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Developmental Vulnerability of Synapses and Circuits Associated with Neuropsychiatric Disorders

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Abstract

Psychiatric and neurodegenerative disorders, including intellectual disability (ID), autism spectrum disorders (ASD), schizophrenia (SZ), and Alzheimer's disease (AD), pose an immense burden to society. Symptoms of these disorders become manifest at different stages of life: early childhood, adolescence, and late adulthood, respectively. Progress has been made in recent years toward understanding the genetic substrates, cellular mechanisms, brain circuits, and endophenotypes of these disorders. Multiple lines of evidence implicate excitatory and inhibitory synaptic circuits in the cortex and hippocampus as key cellular substrates of pathogenesis in these disorders. Excitatory/inhibitory balance – modulated largely by dopamine – critically regulates cortical network function, neural network activity (i.e. gamma oscillations) and behaviors associated with psychiatric disorders. Understanding the molecular underpinnings of synaptic pathology and neuronal network activity may thus provide essential insight into the pathogenesis of these disorders and can reveal novel drug targets to treat them. Here we discuss recent genetic, neuropathological, and molecular studies that implicate alterations in excitatory and inhibitory synaptic circuits in the pathogenesis of psychiatric disorders across the lifespan.

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Introduction

Abnormalities in synapses of excitatory and inhibitory neurons have emerged as key cellular substrates in the pathogenesis of several psychiatric and neurodegenerative disorders (Penzes *et al.* 2011). Indeed, disease-specific disruptions in synaptic morphology and function accompany a large number of brain disorders, suggesting that such alterations may serve as substrates for many psychiatric and neurological disorders, particularly those that involve deficits in information processing. In support of this view, recent studies found altered dendritic spine density on cortical pyramidal neurons in individuals with ID, ASD, SZ and AD (Penzes *et al.* 2011). In addition, structural and functional changes in GABAergic inhibitory circuits have been described in ASD and SZ (Chattopadhyaya and Cristo 2012). Among these, dysfunction of inhibitory parvalbumin-positive (PV-positive) basket cells is thought to play a major role in both ASD and SZ (Lewis and Gonzalez-Burgos 2008; Gogolla *et al.* 2009). Alterations in GABAergic circuits in ASD are supported by findings of significantly reduced GAD65 and GAD67 in the parietal cortex and cerebellum (Fatemi *et al.* 2002; Yip *et al.* 2007) and alterations in $GABA_A$ and $GABA_B$ receptors in post-mortem brains of autistic subjects (Collins *et al.* 2006; Fatemi *et al.* 2009; Oblak *et al.* 2010), combined with reduced benzodiazepine binding to $GABA_A$ receptors (Guptill *et al.* 2007). A reduction in multipolar interneuronal dendritic length and reduced GAD67 levels occur in SZ and may underlie the dysfunction of inhibitory circuits in the disease (Kalus *et al.* 2002; Lewis *et al.* 2005; Akbarian and Huang 2006).

Here we discuss synaptic alterations in ID, ASD, SZ, and psychosis in AD (AD+P). These disorders become manifest at different stages across the life: ID and ASD in early childhood, positive SZ symptoms in adolescence and young adulthood, and AD in late adulthood (Figure 1). Although spine formation and elimination occur throughout a normal lifespan, perinatal and postnatal net synapse proliferation is followed by a period of protracted net synapse elimination that lasts throughout childhood and into adolescence in some brain regions. This is followed by synapse maintenance in the adult brain that preserves circuitry established earlier in life. Disruption of synapse morphogenesis and function during a particular time during development, or in a particular brain region, may dictate the subsequent neuropathological symptoms that arise. Thus, the timing of synapse pathology can lead to disease-specific synaptic and cellular dysfunction, neuronal circuit alterations, and ultimately cognitive and behavioral symptoms.

Consistent with the idea that synaptic circuits are common substrates of mental disorders, a multitude of genetic studies over the past few years have implicated “neuroplasticity” genes in the etiology of these disorders. Indeed, it is now widely accepted that rare (copy number variants and point mutations) and common variants in genes that control the development and plasticity of synapses and dendrites increase risk for mental disorders (Gilman *et al.* 2011; Gai *et al.* 2012; Guilmatre *et al.* 2009; Kirov *et al.* 2012).

Many psychiatric and neurological disorders are associated with disruptions of dendritic spine numbers and morphology. In the mammalian forebrain, most glutamatergic excitatory synapses occur on small protrusions on dendrites called dendritic spines (Figure 2). Changes in spine morphology occur in synaptogenesis, maintenance, plasticity and elimination.

During development, dynamic spines allow dendrites to actively participate in synaptogenesis, thereby contributing to the establishment of connectivity within neuronal circuits (Holtmaat and Svoboda 2009). Activity-dependent spine maintenance or elimination contributes to the remodeling of neuronal circuits during postnatal development and adolescence (Zuo *et al.* 2005; Alvarez and Sabatini 2007). Spines undergo experience-dependent morphological changes in live animals (Holtmaat and Svoboda 2009; Alvarez and Sabatini 2007) and spine morphology is intimately linked to human cognitive development and function (Lewis and Gonzalez 2008). Spine dynamics are regulated by molecular pathways that control cytoskeletal remodeling, trans-synaptic adhesion, receptor trafficking, protein translation, ubiquitination, and gene expression (Penzes *et al.* 2008; Tada and Sheng 2006; Penzes and Jones 2008).

In this mini-review we elaborate on recent findings presented by some of the authors at the 5th Special Neurochemistry Conference entitled “Synapses and dendritic spines in health and disease” held in Buenos Aires, Argentina. We review genetic studies that address etiology, postmortem neuropathological studies that reveal the pathophysiological outcome of the disease process, and functional studies in model systems that investigate the underlying neurobiological mechanisms. We propose that while these disorders have largely distinct symptom profiles, they collectively share the common substrate of abnormal function of synaptic circuits.

Synaptic dysfunction in ID and ASD

One of the most common neurodevelopmental disorders is ID. Patients affected by ID have an intelligence quotient of 70 or below and often exhibit deficits in behaviour related to adaptive functioning, which includes ASD. Over 25% of ID and ASD cases are caused by genetic factors (Rauch *et al.* 2006; Pinto *et al.* 2010) and up to 60% have unknown etiologies. Several single-genes causing syndromic or nonsyndromic ID have been identified over the past 15 years. Most of these genes are located on the X chromosome and are responsible for X-linked intellectual disabilities (XLID). Interestingly, more then 50% of the ID-related proteins that are not transcription or chromatin-remodelling factors are clearly present in the pre- or post-synaptic compartments and appear to be implicated in synaptic functions by regulating actin cytoskeleton rearrangement, synaptic plasticity or synapse formation (Ropers and Hamel 2005). In this review we will describe the molecular mechanisms by which dysfunctions in some of these synaptic proteins – including Shank, IL1RAPL1, oligophrenin-1 and TSPAN7 – contribute to ID and ASD.

