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Dysplasticity, metaplasticity, and schizophrenia: Implications for risk, illness, and novel interventions

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Abstract

In this paper, we review the history of the concept of neuroplasticity as it relates to the understanding of neuropsychiatric disorders, using schizophrenia as a case in point. We briefly review the myriad meanings of the term neuroplasticity, and its neuroscientific basis. We then review the evidence for aberrant neuroplasticity and metaplasticity associated with schizophrenia as well as the risk for developing this illness, and discuss the implications of such understanding for prevention and therapeutic interventions. We argue that the failure and/or altered timing of plasticity of critical brain circuits might underlie cognitive and deficit symptoms, and may also lead to aberrant plastic reorganization in other circuits, leading to affective dysregulation and eventually psychosis. This "dysplastic" model of schizophrenia can suggest testable etiology and treatment-relevant questions for the future.

Since the seminal Special Issue of *Development and Psychopathology* in 1994 (Cicchetti & Tucker, 1994), major advances have taken place in research into brain plasticity and critical periods of development as they inform neuropsychiatric disorders. In this paper, we review the current concept of neuroplasticity as well as the expanding evidence of its aberrations in major psychiatric disorders, with a special focus on schizophrenia and the evolution of risk for this illness. We also examine the potential translational applications of our understanding of neuroplasticity, and how we may harness this in the service of treatment and prevention of serious mental disorders.

Historical Overview and Definitions

The great neurologists of the 19th century, including Ramon Cajal, the father of modern neuroscience, thought that once developed, the adult brain is unlikely to change with experience (Cajal, 1894). However, Cajal later suggested that memories might be formed by strengthening the connections between existing neurons (Stahnisch & Nitsch, 2002). Hughlings Jackson, the father of modern neurology, proposed the hierarchical nature of how the nervous system is organized, and he made the distinction between negative symptoms that result from loss of nervous function and positive symptoms that may represent a failed attempt to compensate for such functional loss by disinhibited activity of lower brain regions (Berrios, 2001). William James, the noted American psychologist, who was inspired by Jackson's work, was among the first to suggest that the brain is not as immutable as previously thought. In his book *The Principles of Psychology*, James wrote, "Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity" (James, 1890). This view was ignored for several decades. Donald Hebb (1949) proposed an idea later referred to as "Hebbian learning," that is, when two neurons repeatedly or persistently fire together, some change takes place in one or both cells such that the efficiency of neuronal activity is increased. This adage that "neurons that fire together wire together" became the cornerstone of the concept of *neuroplasticity*, which refers to how the brain changes (organizes and reorganizes) in response to experience. While the brain shows plasticity throughout an individual's lifetime, its capacity for change may be higher at certain times than others; this led to the concept of critical periods.

Brain plasticity has been defined in a number of different ways (Figure 1). Plasticity can encompass both synaptic plasticity and nonsynaptic plasticity. *Synaptic plasticity* is the ability of a synapse between two neurons to change in strength over time, perhaps due to modifications in synaptic potentials or receptors that transmit chemical signals. Modification of synaptic strength is mediated by long-term potentiation (LTP), a phenomenon whereby repeated signal transmission between two neurons leads to long-lasting enhancement (Lomo, 2003). By contrast, *nonsynaptic plasticity* is a modification of the intrinsic excitability of the neuron, mediated through changes in structures such as the soma, the axon,

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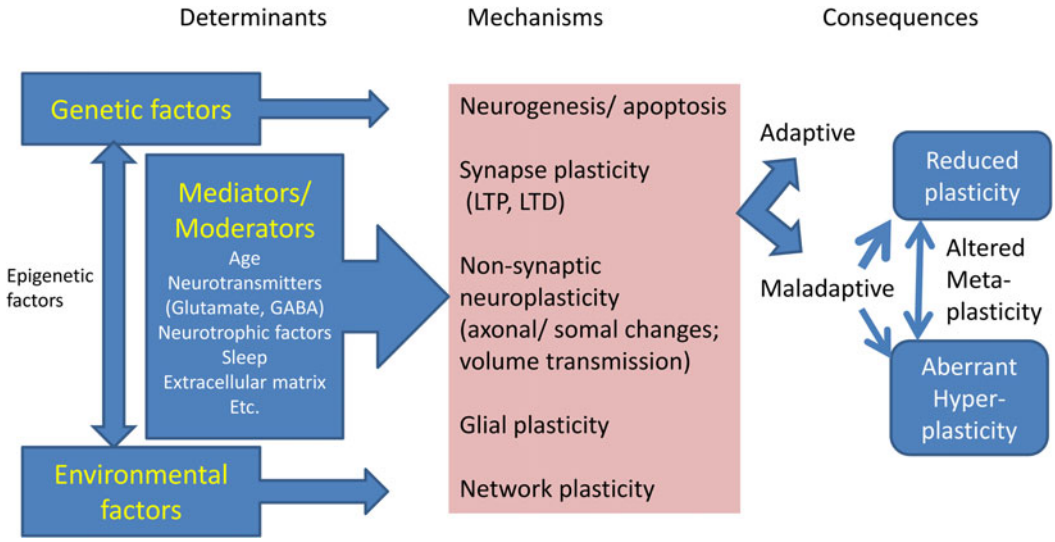

Figure 1. (Color online) Determinants, mechanisms, and consequences of brain plasticity.

or the dendrites. This may occur through neuronal transmission that happens outside of synapses (e.g., by extracellular diffusion processes), using processes such as volume transmission (Vizi, 1979) or via glial and vascular changes (Markham & Greenough, 2004).

Neuroplasticity may occur in at least two (not mutually exclusive) developmental contexts (Figure 2). Very early in development, experience and its resulting neuronal activity can shape neuronal response properties regardless of an organism's attention to a stimulus. This process of *experience-expectant neuroplasticity* (Hubel & Wiesel, 1959) shapes neural representations to reflect statistical regularities in inputs (e.g., from one eye vs. another, and in the environment). Such plasticity is often conceptualized to occur within a finite window, an early "critical period." Maladaptive experiences or insults to the developing brain during these critical periods can have lasting behavioral consequences. By contrast, *experience-dependent neuroplasticity* (Klintsova & Greenough, 1999) occurs *throughout* development. This process involves changes in neuronal activity in relation to experience, leading to lasting neural representations.

