnectivity in schizophrenia.

Schizophrenia has a strong genetic component (heritability of approximately 0.8) as evidenced by family and twin studies. However, the genetics are complex, with no single gene producing a strong effect. Rather, schizophrenia appears to be the result of multiple genes of moderate effect interacting with each other, and the environment, to produce a phenotype (Purcell et al., 2009). Recent research suggests that highly penetrant *de novo* copy number variants (deletions and/or duplications) also contribute to the genetic risk for schizophrenia (Purcell et al., 2009). Linkage and association studies have now implicated several loci in the genome that appear to contain genes conferring risk to schizophrenia (Ross et al., 2006).

Although initial genetic studies provided suggestive evidence for associations between schizophrenia and putative risk genes, the strength of these associations has recently been called into question as hypothesis neutral genome-wide association studies (GWAS) have not confirmed these risk gene associations. However, an important limitation of GWAS is that they examine hundreds of thousands to millions of single nucleotide polymorphisms (SNPs) requiring a substantial correction for multiple comparisons that can compromise statistical power (Cannon, 2010). Thus, there is debate whether negative GWAS findings invalidate the results of candidate gene association studies or that they are insufficiently powered (Cannon, 2010).

Ideally, the evidence for association would come from repeated demonstration of a directional association (even if non-significant), such that pooled- or meta-analyses show a clearly significant directional effect (Norton et al., 2007). However, there have been difficulties in defining what constitutes replication, since many studies vary in their methods, marker sets employed, phenotype definition, and other study design characteristics (Munafo et al., 2008). In addition, when based upon indirect association, replication of particular alleles may not be easily obtained due to a mixture of population differences in allelic heterogeneity at the locus, allele frequencies, patterns of linkage disequilibrium (LD), phenotypic variation relevant to the associated allele, or exposure to environmental variables with which a risk allele interacts (O'Donovan and Owen, 1999). Association to the same allele across studies should be sought, but it cannot be a pre-requisite for considering a study as supportive of association between disease (i.e. schizophrenia) and a particular gene; instead, it is legitimate to consider association to any allele or haplotype as significant evidence for replication at the gene-level, if it both survives appropriate correction for multiple testing and is based on a well-designed quality-controlled study (Norton et al., 2007).

The purpose of this review is to highlight some of the most studied neuroplasticity pathways implicated in the etiology of schizophrenia, both genetically and biologically, and detail the signaling cascades involved in their regulation of synaptogenesis and plasticity. In addition, this review will discuss how different pathways might converge and how perturbations in these pathways might contribute to the pathophysiology of schizophrenia.

2. DISC-1

2.1. DISC1 and schizophrenia

The DISC locus was identified via a balanced (1;11) (q42.1; q14.3) chromosomal translocation in a large Scottish pedigree that segregates in a highly significant manner with a broad range of psychiatric illnesses, including schizophrenia, bipolar disorder, and major depression (St Clair et al., 1990). Two novel genes were identified at this locus and due to the high prevalence of schizophrenia in this family, were named Disrupted-in-Schizophrenia-1/2 (DISC1, DISC2). The human DISC1 genes spans approximately 415 Kb of genomic DNA and consists of 13 exons (Millar et al., 2001, 2000). The chromosomal translocation occurs between exons 8 and 9 of the DISC1 gene on chromosome 1, which has not yet been found in any other families (Ross et al., 2006).

The first independent evidence for the involvement of the DISC1 locus in psychiatric illness came from two Finnish linkage studies. They demonstrated that the 1q32.2-q41 region of chromosome 1, proximal to the *DISC* gene and specifically within intron 9, was associated with an increased risk of schizophrenia and schizoaffective disorder (Ekelund et al., 2004, 2001, 2000; Hovatta et al., 1999). Evidence for this chromosomal association with psychiatric illness has been supported with studies from various populations, including Britain/Iceland, Taiwan and Scotland (Curtis et al., 2003; Detera-Wadleigh et al., 1999; Hamshere et al., 2005; Hwu et al., 2003; Macgregor et al., 2004). In addition, multiple independent association studies support *DISC1* as a risk factor for psychiatric illness (Chubb et al., 2008). Numerous studies have also reported evidence of linkage or association between the *DISC1* locus and impaired cognitive function in both normal and schizophrenic individuals (for review: (Chubb et al., 2008); deficits which are consistent with dysfunction of the DLPFC and hippocampus. *DISC1* haplotypes, including the putative functional SNP (Ser704Cys), are also associated with reduced gray matter volume in hippocampus and cortex (Callicott et al., 2005; Hashimoto et al., 2006; Thomson et al., 2005). Another study demonstrated that from chromosome 1q42 a common haplotype containing three SNP markers near the translocation breakpoint of *DISC1* and a rare haplotype containing four markers from the *DISC1* and translin-associated factor X (*TRAX*) genes, were not only overrepresented among individuals with schizophrenia, but were also associated with several intermediate phenotypes including, short- and long-term memory impairments as well as reduced gray matter density in the PFC (Cannon et al., 2005). In addition to cognition, *DISC1* variants also affect the level of social anhedonia (Tomppo et al., 2009).

The molecular mechanism of the DISC1 translocation is still uncertain and remains controversial. Possible outcomes include haplo-insufficiency or a dominant/negative product, or both, of the C-terminally truncated mutant protein encoded from exons 1 to 8 (Sawa and Snyder, 2005). Evidence for the haplo-insuffiency model comes from the fact that decreased expression of full-length DISC1 and the failure to detect mutant DISC1 in lymphoblastoid cell lines derived from schizophrenic patients (Millar et al., 2005). However, it is uncertain how well lymphoblast DISC1 expression mirrors brain expression and whether the antibodies used were sensitive and/or specific enough to detect truncated DISC1 (Kvajo et al., 2008) or distinguish it from other isoforms (Ishizuka et al., 2007). An additional implication of the balanced translocation is the production of unique fusion transcripts. A novel gene, termed *Boymaw*, was disrupted by the translocation on chromosome 11 and suggested

the generation of two fusion transcripts between the *Boymaw* and *DISC1* genes (Zhou et al., 2008). Recently, fusion transcripts were generated between Boymaw and DISC1 and transfected into a rat hippocampal neuronal cell line (Zhou et al., 2010). Interestingly, the DISC1-Boymaw chimeric proteins showed low expression and punctate staining, while the C-terminal DISC1 protein generated from the Boymaw–DISC1 transcript was more abundantly and diffusely expressed in the cytoplasm. These new findings highlight the possibility that the pathogenesis of the Scottish translocation extends beyond just a loss of DISC1 function (Brandon et al., 2009).

Substantial evidence implicating DISC1 in the pathogenesis of schizophrenia comes from animal models. Although a DISC1 knockout (KO) mouse has yet to be generated, seven DISC1 mutant mouse models have been created, ranging from ENU-induced missense *DISC1* mutants, to truncated human *DISC1* transgenics and bacterial artificial chromosome (BAC) expressing mice (Jaaro-Peled, 2009). All of them display a range of behavioral (disrupted pre-pulse inhibition, PPI; impaired cognitive performance and sociability) and neuroanatomical (enlarged lateral ventricles, reduced spine density and number of parvalbumin interneurons) abnormalities relevant to schizophrenia (for extensive review see: (Desbonnet et al., 2009; Jaaro-Peled, 2009; Jaaro-Peled et al., 2010). However, one important feature to take into account is that the mouse DISC1 is only ~60% identical to the human DISC1 at both the nucleotide and amino acid level (Ma et al., 2002).

A recent study characterized the mRNA expression profile of DISC1 in adult and fetal human brain, as well as in control and schizophrenic subjects (Nakata et al., 2009). This study highlighted the complexity of DISC1 transcription by demonstrating the presence of more than 50 splice variants in the brain. Isoforms Δ 7 Δ 8 (lacking exons 7 and 8), Esv1 (Extra short variant-1; an exon 3 insertion variant), and Δ 3 (lacking exon 3), which all encode truncated DISC1 proteins, were expressed more abundantly during fetal development than during postnatal age, suggesting that they may play important roles in early brain development. Δ 7 Δ 8 and Esv1 were more abundant in the hippocampus of patients with schizophrenia, whereas overall DISC1 expression levels were unchanged. Furthermore, Δ 3 and Δ 7 Δ 8 expression levels were significantly associated with schizophrenia risk-associated polymorphisms [non-synonymous SNPs: rs821616 (Cys704Ser) and rs6675281 (Leu607Phe), and rs821597]. The same allele at rs6675281, which predicted higher expression of these transcripts in the hippocampus, was associated with higher expression of DISC1 Δ 7 Δ 8 in lymphoblasts. These results implicate specific alterations in DISC1 gene processing as a molecular mechanism of genetic risk-associated with the development of schizophrenia (Nakata et al., 2009). However, it should be noted that it is still uncertain how many of these isoforms are actually translated into protein.

2.2. Protein interaction partners

DISC1 is a truly multifunctional scaffolding protein with a diverse cellular distribution. Yeast two-hybrid (Y2H) screens combined with pathway and functional analyses have generated a network of potential protein interaction partners involving DISC1, which include 127 proteins and 158 interactions (Camargo et al., 2007). This network implicates DISC1 in processes related to cell cycle/division, cytoskeletal stability and organization, intracellular transport, and synaptic function. Although future experiments will be needed to determine whether many of these interactions are biologically relevant and involved in the pathophysiology of schizophrenia, this work highlights the complexity of the DISC1 interactome. This section describes DISC1 interactions, many of which were initially identified by Y2H screens that have subsequently been validated *in vivo*.

2.2.1. Centrosomal interactions

The centrosome, the only non-membranous organelle in most vertebrate cells, occupies a tiny volume of the cell near the nucleus and is composed of two main substructures, centrioles (usually two symmetrical, barrel shape structures comprised of microtubules that lie at right angles to one another and in close proximity at one end) and pericentriolar material (interconnected meshwork of fibers and protein aggregates that forms a matrix surrounding both centrioles and is the site of microtubule nucleation) (Doxsey, 2001). Centrosomes are referred to as microtubule organizing centers (MTOCs) because they have the ability to nucleate (the initiation event required for the *de novo* synthesis of microtubules) and organize microtubules (Doxsey, 2001). Features associated with MTOCs include organization of mitotic spindles, formation of primary cilia, and progression through cytokinesis. The centrosome also plays an integral role during neurodevelopment. Establishment of polarity, for which centrosomal position is one key marker, is an essential process during neuronal proliferation, migration, and differentiation (Higginbotham and Gleeson, 2007). The migration of neurons is a crucial step in corticogenesis during brain development. Migration is driven by nucleokinesis (movement of the nucleus towards the centrosome), for which microtubule-based transport is critical. The extension of neurites distally from the centrosome is also dependent, in part, on microtubule-based transport.

2.2.1.1. Microtubule-associated dynein–motor complex. Dynein–motor-associated microtubular dynamics is critical for proper neuronal migration and axonal formation during neuronal development. DISC1 stabilizes the dynein complex at the centrosome, thereby promoting neurite outgrowth *in vitro* and ensuring proper cortical development *in vivo* (Kamiya et al., 2005). Recent *in vivo* findings demonstrated that the C-terminal region, nuclear distribution element like-1 (NDEL1; see below) binding site, and the self-association domain of DISC1 are essential for the proper migration of neurons into the cortical plate during development. *in vitro* over-expression of mutated human DISC1, which lacks the C-terminal domain, acts in a dominant/negative fashion by redistributing wild-type DISC1 through self-association and by dissociating the DISC1–motor complex from the centrosome (Kamiya et al., 2005). *in vivo* over-expression of the C-terminal truncated DISC1 impaired proper neuronal migration in developing mouse (Kamiya et al., 2005) and rat cortex (Young-Pearse et al., 2010).

In addition to DISC1, the structural proteins dynein and dynactin, as well as lissencephaly 1 (LIS1) are part of the dynein–motor complex. NDEL1 is required for dynein function and facilitates the interaction between LIS1 and dynein (Shu et al., 2004). LIS1 mutations inhibit its ability to bind NDEL1, which results in defective neuronal migration, causing lissencephaly (brain malformation; smoothed brain). LIS1 and NDEL1 may exert their effects on neuronal migration via their roles in neurite outgrowth, maintaining nuclear-centrosome attachment, and regulation of microtubule stability and organization, while their effects on neurogenesis might arise from their role in regulating the cell cycle and mitosis (Chubb et al., 2008). Full-length DISC1, but not the putative truncated protein resulting from the Scottish family chromosomal translocation, interacts with NDEL1 at a site independent from the LIS1 binding domain (Brandon et al., 2004; Morris et al., 2003; Ozeki et al., 2003). This complex is neurodevelopmentally regulated, being abundant embryonically and early postnatally, but greatly reduced by adulthood (Brandon et al., 2004). Evidence suggests that NDEL1 serves as a scaffold between DISC1 and LIS1 in order to form a trimolecular complex (Brandon et al., 2004). Functionally, the DISC1–NDEL1 interaction is required for neurite outgrowth, with protein levels of the two being up-regulated during this process (Kamiya et al., 2006).