SHANK3 haploinsufficiency is now considered to be the main cause of the neurobehavioral symptoms of the Phelan-McDermid syndrome (PMS, also called 22q13.3 deletion syndrome), although other genes may also be lost by the chromosomal deletion (Bonaglia *et al.* 2001; Wilson *et al.* 2003; Durand *et al.* 2007; Delahaye *et al.* 2009). Indeed, a number of *de novo* mutations in *SHANK3* (Durand *et al.* 2007; Moessner *et al.* 2007; Gauthier *et al.* 2009), *SHANK2* (Berkel *et al.* 2010), and in *SHANK1* (Sato *et al.* 2012) have been identified in individuals with ASD and ID. A number of knock out mice have been created for the three *SHANK* genes. The first described mouse, lacking Shank1, has small dendritic spines, weakened synaptic transmission, enhanced learning (Hung *et al.* 2008), and defects in social communication (Wöhr *et al.* 2011). In addition, more recent studies show that mice with heterozygous or homozygous disruption of Shank3 have self-injurious repetitive grooming, deficits in social interaction, alterations in learning and memory formation, and defects in synaptic transmission (Bozdagi *et al.* 2010; Peça *et al.* 2011; Wang *et al.* 2011). The behavioral defects correlate with impaired basal synaptic transmission in CA3-CA1 connections, reduced GluR1 clusters and protein levels in the hippocampus, altered activity-dependent AMPAR synaptic plasticity and major changes in striatal and cortico-striatal synapses (Bozdagi *et al.* 2010; Peça *et al.* 2011; Wang *et al.* 2011). Shank3 knocked down in

rodent neuronal cultures by RNA interference (shRNA) specifically reduced the expression of mGluR5 receptors and also impaired DHPG-induced phosphorylation of ERK1/2 and CREB (Verpelli *et al.* 2011). Finally, the Shank2 knockout mice, like their Shank3 knockout counterparts, show abnormalities in behavior tests, impairment in social activities, hyperactivity, and defects in synaptic transmission (Bockers *et al.* 2004; Schmeisser *et al.* 2012; Won *et al.* 2012). These studies demonstrate that mice with mutations in the *SHANK* genes cause alterations in synaptic morphology and signalling, as well as changes in behavior characteristics, indicating that they are good animal models for the study of ID and ASD.

Most of the XLID are attributable to the Fragile X and Rett syndromes; however, mutations of several other genes on the X chromosome have been found to strongly associate with ID, with an estimated 50% of the XLID genes coding for synaptic proteins (Laumonnier *et al.* 2007). For instance, cognitive impairments ranging from nonsyndromic ID to ASD have been found in patients with mutations in the interleukin-1 receptor accessory protein-like 1 gene (*IL1RAPL1*) (Carrie *et al.* 1999; Bhat *et al.* 2008; Piton *et al.* 2008; Franek *et al.* 2011). The IL1RAPL1 protein is structurally formed by three extracellular Ig-like domains, a transmembrane domain, and an intracellular Toll/IL-1R homology domain (TIR domain). IL1RAPL1 binds postsynaptic density protein 95 (PSD-95) and regulates its phosphorylation and synaptic association by activating the c-Jun terminal kinase (JNK) *(Pavlowsky et al. 2010)*. Instead the extracellular domain of IL1RAPL1 induces presynaptic differentiation by binding the receptor tyrosine phosphatase δ (PTPδ), which is localized at the presynaptic terminal, while the TIR domain binds to RhoGAP2 and regulates dendritic spine formation (Valnegri *et al.* 2011b; Yoshida *et al.* 2011). All these findings suggest that the IL1RAPL1 complex mediates trans-synaptic signalling that regulates excitatory synapse formation and function.

Some forms of XLID are caused by mutations or deletions in the synaptic RhoGTPase-activating protein oligophrenin-1 (Nadif Kasri and Van Aelst 2008), indicating that signalling involving member A of the Ras homologue gene family (RhoA) is involved in ID. Oligophrenin-1 is a negative regulator of RhoA, Rac and Cdc42, and also interacts with the postsynaptic adaptor protein Homer (Govek *et al.* 2004). Knockdown of oligophrenin-1 in CA1 pyramidal neurons significantly reduces spine length and this effect is mimicked by a constitutively active form of RhoA and can be rescued by the presence of constitutively dominant negative RhoA, which leads to an inhibition of the RhoA effector Rho-kinase (ROCK1) (Govek *et al.* 2004). Considering the important role of ROCK1 in actin remodelling, these results strongly suggest that RhoA regulates the actin cytoskeleton of spines, possibly through effects on the LIM kinase, myosin light chain (MLC), or MLC phosphatase (Govek *et al.* 2004; Nadif Kasri and Van Aelst 2008). A new role of oligophrenin-1 in regulating the activity of the circadian clock protein Rev-erbα has also recently been shown, suggesting that the etiology of intellectual disability could be related to the interaction between synaptic activity and circadian oscillators (Valnegri *et al.* 2011a). Very recently, Powell et al. showed that oligophrenin-1-deficient mice have changes in the number of vesicles in the readily releasable pool and also have altered availability of secretory vesicles (Powell *et al.* 2012). Thus, alterations in oligophrenin-1 expression result in multiple deficits of synaptic activity and plasticity that depend on oligophrenin-1 being expressed in both the pre- and postsynaptic terminals.

TSPAN7 is directly associated with cognitive defects in humans because several alterations to its gene (*TM4SF2*) – *TM4SF2* inactivation by an X:2 balanced translocation, a premature stop codon TGA (gly218-to-ter), (Zemni *et al.* 2000) and a 2-bp deletion (564delGT) resulting in a premature stop codon at position 192 (Abidi et al. 2002) – are directly associated with non-syndromic intellectual disability. The gly218-to-ter nonsense mutation

and the 2-bp deletion may predict a truncated TSPAN7 lacking cytoplasmic C-terminal tail and the fourth transmembrane domain. TSPAN7 promotes filopodia and dendritic spine formation in cultured hippocampal neurons, and is required for spine stability and normal synaptic transmission. TSPAN7 directly interacts with the PDZ domain of protein interacting with C kinase 1 (PICK1), and associates with AMPAR subunit GluA2 and β1-integrin. Interestingly TSPAN7 regulates AMPA receptor trafficking by modulating the PICK1 and GluA2/3 association. These findings identify TSPAN7 as a key player in the morphological and functional maturation of glutamatergic synapses; possibly explaining why its deletion is strongly associated with ID in humans (Bassani *et al.* 2012).

In conclusion, several genetic and functional studies demonstrate that mutations associated with intellectual disabilities occur in molecules that play an essential role in regulating brain synapse formation and plasticity.

Abnormalities of spiny synapses in schizophrenia

Schizophrenia is a complex developmental psychiatric disorder generally characterized by positive (i.e., hallucinations, disorganized thoughts, delusions) and negative (i.e., diminished affect, social withdrawal) symptoms, and deficits in executive and cognitive functions (Harrison and Weinberger 2005; Owen and O'Donovan 2005). Schizophrenia affects approximately 0.5-1% of the population. Positive symptoms (i.e. hallucinations, delusions) typically emerge in late adolescence or early adulthood, while negative symptoms (i.e. impaired social interactions, low affect) and deficits in cognitive function can be observed earlier in development. Disturbances in glutamate, GABA and dopamine neurotransmission have been implicated in the observed functional ‘dysconnectivity’ in neural circuits observed in schizophrenia (Kantrowitz and Javitt 2010; Bergeron and Coyle 2012; Seeman 2009).

As synapses are the basic units of neural circuits and are intimately involved in neurotransmitter signal transduction, dendritic spine dysfunction may play an important etiological role in schizophrenia. Indeed, structural MRI studies have consistently shown gray matter reductions in schizophrenic patients. Among the ultrastructural changes thought to directly contribute to the lower gray matter are reductions in spine density (Selemon and Goldman-Rakic 1999). Several postmortem studies have examined spine density in brain regions with pronounced gray matter loss. Spine loss has been reported in the dorsolateral prefrontal cortex (DLPFC), particularly in layer 3 neurons (Glantz and Lewis 2000). Schizophrenia patients also show a profound reduction in spine density on pyramidal neurons in the superior temporal gyrus (STG), particularly in the primary auditory cortex (Sweet *et al.* 2009), which could potentially be associated with auditory hallucinations (Barta *et al.* 1990). Several studies have shown reductions in hippocampal volume in schizophrenia (Steen *et al.* 2006). Within the hippocampus, reduced spine density on subicular dendrites, reduced CA3 spine density (Law *et al.* 2004; Kolomeets *et al.* 2005), as well as reduced spine size (Kolomeets *et al.* 2005) have been reported. A lower density of synaptic contacts formed by individual mossy fiber tracts on CA3 pyramidal neurons (Kolomeets *et al.* 2007) has also been reported.