Based on the nature of experience and the state of the organism, the brain can be reshaped in either *adaptive* or *maladaptive* ways. Aberrant plasticity can have a profound impact on neuronal activity (Papa, De Luca, Petta, Alberghina, & Cirillo, 2014; Pirttimaki & Parri, 2013) and may be triggered in pathological conditions such as Alzheimer disease and Huntington disease (Oberman & Pascual-Leone,

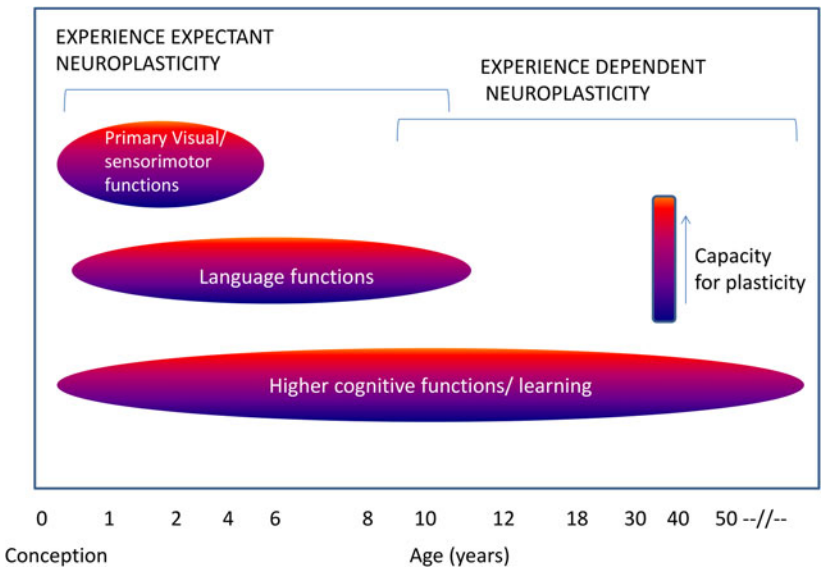

Figure 2. (Color online) Critical windows of neuroplasticity.

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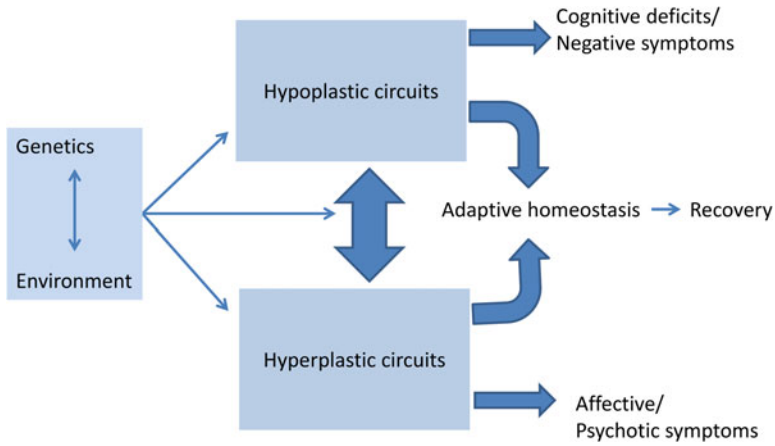

Figure 3. (Color online) Schematic model representing possible ways in which plasticity processes may be impaired in schizophrenia.

2013). Maladaptive excessive plasticity has also been implicated in addiction, posttraumatic stress disorder, and depression (Pittenger, 2013). As we will argue in this paper, the cardinal features of schizophrenia may arise from either diminished plasticity or pathologically excessive plasticity. Through the lens of premorbid and prodromal risk states for schizophrenia, and in an extension of Jackson's model, we propose that failure of plasticity in key brain circuits may result in cognitive and deficit symptoms, while an aberrant hyperplastic response to such deficits might underlie psychosis and emotional dysregulation (Figure 3).

Neurobiological Processes Underlying Plasticity

The nervous system is variably plastic throughout the life span. In this section, we will review the mechanisms of neuroplasticity as they relate to neurogenesis and apoptosis, synaptic formation and pruning, synaptic modulation, nonsynaptic processes, and neuronal support cells.

Neurogenesis

The earliest stages of nervous system development include generation of neurons and glial cells from stem cell progenitors, neural differentiation, and neuronal migration to other locations. After neuronal migration, growth of axons and dendrites occurs through extension of growth cones at their tips. This process is influenced by cell–cell adhesion molecules and other external molecular signals (Alberts et al., 2002). Next, neurons compete for access to neurotrophic factors, and about half of them die through programmed cell death, also called apoptosis (Alberts et al., 2002). Synapses begin to form between neurons, mediated by the release of neurotrophic factors by target tissues. In addition, neurogenesis continues during adulthood in the dentate gyrus of the hippocampus and the subventricular zone (Benarroch, 2013; Lledo, Alonso, & Grubb, 2006).

Synaptic plasticity and role of glutamatergic neurotransmission

Synaptic plasticity is the capacity of synapses to change their strength in response to changes in their activity. LTP, a key mechanism underlying synaptic plasticity, is the strengthening of the transmission across two neurons with repeated stimulation of a synapse, reflected in changes to the amplitude of the postsynaptic potential (Zhang & Linden, 2003). LTP underlies memory formation and learning and occurs in many brain regions, notably the hippocampus. In early phase LTP, which occurs in the first several hours, large quantities of calcium ions are released and protein kinases are activated (Bliss & Collingridge, 1993). In late phase LTP, gene transcription occurs, and proteins are synthesized over the course of hours to days (Lynch, 2004). Brain-derived neurotrophic factor (BDNF) plays an important role in this phase. The molecular mechanisms underlying LTP include activation of *N*-methyl D-aspartate (NMDA) receptors, which serve as coincidence detectors when two neurons fire simultaneously, allowing flow of ions into the neuron. NMDA antagonists block LTP and learning (Morris, Anderson, Lynch, & Baudry, 1986).

Long-term depression (LTD) refers to a long-lasting decrease in synaptic strength. Like LTP, it also involves glutamate signaling on NMDA and AMPA receptors (Collingridge, Peneau, Howland, & Wang, 2010). In contrast to LTP, it is induced by long-lasting low-frequency stimulation, rather than brief high-frequency stimulation (Collingridge et al., 2010). Mechanisms of LTD may include reductions in glutamate release due to both presynaptic and postsynaptic changes, removal of AMPA receptors from the synapse, or changes in the conductance properties of receptors (Collingridge et al., 2010; Malenka, 2003). LTD, like LTP, may also be involved in neuropsychiatric disease. Stress enhances LTD in the hippocampus through activation of NMDA receptors (Kim, Foy, & Thompson, 1996), which may help explain stress-related impairments in memory formation. In addition, LTD has been hypothesized to be involved in synaptic

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refinement processes during development (Collingridge et al., 2010). Thus, disruptions of LTD may lead to aberrant plasticity during development.