In addition to a DISC1–NDEL1 protein interaction, there is also evidence for a genetic interaction between *NDEL1* and *DISC1* variants in schizophrenia risk. There was a significant interaction between rs1391768 (*NDEL1* SNP) and DISC1Ser704Cys, with the effect of *NDEL1* on schizophrenia risk present only against a *DISC1* Ser704 homozygosity background (Burdick et al., 2008). Biochemical evidence also demonstrates that genetic variants of *DISC1* confer different binding affinities for NDEL1 (Burdick et al., 2008; Kamiya et al., 2006).

2.2.1.2. PCM-1. Pericentriolar material-1 (PCM1) is a major constituent of centriolar satellites, non-membranous granules scattered around the centrosome that acts as a scaffold to target proteins to the centrosome in a dynein–motor-dependent manner and modulates microtubular dynamics (Dammermann and Merdes, 2002). Interestingly, although PCM1 is expressed by both neurons and glia, it is found at the centrosome only in glia (Eastwood et al., 2010). PCM1 also interacts with Bardet–Biedl syndrome 4 protein (BBS4), which localizes primarily in the centrosome and contributes to the maintenance of microtubule dynamics. PCM1 forms a complex with DISC1 and BBS4 via discrete binding domains in each protein, whereby DISC1 and BBS4 synergistically recruit PCM1 and associated proteins to the centrosome (Kamiya et al., 2008). Suppression of PCM1, BBS4, or DISC1 in the developing cortex leads to neuronal migration defects, which is exacerbated by the concomitant suppression of the latter two proteins (Kamiya et al., 2008). Recent data demonstrates that *DISC*1 coding variants affect the cellular distribution of PCM1. The *DISC1* Leu607Phe polymorphism negatively affects PCM1 centrosomal localization in SH-SY5Y cells (human neuroblastoma cell line) and white matter glia in the human superior temporal gyrus (STG) (Eastwood et al., 2010), potentially through disruption of the leucine zipper and coiled-coil DISC1 domains (Eastwood et al., 2009). Another *DISC1* SNP, Ser704Cys, also affects PCM1 centrosomal localization in the human STG, with the Cys704 carriers having less localization than Ser704 homozygotes; however, no differences in PCM1 localization were found between controls and schizophrenics with respect to genotype (Eastwood et al., 2010). It is still uncertain whether the effects of these, or other, *DISC1* SNPs influence the localization of centrosomal proteins in addition to PCM1.

The PCM1 gene itself has been associated with increased risk for schizophrenia (Datta et al., 2010; Gurling et al., 2006). A nonsense mutation was also found to segregate with schizophrenia spectrum psychosis in one family (Kamiya et al., 2008). Recent sequencing of individuals who inherited the *PCM1* marker alleles and haplotypes associated with schizophrenia identified three etiological base pair changes that could be pathogenic (Datta et al., 2010). Moreover, subjects with schizophrenia who carried *PCM1* gene susceptibility markers were found to have orbitofrontal gray matter deficits, while non-*PCM1* carrying patients had temporal pole and hippocampal volumetric deficits (Gurling et al., 2006).

2.2.1.3. Kendrin. Kendrin, the human orthologue of mouse pericentrin B, is a large coiled-coil centrosomal protein that mediates microtubule nucleation by anchoring the γ-tubulin ring complex, which initiates assembly of the mitotic spindle apparatus. Kendrin was identified as a DISC1 binding partner by Y2H screening (Miyoshi et al., 2004), for which the C-terminal portion of DISC1 is necessary for this interaction (Shimizu et al., 2008). The binding of DISC1 to kendrin (Miyoshi et al., 2004), as well as the C-terminal portion of DISC1 (Shimizu et al., 2008), is indispensible for the centrosomal localization of DISC1. Furthermore, *in vitro* evidence suggests that the DISC1–kendrin interaction is important for microtubule organization (Shimizu et al., 2008).

2.2.1.4. APP. β-amyloid precursor protein (APP) is a type I transmembrane glycoprotein expressed throughout the developing and adult brain that is proteolytically cleaved and, depending on where that occurs, can release amyloid-β protein 42 ($A\beta_{42}$), a pathological hallmark of Alzheimer's disease. APP was found to also regulate the migration of neural precursors in the developing cortex, where disabled-1 (DAB1), a key neuronal migration factor, was found to be a downstream mediator of APP (Young-Pearse et al., 2007). DISC1 was recently shown to interact with the intracellular domain of APP via its N-terminal domain, which was enriched in the membrane fraction prepared from rat brain (Young-Pearse et al., 2010). Evidence from rescue experiments suggest that DISC1 acts downstream of APP and DAB1 to regulate cortical neuronal migration (Young-Pearse et al., 2010).

In sum, these lines of evidence support a critical role of DISC1 protein interactions for proper functioning of the centrosome and links perturbation of this system to abnormal cortical development associated with schizophrenia.

2.2.2. DBZ

DISC1-Binding Zinc-finger protein (DBZ), which is predicted to have a C_2H_2-type zinc finger motif and coiled-coil domains, was first identified as a potential DISC1 binding partner using a Y2H screen, and was then found to co-immunoprecipitate with DISC1 in rat brain tissue (Hattori et al., 2007). The DISC1 domain responsible for this interaction is near the translocation breakpoint in *DISC1*. DBZ mRNA is selectively expressed in the brain in humans, with high levels of expression in the hippocampus, striatum, and cortex of rats. Evidence suggests that pituitary adenylate cyclase-activating peptide (PACAP) signaling modulates DBZ–DISC1 interaction, which in turn regulates DISC1-dependent neurite outgrowth (Hattori et al., 2007).

2.2.3. FEZ1

Fasiculation and elongation protein ζ-1 (FEZ1) is a mammalian homologue of the *Caenorhabditis elegans* UNC-76 protein that is necessary for normal axonal bundling and elongation of axon bundles in nematodes and are reported to represent a new protein family (Bloom and Horvitz, 1997). FEZ1 has been shown to be an interacting partner of DISC1 by a Y2H screen, and co-localizes with DISC1 in growth cones in cultured hippocampal neurons (Miyoshi et al., 2003). DISC1 also participates in neurite outgrowth of PC12 cells through its interaction with FEZ1 (Miyoshi et al., 2003). Although there is some biological (Lipska et al., 2006) and genetic (Yamada et al., 2004) evidence implicating FEZ1 in the pathophysiology of schizophrenia, other studies have failed to replicate the genetic association (Hodgkinson et al., 2007; Koga et al., 2007; Rastogi et al., 2009).

2.2.4. 14-3-3ε

14-3-3 proteins are critical for many brain functions and are involved in such neurological diseases as Alzheimer's disease (present in neurofibrillary tangles (Layfield et al., 1996)) and Parkinson's disease (interact with α-synuclein (Ostrerova et al., 1999)). 14-3-3ε was detected as a DISC1 binding partner from rat brain cytosol extract (Taya et al., 2007). 14-3-3ε is deleted in Miller–Dieker syndrome, a disorder that includes neuronal migration defects, in part due to the loss of 14-3-3ε binding to NDEL1 and the resultant mislocalization of LIS1 and NDEL1 (Taya et al., 2007). Some evidence suggests that DISC1 acts as a cargo receptor for the 14-3-3ε/LIS1/NDEL1 complex *in vivo* (Taya et al., 2007).

2.2.5. Grb2

Growth factor receptor bound protein 2 (Grb2) was identified as a DISC1 interactor from rat brain membrane extracts, and its binding site on DISC1 is close to that of NDEL1 (Shinoda et al., 2007). In addition, Grb2 competes with NDEL1 for binding to DISC1 (Shinoda

et al., 2007). DISC1 is required for kinesin-dependent movement of Grb2 along microtubules within axonal growth cones (Shinoda et al., 2007). Grb2 is also involved in linking cell-surface receptors to intracellular signaling pathways, including ErbB receptors (Ma et al., 2003), which bind neuregulin and are implicated in molecular pathways that might underlie schizophrenia.

2.2.6. PDE4B

Phosphodiesterase 4B (PDE4B) is a member of the PDE4 family that consists of four genes (A/B/C/D), with alternate mRNA splicing producing at least 20 distinct protein isoforms. These enzymes hydrolyze cyclic adenosine monophosphate (cAMP) and consist of an N-terminal domain that is thought to regulate subcellular distribution, two regulatory domains (upstream conserved regions 1 and 2; UCR1/2), and a catalytic region (Houslay and Adams, 2003). This family of proteins is widely expressed in the CNS in an isoform-specific fashion (Iona et al., 1998), and is important for learning and memory (Davis, 1996), synaptic plasticity (Lee and O'Dowd, 2000), and axonal growth cone motility (Kim and Wu, 1996). PDE4s have also been implicated in the etiology of psychiatric illnesses. They are expressed in many regions linked to mental illness, including the hippocampus and frontal cortex. Genetic studies have found associations between PDE4B (Pickard et al., 2007) and PDE4D (Tomppo et al., 2009) with schizophrenia, while mice with null mutations of PDE4B or PDE4D display an antidepressant-like behavioral profile (O'Donnell and Zhang, 2004), suggesting their involvement in both mood and psychotic disorders.

Immuno-co-precipitation demonstrates that DISC1 directly interacts with the multiple PDE4 isoforms (Millar et al., 2005). It was originally demonstrated that the 71 kDa isoform of DISC1, through its N-terminal head domain, binds to the UCR2 region of PDE4B (Millar et al., 2005). More recently, it was shown that the full-length ~100 kDa DISC1 isoform (fl-DISC1) can bind all four PDE4 family members (Murdoch et al., 2007). DISC1 sequesters PDE4 and prevents it from converting cAMP to adenosine monophosphate, thereby prolonging cAMP-dependent signaling. cAMP is critical for the regulation of protein kinase A (PKA), which plays an important role in neuronal plasticity and function. Therefore, this function of DISC1 is likely to be of importance because PDE4 recruitment to signaling protein complexes confers spatial and temporal regulation of localized cAMP levels (Baillie et al., 2005).

Elevation in cAMP levels causes the dissociation of PDE4 from DISC1. However, there are differences in the cAMP-dependent regulation of the binding between PDE4 isoforms and fl-DISC1. Elevating intracellular cAMP levels causes the release of PDE4C and PDE4D, but not PDE4A and PDE4B, from fl-DISC1 (Murdoch et al., 2007). In contrast, the 71 kDa DISC1 isoform is released from PDE4B when intracellular cAMP levels increase (Millar et al., 2005). These results indicate that the interactions between DISC1 and PDE4 are more complex than originally believed.

2.3. Regulation of embryonic, early postnatal, and adult neurogenesis

DISC1 plays an important role in the generation and integration of new neurons in both early development and adulthood. The expression of DISC1 is highest during critical stages of murine brain development, with peaks at embryonic (E) day E13.5 during the active neurogenesis period in the developing brain, and at postnatal (P) day P35, the period of puberty (Schurov et al., 2004). Protein expression continues into adulthood, with highest levels in the hippocampus, lateral septum, cerebral cortex, hypothalamus, olfactory bulb, and other brain stem regions (Austin et al., 2003). In addition to neurons, DISC1 is expressed in astrocytes, oligodendrocytes, and microglia of the human and rodent cortex (Seshadri et al., 2010).

2.3.1. Embryonic

DISC1 is highly expressed in the developing cerebral cortex (Schurov et al., 2004) where it plays distinct roles in neural progenitor cells and post-mitotic neurons. In the developing cortex, DISC1 suppression *in utero* (day E13) via short hairpin RNA (shRNA) results in decreased neuronal proliferation, premature cell cycle exit and neuronal differentiation, as well as reduced number of cells in ventricular and subventricular zones (Mao et al., 2009). Several lines of evidence suggest that these effects of DISC1 on proliferation are mediated via its regulation of the wingless (Wnt)/β-catenin pathway. Under basal conditions, cytosolic β-catenin levels are kept low due to glycogen synthase kinase-3 beta (GSK3β)-mediated phosphorylation that targets β-catenin for degradation. Upon Wnt activation, β-catenin levels are increased, which leads to the nuclear translocation of β-catenin and the transcription of Wnt-dependent genes. DISC1 acts as a positive modulator of Wnt signaling by directly binding to and inhibiting the activity of GSK3β, thereby preventing the phosphorylation and subsequent degradation of β-catenin (Adachi et al., 2007).