Risk for schizophrenia is associated with a combined effect of multiple susceptibility genes and environmental interactions during development (Stefansson *et al* 2003; Lewis and Levitt 2002; Meyer and Feldon 2009; Rapoport *et al.* 2005; Arango *et al.* 2008). Genetic linkage and genome wide association studies have not identified a clear link between neurotransmitter-associated genes (i.e., for biosynthetic or metabolizing enzymes, receptors) and the etiology of schizophrenia (Harrison and Weinberger 2005). Instead, genetic studies have identified haplotypes and single nucleotide polymorphisms (SNPs) associated with genes regulating neuronal migration, synaptic structure and plasticity (Harrison and

Weinberger 2005), and more recently, genome-wide association studies have identified genes encoding proteins regulating neuronal excitability as potential risk factors for cognitive deficits and numerous psychiatric disorders (Weissflog *et al.* 2012; Franke *et al.* 2009; Casamassima *et al.* 2010; Bhat *et al.* 2012; Meier *et al.* 2012). Here we will summarize recent findings on some of the most prominent ones and explore their roles in spine dynamics.

A large number of genetic linkage and association studies have suggested that the NRG1 and ERBB4 genes may be risk factors for schizophrenia (Stefansson *et al.* 2002; Munafo *et al.* 2008; Munafo *et al.* 2006; Hall *et al.* 2006; Silberberg *et al.* 2006; Law *et al.* 2007; Tan *et al.* 2010; Nicodemus *et al.* 2010) and its endophenotypes (Greenwood *et al.* 2012; Greenwood *et al.* 2011). These genes also regulate several biological processes altered in schizophrenia (Buonanno and Fischbach 2001; Mei and Xiong 2008; Buonanno 2010). While many genes have been associated with a risk for schizophrenia and regulate biological process similar to NRG1 and ErbB4, few show the same degree of biological plausibility and reproducible association with the disease. In particular, a functional NRG1 SNP associated with schizophrenia (Walss-Bass *et al.* 2006) that substitutes a valine in the NRG1 (type III) transmembrane domain necessary for gamma-secretase-dependent cleavage (Chen *et al.* 2010) constitutes an important “at risk” variant for the disorder. In addition, a second NRG1 polymorphism (SNP8NRG243177) within the original HAP_{ICE} “at risk” Icelandic haplotype (Stefansson *et al.* 2002), a large region of DNA that is hyper-variant in schizophrenia and associated with transcriptional regulation of type III NRG1 (Weickert *et al.* 2012), is highly associated with risk for developing psychotic symptoms, decreased premorbid IQ and activation of frontal and temporal lobes (Hall *et al.* 2006). Moreover, studies that have evaluated 94 candidate genes for schizophrenia and ten quantitative endophenotypes, such as pre-pulse inhibition, P50 suppression and the Wisconsin Card Scoring Test, identified *NRG1* and *ERBB4* as schizophrenia susceptibility genes (Greenwood *et al.* 2012; Greenwood *et al.* 2011).

Both NRG1 and ErbB4 regulate synaptic structure and function. ErbB4 is expressed in interneurons, and potentially less abundantly, in cortical pyramidal cells and spines of excitatory neurons (see below). Long-term NRG1 treatment increases pyramidal neuronal spine density and the preponderance of spines with mature phenotypes (Barros *et al.* 2009). ErbB4 overexpression increases spine density, area, and excitatory synaptic transmission (Li *et al.* 2007). Conversely, erbB4 knockdown reduces spine density and size (Li *et al.* 2007). Mice deficient in NRG1 type III show reductions in spine density in hippocampal neurons (Chen *et al.* 2008). Mice lacking erbB2 and erbB4 in the CNS show reduced spine density in both the hippocampus and cortex (Barros *et al.* 2009). In both these mice, spine morphological deficits co-occur with schizophrenia-related behavioral phenotypes.

The initial link of the disrupted in schizophrenia 1 (DISC1) gene to schizophrenia was identified in a Scottish pedigree with a disruption of the DISC1 open reading frame. Polymorphisms and frame shift mutations of DISC1 have been linked to schizophrenia in other lineages (Schumacher *et al.* 2009). As DISC1 has been associated with several psychiatric disorders, including bipolar disorder, depression, and autism, it seems likely that it constitutes a general psychiatric vulnerability gene. DISC1 is highly abundant in spines (Kirkpatrick *et al.* 2006). In cortical neurons, long-term knockdown reduces spine area (Hayashi-Takagi *et al.* 2010), whereas its short-term knockdown increases spine density and size. The effects of DISC1 mutations in mice on spine density reflect brain region and developmentally influenced effects. Namely, spine numbers in dentate gyrus granule cells are reduced in a mouse model of disease-associated chromosomal translocation (Kvajo *et al.* 2008), and dendrite complexity is reduced by early postnatal expression of DISC1 C-terminus in mice (Li *et al.* 2007). Spine density in cortical pyramidal neurons was increased

by prenatal expression of mutant DISC1, while combined prenatal and postnatal expression increased spine density in hippocampal granule cells (Ayhan *et al.* 2011).

While DISC1 mRNA levels seem unaffected in schizophrenia patients (Dean *et al.* 2007; Lipska *et al.* 2006), the expression of DISC1 interacting proteins was reduced in patients carrying high-risk DISC1 SNPs (Lipska *et al.* 2006), suggesting that DISC1 function might be affected in schizophrenia. Disruption of DISC1's ability to scaffold proteins in spines would be expected to have deleterious consequences on spine morphogenesis. Indeed, DISC1 is known to interact with several well-established regulators of spine morphogenesis, most prominently the RacGEF kalirin-7 (Millar *et al.* 2003). Recently kalirin-7, via activation of its downstream effector Rac1, was found to directly regulate the effects of DISC1 on spine morphology (Hayashi-Takagi *et al.* 2010). Interestingly, the expression of kalirin mRNA was reduced in the DLPFC of patients with schizophrenia, irrespective of antipsychotic treatment (Hill *et al.* 2006). This suggests a potential role for small GTPase pathways in spine pathology in schizophrenia. Indeed, the expression of Cdc42 mRNA was also reduced in postmortem schizophrenic DLPFC (Hill *et al.* 2006; Ide *et al.* 2010). Loss of kalirin and Cdc42 strongly correlates with spine loss in layer 3 PFC neurons (Hill *et al.* 2006). Because of kalirin's important synaptic functions, its interactions with DISC1 and its reduced expression in schizophrenia, recent studies have examined how kalirin loss impacts spines and behavior. Interestingly, kalirin KO mice show severe reductions in spine density and dendrite complexity in the frontal cortex, as well as schizophrenia-related impairments in working memory, sociability, and prepulse inhibition (Cahill *et al.* 2009; Xie *et al.* 2010). Remarkably, both spine loss and behavioral dysfunction emerged during adolescence and were absent in juvenile KO mice (Cahill *et al.* 2009). This is interesting given the onset of schizophrenia symptoms in adolescence in humans, and points to a tight association between the onset of spine loss and the onset of behavioral impairments in these animals.

The 22q11.2 microdeletion syndrome is the most common CNV associated with schizophrenia, accounting for 1-2% of cases (Stark *et al.* 2008). Primary hippocampal neurons from mice engineered to carry hemizygous deletion of the 1.3-Mb orthologous chromosomal region (*Df(16)A*$^{+/-}$) showed reduced spine density and sizes (Mukai *et al.* 2008). Interestingly, loss of either of two genes within this region (ZDHHC8 and Dgcr8) was sufficient to impair spine and dendrite morphology (Stark *et al.* 2008; Mukai *et al.* 2008). ZDHHC8 is a palmitoyl transferase which palmitoylates PSD-95; its loss results in reduced spine density and simpler dendrites, and its replacement into *Df(16)A*$^{+/-}$ neurons rescued spine and dendrite deficiency (Mukai *et al.* 2008). Dgcr8 is involved in miRNA processing, and its loss results in smaller spines and simpler dendrites (Stark *et al.* 2008). Mice modeling the 22q11.2 microdeletion syndrome (*Df(16)A*+/-) showed reduced hippocampal spine density and sizes (Mukai *et al.* 2008). Mice deficient in individual genes within this region (ZDHHC8 and Dgcr8) showed simplified dendritic trees and reduced spine density (Mukai *et al.* 2008), or smaller spines (Stark *et al.* 2008), respectively.