Nonsynaptic plasticity and role of glia

Nonsynaptic plasticity includes a wide range of processes affecting the intrinsic excitability of neurons (Daoudal & Debanne, 2003). Mechanisms may include changes to the neuronal soma (cell body), dendrites, axons, and components of the neuronal membrane, such as resting and voltage-gated ion channels (Mozzachiodi, Lorenzetti, Baxter, & Byrne, 2008). Nonsynaptic plasticity may impact serotonin, acetylcholine, metabotropic glutamate, kainite, and NMDA receptors, voltage-gated calcium channels, and cellular signaling (Daoudal & Debanne, 2003; Zhang & Linden, 2003). Volume transmission, another aspect of nonsynaptic plasticity, involves both activation of extrasynaptic receptors and induction of activity by diffusion of molecules from the extracellular fluid into synaptic clefts. The role of nonsynaptic plasticity in memory and learning is still unclear.

Glial cells are nonneuronal cells that help maintain and support neurons, providing structural support and insulation, among other functions. While glial cells were generally considered as "support cells," glia can dynamically respond to environmental input and influence neuronal function by releasing neurotransmitters (gliotransmitters). Astrocytes, a type of glial cell, wrap their membranous projections around synapses and release substances such as neurotransmitters (Paixao & Klein, 2010), and D-serine, which influences LTP and LTD (Henneberger, Papouin, Oilet, & Rusakov, 2010). Glutamate transporters on astrocytes remove excess glutamate from the extracellular space, preventing the excitotoxicity that can result from excessive glutamate stimulation of the synapse (Rothstein, 1996). Genetic or molecular changes that alter glutamate transporters in glia result in impairment of LTP (Filosa et al., 2009) and LTD (Omrani et al., 2009).

Neurotrophins and other trophic proteins

Neurotrophins are signaling proteins that prompt neurons to grow and differentiate, and thus they are essential to neurodevelopment and neural plasticity. Several major neurotrophins have been studied in depth: BDNF, nerve growth factor, neurotrophin-3, and neurotrophin-4. The most investigated neurotrophin, BDNF, influences synaptic regulation and growth (Kleim et al., 2006) and neuronal migration and differentiation (Huang et al., 1999). BDNF is involved in late-phase LTP (Tartaglia et al., 2001) and may work partly by enhancing the response of synapses to tetanic stimulation (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996).

Sleep, electrophysiology, and neuroplasticity

An important mediator of synaptic plasticity is sleep. According to the sleep homeostasis hypothesis, the extensive learning experiences and synaptic strengthening that occur during wakeful states results in synaptic fatigue at a cellular level, which is restored during sleep (Tononi & Cirelli, 2014). It is interesting that sleep spindles are thought to play a role in synaptic changes and sleep-dependent memory consolidation (Fogel et al., 2012). Spindles are nonrapid eye movement sleep EEG rhythms (7–14 Hz). Spindle-associated spike discharges have been shown to induce LTP-like synaptic plasticity, thus playing an important role in sleep-dependent memory consolidation (Rosanova & Ulrich, 2005). Moreover, a simultaneous EEG functional magnetic resonance imaging (fMRI) study showed that the functional connectivity of the hippocampal formation with the neocortex was the strongest during Stage 2 nonrapid eye movement sleep when spindles were present (Andrade et al., 2011).

Electrophysiology has been used to assess LTP in the human cortex in the waking state as well. In normal individuals, repetitive auditory stimulation or visual stimulation has been associated with increases in the amplitude of the auditory and visual evoked potentials, respectively (Clapp, Hamm, Kirk, & Teyler, 2012; Clapp, Kirk, Hamm, Shepherd, & Teyler, 2005), suggesting the induction of LTP. This type of LTP generally lasts more than an hour and can be blocked by NMDA receptors in animal models (Clapp et al., 2012). As will be discussed in detail later, the combination of transcranial magnetic stimulation and EEG is now being used to identify deficits of LTP in neuropsychiatric disease.

Network plasticity

The existence of cortical network plasticity is supported by functional neuroimaging studies of cortical remapping during learning. When a specific motor task is practiced repeatedly, the amount of motor cortex activated during performance of that task widens in comparison with performance of different, unpracticed tasks (Karni et al., 1995). However, it is not known whether this cortical remapping of a learned task is permanent or a temporary part of the learning process. A recent expansion–normalization model (Kilgard, 2012) suggests that changes in cortical mapping during learning are transient states that facilitate the learning process. Through a temporary increase in the availability of neurons to engage in a novel task, the optimal neural circuitry for the task can then be recruited and refined (Kilgard, 2012).

Studies of brain injury also demonstrate the brain's adaptive cortical plasticity. Following a stroke, brain regions adjacent to the injured region are recruited to perform the tasks formerly performed by the injured region (Xerri, Merzenich, Peterson, & Jenkins, 1998). Active rehabilitation training may enhance this process of cortical reorganization (Nudo & Milliken, 1996). Over time, this task-related activation decreases and becomes restricted to fewer regions, implying an initial compensatory expansion of activation, followed by cortical reorganization (Ward, Brown, Thompson, & Frackowiak, 2003).

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Genes, environment, and plasticity

Genetic variation can influence plasticity processes, including neurogenesis and LTP. For example, mutations in the disrupted in schizophrenia 1 (*DISC1*) gene, which is associated with schizophrenia, can disrupt hippocampal neurogenesis, leading to creation of neurons with abnormal morphology or premature axonal and dendritic development (Duan et al., 2007; Eisch et al., 2008). Epigenetic mechanisms can also impact neuroplasticity. Epigenetics refers to heritable changes in gene expression that do not involve changes in actual DNA sequences. Three major mechanisms of epigenetic changes include DNA methylation, histone modification (such as acetylation), and noncoding RNAs (Hsieh & Eisch, 2010). Noncoding RNAs have been shown to regulate the proliferation of neural stem cells, either stimulating division of neural progenitor cells or promoting the apoptosis of cells (Iyengar et al., 2014). Deficiency in growth arrest in DNA-damage-inducible beta (*Gadd45b*), a gene that promotes DNA demethylation, has been associated with deficits in neurogenesis and dendritic growth of neurons (Ma et al., 2009). Late-phase LTP is dependent on gene transcription, which in turn depends on epigenetic processes. Thus, deletion of the gene coding for cAMP response element binding protein (CREB), which activates transcription through histone acetylation, results in impairments of late-phase LTP in animal models (Alarcon et al., 2004). In a related fashion, histone deacetylase inhibitors can enhance the induction of LTP by promoting gene transcription (Levenson & Sweatt, 2005).