In addition to regulating cell proliferation in the developing brain, DISC1 also affects post-mitotic neurons. Knockdown of DISC1 expression by shRNA or expressing the C-terminal truncated mutant form of DISC1 using *in utero* electroporation on day E15, when radial neuronal migration becomes more prominent, resulted in the delayed migration of cortical neurons (Kamiya et al., 2005). Moreover, these manipulations impaired the orientation, polarity and degree of dendritic arborization of those neurons that migrated into the proper position (Kamiya et al., 2005).

2.3.2. Early postnatal

Recent evidence has now emerged detailing how DISC1 regulates the migration, maturation, and positioning of dentate granule cells in the development of the postnatal dentate gyrus (Enomoto et al., 2009). DISC1 interacts with an actin binding protein, which serves as the girder for actin filaments (*girdin*). Girdin (also known as KIAA1212) is expressed in neurons, but not progenitor cells, in the dentate gyrus of the hippocampus of the postnatal mouse brain. DISC1 interacts with girdin and regulates axonal development *in vitro* and *in vivo*. Girdin-deficient mice have abnormal cytoarchitecture of the dentate gyrus, including a dispersed granule cell layer, multilamination of the CA1 region, and impairment in the development and lamination of mossy fibers. Girdin deficiency, siRNA-mediated knockdown of girdin expression, and inhibition of DISC1/girdin interaction all resulted in overextended migration and mispositioning of dentate granule cells. These manipulations, however, did not significantly affect dendritic morphology or the electrophysiological properties of these cells. Finally, DISC1 expression was unable to rescue the mispositioning of girdin-deficient dentate granule cells. In sum, these findings suggest that DISC1 acts upstream of girdin to regulate postnatal hippocampal development.

2.3.3. Adult

It is well established that dentate gyrus of the hippocampus in the adult mammalian brain provides the proper milieu to sustain progenitor cells and is permissive to neuronal fate determination (Balu and Lucki, 2009). Moreover, this process, at the level of cell proliferation, is reduced in patients with schizophrenia (Reif et al., 2006). In the adult dentate gyrus, DISC1 is expressed in neural progenitors and neurons, but not in astrocytes (Mao et al., 2009). Given the important role DISC1 plays during early brain development and the resemblance of the adult neurogenic dentate gyrus to the developing brain, it is not surprising that DISC1 is also an integral regulator of adult hippocampal neurogenesis. The roles DISC1 plays in regulating adult neurogenesis have been teased apart using viral-mediated RNA interference specifically in the adult dentate

gyrus, which suppresses DISC1 expression in actively dividing cells. Suppression of DISC1 reduced proliferation of neural progenitors in the dentate gyrus through its direct interaction and inhibition of GS3K-β activity (Mao et al., 2009). Interestingly, similar DISC1 manipulation led to soma hypertrophy, accelerated dendritic outgrowth with the appearance of ectopic dendrites and mispositioning from overextended migration into the outer-third layer of granule cell layer (Duan et al., 2007). These morphological changes were not due to altered neuronal fate specification (Duan et al., 2007). Functionally, new neurons with reduced DISC1 displayed enhanced intrinsic excitability and accelerated synapse formation (Duan et al., 2007). These results demonstrate that in the adult hippocampus, DISC1 acts not only as a facilitator of neural proliferation, but also orchestrates the timing of functional neuronal integration. It should be noted that DISC1 mutant mouse models do not exactly recapitulate what is observed with shRNA manipulations of DISC1. Although the migration of immature dentate granule cells was abnormal in both types of manipulations, there were no differences in soma size or dendritic morphology of immature dentate granule cells in mutant mice carrying a truncated lesion in the endogenous *DISC1* orthologue (Kvajo et al., 2008). However, the manner and the cell population in which DISC1 was suppressed between studies were very different and likely contributed to the varied morphological phenotype.

Recent studies have begun to elucidate the signaling cascades downstream of DISC1 involved in mediating its effects on adult neurogenesis. One such pathway is the Akt-mammalian target of rapamycin (mTOR) cascade. Suppression of DISC1 in newborn neurons of the adult hippocampus increased activation of Akt (Arguello and Gogos, 2008) and its downstream effector, S6 ribsomal protein (S6), during their maturation process (Kim et al., 2009). As mentioned above, DISC1 directly interacts with girdin, which is expressed in dentate granule cells of the adult hippocampus. Evidence suggests that the DISC1-girdin interaction prevents activation of Akt signaling (Kim et al., 2009). Moreover, genetic manipulations that enhance Akt signaling in adult born hippocampal neurons mimics the morphological effects observed with DISC1 suppression (soma hypertrophy, mispositioning of newborn neurons, increased dendritic arborization). Pharmacological inhibition of mTOR, a downstream effecter of Akt, blocked the morphological effects of DISC1 suppression and Akt over-activation. On the other hand, inhibition of GS3K-β activity did not reverse the changes caused by DISC1 suppression. In sum, these results suggest that DISC1 regulates different stages of neurogenesis in the adult hippocampus by distinct molecular mechanisms. DISC1 regulates the proliferation of neural progenitors via the Akt–GS3K-β pathway, while it modulates new neuron development and functional integration, in part, via its interaction with girdin and subsequent modulation of the Akt–mTOR pathway.

As described in this section, the role of DISC1 in regulating neurogenesis is quite complex and depends on numerous factors including brain region and stage of development. However, these recent findings shed light on several signaling pathways that are associated with DISC1 and are implicated in the pathophysiology schizophrenia.

2.4. Maturation of the dopaminergic system in the frontal cortex

The role DISC1 plays during development is important for proper neural functioning in adulthood. Recent evidence demonstrated that transient disruption of DISC1 *in utero*, mainly confined to pyramidal neurons of the PFC, led to circuitry perturbations in this region (Niwa et al., 2010). Dendritic abnormalities and electrophysiological properties of pyramidal neurons in the PFC were altered by the early postnatal period. However, the impaired maturation of the mesocortical dopamine system (PFC: reduced dopamine content and release, reduced tyrosine hydoxylase levels) and altered GABAergic development (PFC: reduced number of parvalbumin (PV) interneurons) did not become manifest until after puberty. These results suggest that impaired DISC1 signaling during development could contribute to the alterations of dopaminergic and GABAergic signaling in the PFC associated with schizophrenia.

2.5. Regulation of dendritic spine plasticity

DISC1 is enriched in the postsynaptic density (PSD) fraction of dendritic spines in the adult brain, where it interacts with one of the major scaffolding proteins, PSD 95 kDa (PSD95) (Hayashi-Takagi et al., 2010). DISC1 also interacts with Kalirin-7 (Kal-7), a GDP/GTP exchange factor for the small G protein Rac1, a well-known regulator of spine morphology and plasticity (Hayashi-Takagi et al., 2010). Evidence suggests that DISC1 anchors Kal-7 to PSD95, thereby sequestering Kal-7 to the PSD and preventing it from activating Rac1. This complex is modulated by neuronal activity, particularly NMDA receptor-dependent activity, which regulates Rac-1 mediated changes in spine morphology.

2.6. Regulation of cell–cell and cell–matrix adhesion

Recent evidence suggests that DISC1 regulates cell–cell adhesion as well as cell–matrix adhesion by regulating adhesion molecule expression (Hattori et al., 2010). DISC1 over-expression in PC-12 cells increased cell–cell adhesion by increasing the mRNA and protein expression of N-cadherin (Hattori et al., 2010), which belongs to the cadherin superfamily of proteins that is involved in the formation of adherence and synaptic junctions in the nervous system (Tepass et al., 2000). DISC1 over-expression in PC-12 cells also enhanced cell–matrix adhesion and neurite outgrowth by increasing the protein levels of β1-integrin, a transmembrane receptor that recognizes extracellular matrix and cell-surface proteins; integrins are important for synapse formation and axonal guidance during neurodevelopment (Reichardt and Tomaselli, 1991). Furthermore, DISC1 regulated the protein levels of N-cadherin and β1-integrin in primary hippocampal neurons. However, the mechanisms underlying the regulation of N-cadherin and β1-integrin expression by DISC1 are currently unclear.

3. Neuregulin 1 and ErbB4 signaling

3.1. Neuregulin 1, ErbB4, and schizophrenia

Neuregulin 1 (NRG1) was first identified as a candidate schizophrenia risk gene by extensive fine-mapping of the 8p locus (*NRG1* lies in the 8p12–8p21 region), a previously identified schizophrenia risk locus, and haplotype-association analysis of affected Icelandic families. This original core haplotype (Hap_{ICE}) consisted of five SNPs and two microsatellites covering 290 kb and containing the first 5′ exon of the type IV isoform and the first 5′ exon of the type II isoform GGF2 of *NRG1*. Many studies since then from diverse populations have supported the genetic association between *NRG1* and schizophrenia and identified 80 SNPs, which are localized to the 5′ and 3′ region of *NRG1* (Alaerts et al., 2009; Mei and Xiong, 2008; Walker et al., 2010). Nevertheless, there are studies from Japanese, Irish, and Spanish cohorts that have shown poor associations (Iwata et al., 2004; Rosa et al., 2007; Thiselton et al., 2004). Functional polymorphisms associated with schizophrenia have been identified; one in the 5′ promoter region that predicted reduced expression of NRG1 type III in the hippocampus of post mortem brain (Nicodemus et al., 2009), while another SNP was found to influence NRG1 type IV expression (Tan et al., 2007). Several meta-analyses that examined the strength of association between *NRG1* and schizophrenia have provided mixed results.

One found a strong positive correlation between the six most frequently analyzed *NRG1* markers from population and family-based association studies (Li et al., 2006), while a more recent meta-analysis found that only one SNP and the two microsatellite polymorphisms in the core risk haplotype (HAP_{ICE}) showed significant association (Gong et al., 2009). Two others produced negative results when only the most commonly reported single marker *NRG1* (SNP8NRG221533) was analyzed, but found when haplotype-based *P*-values were combined, there was evidence in support of an association of *NRG1* with schizophrenia (Munafo et al., 2008, 2006).

ErbB4 is one of the receptors to which NRG1 binds. *ErbB4* spans 1.15 megabases on chromosome 2q34 and has been nominated as a susceptibility gene for schizophrenia in certain populations, including Caucasians, African Americans, and Ashkenazi Jews (Mei and Xiong, 2008), with the SNPs in this gene being mainly clustered around exon 3 and in front of exon 13. However, few studies have replicated the association of *ErbB4* with schizophrenia as compared to *NRG1*. To date, no coding mutations have been identified in the *ErbB4* gene and all reported schizophrenia-associated risk SNPs are non-coding intronic variants, which suggests that risk might be conferred through alternative splicing regulation (Law et al., 2007).

Brain imaging studies have found genotype–phenotype effects with allelic variants of *NRG1* and *ErbB4*. One particular *NRG1* risk allele was associated with decreased activation of the temporal and frontal lobe regions, increased development of psychotic symptoms and decreased premorbid IQ (Hall et al., 2006). As NRG1–ErbB4 signaling is implicated in myelination (see below), diffusion tensor imaging (DTI) studies have been used to measure fractional anisotropy (FA), a putative marker of neuronal myelination, in subjects carrying *NRG1* and *ErbB4* risk genotypes. Two recent DTI studies have found deficits in WM integrity in unaffected subjects carrying *NRG1* risk SNPs (McIntosh et al., 2008; Winterer et al., 2008). In healthy subjects carrying an *ErbB4* schizophrenia risk haplotype, left temporal lobe white matter abnormalities were found, which correlated with impaired working memory (Konrad et al., 2009).

The studying of NRG1 and ErbB4 levels in schizophrenia has been complicated by the complex transcriptional regulation of these genes and the production of multiple protein isoforms. In schizophrenia, the NRG and ErbB4 mRNA levels in the PFC have been shown to be up-regulated in an isoform-specific manner (Law et al., 2007, 2006; Silberberg et al., 2006). At the protein level, however, the results have not been as uniform. One study found that the number of neurons positive for the NRG1α isoform was reduced in the PFC of patients (Bertram et al., 2007), while another found that certain immunoreactive bands of NRG1 and ErbB4 were increased in the PFC of patients (Chong et al., 2008). Others have found that even though protein levels of NRG1 and ErbB4 in the PFC were not altered in schizophrenia, NRG1-induced activity of ErbB4 signaling was enhanced in post mortem brain tissue from schizophrenia subjects (Hahn et al., 2006). This enhanced ErbB4 signaling led to suppression of NMDA receptor signaling in the PFC, in agreement with what has been observed in rodent studies (Pitcher et al., 2008).