Abnormalities in inhibitory circuits in SZ

The synchronization of neuronal network activity in the human cortex and hippocampus at gamma frequencies (30-80 Hz) is important for cognition, learning and memory (Engel and Singer 2001) and is altered in schizophrenia (Herrmann and Demiralp 2005; Spencer 2009; Gonzalez-Burgos and Lewis 2008). Gamma oscillations emerge from the synchronized firing of interconnected excitatory glutamatergic and primarily inhibitory fast-spiking GABAergic PV+ interneurons (Cobb *et al.* 1995), and their power (i.e. amplitude) is modulated by the E/I balance at distinct synaptic sites in the circuit and the intrinsic excitable properties of the neurons (Bartos *et al.* 2007). Event-related gamma oscillation power is reduced in subjects diagnosed with schizophrenia (Kwon *et al.* 1999; Wilson *et al.* 2008), and the regional reaction time phase-lock of oscillations is correlated with either

positive or negative symptoms (Spencer *et al.* 2004). Importantly, GABAergic fast-spiking interneurons and levels of the GABA biosynthetic enzyme GAD67 are reduced in PV+ interneurons in postmortem brains from affected individuals, suggesting that specific neural circuits may be associated with schizophrenia (Akbarian *et al.* 1995; Woo *et al.* 1998; Woo *et al.* 2004) also see (Gonzalez-Burgos and Lewis 2008). Altered functionality of PV+ basket cell GABAergic interneurons, which provide perisomatic inhibition to pyramidal neurons, may account for the observed reduction in neural network oscillations that are important for working memory (Gonzalez-Burgos and Lewis 2012; Spencer 2009).

Determining the cellular and subcellular localization of ErbB4 and its function at pre- and post-synaptic sites is critically important for understanding the role of this signaling pathway in modulating E/I balance and neuronal network activity. ErbB4 mRNA expression patterns have long been known to correspond to GABAergic neurons in the neocortex and hippocampus (Lai and Lemke 1991; Steiner *et al.* 1999; Gerecke *et al.* 2001; Fox and Kornblum 2005; Thompson M. *et al.* 2007), and unlikely to be expressed in glutamatergic neurons as demonstrated by single-cell PCR from electrophysiologically identified neurons (Vullhorst *et al.* 2009). Recently, using highly specific polyclonal and monoclonal antibodies, ErbB4 receptor protein was detected in the somato-dendritic region of distinct GABAergic neuronal subtypes in the hippocampus (Fisahn *et al.* 2009; Yau *et al.* 2003) and the neocortex of rodents and primates (Neddens *et al.* 2011; Neddens and Buonanno 2011). Of importance, ErbB4 is expressed in approximately 50% hippocampal (Fisahn *et al.* 2009) and nearly all neocortical PV+ fast-spiking GABAergic interneurons (Neddens and Buonanno 2011). The receptor is also expressed in cholecystokinin (CCK)-positive GABAergic basket cells, another interneuron subtype that contributes to gamma oscillations (Tukker *et al.* 2007).

Soma targeting basket and axoaxonic AIS targeting chandelier GABAergic interneurons, respectively, can regulate E/I balance and neuronal network activity by regulating the excitability and firing frequency of glutamatergic pyramidal neurons. In contrast to the consistent observation that ErbB4 is expressed in the somatodendritic compartment of interneurons, its presence at presynaptic GABAergic terminals has been more controversial. Activation of ErbB4 by exogenously added NRG1 was reported to promote depolarization-dependent release of GABA purportedly by activation of presynaptic ErbB4 receptors on terminals of basket cells innervating prefrontal cortical pyramidal neurons (Wen *et al.* 2010); a similar conclusion was reached after analysis of mini inhibitory postsynaptic potentials (mIPSCs) from chandelier GABAergic neurons onto pyramidal neocortical neurons (Fazzari *et al.* 2010). However, as discussed in more detail below, studies using two highly characterized monoclonal antibodies raised against the extracellular and intracellular domains of ErbB4 (Vullhorst *et al.* 2009) failed to detect immunoreactivity for the receptor at GABAergic presynaptic terminals innervating either the soma or axon initial segment of pyramidal neurons in the hippocampus or frontal cortex of rodents and primates (Neddens *et al.* 2011; Neddens and Buonanno 2011). The reasons for these disparate findings may result from the use of commercial polyclonal antisera (Wen *et al.* 2010; Fazzari *et al.* 2010) vs. non-commercial monoclonal antibodies (Vullhorst *et al.* 2009; Neddens and Buonanno 2011; Neddens and Buonanno 2009) or possibly from fixation and unmasking techniques that expose limited amounts of epitope.

An important observation that potentially associates schizophrenia at-risk genes with altered network activity, is the recent demonstration that perfusion of acute hippocampal slices with 1nM NRG1 dramatically increases the power (amplitude) of kainate-induced gamma oscillations (Fisahn *et al.* 2009). This effect of is blocked by the pan-specific ErbB receptor antagonist PD158780 and totally absent in acute slices prepared from ErbB4 knockout mice. Of importance, the endogenous power of kainate-induced gamma oscillations in slices

prepared from ErbB4 null mice was reduced by 60% and coincided with a loss of approximately 50% of hippocampal PV+ GABAergic interneurons (Fisahn *et al*. 2009).

While some have focused on the potential role of *presynaptic* ErbB4 receptors on PV+ GABAergic interneurons for regulation of network activity and behavior (Wen *et al*. 2010; Fazzari *et al*. 2010), based on studies using monoclonal ErbB4 antibodies and electron microscopy analysis, a hypothesis favored by others (Buonanno 2010; Neddens and Buonanno 2009) is that *postsynaptic* ErbB4 receptors expressed on dendrites of PV+ GABAergic interneurons, which receive glutamatergic inputs and exhibit the highest levels of ErbB4 immunoreactivity, are a major site for modulation of E/I balance and neuronal network activity. Consistent with the latter hypothesis, targeted ablation of either the AMPA receptor GluR1 or GluR4 subunit at glutamatergic postsynaptic sites of GABAergic interneurons results in the reduction of kainite-induced gamma oscillation power (Fuchs *et al*. 2007) that are similar to those in ErbB4 null mice (Fisahn *et al*. 2009). In addition, ablation of the obligatory NMDA receptor NR1 subunit at glutamatergic synapses in approximately 50% of cortical and hippocampal GABAergic interneurons reduces neuronal synchrony and elicits “schizophrenia-like” behaviors in mutant mice (Belforte *et al*. 2010). Interestingly, mice with either full mutation of ErbB4 or targeted ablation in PV+ interneurons exhibit several behavioral deficits associated with rodent models for schizophrenia (Wen *et al*. 2010; Shamir *et al*. 2012). Therefore, regulation of glutamatergic transmission at excitatory synapses on inhibitory neurons is a major site for modulation of neuronal network activity and, as discussed below, NRG/ErbB4 signaling may be a major regulator at glutamatergic synapses driving GABAergic basket cells.

The C-terminal tail of ErbB4 interacts directly with the MAGUK family of postsynaptic proteins including PSD-95 (Garcia *et al*. 2000; Huang *et al*. 2000) and accumulates at synaptic puncta on inhibitory neurons (Vullhorst *et al*. 2009; Fisahn *et al*. 2009; Longart *et al*. 2007). Ultrastructural analysis in CA1 interneurons using immunoelectron microscopy revealed abundant ErbB4 expression at, and adjacent to, glutamatergic postsynaptic sites (Vullhorst *et al*. 2009). By contrast, there is no evidence for presynaptic expression in cultured GAD67-positive hippocampal interneurons and in CA1 basket cell terminals (Vullhorst *et al*. 2009; Fisahn *et al*. 2009; Longart *et al*. 2007). The localization of ErbB4 at excitatory synapses on GABAergic neurons, but not excitatory neurons, identifies these synapses as a primary target of NRG signaling in the hippocampus and indicates that ErbB4 serves as a selective marker for PSDs on GABAergic neurons (Vullhorst *et al*. 2009). Taken together, these findings strongly support a role for *postsynaptic* somatodendritic ErbB4 receptors on PV+ GABAergic interneurons in modulating glutamatergic drive onto these cells for regulating gamma oscillation power and “schizophrenia-like” behaviors observed in ErbB4 mutant mice (Buonanno 2010; Vullhorst *et al*. 2009; Neddens and Buonanno 2009).