LTP and LTD can also be impaired by various genetic mutations and deletions. For example, deletions in the genes coding for GluN2A subunit of the NMDA receptor (Kannangara et al., 2014) and subunits of calcium/calmodulin-dependent protein kinase II (Malenka & Nicoll, 1999) result in impairments in LTP. Numerous other genes that have been linked to LTP and LTD, including *CREB1* (Bourtchuladze et al., 1994), mammalian target of rapamycin (*mTor*; Hoeffer & Klann, 2010), and glycogen synthase kinase-3 beta (*GSK-3B;* Bradley et al., 2012),

The Val66Met polymorphism in the *BDNF* gene results in the substitution of the amino acid valine with methionine, and is associated with changes in cortical morphology and hippocampal activity. The methionine allele has been associated with volumetric reductions in the hippocampus and prefrontal cortex (Pezawas et al., 2004; Szeszko et al., 2005), and poorer performance in episodic memory tasks in normal individuals (Egan et al., 2003). This polymorphism may affect plasticity by impairing NMDA-receptor mediated LTP (Ninan et al., 2010).

Environmental factors can substantially impact neurogenesis. Maternal infectious exposure in rats is associated with decreased neurogenesis in the dentate gyrus of the hippocampus (Cui, Ashdown, Luheshi, & Boksa, 2009) and diminished cognitive performance in offspring after birth (Jiang et al., 2013). This correlation may be mediated by immune system activation (De Miranda et al., 2010). Prenatal exposure to substances of abuse, such as alcohol, can also lead to dysmorphic brain development (Gil-Mohapel, Boehme, Kainer, & Christie, 2010). In addition, rodent models of chronic stress demonstrate decreases in hippocampal progenitor cells (Hsieh & Eisch, 2010; Pham, Nacher, Hof, & McEwen, 2003).

While many variables have been observed to inhibit adult neurogenesis, other factors may enhance it. Deep brain stimulation, antidepressants, and exercise have been shown to increase adult neurogenesis in rodent models (Eisch et al., 2008). While promising, most research on this topic has been conducted on animal models. New techniques are being developed for in vivo visualization of neurogenesis in humans, such as the use of metabolic biomarkers to identify neural stem cells using proton magnetic resonance spectroscopy (Manganas et al., 2007). Further technical advances may allow for direct study of neurogenesis in human neuropsychiatric illness.

Critical periods and timing of onset and closure of neuroplasticity

Environment can shape brain function substantively across the life span. Plasticity is at its greatest during key epochs early in development (critical periods), and this presents developmental psychopathologists with new avenues for understanding vulnerability of the brain and intervening in a timely manner (Cicchetti & Toth, 2009). Studies of critical periods in the visual cortex have shown that among other processes, maturation of specific GABA circuits may determine the onset of certain critical periods. Timing and duration of critical periods may be modifiable by pharmacological manipulation of these and similar circuits (Takesian & Hensch, 2013). The onset of critical periods may be triggered by factors such as polysialic acid and neural cell adhesion molecule, which limit function of parvalbumin containing GABA circuits. Neural networks refined by experience are then actively stabilized by extracellular milieu factors, such as perineural nets, which serve as "brakes" for pruning processes (Wang & Fawcett, 2012). An understanding of such factors is likely to shed light on disorders of neuroplasticity such as schizophrenia, and motivate potentially novel treatment targets (Bitanihirwe & Woo, 2014).

Effects of age: Plasticity across the life span

The brain maintains some plasticity throughout life, but the capacity to change, which is at its peak early in life, gradually declines with age after young adulthood. The degree, slope, and timing of such decline, however, varies between individuals, is determined by both genetic and environmental factors, and may underlie risk for neuropsychiatric disorders (Oberman & Pascual-Leone, 2013).

Metaplasticity

The concept of metaplasticity refers to the plasticity of synaptic plasticity; that is, the ability of a synapse to engage in LTP

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or LTD can itself be modulated in a dynamic fashion (Abraham & Bear, 1996). Metaplasticity involves a priming stimulus that alters the subsequent response of a neuron to a plasticity-inducing stimulus. An important feature of metaplasticity is a time gap between the priming signal that stimulates metaplastic mechanisms and subsequent events that induce synaptic plasticity. Several mechanisms may enable metaplasticity. NMDA receptor activation, which induces LTP, also *inhibits* subsequent LTP for some time afterward (Abraham, 2008). Another mechanism may be metabotropic glutamate receptor activation, which enhances the induction of LTP in the hippocampus (Cohen, Coussens, Raymond, & Abraham, 1999). Finally, mechanisms of nonsynaptic plasticity (i.e., intrinsic plasticity) may also be categorized as a type of metaplasticity (Abraham, 2008). One possible function of metaplasticity may be to protect against excitotoxic damage to neurons that could occur through unopposed LTP (Abraham, 2008).

Summary

The brain maintains plasticity throughout life, though in varying degrees at the different epochs of age. This remarkable ability of the brain is orchestrated by the inherent properties of neurons, synapses, and glia, and by neurotransmitter systems such as glutamate, GABA, and neurotrophic factors. As a result, cortical reorganization occurs in response to learning and to injury throughout life. The extent to which the brain can dynamically change with learning and exogenous exposures is determined by genetic, epigenetic, and environmental factors; such plastic change could be adaptive or represent maladaptive cascades secondary to genetic and environmental inputs, as we will see in the next section.

Plasticity Alterations in Schizophrenia

Schizophrenia is a common, chronic complex illness typically beginning in adolescence and characterized by positive symptoms (hallucinations, delusions, and disorganized thinking), negative symptoms (social withdrawal, affect flattening, and motivational deficits), and impaired cognition across several domains (attention, executive function, memory, and social cognition; Tandon, Keshavan, & Nasrallah, 2008). It is widely held that schizophrenia is a developmental brain disorder, involving several processes affecting brain plasticity: early (neurogenesis, neural migration, and synaptogenesis; Murray, Lewis, Owen, & Foerster, 1988; Weinberger, 1987) and late in brain development (synaptic pruning, and myelination; Feinberg, 1982; Keshavan, Anderson, & Pettegrew, 1994; Murray et al., 1988; Weinberger, 1987). We herein review extant literature on alterations in schizophrenia that bear upon these neuroplasticity processes. There is evidence for diminished plasticity as well as aberrant excessive plasticity, as our review will show.

Neurons and synapses

Schizophrenia has been associated with a number of neuropathological abnormalities, which may also reflect deficiencies in plasticity. While neuroimaging studies demonstrate subtle reductions in gray matter volume in schizophrenia, postmortem studies indicate that this reduction is due to loss of cortical neuropil and dendritic arborization, rather than loss of neurons (Selemon, Mrzljak, Kleinman, Herman, & Goldman-Rakic, 2003). The most consistent neuropathological findings in schizophrenia are reduced density of dendritic spines (Glantz & Lewis, 2000; Harrison, 1999) and smaller cell bodies of neurons in the dorsolateral prefrontal cortex (Pierri, Volk, Auh, Sampson, & Lewis, 2001) and the hippocampus (Bennett, 2011). Adolescence, when schizophrenia typically begins, is a period during which the synaptic density is normally pruned by 50% (Anderson, Classey, Conde, Lund, & Lewis, 1995; Woo, 2013). Consequently, it has been suggested that dysfunctional or excessive synaptic pruning in the prefrontal cortex during adolescence may serve to diminish plasticity in schizophrenia (Keshavan et al., 1994).