Mutant mouse models have also strengthened the involvement of disregulated NRG1–ErbB4 signaling in the schizophrenia disease process. As the detailed phenotypes of these models are beyond the scope of this review, they do recapitulate many of the behavioral (disrupted PPI and hyperactivity) and structural brain abnormalities (lateral ventricle enlargement and reduced dendritic spine density) that are observed in schizophrenia (for extensive review see: (Desbonnet et al., 2009; Jaaro-Peled et al., 2010).

3.2. Molecular biology

NRG1 is the best characterized member of a family of growth factors that are encoded by four individual genes (NRG1–4), which all share a common epidermal growth factor (EGF)-like domain. The EGF-like domain is both necessary and sufficient for activation of its cognate receptor, ErbB. The *NRG1* gene is very complex, with at least 25 exons distributed over a megabase. Due to alternative splicing, *NRG1* generates six protein types (I–VI; defined by their 5′ exon) and at least 31 isoforms, with each protein type having a distinct amino-terminal region. NRG1 isoforms are differentially expressed both at their level and pattern in various tissues, including brain (Meyer et al., 1997), although the full panel of expressed NRG1 protein variants remains to be determined since many of the isoforms have only been identified at the transcript level (Harrison and Law, 2006). NRG1 type IV, which is specific to human, has gained notoriety due to a functional HAP_{ICE}SNP associated with schizophrenia that regulates its expression (Tan et al., 2007). A recent study demonstrated that the type IV isoform mRNA is translated, the protein processed in a PKC-dependent fashion, stimulates ErbB receptors, and activates downstream signaling cascades (Shamir and Buonanno, 2010). Moreover, in hippocampal neurons, NRG1 type III and IV proteins are targeted to the soma, dendrites, and axon initial segments, while only the type III isoform is transported to distal axons, implicating distinct roles the NRG1 isoforms might have in neurodevelopment and disease, like schizophrenia (Shamir and Buonanno, 2010).

3.2.1. ErbB4 signaling

Most of the isoforms are synthesized as membrane-bound precursors, called pro-NRG1s, which are then proteolytically cleaved by three different transmembrane proteases to release the diffusible, mature form (NRG), except in the case of type III NRG1 (Harrison and Law, 2006). The expression and processing of pro-NRG1 is tightly regulated spatially and temporally, as well as by neuronal activity. NRG1 signals by binding to the single-transmembrane ErbB tyrosine kinase receptor, of which there are four types (ErbB1–4) that share homology with the EGF receptor. NRG1 preferentially binds to ErbB3 and ErbB4 receptors via its EGF domain (Harrison and Law, 2006). ErbB4 is best characterized for it CNS function, and due to alternative splicing has four isoforms that trigger distinct signaling cascades. Upon binding of NRG1, ErbB proteins dimerize to form homodimers and heterodimers, which in turn lead to tyrosine kinase activation and auto- and trans-phosphorylation of intracellular domains. These phosphorylated domains serve as docking sites for adaptor proteins such as Grb2 and Shc that activate the Raf-mitogen activated protein kinase (MAPK) pathway, as well as the phosphatidyl inositol-3-kinase (PI3K) pathway that leads to downstream Akt signaling. In addition to these canonical signaling pathways, there are also non-canonical forward (ErbB4 receptor is cleaved, releasing an intracellular domain that translocates to the nucleus and alters gene transcription) and backward (pro-NRG1 is cleaved twice, releasing a C-terminal fragment that can translocate to the nucleus and alter gene transcription) NRG1 signaling mechanisms.

3.3. Neuronal development

3.3.1. Cell proliferation

NRGs and ErbBs are expressed in regions of the developing brain that undergo proliferation. NRG1 stimulates the proliferation of neuronal progenitors *in vitro* from embryonic neural stem cells (Liu et al., 2005), while conditional ErbB4-deficient mice are resistant to the proliferative enhancing effects of NRG in the subventricular zone *in vivo* (Ghashghaei et al., 2006). These findings lend credence to the hypothesis that NRG1–ErbB4 signaling is important for regulating the proliferative activity of progenitor cells.

3.3.2. Neuronal migration

NRG1 plays important roles in neuronal migration across multiple systems. In the developing hindbrain, NRG1 signaling provides

patterning information to the cranial paraxial mesenchyme that is essential for the proper migration of neural crest cells (Golding et al., 2000). In the developing cortex, NRG1 contributes to the establishment of the radial glial scaffold (Schmid et al., 2003) that guides the radial migration of glutamatergic neurons to their ultimate position in the cortex (Anton et al., 1997). NRG1 is also crucial for the tangential migration of GABAergic interneurons (Flames et al., 2004). NRG1–ErbB4 interactions mediate the short and long-range attraction for the tangentially migrating interneurons. ErbB4 is expressed in a subpopulation of interneurons that migrate tangentially towards the cortex through a permissive corridor that expresses type III NRG1 (Duan et al., 2007; Wood et al., 2009). In the adult rodent brain, ErbB4 in part, regulates the migration of immature neuroblasts that travel from the subventricular zone along the rostral migratory stream to the olfactory bulb, as well as their placement and differentiation into interneurons (Anton et al., 2004).

3.3.3. Axon guidance

NRG1 is a facilitator of neurite outgrowth, as application of NRG1 stimulates this process in many types of primary neurons. Moreover, NRG1 and ErbB4 are required for proper axon guidance of thalamocortical axon (TCA) projections (Lopez-Bendito et al., 2006), which convey sensory and motor input to the cerebral cortex.

3.3.4. Myelination

Although the role of NRG1, particularly type III, is well established in myelination in the peripheral nervous system, its role in myelination in the CNS has not been well characterized. NRG1 is thought to serve as an axon-derived signal for oligodendrocyte development (Mei and Xiong, 2008). *in vitro* and zebrafish studies support the notion that NRG1 promotes oligodendrocyte differentiation and myelination. In transgenic mice expressing a dominant-negative ErbB4, there was reduced myelin thickness, a slower conduction velocity in their CNS axons, and a larger number of smaller oligodendrocytes, each myelinating less axonal surface (Roy et al., 2007). However, conditional null mutants that completely lack NRG1 beginning at different stages of neural development all showed normal myelination, casting some doubt on the importance of NRG1 signaling for CNS myelination (Brinkmann et al., 2008).

3.3.5. Synapse formation

In the CNS, type III NRG1 influences the expression of acetylcholine receptors, whereas the type I and II isoforms regulate the expression of $GABA_A$ receptors (Liu et al., 2001; Yang et al., 1998). Moreover, signaling by type I–III isoforms of NRG1 has been shown to alter the levels and profiles of various NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors (Bjarnadottir et al., 2007; Ozaki et al., 1997), while mice with heterozygous deletion of NRG1 have a reduced number of functional forebrain NMDA receptors (Stefansson et al., 2002).

Both spine formation and elimination of glutamatergic synapses are regulated in a neuronal activity-dependent manner. Postsynaptic ErbB4 signaling is required for this activity-dependent spine control (Li et al., 2007). Synaptic activity triggers NRG1–ErbB4 signaling that recruits/stabilizes ErbB4 at the synapse in a PSD95-dependent manner and stabilizes AMPA receptors. Interruption of NRG1–ErbB4 signaling results in the destabilization of synaptic AMPA receptors and spine structure, which leads to impairment of plasticity and to the eventual loss of spines and NMDA receptors.

3.3.6. Development of the dopaminergic system

ErbB4 receptor mRNA is localized to midbrain dopaminergic neurons in mice (Abe et al., 2009). Recent evidence demonstrates that type I NRG1 is a potent regulator of the dopaminergic system during development (Kato et al., 2010). Administration of NRG-1 to neonatal mice produced a hyperdopaminergic state, particularly in the medial PFC, during the early postnatal period and persisted into adulthood. This state manifested as elevated levels of tyrosine hydroxylase (TH) and dopamine, increased enzymatic activity of TH, and increased release of dopamine evoked by depolarization. This suggests that augmented NRG1 signaling during development could lead to life-long perturbations of the dopaminergic system that could contribute to the pathogenesis of schizophrenia.

3.3.7. Regulation of DISC1 expression

Recent evidence suggests that NRG1 and NRG2, but not NRG3, positively regulate the expression of the 130 kDa DISC1 isoform (Seshadri et al., 2010). This effect is mediated in an ErbB2 and ErbB3, but not ErbB4 dependent manner, and requires downstream PI3K/Akt signaling. Heterozygous NRG1-KO mice at birth had reduced cortical levels of the 130 kDa DISC1 isoform. In addition, a similar decrease in DISC1 was observed in another genetic model with reduced NRG1/Akt signaling, the β-site amyloid precursor protein cleaving enzyme-1 (BACE1) knockout mouse. These findings suggest a crosstalk between NRG/DISC1/Akt and identify a potential common pathway in these cascades that are implicated in the pathophysiology of schizophrenia.

3.4. Synaptic plasticity in the adult brain

NRG1 and ErbB4 are expressed in many regions of the adult brain (Lai and Lemke, 1991; Yau et al., 2003). In the cortex, the expression of NRG1 isoforms is laminar specific and mainly non-overlapping, with type I and II isoforms expressed in layers 2, 3 and 6b, and the Type III isoform in layer 5. Types I–III are also expressed in the piriform cortex, reticular nucleus of the thalamus, and the hippocampus. On the other hand, ErbB4 expression is found in cortical layers 2-6b and at high levels in regions where interneurons are enriched. These findings suggest that NRG1–ErbB4 signaling is also important for proper functioning of the adult brain.

3.4.1. Glutamatergic transmission

ErbB4 interacts and co-localizes with the scaffolding protein PSD95, a protein that is crucial for the assembly and function of glutamatergic synapses. Its interaction with PSD95 enhances NRG1 intracellular signaling (Huang et al., 2000). Evidence suggests that NRG1 through ErbB4 signaling suppresses the induction and expression of long-term potentiation (LTP) at glutamatergic synapses between Schaeffer collateral afferents and CA1 pyramidal neurons (SC-CA1) in the hippocampus (Huang et al., 2000; Pitcher et al., 2008). However, recent studies in mice detected ErbB4 (mRNA and protein) in GABAergic interneurons (mainly PV-expressing cells), but not in pyramidal neurons of the hippocampus and neocortex (Fazzari et al., 2010; Vullhorst et al., 2009). Ultrastructural analysis of CA1 interneurons revealed abundant ErbB4 expression in the somatodendritic compartment adjacent to glutamatergic postsynaptic sites, which are required for PV-expressing interneurons to receive proper excitatory input (Fazzari et al., 2010). These results implicate glutamatergic synapses onto GABAergic interneurons as a primary target of NRG1–ErbB4 signaling in the adult CA1, a finding that has important functional implications for understanding the effects of NRG1 on glutamatergic transmission and plasticity, as well as its involvement in the pathophysiology of schizophrenia.

3.4.2. GABAergic transmission

ErbB4 is expressed in many PV-containing chandelier and basket cells where it localizes to axon terminals and postsynaptic densities receiving glutamatergic input (Fazzari et al., 2010). Elimination of ErbB4 reduces the number of axo-axonic cortical synapses

made by chandelier cells on to pyramidal neurons (Fazzari et al., 2010). ErbB4 is present in the presynaptic terminals of GABAergic interneurons, and stimulation of these presynaptic receptors by NRG1 enhances activity-dependent GABA release in the mouse prefrontal cortex through presently unidentified mechanisms (Woo et al., 2007). In the CA3 region of the hippocampus, NRG1–ErbB4 signaling increases the power of kainate-induced gamma oscillations, suggesting that ErbB4 is involved in the synchronization of CA3 pyramidal cell firing by local PV-expressing interneurons, many of which express ErbB4 (Fisahn et al., 2009). Consistent with this finding, both the number of PV-interneurons and the power of kainate-induced gamma oscillations are reduced in mice lacking the ErbB4 receptor (Fisahn et al., 2009). Furthermore, in the prefrontal cortex, NRG1 inhibits pyramidal neurons by stimulating GABA release from interneurons (Wen et al., 2010). In mice lacking ErbB4 specifically in PV-positive interneurons (starting at P10), NRG1 failed to stimulate activity-dependent GABA release and suppress pyramidal neuron activity (Wen et al., 2010). These findings highlight the importance of NRG1–ErbB4 signaling in balancing the activity of brain regions known to be affected in schizophrenia.