Because ErbB4 is expressed in the somatodendritic region of GABAergic interneurons, it was important to investigate if receptor activation acutely regulates the intrinsic excitability and firing properties of ErbB4-positive interneurons. Interneuron output is shaped by the modulation of action potential (AP) waveform and firing rates. Voltage-gated potassium (K_v) and sodium (Na_v) channels modulate several aspects of neuronal excitability including AP waveform, duration and firing frequency (Lawrence *et al*. 2006; Yu *et al*. 2006; Bean 2007; Milescu *et al*. 2010). Therefore, regulation of these currents affects AP threshold and neuronal excitability (Matzner and Devor 1992) that can modulate E/I balance and network activity. Two recent studies reported on the effects of NRG/ErbB4 signaling on the intrinsic properties of identified GABAergic interneurons in acute cortical slices from adult mice (Li *et al*. 2012) and in dissociated hippocampal cultured neurons (Janssen *et al*. 2012). Li et al. found that acute NRG1 application in cortical slices increased the intrinsic excitability of PV + interneurons, presumably ErbB4-positive neurons because most cortical PV neurons

express the receptor (see (Neddens and Buonanno 2011)), by decreasing AP threshold via $K_v1.1$ channel blockade; effects on Na_v currents were not analyzed (Li *et al.* 2012). On the other hand, by recording from pharmacologically isolated and labeled ErbB4-positive interneurons in dissociated hippocampal cultures, Janssen et al. demonstrated that NRG1 reduces the excitability of dissociated ErbB4+ interneurons, depolarizes the AP threshold, and decreases maximum Na_v channel somatic current. These effects observed only in GABAergic ErbB4-expressing neurons, but not glutamatergic neurons, were totally blocked by the ErbB blocker PD158780. In these experimental conditions no effects of acute NRG1 treatment were observed on macroscopic K^+ current or AP duration (Janssen *et al.* 2012). The apparent discrepancies between these studies may be due to several experimental differences, such as: a) the study by Li et al. was conducted in slices where NRG1-mediated release of dopamine (see below; (Kwon *et al.* 2008)) or other neuromodulators may affect K_v channels and increase excitability (Govindaiah *et al.* 2010), while the study by Janssen et al. used dissociated hippocampal cultures that are devoid of afferents; b) The study by Li et al. was restricted to PV+ neurons, whereas the other study recorded from identified ErbB4-positive interneurons that encompass a heterogeneous population of GABAergic neurons (Neddens and Buonanno 2009); and c) the two studies used interneurons of different ages and from distinct brain structures. Additional studies will be necessary to determine if the acute effects of NRG1 on increasing adult interneuron excitability by reducing Kv1.1 result from an intrinsic effect of ErbB4 activation in PV+ GABAergic neurons or from indirect effects of NRG1 produced by augmenting extracellular dopamine (Kwon *et al.* 2008) and activating D4Rs on this interneuron population (see below, (Andersson *et al.* 2012)).

Dopamine effects are mediated by D1-type (D1R and D5R) and D2-type (D2R, D3R and D4R) receptors that are positively and negatively coupled to adenylate cyclase, respectively. Most antipsychotics used to date target D2-types receptors. Because mice with reduced levels of NRG1, ErbB4 and NMDA receptor subunits share several “schizophrenia-like” behavioral abnormalities that are reversed or ameliorated by the antipsychotic clozapine (Stefansson *et al.* 2002; Shamir *et al.* 2012; Mohn *et al.* 1999), a possible functional link between NRG1/ErbB signaling and dopamine neurotransmission was investigated. Delivery of NRG1 by reverse-microdialysis in freely moving rats causes a dramatic and rapid accumulation of dopamine and its metabolites in the dorsal hippocampus, and this increase is blocked by PD158780 (Kwon *et al.* 2008). NRG1-induced increases in dopamine can reverse synaptic potentiation in the hippocampus through activation of D4Rs. Consistent with these findings, the effects of NRG1 on synaptic potentiation are blocked by the D4R-specific antagonist (PD168077) and clozapine, an antipsychotic that preferentially targets D4Rs, and are absent in D4R knockout mice (Kwon *et al.* 2008). While ErbB4 transcripts are expressed in the ventral tegmental area (Steiner *et al.* 1999; Gerecke *et al.* 2001), which sends afferent dopaminergic projections to the hippocampus (Gasbarri *et al.* 1994; Gasbarri *et al.* 1997), ErbB4 immunoreactivity was undetectable on dopaminergic axons (Kwon *et al.* 2008) but can be detected on the cell bodies of mesocortical- and nigrostriatal-projecting TH-positive neurons (Neddens and Buonanno, unpublished). Therefore, the possibility that ErbB4 is present at low levels on dopaminergic axons cannot be excluded presently; alternatively, NRG1 could promote dopamine release in the hippocampus by acting indirectly via GABAergic neurons.

Surprisingly little is known about the effects of dopamine on gamma oscillation activity in the hippocampus and PFC, although it has long been appreciated that dopamine modulates attention, cognitive salience and working memory (Winterer and Weinberger 2004), and that its levels are altered in schizophrenia (see Furth *et al.*, under review). The rodent frontal cortex and hippocampus receive sparse dopaminergic innervation from the VTA that regulates synaptic transmission, plasticity and working memory (Lisman *et al.* 2008; Andersson *et al.* 2012; Jay 2003; Lisman and Grace 2005). Based on the aforementioned

studies showing that NRG/ErbB4 signaling increases extracellular DA levels and regulates hippocampal synaptic plasticity via D4Rs (Kwon *et al.* 2008), and that targeted ablation of ErbB4 in PV+ GABAergic interneurons results in "schizophrenia like" behaviors similar to those observed in null ErbB4 mice (Shamir *et al.* 2012), the effects of dopamine on kainate-induced gamma oscillations in hippocampal slices were investigated (Andersson *et al.* 2012).

Interestingly, the selective activation of D4Rs, but not of D1/D5Rs and D2/D3Rs, increases gamma oscillation power, and this effect is blocked by a highly specific D4R antagonist (L-745,870). Consistent with the effects of D4R on gamma rhythms, receptor mRNA and protein are expressed in GAD67-positive GABAergic interneurons, but not in glutamatergic hippocampal neurons, and dopamine D4 and ErbB4 receptors are coexpressed in 71% of PV + basket cells. Of importance, we found that D4R activation is essential for the effects of NRG-1 on gamma oscillation power as the selective D4R anatagonist, as wells as the D4R-preferring atypical antipsychotic clozapine, dramatically reduced the NRG-1-induced increase in gamma oscillation power (Andersson *et al.* 2012). This study provides a novel link between D4R and ErbB4 signaling on gamma oscillation power, and the coexpression of both receptors in PV+ GABAergic basket cells, suggests a cellular mechanism that may be compromised in different psychiatric disorders affecting cognitive control. These findings suggest potential benefits of D4R modulators for targeting cognitive deficits as the 7-repeat D4R functional variant in humans (DRD4-7R) is associated with alterations in attention, working memory and gamma band activity (Demiralp *et al.* 2007) and with ADHD (DiMaio *et al.* 2003).