Altered neurotransmission

NMDA receptors and glutamatergic pathways play a crucial role in modulating synaptic plasticity (Butefisch et al., 2000); they have also been implicated in schizophrenia (Moghaddam & Javitt, 2012; Woo, 2013) based on studies of NMDA antagonists causing psychotic and cognitive symptoms and electrophysiological changes in healthy individuals (Javitt, Steinschneider, Schroeder, & Arezzo, 1996), and diminished cortical NMDA receptor subunit expression in individuals with schizophrenia (Harrison, Law, & Eastwood, 2003). NMDA receptor hypofunction may cause glutamatergic excess and damage to pyramidal neurons, which may manifest as loss of dendritic arborization (Woo, 2013), leading to diminished neuroplasticity.

Impairments in GABAergic systems may also disrupt plasticity in schizophrenia. Inhibitory parvalbumin-containing neurons promote the normal maturation of neuronal circuits, and are abnormal in schizophrenia (Woo, 2013). In postmortem brains of schizophrenia patients, parvalbumin-containing neurons demonstrate diminished expression of glutamic acid decarboxylase 67 (GAD67), an enzyme that helps synthesize the inhibitory neurotransmitter GABA (Akbarian et al., 1995). Thus, in patients with schizophrenia, these neurons may fail to regulate synaptic pruning. GABA activity may be decreased in certain brain regions in schizophrenia (Barr et al., 2013), which may lead to reduced cortical plasticity (Butefisch et al., 2000; Voineskos, Rogasch, Rajji, Fitzgerald, & Daskalakis, 2013) and abnormal pruning. In addition, maturation of the extracellular matrix, comprising perineuronal nets, may be critical for termination of synaptic pruning processes (Woo, 2013); failure of such maturation may lead to "runaway" pruning.

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Glial alterations

Alterations in microglia, a type of neuronal support cell, may also contribute to impaired plasticity in schizophrenia. Both imaging and postmortem studies have observed increased activation of microglia in patients with schizophrenia. This has been noted in both the frontal cortex and the hippocampus (Doorduin et al., 2009). In an analysis of publicly available gene pathways related to glial cell function from the Psychiatric Genomics Consortium data, the glia–oligodendrocyte pathway was specifically associated with schizophrenia, indicating how oligodendrocyte dysfunction may contribute to the myelination abnormalities seen in schizophrenia (Duncan et al., 2014).

Alterations in neurotrophins

Deficits in neurotrophins, particularly BDNF, may underlie diminished plasticity in schizophrenia. Levels of BDNF are lower in schizophrenia than in healthy controls and are associated with severity of both positive (Pillai et al., 2010) and negative symptoms (Chen et al., 2014). As discussed earlier, the Val66Met polymorphism may impair the cellular transport of BDNF. Data on the association of this polymorphism with schizophrenia is inconsistent. One meta-analysis found that homozygosity for the infrequent methionine/methionine genotype was associated with elevated risk of schizophrenia (Gratacos et al., 2007), though other meta-analyses have not confirmed this finding (Kanazawa, Glatt, Kia-Keating, Yoneda, & Tsuang, 2007; Naoe et al., 2007).

BDNF appears to have an intricate relationship with the dopamine neurotransmitter system. While BDNF mediates expression of D1 and D5 dopamine receptors, removal of dopaminergic neurons in the midbrain is associated with diminished levels of BDNF, suggesting that these neurons influence *BDNF* gene expression (Favalli, Belmonte-de-Abreu, Wong, & Daskalakis, 2012). BDNF levels may rise with antipsychotic treatment, though again, evidence is inconsistent (Favalli et al., 2012; Grillo et al., 2007).

Abnormal sleep spindles and EEG findings

Patients with schizophrenia demonstrate significant reductions in density, number, and coherence of sleep spindles. Synchronous oscillations of neural circuits during spindle sleep have been thought to contribute to learning-related synaptic plasticity. Motor procedural learning during sleep, normally seen in healthy individuals, is impaired in schizophrenia, and this deficit is related to spindle reductions. (Wamsley et al., 2012). Spindle reductions appear to be related to cognitive impairments in early course patients with schizophrenia (Keshavan, Montrose, Miewald, & Jindal, 2011).

Some EEG abnormalities seen in schizophrenia may reflect impaired plasticity. For example, prepulse inhibition of the startle response refers to a decrease in the amplitude of the startle response that occurs when the startling stimulus is preceded by a weak stimulus. In schizophrenia, the startle response does not decrease as much as it does in healthy controls (Braff, Geyer, & Swerdlow, 2001), implying failure of habituation to a stimulus. This diminished habituation may reflect abnormal plasticity, in that the brain is unable to efficiently adapt to environmental change. Mismatch negativity, which represents an evoked response to an unexpected deviant stimulus, is also impaired in schizophrenia, and has been thought to reflect abnormal NMDA mediated short-term plasticity.

Diminished LTP and LTD-like network plasticity

As reviewed in the earlier section, functional MRI studies have demonstrated evidence of cortical plasticity in humans. This cortical remapping is observed in both healthy individuals following motor learning tasks and subjects with brain injury. It is also believed to underlie important perceptual and motor learning abilities (Reed et al., 2011). The cellular substrate of such cortical map plasticity is hypothesized to be related to the better demonstrated synaptic plasticity (Buonomano & Merzenich, 1998). Reduced neuroplasticity in schizophrenia could lead to deficit states such as cognitive deficits, negative symptoms, and functional disability (Fett et al., 2011; Green et al., 2004; Sergi et al., 2007). Evidence to support reduced cortical plasticity in schizophrenia comes from novel neuroimaging experiments that incorporate brain stimulation and EEGs.

Transcranial magnetic stimulation (TMS) has been used to study in vivo cortical plasticity in schizophrenia. This method uses focal magnetic fields to penetrate the cranium. The resultant electric currents then depolarize the underlying cortex, thus inducing action potentials in targeted brain regions (Kobayashi & Pascual-Leone, 2003). The output of cortical activation (in this case motor cortex) is measured using electromyographic recordings of hand muscle contractions. The most common method has been to compare motor evoked potentials (MEP) and motor thresholds before and after repetitive brain stimulation, with repetitive TMS (rTMS) or transcranial direct current stimulation (tDCS), which uses direct currents to shift the resting membrane potentials of underlying neurons (Nitsche & Paulus, 2000). These techniques use synaptic plasticity-inducing protocols that result in cortical excitability changes mirroring LTP (high-frequency rTMS and anodal tDCS) or LTD (low-frequency rTMS and cathodal tDCS).