3.4.3. Dopaminergic transmission

Dopamine is an important modulator of LTP at glutamatergic synapses throughout the brain (Jay, 2003), not only in the striatum and PFC, which are heavily innervated by dopaminergic fibers, but also in the hippocampus, which receives diffuse inputs from the ventral tegmental area (VTA). In the adult murine hippocampus, NRG1 regulates glutamatergic plasticity at SC-CA1 via modulation of dopaminergic transmission (Kwon et al., 2008). NRG1 stimulates dopamine release in the hippocampus and reverses early-phase LTP at SC–CA1 synapses via activation of dopamine D4 receptors. Although the mechanism by which NRG1 stimulates dopamine release is uncertain, the presence of ErbB4 receptors on GABAergic interneurons favors a mechanism that involves local inhibitory interneurons (Kwon et al., 2008).

4. Dysbindin

4.1. Dysbindin and schizophrenia

Evidence for dystrobrevin binding protein 1 gene (*DTNBP1*; dysbindin) as a putative schizophrenia risk gene came from systematic LD mapping across a linkage region on 6p in the 270 multiply affected pedigrees from the Irish Study of High Density Schizophrenia Families (Straub et al., 2002). Subsequent reanalysis of these data found a single high-risk haplotype containing eight SNPs covering 30 kb (van den Oord et al., 2003). A subsequent large case-control study found strong evidence for association of a three-marker haplotype (Williams et al., 2004), although it failed to find association with previously implicated haplotypes (Schwab et al., 2003; Straub et al., 2002). As of 2008, there have been 45 follow-up association studies, 18 of them with positive results, which are annotated in the Schizophrenia Gene Database (Allen et al., 2008). A large, recent case-control study and family-based sample of German ancestry failed to find an association between *DTNBP1* (38 SNPs genotyped) and schizophrenia (Strohmaier et al., 2010). Meta-analysis of *DTNBP1* (rs1011313) yielded significant summary odds ratios suggesting a nominally significant increase in risk for schizophrenia (Allen et al., 2008). Recent examination of the Irish Case Control Study of Schizophrenia (ICCSS) sample found four SNPs that gave evidence of association, most strongly with the common allele at rs760761 (Riley et al., 2009). Association was also found for a haplotype of the common alleles of five markers (including rs760761) and the minor allele of rs2619538 overlapping the 5′ end of *DTNBP1* (Riley et al., 2009). Although there are inconsistencies in the reported alleles/haplotypes between studies (Desbonnet et al., 2009), the associations do cluster in eight commonly typed SNPs that yield six common haplotypes (Riley et al., 2009). These inconsistent findings have triggered skepticism towards their validity for several reasons (Mutsuddi et al., 2006): the DTNBP1 haplotypes associated with schizophrenia have differed among studies, the same SNPs have not been genotyped in every association study, causal variants that might contribute to schizophrenia have not been found, and a demonstrated function associated with any of the risk haplotypes has not been identified (Strohmaier et al., 2010). *DTNBP1* has also been associated with other illnesses including bipolar disorder and Hermansky–Pudlak syndrome type 7, a complex genetic disorder related to lysosome biogenesis (Li et al., 2003).

Several studies have independently described an association between *DTNBP1* SNPs and haplotypes with a higher level of negative and cognitive symptoms in schizophrenia (DeRosse et al., 2006; Fanous et al., 2005; Wessman et al., 2009; Wirgenes et al., 2009). When compared with non-carriers, patients carrying *DNTBP1* SNPs showed a greater decline in general cognitive ability from the premorbid to the clinical state (Burdick et al., 2007) and a lower general cognitive ability in the clinical state (Burdick et al., 2006). These findings are in agreement with other evidence of *DTNBP1* haplotypes influencing prefrontal brain function (Donohoe et al., 2007; Fallgatter et al., 2010; Luciano et al., 2009; Markov et al., 2009), as well as an association of a three-marker C–A–T dysbindin haplotype with significant reductions of gray matter volumes in both the right dorsolateral prefrontal and left occipital cortices (Donohoe et al., 2009).

Dysbindin-1 mRNA and protein expression are reduced in the DLPFC (Weickert et al., 2004) and hippocampus (Talbot et al., 2004; Weickert et al., 2008) of schizophrenic patients. The changes in mRNA were associated with *DNTBP1* risk haplotypes, suggesting these variants would act as *cis*-elements to decrease dysbindin-1 mRNA levels (Bray et al., 2005; Weickert et al., 2008, 2004). A recent study demonstrated that American schizophrenia patients had less dysbindin-1C protein, but not dysbindin-1A or -1B, in the DLPFC. However, the protein change was not associated with reductions in dsybindin-1C mRNA expression or the only *DNTBP1* risk haplotype reported in the United States (Tang et al., 2009a).

4.2. Molecular biology

The human *DTNBP1* gene spans approximately 140 kb on chromosome 6p22.3, has 10 exons, and has yet to be classified into any known gene family. It encodes the first known member of the dysbindin protein family, dysbindin-1, a coiled-coil-containing protein that is widely distributed in the brain (Guo et al., 2009). It is concentrated in synapses of brain areas commonly affected in schizophrenia, including the hippocampus, striatum, and cortex (Benson et al., 2001; Talbot et al., 2006); gene expression occurs in cortical pyramidal neurons (Talbot et al., 2004). There are three major dsybindin-1 isoforms, dysbindin-1A, -1B, -1C that are the product of *DNTBP1* (Tang et al., 2009a). These isoforms have distinct distribution patterns in human brain syanptosomes. Dysbindin-1A is almost exclusively associated with PSDs, dysbindin-1B is nearly found only with synaptic vesicles, and dysbindin-1C is mainly associated with the PSD and to a lesser extent with synaptic vesicles (Tang et al., 2009a). Isoform A is the full-length dysbindin-1 (315 amino acids in humans). Isoform B (303 amino acids) is not expressed in the mouse and differs from A only in its C-terminal region, while isoform C (270 amino acids) differs from isoform A only in the absence of an N-terminus region in its coiled-coil domain (Tang et al., 2009a).

In mouse brain, specifically the cortex and hippocampus, endogenous levels of dysbindin protein are developmentally reg-

ulated, with higher levels observed during embryonic and early postnatal periods than in young adulthood (Ghiani et al., 2009). This time-course of expression suggests that dysbindin is important for proper neural development. Moreover, using an electrophysiology-based genetic screen in Drosophila (the neuromuscular junction of Drosophila is a glutamatergic synapse used as a model of homeostatic signaling in the nervous system), it was found that dysbindin is essential for adaptive neuroplasticity, such that it is required presynaptically for the retrograde, homeostatic modulation of neurotransmission and functions downstream or independently of calcium influx (Dickman and Davis, 2009).

4.3. Protein interactions

4.3.1. Dystrophin-associated protein complex

Dysbindin-1 was initially found to interact with α- and β-dystrobrevin (DTNA, DTNB) in the muscle and brain of mice, respectively (Benson et al., 2001). DTNA is highly expressed in skeletal muscle, while DTNB is abundantly expressed in the brain (particularly in the hippocampus and cortex), kidney, liver, and lung. DTNA and DTNB are members of the multifunctional dystrophin-associated protein complex (DPC) that links the cytoskeleton to the extracellular matrix and serves as a scaffold for signaling proteins (Benson et al., 2001).

4.3.2. Biogenesis of lysosome-related organelle complex-1

Dsybindin is also a critical component of the biogenesis of lysosome-related organelle complex-1 complex (BLOC-1), a 200-kDa ubiquitously expressed soluble protein complex involved in intracellular membrane trafficking and organelle biogenesis. Dsybindin-1 interacts with all seven known components of BLOC-1 (Nazarian et al., 2006). Recent biochemical evidence suggests that in mouse brain, the bulk of dysbindin exists as a stable component of BLOC-1 (Ghiani et al., 2009). Six proteins that are predicted to interact with BLOC-1 are involved in membrane fusion of the synaptic vesicle (Guo et al., 2009). Brain-derived BLOC-1 interacts with a few members of the soluble *N*-ethalmaleimide-sensitive factor attachment protein receptor (SNARE) superfamily of proteins including, SNAP-25 and syntaxin 13, which control membrane fusion (Ghiani et al., 2009). In addition, BLOC-1 plays a role in neurite outgrowth, as neuronal cultures derived from BLOC-1 deficient mice displayed impairment in this process (Ghiani et al., 2009).

4.4. Sandy mice

Sandy mice arose from spontaneous mutation in a DBA/2J stock and carry a *DTNBP1* allele encoding a protein with an in-frame 22-residue deletion (Li et al., 2003). These null mice display behavioral abnormalities consistent with certain schizophrenia intermediate phenotypes, including deficits in social interaction (Feng et al., 2008), enhanced stimulant sensitization (Bhardwaj et al., 2009), and poor performance in certain simple memory tasks (Bhardwaj et al., 2009; Cox et al., 2009). They also have deficits in working memory tasks, such as an operant delayed-non-match to position tasks (Jentsch et al., 2009) and a T-maze forced alternation task (Takao et al., 2008).

4.5. Regulation of neurotransmission

Circuits involving glutamatergic pyramidal neurons and local inhibitory interneurons within the PFC have essential roles in the encoding and maintenance of information in working memory (Fuster, 2001). Glutamate-dependent recurrent excitation within this circuit has been attributed to the increased activity in the PFC during maintenance of information within memory (Compte et al., 2000). Electrophysiological recordings from deep layer pyramidal neurons in the mPFC of Sandy mice revealed reductions in paired pulse facilitation as well as evoked and miniature excitatory postsynaptic currents, which are indicative of deficiencies in the functioning of presynaptic glutamatergic terminals (Jentsch et al., 2009). The electrophysiological impairments in Sandy mice are in agreement with previous findings of dysbindin acting as a positive modulator of glutamate release (Chen et al., 2008; Numakawa et al., 2004). These data provide evidence of a role for dysbindin in modulating glutamatergic transmission in the PFC, potentially through a presynaptic mechanism, thereby regulating cognitive processes dependent on this brain region.

The role of dysbindin in regulating prefrontal circuitry was also investigated in regard to dopaminergic and GABAergic transmission (Ji et al., 2009). Cortical neurons cultured from dysbindin knockout mice (derived from original Sandy mice) showed robust increases in the D2 dopamine receptor, but not the D1 dopamine receptor, on the cell surface. The elevated surface level of D2 receptors was due to enhanced recycling and insertion, rather than reduced endocytosis. Consistent with elevated D2 signaling, dysbindin deficiency decreased inhibitory input to pyramidal neurons in layer V of the PFC, while fast-spiking interneurons in the PFC from dysbindin knockout mice were more sensitive to D2 agonists in regard to firing frequency. Moreover, dysbindin knockout mice had reduced excitability of fast-spiking GABAergic interneurons in both the PFC and striatum. In sum, these results suggest that dysbindin regulates PFC function by facilitating D2-mediated modulation of GABAergic transmission.

In addition to regulating cell-surface expression of D2 receptors, dysbindin also controls the trafficking of NMDA receptors in the hippocampus (Tang et al., 2009b). Dysbindin null mice had increased NR2A, but not NR2B, subunit surface expression that was accompanied by increased NR2A-mediated synaptic currents and enhanced LTP at CA1 synapses. However, basal AMPA receptor currents, basal synaptic transmission, presynaptic properties and LTD were unaffected in dysbindin deficient mice. These findings identify a link between dysbindin and NMDA receptor function via trafficking.

5. AKT1

5.1. Akt1 and schizophrenia

The first evidence for an association between variants of V-akt murine thymoma viral oncogen homolog 1 (*AKT1*) and schizophrenia came in 2004 (Emamian et al., 2004). In families of European descent, the most significantly associated SNP was rs3730358 in intron 3, with one haplotype (rs1130214–rs3730358–rs2498799, alleles T–C–G) spanning introns 2–7 that was over-transmitted to affected offspring (1.8:1). Since the initial report, the association between *AKT1* and schizophrenia has been replicated in multiple independent studies from diverse populations, including European (Schwab et al., 2005; Tan et al., 2008; Thiselton et al., 2008), Japanese (Ikeda et al., 2004), Chinese (Xu et al., 2007b), and Iranian (Bajestan et al., 2006). However, not all studies have replicated this association, including those sampling Asian and Finnish populations (Ide et al., 2006; Liu et al., 2006; Ohtsuki et al., 2004; Turunen et al., 2007). Another study found that although there was no association between schizophrenia and single markers of *AKT1*, they found weak evidence for association with two previously studied haplotypes, suggesting that the evidence for association of *AKT1* as a susceptibility gene for schizophrenia is weakly positive (Norton et al., 2007). Given the diverse range of ethnicities studied so far, lack of consistency of the patterns of association between studies is potentially explicable in terms of population differences in LD and modest power to detect weak genetic effects (Norton et al., 2007).