In summary, the colocalization of D4R and ErbB4 receptors on PV+ interneurons, activity of which is critically important for regulating E/I balance and cognitive functions (Yizhar *et al.* 2011), perhaps by optimizing "signal-to-noise" ratio of cortical microcircuits (see (Winterer and Weinberger 2004) and Furth *et al.*, in review), makes these receptor systems attractive novel targets for modulating network activities that underlie cognition. These studies identify PV+ GABAergic interneurons as a potential novel cellular target for modulating gamma oscillations and related cognitive functions deficient in psychiatric disorders, and suggest that NRG/ErbB4 and dopamine signaling pathways (and potentially other schizophrenia liability genes) may converge in these cells to modulate the activity of microcircuits altered in psychiatric disorders.

Psychosis in Alzheimer Disease and Excess Vulnerability of Cerebral Cortical Synapses

Synapse pathology in AD has been extensively reviewed in the recent literature. However, psychosis occurring in AD has received much less attention. In a review of 55 studies comprising of 9,749 subjects, the median prevalence of psychosis in subjects with AD (AD +Psychosis, AD+P) was 41% (Ropacki and Jeste 2005). Interestingly, AD+P patients consistently showed faster cognitive decline compared to AD without psychosis (AD-P) patients (Ropacki and Jeste 2005). Nine of nine studies found a significant association between a greater rate of cognitive decline and the presence of AD+P. Recent studies have continued to support the relationship between more rapid cognitive decline and AD+P (Emanuel *et al.* 2011; Sweet *et al.* 2012).

Several lines of evidence indicate that psychosis in AD has a specific neurobiology. Perhaps the most compelling is evidence that AD+P risk is transmitted in families (Sweet *et al.* 2002a), now replicated in two additional cohorts (Hollingworth *et al.* 2007; Sweet *et al.* 2010). The heritability of psychosis within AD is estimated as 61% (Bacanu *et al.* 2005). There are two important implications of these findings. First, and most direct, is that the risk for AD+P is likely to be influenced by genetic variation. Second, is that AD+P results from a distinctive underlying neurobiology. That is, AD+P cannot be seen as arising solely as a

non-specific consequence of AD progression. Nor can it arise solely due to a serendipitous accumulation of neurodegenerative lesions in vulnerable “psychosis” brain regions. AD+P has a genetic architecture most consistent with disease modification rather than an independent syndrome. That is, genes which increase the risk for AD itself are found equivalently in AD+P and AD without psychosis, while additional genetic variants which predispose to psychosis are present in AD+P, with some limited overlap of these variants with other psychoses. For example, there is strong evidence against an association of AD+P (in comparison to AD without psychosis) and *APOE* and *TOMM40* (DeMichele-Sweet *et al*. 2011b; Hollingworth *et al*. 2011; Chu *et al*. 2011). Similarly AD+P is not associated with variation in recently identified AD risk genes *CLU, PICALM, CR1, BIN1, ABCA7, MS4A, CD2AP, CD33* and *EPHA1* (Hollingworth *et al*. 2011) nor with other genes that may contribute to neurodegeneration risk: *APP, BACE1, SORL1*, and *MAPT* (DeMichele-Sweet *et al*. 2011a). In contrast, the first GWAS of AD+P was recently completed, which identified *VSNL1* (the gene encoding Vilip1), and other novel loci (e.g. *STK11*, *RIMBP2*) (Hollingworth *et al*. 2011). This study also, albeit to a lesser extent, found evidence for association of AD+P with a group of SNPs that appear to contribute to risk for schizophrenia (Hollingworth *et al*. 2011).

It has been appreciated for a number of years that the strongest correlate of cognitive impairment in individuals with AD is loss of synapses across neocortical regions (Terry *et al*. 1991; Scheff and Price 2003), with excitatory synapses onto dendritic spines particularly affected (Baloyannis *et al*. 2007; Grutzendler *et al*. 2007). This has led to the hypothesis that the more rapid cognitive deterioration seen in AD+P reflects greater vulnerability of neocortical synapses than in AD-P (Sweet *et al*. 2002b). Evidence in support of this hypothesis is described below.

In vivo neuroimaging studies of individuals with AD indicate there is increased disruption of neocortical gray matter is subjects with psychosis. In contrast, findings are largely negative with regard to medial temporal lobe (hippocampal formation) differences between AD+P and AD-P subjects. Delusions were associated with decreased gray matter density in the left frontal lobe and in the right frontoparietal cortex (Bruen *et al*. 2008). Single photon emission computed tomography (SPECT) studies of regional perfusion in AD+P (in comparison to AD-P) have found lower regional perfusion in bilateral dorsolateral prefrontal cortex (DLPFC), (Mega *et al*. 2000) left anterior cingulated gyrus (Mega *et al*. 2000), right frontal (Moran *et al*. 2008), left frontal (Kotrla *et al*. 1995), right temporal (Moran *et al*. 2008), and bilateral temporal cortices (Starkstein *et al*. 1994). Studies of brain metabolism using 18F-fluorodexoxyglucose imaging have provided further evidence for frontal cortex abnormalities in AD+P, including a relationship between severity of delusions and reduced cerebral metabolism in right DLPFC, right inferior frontal pole, and right lateral orbitofrontal cortex (Sultzer *et al*. 2003; Mentis *et al*. 1995).

Using magnetic resonance spectroscopy to examine postmortem brain tissue sample from AD+P and AD-P subjects, significant elevations in concentrations of the phosphodiester membrane breakdown product, glycerol-phosphoethanolamine have been reported (Sweet *et al*. 2002b). Elevations were present across the neocortex, with DLPFC, superior temporal gyrus (STG), and inferior parietal cortex (IPC) most affected. In contrast, medial temporal cortex (amygdala) and cerebellum were unaffected (Sweet *et al*. 2002b). These changes were interepreted as evidence of excess synaptic disruption in AD+P, in a pattern consistent with generalized neocortical involvement.

More recently, the dendritic spine associated protein, kalirin, was examined in post-mortem gray matter protein extracts from the dorsolateral prefrontal cortex of subjects with AD+P and AD-P. Kalirin is found in adult human cerebral cortex gray matter as one of four

predominant isoforms, kalirin-5, -7, -9, and -12 (Deo *et al.* 2011). Significant reductions in levels of kalirin-7, -9, and -12 were found in AD+P (Murray *et al.* 2012). In contrast, levels of the kalirin-5 isoform were unchanged (Murray *et al.* 2012). Because all four isoforms are found in post-synaptic density fractions (Deo *et al.* 2011), the absence of reduction in kalirin-5 suggest that the reductions in kalirin-7, -9, and -12 are better interpreted as evidence of synaptic dysfunction than of frank synapse loss (Murray *et al.* 2012).

Substantial evidence now indicates that aggregation of Aβ into soluble oligomers (dimers→protofibrils) is a primary source of synaptotoxicity in Alzheimer's disease (Selkoe 2002; Selkoe 2008; Walsh and Selkoe 2007; Koffie *et al.* 2011). This includes evidence from human postmortem tissue that cortical synapse loss is an early pathologic event and that cognitive impairments and synapse loss correlate most strongly with soluble Aβ (Lue *et al.* 1999), even in subjects with early disease (Naslund *et al.* 2000).

Studies of the synaptic effects of Aβ are further elucidating a model of how Aβ acts to eliminate dendritic spines. Though reductionistic, the predominant model proposes that Aβ shifts the balance within spines from LTP→LTD, through mechanisms including reduced NMDA receptor dependent Ca^{++} influx, mGluR activation, and low level caspase-3 activation (Selkoe 2008; Koffie *et al.* 2011). The final common mechanism for these pathways converge on altered endocytotic recycling of glutamate receptors, resulting in reduced synaptic expression of GluR1 and GluR2 containing AMPA receptors and synaptic NMDAR (Hsieh *et al.* 2006). The net result of these effects is loss of dendritic spines (Hsieh *et al.* 2006).