Compared to healthy controls, reduced LTD-like plasticity has been reported in schizophrenia patients by demonstrating lack of expected changes in MEP (reduction in amplitude) and motor thresholds (increase) as induced by low-frequency rTMS, delivered to the premotor (Oxley et al., 2004) and motor (Fitzgerald et al., 2004) cortices, as well as by cathodal tDCS delivered to the motor cortex (Hasan, Nitsche, et al., 2012). It is interesting that these deficits were also demonstrated in recordings from the nonstimulated hemisphere (Hasan, Aborowa, et al., 2012), suggesting an association

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between LTD-like cortical plasticity and interhemispheric connectivity.

Possible impairments in LTP-like plasticity have also been demonstrated using similar study designs. Lesser enhancement of MEP was observed after anodal tDCS to the contralateral motor cortex in chronic schizophrenia patients relative to recent-onset patients and healthy controls (Hasan et al., 2011). Frantseva et al. (2008) used a different strategy to measure LTP-like plasticity by pairing (within 25 ms) median nerve electric stimulation with TMS over the contralateral motor cortex, in what is referred to as paired associative stimulation. Schizophrenia patients showed lesser facilitation of MEPs, when compared to healthy individuals. It is interesting that these patients also demonstrated motor learning deficits, and there was a significant association between the measure of LTP and motor skill learning. Use-dependent plasticity is another TMS measure that may reflect LTP-like plasticity (Classen, Liepert, Wise, Hallett, & Cohen, 1998). Here, the spontaneous direction of TMS-induced thumb movements is first measured. Subjects are then trained with 30 min of motoric practice of thumb movements in a direction that is opposite (by 180 degrees) to the actual thumb movements. Postpractice thumb movement direction elicited by TMS is then evaluated. Using this experiment, Daskalakis, Christensen, Fitzgerald, and Chen (2008) found that schizophrenia patients had significantly attenuated motor reorganization compared to healthy subjects.

Stimulus-specific plasticity paradigms using event-related potentials have also been used to quantify occipital (visual) and temporal (auditory) lobe LTP-like plasticity (Clapp, Kirk, et al., 2005; Clapp, Zaehle, et al., 2005). Here, repetitive high-frequency visual or auditory stimuli are used to produce a lasting facilitation of visual or auditory evoked potentials, respectively. Using this paradigm, researchers have demonstrated lesser facilitation of visual (Cavus et al., 2012) and auditory (Mears & Spencer, 2012) evoked potentials in schizophrenia patients as compared to healthy controls.

Overall, these findings not only provide evidence for deficient cortical plasticity that represent both LTD and LTP-like synaptic plasticity but also link these deficits to impairments in cognitive functions like learning and memory (Frantseva et al., 2008; Wamsley et al., 2012).

Genes, environment, and impaired plasticity in schizophrenia

Schizophrenia is highly heritable. In recent years, several genetic loci with small to moderate effects have been identified in genomewide association studies. It is interesting that these genes not only regulate glutamatergic, GABAergic, and dopaminergic transmission but also regulate several aspects of brain development and plasticity discussed above (Balu & Coyle, 2011). Alterations in the *DISC1* gene, expressed during both prenatal and adult hippocampal neurogenesis (Jun, Hussaini, Rigby, & Jang, 2012) have demonstrated signs of maladaptive plasticity (mistargeted formation of synapses and reduced dendritic arborization) in mice (Kvajo et al., 2011; Pletnikov et al., 2008). Time-specific transient alterations (e.g., in utero) of *DISC1* have shown to adversely affect postnatal maturation of prefrontal dopaminergic and GABAergic neurotransmission (Niwa et al., 2010). The neuregulin 1 gene (*NRG1*), which codes for the protein neuregulin 1, is involved in adult neurogenesis. *NRG1* has been shown to stimulate proliferation of hippocampus-derived neural progenitor cells (Lai & Feng, 2004), and partial deletions of this gene are associated with stress sensitivity in animal models (Chohan et al., 2014). Thus, genetic alterations in the capacity for neurogenesis may weaken the brain's response to environmental stress, elevating the risk for development of neuropsychiatric disorders.

One novel line of work has used human induced pluripotent stem cells to examine alterations in neurogenesis in schizophrenia. In this method, fibroblasts are obtained from individuals and reprogrammed into pluripotent stem cells. In one such study in patients with schizophrenia, these neurons displayed a significant decrease in the number of neurites and neuronal connectivity (Brennand et al., 2011). Abnormalities in gene expression were also observed, such as decreased expression of the protein PSD95 and increased expression of *NRG1*. Of the several hundred genes that demonstrated abnormal expression, 13% were reported to be abnormal in schizophrenia in previous publications (Brennand et al., 2011).

Environmental factors may mediate the dendritic spine reductions observed in schizophrenia. Chronic stress and prenatal stress have been correlated with reduced dendritic arborization in animal models (Markham, Mullins, & Koenig, 2013), while environmental enrichment and learning are associated with increased dendritic arborization (O'Malley, O'Connell, Murphy, & Regan, 2000). In summary, plasticity in schizophrenia may be abnormal due to genetically mediated changes in NMDA receptor function, GABA-mediated inhibition, and neurogenesis. These abnormalities eventually lead to observable neuropathological abnormalities in dendritic spine density and complexity. Epigenetic factors may mediate the impact of environmental factors on plasticity processes via noncoding RNAs (Spadaro & Bredy, 2012).

Aberrant excessive neuroplasticity in schizophrenia?

In contrast to diminished plasticity, aberrant excessive synaptic plasticity in neural networks may underlie positive symptoms of schizophrenia; this may result from dysregulated metaplasticity secondary to either genetically controlled reduced synaptic plasticity in key cortical regions or environmental effects like stress or substance abuse. For instance, Hoffman has suggested that social withdrawal or "deafferentation" may trigger the initial active phase of schizophrenia (Hoffman, 2007) by plastic reorganization by the "social brain" to generate spurious meaning from social cues that may manifest as hallucinations or delusions (Hoffman, 2008). This may reflect metaplastic effects (Abraham,

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2008) on social brain regions. Animal experiments suggest that social isolation enhances the surface trafficking of NMDA receptors in dendritic spines of principal neurons in the amygdala, thus leading to aberrant plasticity and emotion dysregulation (Gan, Bowline, Lourenco, & Pickel, 2014). These findings are also in sync with the observation that sensory deafferentation induces hyperplastic brain changes that may be mediated either by removal of GABA-related cortical inhibition or by LTP-like mechanisms (Ziemann, Hallett, & Cohen, 1998).