Additional evidence in humans linking Akt1 to the pathophysiology of schizophrenia comes from biochemical and imaging studies. Akt1 protein levels and phosphorylation of one of its substrates, GSK3β, were reduced in the hippocampus and frontal cortex, as well as in the peripheral lymphocytes of patients with schizophrenia (Emamian et al., 2004). Moreover, the same study found that the *AKT1* core risk haplotype (rs1130214–rs3730358, T–C) was associated with lower Akt1 protein levels in lymphocyte-derived cell lines of schizophrenia patients. *Post mortem* data revealed that Akt1, but not Akt2 or Akt3, mRNA expression was lower in the prefrontal cortex of patients with schizophrenia, but not in bipolar disorder (Thiselton et al., 2008). Individuals carrying a haplotype associated with schizophrenia had significantly reduced Akt1 protein levels in the PFC as compared to non-carriers, although there was no difference in Akt1 protein levels when the comparison was made between controls and subjects with schizophrenia (Karege et al., 2010). Finally, healthy subjects that were minor allele (G/A) carriers of the synonymous coding SNP rs1130233 in *AKT1* (associated with increased risk for schizophrenia in a family-based associated study) had impaired cognitive performance, reduced protein levels of Akt1 in peripheral lymphoblasts, inefficient task-related activation of the DLPFC, and reduced gray matter volume in the bilateral caudate and right PFC (Tan et al., 2008).

Furthermore, Akt1 KO mice strengthen the argument for the involvement of this kinase in the etiology of schizophrenia (Balu et al., 2010) Mice lacking Akt1 display behavioral and neuronal abnormalities pertinent to schizophrenia, such as impaired PPI and working memory, as well as reduced synaptic plasticity and dendritic spine density (for review see: Desbonnet et al., 2009).

5.2. Molecular biology

In rodents and humans, there are three isoforms of the serine/threonine kinase Akt: Akt1/PKBα, Akt2/PKBβ, and Akt3/PKBγ, which share a high degree of sequence homology and are encoded by distinct genes (Coffer et al., 1998; Murthy et al., 2000). Akt shows the most similarity to protein kinase A (PKA) and protein kinase C (PKC), and thus has also been termed protein kinase B (PKB). Akt2 and Akt3 are approximately 82% identical with Akt1, although Akt3 lacks 23 amino acids at the C-terminus compared with the others (Konishi et al., 1995). Preliminary analyses of the three gene products support the notion that these isoforms have similar biochemical characteristics (Coffer et al., 1998). However, despite their significant homology, mouse genetics have revealed that the Akt isoforms regulate distinct physiological functions. Akt1 deficient mice display impaired overall growth (Cho et al., 2001b), whereas Akt2 null mice are insulin intolerant, demonstrating a diabetes-like syndrome (Cho et al., 2001a). Akt3 deficient mice display normal growth and glucose homeostasis, but have a selective reduction in brain size (Easton et al., 2005).

5.3. Akt signaling and neuroplasticity

Canonical Akt activation involves its recruitment to the plasma membrane by phosphorylated 3,4,5-phosphatidylinositol, followed by phosphorylation of its regulatory sites by phosphatidylinositol-dependent kinase-1 (PDK-1) on threonine 308 and by PDK-2/rictor-mTOR complex on serine 473 (Beaulieu et al., 2009).

The PI3K-Akt cascade receives input from many extracellular stimuli, including growth and neurotrophic factors, as well as neuronal activity. Akt phosphorylates (activates) the mTOR–raptor complex, which facilitates protein synthesis needed for such processes as synapse formation and cell growth (Asnaghi et al., 2004). Akt also phosphorylates (inhibits) the constitutively active serine/threonine kinase GSK3, of which there are two isoforms, GSK3α and GSK3β. Inhibition of GSK3 changes the ratio between anti-apoptotic protein BCL2 and the pro-apoptotic protein Bax, leading to increased cell survival. Inhibition of GSK3 also prevents the catabolism of multiple proteins, including β-catenin, a multifunctional protein that can serve as a transcription factor as well as a scaffolding protein in the formation of adherens junctions. As a scaffolding molecule, β-catenin interacts with cadherins and α-catenin to anchor the junctional complex with the actin cytoskeleton. β-catenin is recruited to dendritic spines following depolarization, suggesting it plays an important role in activity-dependent synaptic plasticity (Murase et al., 2002). As a transcription factor, β-catenin promotes the transcription of Wnt-dependent genes that regulate various aspects of central nervous system development (Ciani and Salinas, 2005; Logan and Nusse, 2004).

5.4. Akt and dopaminergic transmission

In addition to lying downstream of growth factor and neurotrophin receptors, Akt is also directly downstream of dopamine receptor activation. Genetic (mice lacking the dopamine transporter) and pharmacologic (treatments with methamphetamine or apomorphine) manipulations that stimulate dopaminergic neurotransmission, reduce Akt phosphorylation/activity and activate both GSK3α/β in the striatum (Beaulieu et al., 2004). Further investigation revealed that Akt and GSK3α/β are regulated by D2-, but not D1-class dopamine receptors. Regulation of this pathway is independent of cAMP signaling (Beaulieu et al., 2004), and is instead mediated by β-arrestin2. D2-receptor activation results in the formation of a complex of at least β-arrestin2, protein phosphatase-2 (PP2A), and Akt, whereby PP2A deactivates Akt and stimulates GSK3 signaling (Beaulieu et al., 2005). This inverse relationship is further substantiated by the fact that mice treated with the first-generation antipsychotic haloperidol, a D2 receptor antagonist, displayed increased phosphorylation of both total Akt and GSK3β in the brain (Emamian et al., 2004). Data from mice deficient in Akt1, suggest that Akt function is also important for proper dopaminergic neurotransmission as well as dopamine-dependent behaviors (Emamian et al., 2004; Lai et al., 2006).

6. Brain-derived neurotrophic factor

6.1. BDNF and schizophrenia

Variants in the gene encoding brain-derived neurotrophic factor (BDNF), which is located on chromosome 11p13, have been studied extensively for association with schizophrenia. The most extensively studied SNP is rs6265 that produces a G/A amino acid substitution (Valine to Methionine) at codon 66 (Val66Met). Val66Met is a functional polymorphism that affects the activity-dependent secretion of BDNF in neuronal cell cultures (Chen et al., 2006). Allele status affects human hippocampal function (Egan et al., 2003) and episodic memory (Dempster et al., 2005; Egan et al., 2003). Association studies between the functional SNP Val66Met and schizophrenia have generated conflicting results. While modest associations between rs6265 were found in Chinese (Hong et al., 2003) and Caucasian (Neves-Pereira et al., 2005) populations, many other studies have reported negative findings (Gratacos et al., 2007; Jonsson et al., 2006; Kanazawa et al., 2007; Xu et al., 2007a), suggesting the existence of an association, albeit of low increased risk and likely including multiple causal variants. A $(GT)_n$ dinucleotide repeat was identified 1 kb upstream from the transcription start site in BDNF (Proschel et al., 1992). This repeat was found to be associated with schizophrenia in Caucasian subjects (Muglia et al., 2003), but other studies have not found such an association (Hawi et al.,

1998; Virgos et al., 2001). Another study found SNP C270T in the 5′ non-conding region and detected a significant association with schizophrenia in Japanese subjects (Nanko et al., 2003). A recent meta-analysis indicated that the T allele of C270T and the rs6265 homozygous state were associated with the disorder (Jonsson et al., 2006).

Association between the *BDNF* alleles and brain morphology in schizophrenia have indicated that Met-allele carriers as compared to Val-homozygotes tend to have reduced gray matter volumes in the hippocampus (Takahashi et al., 2008), as well as in the temporal and occipital cortices (Ho et al., 2006); although not all studies have found such an association (Koolschijn et al., 2009). In patients with schizophrenia, Met-carriers had greater reductions in frontal gray matter volume and excessive increases in lateral ventricle and sulcal CSF volume over time compared with Val-homozygotes (Ho et al., 2007). Although a recent study found that schizophrenic patients had smaller hippocampal volumes compared with healthy controls at baseline, BDNF genotype was not associated with hippocampal volume change over time in patients or healthy controls (Koolschijn et al., 2009).

The ability of BDNF to cross the blood-brain barrier (Pan et al., 1998) suggests that BDNF blood levels may reflect BDNF levels in the brain. The majority of studies report decreased serum BDNF levels in first-episode (Buckley et al., 2007; Chen et al., 2009; Rizos et al., 2008) and chronically treated (Grillo et al., 2007; Ikeda et al., 2008; Zhang et al., 2007) schizophrenic patients, suggesting that peripheral BDNF levels could serve as a potential biomarker for the disease.

In *post mortem* studies, the expression of BDNF mRNA (Weickert et al., 2003), particularly in layers II, III, and V/VI, and protein (Hashimoto et al., 2005; Weickert et al., 2003) was reduced in the DLPFC of subjects with schizophrenia. There was also a positive correlation between reduced BDNF mRNA levels and reduced spine density on basilar dendrites of deep layer 3 pyramidal neurons in the same subjects with schizophrenia (Hill et al., 2005). It was recently demonstrated that expression of a particular BDNF transcript, BDNF II–IX, as well as protein levels (pre-pro, pro, and mature BDNF) were reduced in the DLPFC of patients with schizophrenia (Wong et al., 2010). However, other studies have found an increase (Durany et al., 2001) or no change (Takahashi et al., 2000) in BDNF protein levels in the frontal cortex of schizophrenic patients. The amount of mRNA (Hashimoto et al., 2005; Weickert et al., 2005) and protein (Takahashi et al., 2000) of tropomysin receptor kinase B (TrkB), the cognate receptor of BDNF, were reduced in the hippocampus and cortex of subjects with schizophrenia. The reductions in mRNA expression levels of TrkB and glutamic acid decarboxylase of 67 kDa (GAD67) were significantly correlated with each other in the same individuals with schizophrenia; this correlation was significantly stronger than that between BDNF and GAD67 mRNAs (Hashimoto et al., 2005).

6.2. Molecular biology

6.2.1. Transcriptional regulation

The *BDNF* gene is comprised of at least eight distinct promoters leading to the transcription of numerous unique mRNA transcripts, in a developmental, tissue-specific, and activity-dependent manner. Each transcript contains one of eight alternative 5′ untranslated exons spliced to a common 3′ coding exon (IX) that contains the entire open reading frame for the BDNF protein (Aid et al., 2007). *BDNF* transcripts are also polyadenylated at either of two alternative sites that leads to two populations of mRNAs (Timmusk et al., 1993), one containing a short 3′ untranslated region (UTR) that is restricted to the soma, and the other with a long 3′ UTR that is targeted to dendrites for local translation (An et al., 2008). This complex regulation at the level of promoters, splicing, and polyadenylation sites results in the production of at least 18 transcripts, all of which encode one identical BDNF protein product.

6.2.2. Protein regulation

The cellular actions of BDNF can also be regulated at the level of peptide processing. BDNF is initially synthesized as a precursor protein (preproBDNF) in the endoplasmic reticulum.

Once the signal peptide is cleaved, proBDNF is transported to the Golgi apparatus for sorting into either constitutive or regulated secretory vesicles. ProBDNF can be converted into mature BDNF (mBDNF) intracellularly in the trans-Golgi by endoproteases or in immature secretory granules by proprotein convertases (Mowla et al., 1999). Recent evidence suggests that secreted proBDNF is converted extracellularly to mature BDNF by tissue plasminogen activator (tPaA), a serine protease, in an activity-dependent manner (Nagappan et al., 2009).

6.2.3. Intracellular signaling

BDNF plays an important role in neuronal differentiation during development, as well as in synaptic plasticity and neuronal survival in the adult brain (Binder and Scharfman, 2004). Mature BDNF regulates this vast array of processes by signaling through its high-affinity receptor, TrkB. Each receptor traverses the membrane once and is terminated with a cytoplasmic domain that contains a tyrosine kinase domain surrounded by several tyrosines that serve as phosphorylation-dependent docking sites for cytoplasmic adaptors and enzymes. BDNF binding causes the TrkB receptor to dimerize, resulting in activation through trans-phosphorylation of the kinases present in their cytoplasmic domains. However, due to differential splicing, there are two additional TrkB isoforms that have comparatively short cytoplasmic domains that lack tyrosine kinase activity (Reichardt, 2006). These truncated receptors can inhibit BDNF-mediated dimerization and activation of full-length receptors (Eide et al., 1996), but there is evidence that the BDNF can activate and signal via the truncated TrkB isoform (Rose et al., 2003).