Despite these advances, unresolved questions persist. For example, it is clear that shifting the balance from LTP→LTD leads to net removal of GluR and NMDAR from synapses. However, it is not resolved whether signaling through specific NMDAR subtypes (i.e. NMDAR2A vs NMDAR2B), or signaling through NMDAR in specific locations (synaptic versus extrasynaptic) are associated uniquely with generation of LTP versus of LTD (Fetterolf and Foster 2011). Similarly, although studies clearly indicate phosphoTau is a necessary downstream mediator of Aβ impairments of LTP (Shipton *et al.* 2011), its dendritic mechanisms are just emerging (Zempel *et al.* 2010), leaving unclear how it may interact with other LTP and LTD mediators impacted by soluble Aβ. The exact species of soluble Aβ oligomers most relevant for spine toxicity is also not known as species from dimers to protofibrils are typically present in varying degrees. Similarly, soluble Aβ oligomers exist in equilibrium with fibrillar deposits of Aβ in plaques, and thus plaques may serve as reservoirs of soluble Aβ (Walsh and Selkoe 2007; Koffie *et al.* 2009). Plaques may themselves contribute to spine toxicity through a mechanism that differs from soluble Aβ (see(Bittner *et al.* 2010)) and serve as a site for inflammatory responses (Spires-Jones *et al.* 2007). How inflammation contributes to synapse loss is itself an emerging field (Rosen and Stevens 2010).

For AD+P, then, the important residual question is whether the greater cortical synaptic disruption in these subjects reflects enhanced Aβ drive, an increased response of downstream mediators of Aβ-induced synaptotoxicity, or additional independent synaptotoxic pathologies. There is no consistent evidence that AD+P is associated with a higher burden of neocortical deposition of fibrillar Aβ (2000;2000). Similarly, AD+P was not associated with increased neocortical concentrations of soluble $Aβ_{1-42}$, and the concentrations of soluble $Aβ_{1-40}$ were reduced in AD+P (Murray *et al.* 2012). However, the ratio of $Aβ_{1-40}$: $Aβ_{1-42}$ was elevated in the dorsolateral prefrontal cortex in AD+P subjects (Murray *et al.* 2012). Because $Aβ_{1-40}$ can inhibit the oligomerization of $Aβ_{1-42}$ into more toxic species by sequestering it into stable mixed tetramers (Murray *et al.* 2009), it remains possible there is heightened Aβ drive in AD+P.

In contrast, there is substantial evidence for an association of AD+P with at least one mediator of Aβ effects, neocortical phospho-tau pathology. Neurofibrillary tangle density is increased in AD+P in dorsolateral prefrontal, superior temporal, and inferior parietal cortex, but not in medial temporal lobe. Similarly, increased aggregated tau protein has been found in cortical gray matter extracts from subjects with AD+P (Rakic *et al.* 1986). More recently, measures of spread of phospho-tau pathology and phospho-tau concentration were evaluated in within dorsolateral prefrontal cortex from subjects with AD+P and AD-P. While only phospho-tau concentration differed significantly between groups, both measures were correlated with degree of cognitive impairment, suggesting they also contribute to greater synapse loss in these subjects (Murray *et al.*, AJGP, abstract).

There is evidence for reduced expression of multiple kalirin isoforms in AD-P, with further reductions in AD+P (Murray *et al.* 2012). Kalirin plays an integral role in dendritic spine growth, morphogenesis, and activity-dependent plasticity (Cahill *et al.* 2009; Xie *et al.* 2007). Importantly, kalirin reduction is known to deplete PSD GluR1, NMDAR2B, and cause spine loss (Xie *et al.* 2007; Ma *et al.* 2008), and conversely, increased expression of kalirin-7 and -9 increases spine density (Deo *et al.* 2011; Ma *et al.* 2008). An important downstream target of kalirin signaling, p21-activated kinase (PAK), shows reduced activation in response to Aβ *in vitro* and *in vivo*, and contributes to dendritic spine loss (Zhao *et al.* 2006). However, whether kalirin reductions are intermediate between Aβ and these effects of PAK, and therefore contribute to excess dendritic spine loss in AD+P, awaits experimental verification.

The data reviewed above support a model of AD+P summarized in Figure 3. Importantly the existing imaging and postmortem data suggest that it is neocortex, but not medial temporal cortex, that is most affected in AD+P, with the most consistent findings in the dorsolateral prefrontal cortex. The vulnerability to AD+P, due to underlying genetic factors, may affect the cascade of pathology in AD in any of several ways. The net result of these effects is enhanced drive of the pathologic cascade, increasing pTau, and leading to reductions in kalirin, removal of post-synaptic GluR and NMDAR, and spine loss. These effects are manifest as a greater rate of cognitive deterioration with subsequent emergence of psychotic symptoms.

Conclusions

Disorders such as ID, ASD, SZ, and AD+P have complex etiologies with heterogeneous symptomatology. An interesting observation that has recently emerged is that a significant overlap exists in the genetic etiology of these disorders. Based on such findings it has been hypothesized that disorders historically considered distinct might share at least partially overlapping pathogenic mechanisms, and differential manifestations of alterations in shared cellular substrates might underlie the phenotypic variability (Burbach and van der Zwaag 2009; Girirajan and Eichler 2010; O'Roak and State 2008; Penzes *et al.* 2011; Poot *et al.* 2011). However, there is also a significant phenotypic divergence between these disorders, most notably in the ages of onset spanning infancy, early childhood, adolescence and senescence. How overlapping genetics may lead to such diverse manifestations remains to be identified, although could be conceptualized as resulting from progressively less severe molecular alterations, such that developmental onset is in some cases delayed (e.g. schizophrenia), or requires the presence of an additional neuronal pathology before being manifest (e.g. AD+P). Consistent with this idea, the divergence among these syndromes is already apparent at the cellular level, manifested by differential alterations in dendrites and spines (Penzes *et al.* 2011; van Spronsen and Hoogenraad 2010). Such findings highlight the importance of finding common final molecular and cellular mechanisms, as well as mechanisms of molecular convergence and divergence. Recent breakthroughs in the

characterization of regulators of synaptic circuits have provided opportunities to identify molecular changes that could directly contribute to pathology. The molecular networks that control spines provide a framework for understanding how a large number of genetic perturbations can interact to disrupt synaptic function, neuronal circuit organization, and behavioral output in a disease-specific manner. As the pace of discovery in psychiatric genetics is very rapid, elucidating the functions of newly identified disease-associated genes within synaptic molecular networks is a key step to translating genetic findings into biological understanding and clinical applications. Understanding the causal links between synaptic pathology and disease phenotypes, and the identification of novel drug targets based on these links, will also facilitate the development of effective treatments for these disorders.

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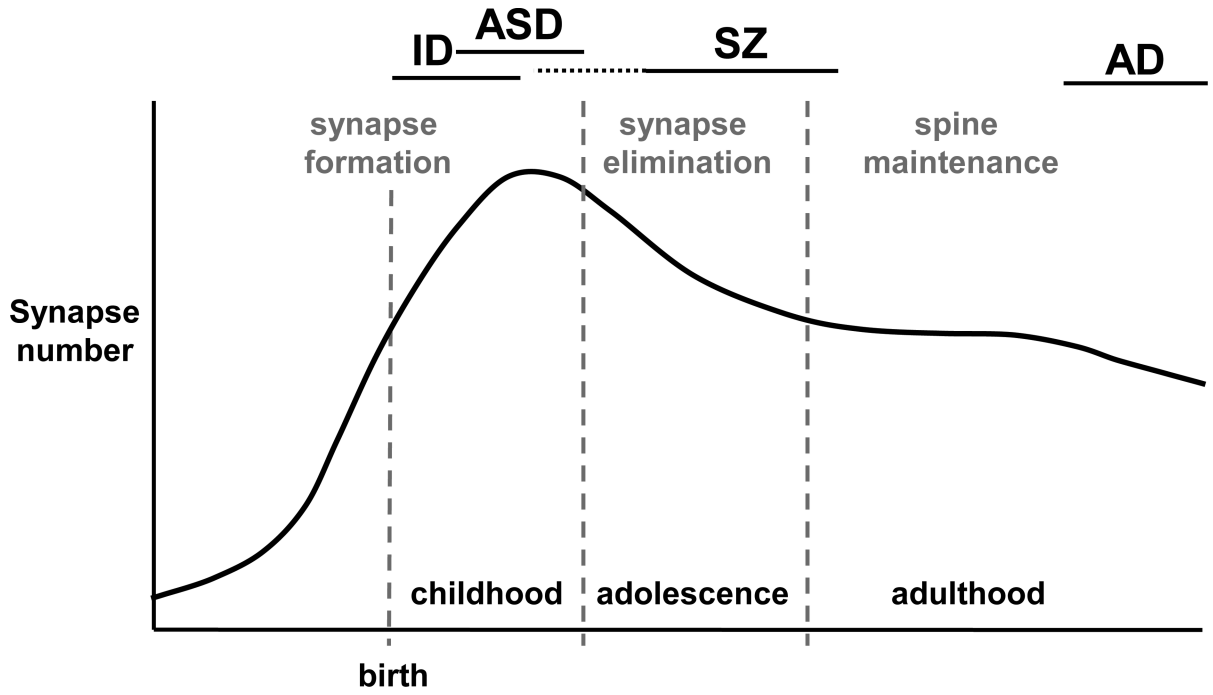