Support for aberrant excessive plasticity also comes from neuroimaging studies examining the dysconnection hypothesis of schizophrenia (Stephan, Friston, & Frith, 2009). Diffusion tensor imaging has revealed greater white matter connectivity in schizophrenia patients with auditory hallucinations, in contrast to those without in the arcuate fasciculus, which connects the primary auditory cortex with language areas, and the cingulate bundle, a part of the limbic cortex (Hubl et al., 2004). This aberrant connectivity could underlie the abnormal coactivation of regions that normally process external auditory stimuli and language-related areas (Dierks et al., 1999). Moreover, patients with both auditory and visual hallucinations show higher white matter connectivity in the pathways connecting the visual areas to the hippocampal formation (Amad et al., 2014) and the amygdala (Ford et al., 2014), when compared to patients with only auditory hallucinations. Similarly, patients with auditory hallucinations show increased resting-state functional connectivity between the hippocampal formation and the language regions (Sommer, Clos, Meijering, Diederen, & Eickhoff, 2012). These findings partially support earlier observations of heightened regional hippocampal blood flow in schizophrenia patients at rest and during a cognitive task (Medoff, Holcomb, Lahti, & Tamminga, 2001) and emerging evidence on correlations between hippocampal volumes and psychotic symptoms (Mathew et al., 2014). In another study that combined resting-state and task (working memory) based functional imaging, patients with schizophrenia and their relatives demonstrated hyperactivation (reduced task-related suppression) and hyperconnectivity of the default mode network (Whitfield-Gabrieli et al., 2009) when compared to healthy subjects. These abnormalities were associated with severity of psychopathology and cognitive deficits (Whitfield-Gabrieli et al., 2009). Finally, structural MRI studies have demonstrated significantly increased cortical thickness in regions related to self-monitoring (the left insular cortex, cingulate gyrus, and dorsal middle frontal gyrus and hippocampal formation) in schizophrenia patients with auditory hallucinations than those without (Amad et al., 2014; van Swam et al., 2012). It is interesting that auditory hallucinations have been linked to a failure to activate areas concerned with the monitoring of inner speech (McGuire et al., 1995); impaired corollary discharges, which are neural signals that coincide with self-generated thoughts/movements (Crapse & Sommer, 2008), may underlie increased cortical activity to self-induced sensory stimuli observed in patients with schizophrenia (Whitford et al., 2011). It has been speculated that the mirror neuron system plays a role in the generation of these corollary discharges (Prather, Peters, Mowicki, & Mooney, 2008; Tchernichovski & Wallman, 2008). Mirror neuron system activity is reduced in schizophrenia (Kato et al., 2011; Mehta, Agarwal, et al., 2013). These deficits were also found to be associated with social cognitive deficits in these patients (Mehta, Basavaraju, Thirthalli, & Gangadhar, 2012; Mehta, Thirthalli, Bassavaraju, Gangadhar, & Pascual-Leone, 2013).

The 22q11 microdeletion syndrome is the strongest known link between any genetic anomaly and schizophrenia, with as many as 30% developing symptoms of schizophrenia (Pulver et al., 1994). Mouse models of the 22q11 microdeletion syndrome show a dramatic enhancement in short- and long-term potentiation of synaptic transmission in an age-dependent manner in the hippocampus of these mice, as compared to the wild-type mice (Earls et al., 2010). The 22q11 microdeletion may lead to a reduction in the *Dgcr8* gene, resulting in an elevated Serca2 expression causing abnormally excessive synaptic plasticity (Earls & Zakharenko, 2013). Another mechanism through which 22q11 microdeletion syndrome manifests is haploinsufficiency of the transcription factor TBX1. This transcription factor interacts with several signaling pathways, including β-catenin, a protein that functions as the "molecular glue" to keep synapses together (Papangeli & Scambler, 2013). Recent evidence from mice experiments has demonstrated that excessive hippocampal beta-catenin can potentially lead to "sticky synapses" that have impaired LTD-like plasticity, which result in impaired cognitive flexibility (Mills et al., 2014). This process may yield itself as a mechanistic basis to understand the inflexible nature of persistent delusions in schizophrenia.

As reviewed earlier, mutations in the *DISC1* gene are considered risk factors for schizophrenia (Harrison & Weinberger, 2005). *DISC1* knockdown models have demonstrated an accelerated hippocampal neurogenesis, as well as increased dendritic development and synapse formation. These aberrant morphological changes result in an accelerated formation of functional GABAergic and glutamatergic synaptic inputs to new neurons, as well as enhanced excitability of the hippocampal neurons (Duan et al., 2007). *DISC1* thus appears to be a critical regulator of the aberrant excessive synaptic plasticity observed in schizophrenia. Yet another animal model of schizophrenia that employs phospholipase C-β1 knockout mice has also demonstrated significantly enhanced adult hippocampal neurogenesis in these mice when compared with the wild-type littermates (Manning, Ransome, Burrows, & Hannan, 2012).

Together, the above synthesis of evidence for aberrant excessive synaptic plasticity in limbic regions against a background of reduced cortical plasticity provides a framework to understand different symptom dimensions of schizophrenia within the broad purview of the "dysplastic" model.

Summary

Several lines of evidence point to diminished neuronal plasticity in widespread brain regions in schizophrenia, including

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reductions in dendritic and glial density; altered glutamatergic, GABAergic, and neurotrophic function; and in vivo evidence of diminished LTP and LTD-like plasticity. While these changes may account for the core deficit symptoms of schizophrenia, positive symptoms might result from excessive neuroplasticity causing aberrant reorganization in limbic circuits. Genetic, epigenetic, and environmental factors, as discussed below, may influence the nature, extent, timing, and persistence of such abnormalities.

Aberrant Plasticity and the Schizophrenia Risk State

Schizophrenia has been linked to a plethora of genetic as well as socioenvironmental risk factors (Morgan, McKenzie, & Fearon, 2008; Shah, Mizrahi, & McKenzie, 2011; Sullivan, 2005), which may impact (either directly or indirectly) the kinds of neuroplastic processes described in previous sections. The extant neurodevelopmental hypotheses of schizophrenia (Fatemi & Folsom, 2009; Keshavan, 1999; McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2003; Murray, 1994) suggest that developmental brain changes may occur during the prenatal or in postnatal life extending into adolescence or early adulthood. Such alterations could profoundly alter *early* brain developmental processes such as neuronal proliferation, migration, apoptosis, and synaptogenesis, and/or *later* processes of synaptic pruning and myelination. These processes are further impacted by hormonal changes, and exogenous insults such as trauma, neglect, and substance abuse during childhood or adolescence (Keshavan, 1999; Paus, Keshavan, & Giedd, 2008; Piper et al., 2012). As the combination of "hits" individuals encounter increases, their brains are vulnerable to becoming prone to more distressing symptoms and worsening functional impairment (Owen, Donovan, Thapar, & Craddock, 2011). The role of certain chronic risk factors (such as negative life events, daily hassles, or substance misuse) appears to be additive and cumulative (Collip, Myin-Germeys, & van Os, 2008). We suggest that it is not only the cumulative adverse exposures per se but also *repeated* exposure that plays a role via altered brain plasticity in promoting liability to brain changes, symptoms, and impairment.