Phosphorylation of other tyrosine residues creates docking sites for adaptor molecules containing phosphotyrosine binding (PTB) or Src-homology-2 (SH2) domains. The three major intracellular signaling pathways activated by the Trk receptors are: the Ras–MAPK pathway, PI3K–Akt pathway, and the phospholipase Cγ1 (PLCγ1)–Ca^{2+} pathway (Huang and Reichardt, 2003), all of which can regulate gene transcription. MAPK signaling promotes neuronal differentiation and growth via MAPK/ERK kinase (MEK) and extracellular signal-related kinase (ERK), while PI3K promotes the survival and growth of neurons, as well as axon growth and pathfinding. PLCγ1-dependent generation of IP3 and diacylglycerol (DAG) results in the mobilization of Ca^{2+} stores and subsequent activation of Ca^{2+}/calmodulin dependent kinases (CaMKs; CaMKII, CaMK kinase, CaMKIV) and protein kinase C (PKC) isoforms, respectively.

ProBDNF signals through the pan neurotrophin receptor 75 ($p75^{NTR}$). It is a member of the tumour necrosis receptor superfamily with an extracellular domain, a single-transmembrane domain, and a cytoplasmic domain that includes a 'death' domain (important for apoptotic signaling) similar to those present in other members of this family. Although this receptor does not contain a catalytic motif, it interacts with several proteins that transmit signals important for regulating neuronal survival and differentiation and synaptic plasticity.

6.3. Regulation of the GABAergic system

6.3.1. Developmental regulation of interneurons

Proper functioning of the CNS results from the establishment of precise synaptic connections between neurons during devel-

opment. This occurs through a complex, multistep process that involves neurogenesis, migration, differentiation, and synaptogenesis. BDNF has been implicated in regulating many of these processes for the development of GABAergic interneurons in the cortex, even though interneurons only express TrkB receptors, not BDNF (Gorba and Wahle, 1999). BDNF promotes dendritic elongation and branching of interneurons (Kohara et al., 2003), as well as the formation of inhibitory synapses (Vicario-Abejon et al., 1998). BDNF elicits changes in presynaptic GABAergic terminals, including the up-regulation of the presynaptic proteins syntaxin, synaptobrevin, and synaptophysin (Yamada et al., 2002), as well as the rate-limiting enzyme of GABA synthesis, GAD67 (Mizuno et al., 1994). Postsynaptically, BDNF up-regulates the protein levels of $GABA_A$ receptors (Yamada et al., 2002). BDNF also affects the maturation of GABAergic interneurons. In transgenic mice over-expressing BDNF, the maturation of PV-positive interneurons was significantly accelerated (Huang et al., 1999).

TrkB itself is also an important regulator of GABAergic development. TrkB hypomorphic mice had significantly reduced levels of GAD67 and PV, but not calretinin mRNA in the PFC (Hashimoto et al., 2005). The density of neurons with detectable levels of GAD67 mRNA was reduced, but the expression level per neuron was unchanged (Hashimoto et al., 2005). However, the role BDNF plays in regulating the expression levels of PV and GAD67 mRNAs is less well defined. While adolescent homozygous BDNF knockout mice had fewer PV-positive interneurons than wildtype mice (Altar et al., 1997; Jones et al., 1994), there were no differences in the expression of GAD67 or PV mRNAs in the PFC of adult mice lacking BDNF specifically in neurons, either when BDNF knockdown occurred during embryogenesis or adulthood (Hashimoto et al., 2005). However, a recent study found that specific disruption of promoter IV-dependent BDNF transcription reduced the number of PV interneurons in the PFC, but not in the motor cortex (Sakata et al., 2009).

6.3.2. GABAergic transmisson

TrkB is more abundantly expressed in PV-containing interneurons than in calbindin or calretinin-positive interneurons (Gorba and Wahle, 1999). There are two major types of PV interneurons that regulate the activity of a large number of excitatory pyramidal neurons: basket cells that innervate somatic segments and chandelier cells that innervate axon initial segments (Benes and Berretta, 2001). Both classes of PV cells have strong negative control over pyramidal cells due to their ability to generate high-frequency, non-adapting (fast-spiking) action potentials (Lewis and Gonzalez-Burgos, 2008). It is this unique feature that allows these interneurons to synchronize large-scale network oscillations (Woo and Lu, 2006). Neuronal synchronization is believed to be important for PFC-mediated working memory (Chudasama and Robbins, 2006).

Recent studies have examined the ability of BDNF to regulate the excitability of interneurons both in the PFC and the hippocampus. BDNF promoter IV is well characterized in its role as being responsive to activity-mediated transcription (Greer and Greenberg, 2008). In addition to affecting the number of PV interneurons, specific disruption of promoter IV transcription impaired inhibitory (amplitude and frequency of spontaneous inhibitory postsynaptic currents; sIPSCs), but not excitatory synaptic transmission in layer V PFC pyramidal neurons (Sakata et al., 2009). Interestingly, BDNF appears to exert the opposite effect on inhibitory transmission in dentate gyrus granule cells of the mouse hippocampus (Holm et al., 2009). Mature, but not pro-, BDNF decreased sIPSC frequency of granule cells and reduced the excitability of fast-spiking GABAergic interneurons in the dentate gyrus. Moreover, the effects of BDNF on dentate GABAergic transmission were mediated by the TrkB receptor, not the $p7^{NTR}$; PV interneurons in the dentate gyrus do not express $p75^{NTR}$. However, it should be noted that the methods used to manipulate BDNF signaling between the PFC and hippocampal studies were quite different. These results highlight the complexity of BDNF signaling on inhibitory neurotransmission and demonstrate the brain region, cell-type, and activity-dependent specificity of its effects.

6.4. Regulation of glutamatergic transmission

Many of the effects of BDNF on synaptic plasticity at glutamatergic synapses are believed to occur through the activation of TrkB-dependent signaling cascades that regulate ion channels (Minichiello, 2009). TrkB receptors have been found in the axons, nerve terminals, and dendritic spines of glutamatergic pyramidal neurons and granule cells in the hippocampus (Drake et al., 1999), as well as in the dendritic spines of cortical neurons (Aoki et al., 2000). BDNF modulates glutamatergic synaptic transmission through both presynaptic and postsynaptic mechanisms. Biochemical (Sala et al., 1998) and electrophysiological (Tyler and Pozzo-Miller, 2001) evidence suggests that BDNF facilitates the release of presynaptic glutamate via TrkB receptor activation, although the mechanism by which this occurs remains largely unknown (Minichiello, 2009). Postsynaptically, TrkB receptor activation directly and indirectly modulates glutamate receptor function. NMDA receptor channel open-probability is increased by either increased NR2B subunit tyrosine phosphorylation or by the protein tyrosine kinase Fyn, which when activated by TrkB, interacts with the NMDA receptor to modulate activity (Levine et al., 1998). BDNF/TrkB-dependent cation influx through transient receptor potential channels (TRPC), which alters membrane potentials, could also facilitate synaptic Ca^{2+} entry through NMDA receptors (Minichiello, 2009). BDNF has been shown to modulate AMPA receptor expression and trafficking (Caldeira et al., 2007), with the latter dependent on Ca^{2+} mobilization from IP3-sensitive internal stores (Nakata and Nakamura, 2007).

6.4.1. Long-term potentiation

LTP, which is defined as a persistent increase in synaptic strength, can be either NMDA receptor-dependent or NMDA receptor-independent. LTP can also be divided into three sequential phases: short term potentiation, early LTP (E-LTP), and late LTP (L-LTP). Short-term and E-LTP, unlike L-LTP, are both transient and do not require gene transcription and *de novo* protein synthesis (Kandel, 2001). There has been much recent evidence demonstrating the importance of BDNF–TrkB signaling in regulating adult hippocampal LTP, particularly during the E-LTP and L-LTP phases (Minichiello, 2009). BDNF appears to facilitate L-LTP by stimulating the synthesis and rapid dendritic trafficking of mRNA encoded by the immediate early gene, activity-regulated cytoskeleton-associated protein (Arc) (Messaoudi et al., 2007). In addition to hippocampal LTP, BDNF–TrkB signaling modulates synaptic plasticity in other brain regions, including the amygdala (Ou and Gean, 2006) and nucleus accumbens-VTA (Russo et al., 2009).

6.4.2. Long-term depression

Long-term depression (LTD) is another form of excitatory synaptic plasticity that is defined as a persistent decrease in synaptic strength, and like LTP, can be NMDA receptor-dependent and independent. Activation of $p75^{NTR}$ by pro-BDNF has been shown to facilitate NMDA receptor-dependent LTD in the hippocampus (Woo et al., 2005) and genetic perturbation of $p75^{NTR}$ leads to altered protein expression of certain AMPA receptor (Rosch et al., 2005) and NMDA receptor subunits (Woo et al., 2005).

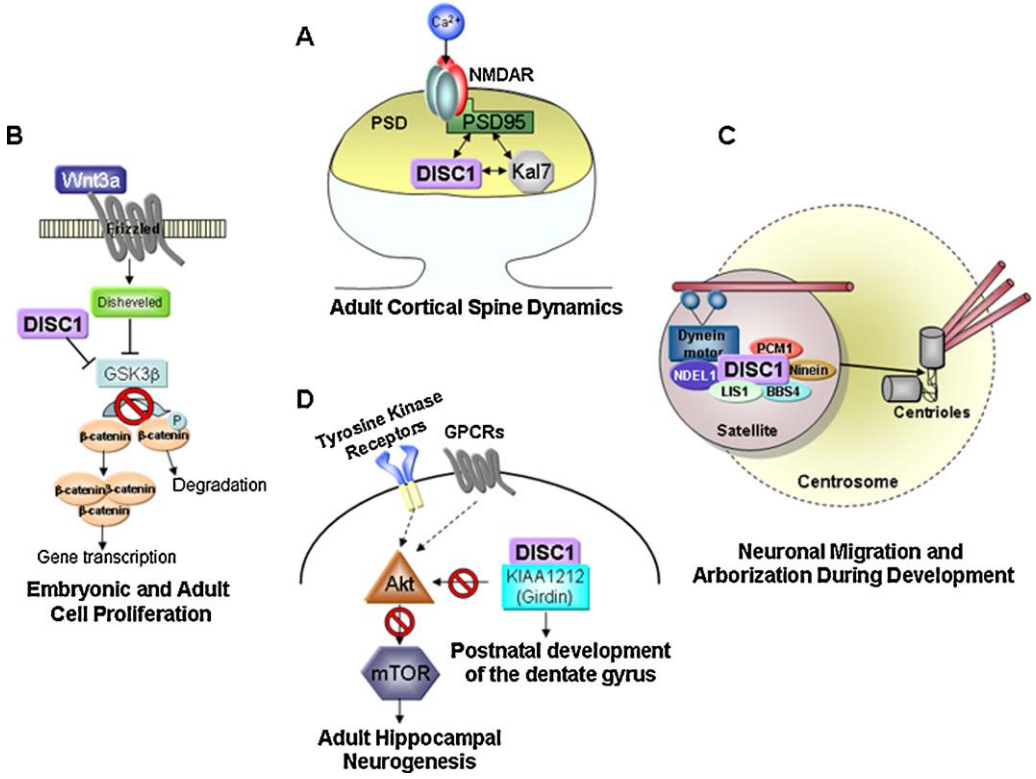


Fig. 1. DISC1 regulates many aspects of neuroplasticity during development and adulthood. (A) Disrupted in schizophrenia 1 (DISC1) is located in the postsynaptic density (PSD) of excitatory cortical neurons. It directly interacts with the anchoring molecule PSD 95 kDa (PSD95) and kalirin-7 (Kal-7), a GDP/GTP exchange factor for the small G protein Rac1, a well-known regulator of spine morphology and plasticity. This complex is modulated by *N*-methyl-D-aspartate receptor (NMDAR)-dependent activity, which regulates Rac-1 mediated changes in spine morphology. (B) DISC1 regulates proliferative activity during development and in the adult hippocampus via modulation of the canonical Wnt/β-catenin signaling pathways. DISC1 directly binds to, and inhibits the activity of glycogen synthase-3β (GSK3β). This consequently increases the cytosolic concentration of β-catenin, potentiates Wnt3a signaling, and increases cell proliferation. (C) DISC1 is part of the centrosome, where it anchors other proteins such as pericentriolar material 1 (PCM1), nudE-like 1 (NDEL1), lissencephaly 1 (LIS1), Bardet–Biedl syndrome protein 4 (BBS4), and ninein to the dynein–motor complex. DISC1 is important for proper functioning of this complex, which is critical for neuronal migration and neurite outgrowth. (D) In the postnatal hippocampus, through its interaction with the actin binding protein, girdin, DISC1 regulates neuronal positioning and migration, as well as axonal development. DISC1 modulates neurogenesis in the dentate gyrus of the adult hippocampus, a brain region that retains the capacity to produce neurons throughout adulthood. DISC1 controls the timing of integration, dendritic arborization, and soma size of the newborn neurons. It does this by binding to, and inhibiting KIAA1212 (also known as girdin), an activator of Akt. This leads to reduced Akt signaling and reduced activation of its downstream substrate, mammalian target of rapamycin (mTOR).