Figure 1. Trajectory of synapse number across the lifespan

Synapse numbers increase before and after birth; synapse are selectively eliminated during childhood and adolescence to adult levels. Bars on the top indicate the period of emergence of symptoms of specific disorders.

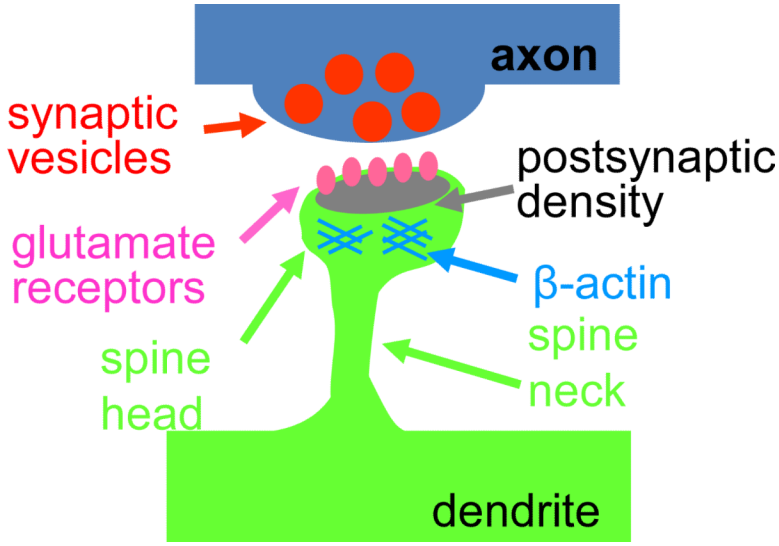

Figure 2. Schematic structure of a spiny synapse

Alterations in the mechanisms that control the formation, maintenance, and elimination of spiny synapses are likely to contribute to synaptic pathology in mental disorders.

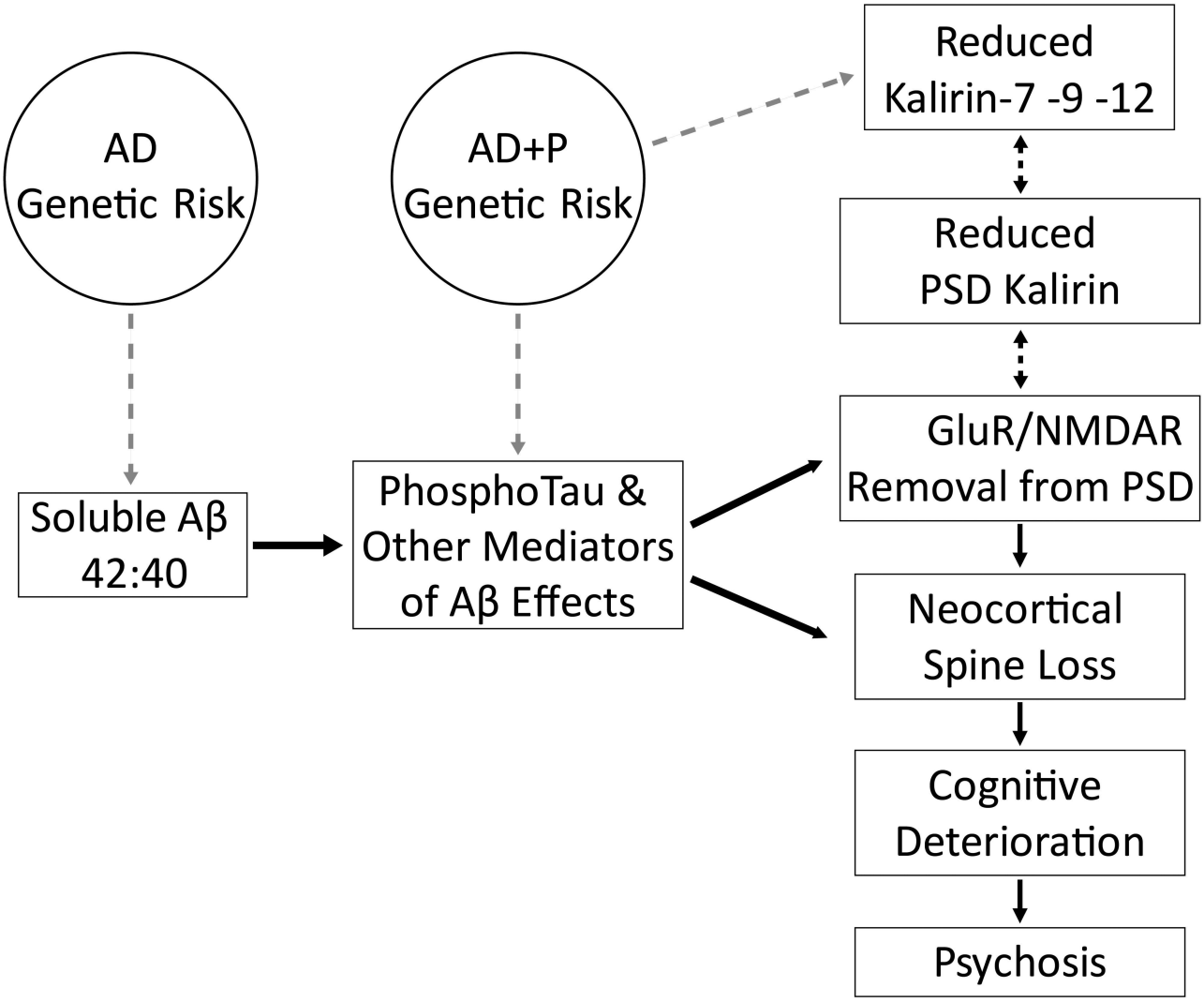

Figure 3. Summary diagram of synaptic vulnerability in Alzheimer Disease with Psychosis (AD +P)

Effects for which there is existing evidence are shown as unidirectional solid black arrows. Gray arrows indicate hypothesized effects.

Table 1

Summary of important genes associated with X-linked intellectual disabilities.

Protein name	Chromosome	Protein function	Phatology
Shank	22	scaffold	Phelan-McDremid Syndrome, autism
IL1RAPL1	X	synaptic adhesion	non syndromic XLID
Oligophrenin-1	X	RhoGAP	syndromic XLID
TSPAN7	X	tetraspanin	non syndromic XLID

Table 2

Summary of genes discussed in this review associated with schizophrenia.

Protein name	Chromosome	Protein function
NRG1	8	neuronal growth and differentiation
ErbB4	2	receptor tyrosine kinase
DISC1	1	scaffold
ZDHHC8 (22q11.2)	22	palmitoyl transferase
Dgcr8 (22q11.2)	22	miRNA processing