7. NMDA receptor

7.1. NMDA receptor and schizophrenia

Dissociative anesthetics such as ketamine and phencyclidine (PCP) have been known for 50 years to produce in adults a syndrome difficult to distinguish from schizophrenia (Luby et al., 1959). While these drugs have complex interactions in the nervous system, it was noted that the psychotomimetic effects of PCP occurred at plasma concentrations that cause a non-competitive, use-dependent antagonism of NMDA receptors (Javitt and Zukin, 1991). Ketamine infused in normal volunteers produces the full range of signs and symptoms of schizophrenia (Krystal et al., 1994), as well as the physiologic abnormalities associated with schizophrenia, including abnormal event-related potentials (Umbricht et al., 2000), eye-tracking abnormalities (Radant et al., 1998) and enhanced subcortical dopamine release (Kegeles et al., 2000). Moreover, individuals with stabilized schizophrenia exhibit marked sensitivity to ketamine with recurrence of individual specific symptoms (Lahti et al., 2001).

Recent genetic studies support a role for NMDA receptors in the etiology of schizophrenia. Most of the evidence is derived from association studies, although this strategy has come under criticism by advocates of "unbiased" GWAS strategy. Meta-analysis has strongly implicated the gene encoding D-amino acid oxidase (DAAO), which regulates the availability of D-serine, as well as G72, a gene encoding a protein that binds to and inhibits DAAO (Lisman et al., 2008). Meta-analysis has also pointed to the NR2B subunit, a component of the NMDA receptor, as a risk gene for schizophrenia (Allen et al., 2008).

7.2. Structure and function of the NMDA receptor

The NMDA receptor is a critical postsynaptic mediator of activity-dependent synaptic plasticity. Throughout most of the brain, the heterotetrameric receptor is composed of two NR1 subunits and two NR2 subunits, all of which contribute transmembrane domains to the pore of the ion channel that is characterized by high Ca^{2+} permeability. The NR1 subunit has eight different splice variants, which may affect channel function differently by associating with different intracellular signaling pathways (Bradley et al., 2006). NR2 subunits may be expressed in four different forms (NR2A-D), and in some regions of the nervous system may be substituted by two different forms of NR3 subunits, each of which confer different biophysical and pharmacologic properties to the channel (Lynch and Guttmann, 2001). NMDA receptors are considered "molecular coincidence detectors" because activation requires postsynaptic depolarization (removes Mg^{2+} block in pore at resting membrane potential), and the binding of two agonists, glutamate, and either glycine or D-serine, at the glycine modulatory site (GMS; (Tsien, 2000)). The influx of Ca^{2+} through the NMDA receptor triggers a cascade of intracellular events that regulate many types of

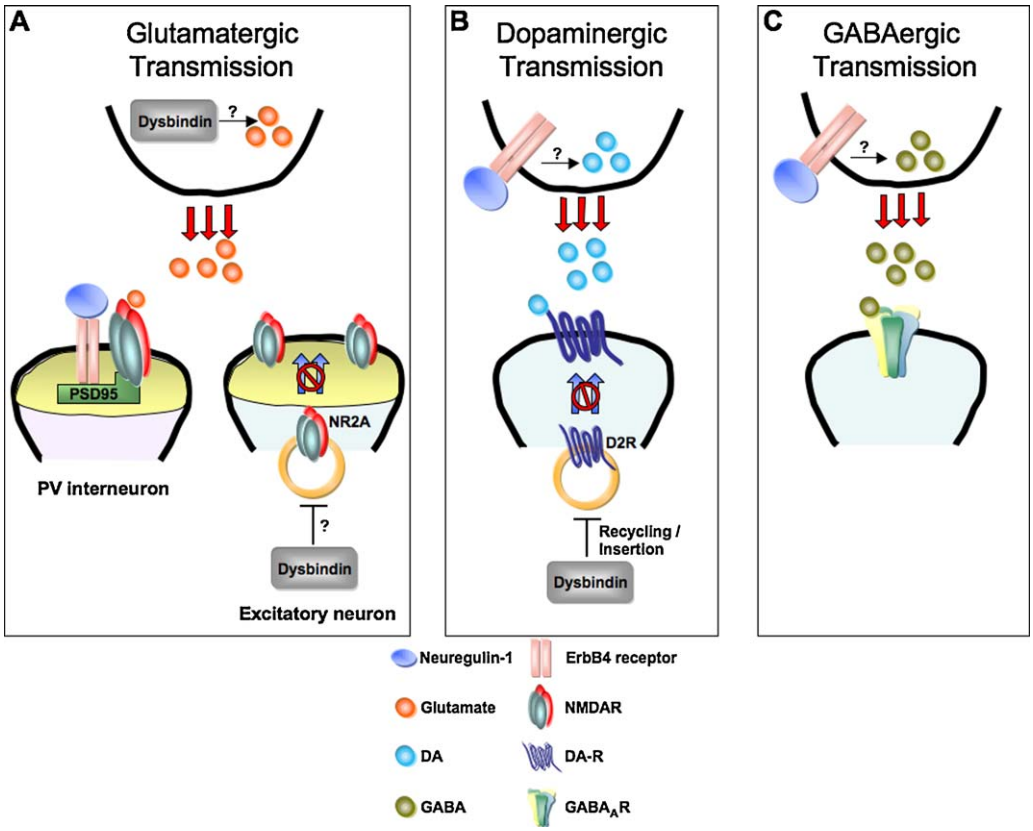


Fig. 2. Dysbindin and Neuregulin1/ErbB4 regulate multiple neurotransmitter systems. (A) Glutamatergic transmission is modulated both pre- and postsynaptically by neuregulin-1 (NRG1) and dysbindin. In the presynaptic neuron, dysbindin increases glutamate release, while postsynaptically it inhibits the surface expression of NR2A, but not NR2B, subunit containing *N*-methyl-D-aspartate receptors (NMDARs). The mechanism underlying these trafficking effects is unknown. ErbB4 interacts and co-localizes with the scaffolding protein postsynaptic density 95 kDa (PSD95). NRG1 through ErbB4 signaling suppresses the induction and expression of long-term potentiation (LTP) at glutamatergic synapses in the hippocampus. Recent evidence suggests that NRG1/ErbB4 signaling most critically impacts glutamatergic transmission onto GABAergic interneurons, namely those expressing parvalbumin (PV+). (B) With respect to dopaminergic signaling, dysbindin negatively regulates the surface expression of dopamine type-2 (D2), but not D1 receptors by affecting recycling and insertion, rather than endocytosis. NRG1 stimulates hippocampal dopamine release, however the mechanism is unknown. (C) ErbB4 is present in the presynaptic terminals of GABAergic interneurons and stimulation of these receptors by NRG1 enhances activity-dependent GABA release through presently unidentified mechanisms. In PV+ chandelier and basket cells, ErbB4 is also localized to axon terminals and PSDs that receive glutamatergic input. Furthermore, evidence suggests that NRG1/ErbB4 signaling in PV+ interneurons is important for synchronizing pyramidal cell activity in several brain regions.

neuroplasticity (Greer and Greenberg, 2008; Wayman et al., 2008), including LTP, dendritic patterning, spine elaboration and synaptogenesis, which are perturbed in schizophrenia and animal models of the disease.

D-Serine appears to be the co-agonist at NMDA receptors in the cortical limbic regions of the brain. To study the effects of reduced D-serine availability presumably associated with G72 risk variants, the gene encoding serine racemase (SR) has been knocked-out. Homozygote SR−/− mice exhibited reduced spontaneous NMDA receptor function and impaired hippocampal LTP, as well as memory impairments that are consistent with an intermediate phenotype of schizophrenia (Basu et al., 2009). At the neuroanatomical level, SR−/− mice had reduced dendritic complexity and spine density in the mPFC such that an absolute reduction of synapses approaches 50% in certain sectors. These dendritic abnormalities were accompanied by specific cognitive deficits associated with impaired prefrontal function (DeVito et al., 2010). Given that the NMDA receptor sits between presynaptic and postsynaptic risk genes described above, it may be the critical mediator of synaptic disconnection in schizophrenia.

8. Functional convergence of schizophrenia risk pathways

Schizophrenia is a disorder of complex genetics that is the product of multiple risk genes with moderate effects, combined with environmental interactions. There is substantial evidence that schizophrenia is associated with perturbations in synaptogenesis and neuroplasticity, such as deficiencies in dendritic arborization, cortical thinning, and altered connectivity of neural networks. The putative schizophrenia risk genes highlighted in this review are important regulators of neural plasticity. Not only is a single risk gene involved in numerous signaling cascades, but multiple risk genes converge to affect the same signaling pathways and biological processes. For example, the pathways highlighted here regulate NMDA receptor-dependent signaling through both presyanptic and postsynaptic mechanisms, and likely contribute to and/or are a downstream consequence of the NMDA receptor hypofunction observed in this disorder. Therefore, disturbances in one of these genes could potentially have significant effects on brain function, resulting in an intermediate phenotype, as has been demonstrated with allelic variants of the genes described here. The presence of two or more risk alleles could have multiplicative effects, especially if they functionally converge on the same processes.

There are common themes that apply to the putative risk genes outlined in this review. First, these genes regulate glutamatergic, GABAergic, and dopaminergic transmission, all of which are disregulated in schizophrenia. They do so at varying levels, from modulating presynaptic neurotransmitter release, to affecting postsynaptic receptor levels and downstream intracellular signaling cascades (Figs. 1 and 2). The alterations in synaptic transmission associated with these risk genes likely contribute to the abnormalities in brain activity and sensory processing observed

in schizophrenia. Another common theme is their importance for neuronal development, particularly migration, connectivity and cell maturation/survival. Since schizophrenia is believed to be a neurodevelopmental disorder (Weinberger, 1987), disturbances in one or more of these pathways would likely contribute to disease progression. DISC1 and NRG1/ErbB4 are critical for proper brain development, and evidence suggests that these pathways might be functionally convergent (Jaaro-Peled et al., 2009). They can both localize to the nucleus to regulate gene transcription (NRG1/ErbB4 by cleaved intracellular domains; DISC1 via activating transcription factor 4(ATF4)/promyelocytic leukemia protein (PML) transcriptional machinery), and both are constituents in the PSD of excitatory synapses (Jaaro-Peled et al., 2009). Furthermore, in the zebrafish embryo, both DISC1 and NRG1 ErbB-dependent signaling are essential for the development of oligodendrocytes (Wood et al., 2009). In addition to NRG1 signaling, Y2H screens with dysbindin have shown that it shares common protein–protein interactions with DISC1, thematically involving microtubule organization, cell division, and exocytosis, which suggests the possibility of convergence in their biological functions. Although it is tempting to speculate that aberrant functioning of DISC1 and dysbindin contribute to an increased risk for developing schizophrenia, more *in vivo* evidence is needed to test this hypothesis.

In order to determine how disregulation of common biological functions underlie the neurobiology of schizophrenia, work needs to be done to delineate exactly which pathways are convergent, when during brain development their crosstalk is critical, and where intracellularly they intersect. Making this task quite difficult is the complex transcriptional and translational regulation, as well as the time- and brain region-dependent expression of many of these proteins.

9. Concluding remarks

Elucidating the functions of putative schizophrenia risk gene products under normal conditions and how their functions are altered in schizophrenia, as well as understanding how they interact with each other and environmental risk factors, will provide new insight into the neurobiological underpinnings of schizophrenia. Moreover, this information will likely lead to an emergence of novel targets for therapeutic intervention directed at reversing deficiencies in neuroplasticity with hopefully improved clinical outcomes. Recent proof of this are agents that activate the GMS on the NMDA receptor, such as glycine, D-serine and D-cycloserine that have been shown in preclinical studies and in clinical trials (Davis et al., 2006) to enhance cognition as well as reduce negative symptoms in schizophrenia (Tsai and Lin, 2010).

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