Trajectory of premorbid psychopathology in high-risk subjects may be linked to critical periods of vulnerability

If insults to core neurobiological processes contribute to the schizophrenia phenotype many years later, the neurodevelopmental hypothesis holds that such processes are both unfolding and especially susceptible to perturbation during critical periods. These periods may include specific windows of prenatal life, childbirth, childhood, and adolescence at which particular risk exposures have been identified. At the earliest stages of conception, for example, advanced paternal age, presumably through de novo mutations, appears to confer susceptibility (Malaspina, 2001). During the prenatal period, maladaptive infectious exposure may influence maternal immune response and/or fetal physiology in an experience-expectant fashion to contribute to a modest but still significant risk for psychosis (Brown & Derkits, 2010). In childhood and adolescence, experience-dependent factors such as abuse, use of psychotropic substances and bullying also increase risk (Addington et al., 2013; Shah et al., 2012; van Dam et al., 2012).

The concept of combinations of exposures/insults at specific critical periods maps onto observations that the timing and course of development may differ across brain regions or circuits (Lewis & Akil, 1997). For example, synaptic density in the visual cortex reaches adult levels by preschool age (Toga, Thompson, & Sowell, 2006), whereas higher order disruption in executive function has repeatedly been localized to the prefrontal cortex, an area that is among the last to complete maturation (Gogtay, 2008). If endogenous or exogenous insults lead to disrupted neural processes that compromise neuroplasticity, then phenotypic manifestations may reflect the neural circuits maximally affected by failed, aberrant, or excessive plasticity.

The earliest detectable phases of psychotic illness (i.e. the component signs and symptoms with which it is consistently associated) tend to emerge after, rather than before, the accumulation of critical periods of exposure and brain maturation. This has allowed researchers to focus new attention on the trajectory of the premorbid and subthreshold stages in children and adolescents at high clinical and/or familial risk for schizophrenia. Individuals at familial high risk (FHR) have an 8%–12% chance of converting to psychosis over the life span; in contrast, in clinical studies, distressed and help-seeking clinical high-risk (CHR) subjects have a 15%–40% rate of conversion over a 2- to 3-year period (Fusar-Poli et al., 2013; Tandon, Keshavan, & Nasrallah, 2008). However, a broad spectrum of nonpsychotic psychopathology is substantively more common in the premorbid phase. In an ongoing prospective study of FHR relatives (Shah et al., unpublished data), we have observed that cognitive/learning disorders appear to emerge earliest, followed by anxiety and affective disorders, before social withdrawal and subthreshold psychotic-like symptoms and impaired cognition set in (Figure 4). The emergence of such a "classic" trajectory may reflect that the neural circuits underlying attention and sensorimotor function mature (i.e., show diminishing plasticity) earliest, followed by the maturation of limbic/striatal and eventually higher association brain regions such as the prefrontal cortex. However, as will be discussed further, the sequence, timing, and slope of such trajectory may vary greatly between individuals, in relation to genetic and environmental factors.

Neuroplasticity may be altered in subjects at risk for psychosis

We herein review the relatively limited evidence suggesting that neurodevelopmental processes involved in schizophrenia etiopathogenesis reflect not only an altered trajectory of otherwise determined brain development but also disruptions to neuroplastic processes themselves.

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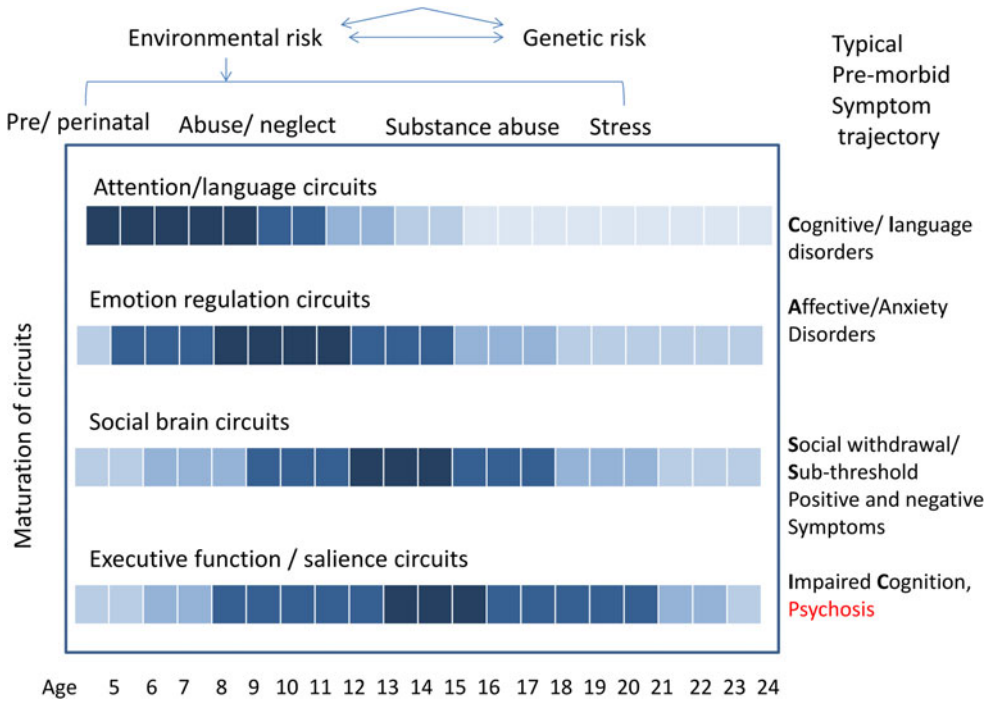

Figure 4. (Color online) Trajectory of phenotypic manifestations among individuals deemed to be at high risk for schizophrenia and the genetic and environmental predisposing factors.

Gray matter changes. While few neuropathological data exist, progressive gray matter loss seen in high-risk subjects indirectly suggests alterations in brain plasticity. CHR individuals who later developed psychosis had decreased gray matter volumes in some neuroanatomical structures compared with controls and nonconverters, as well as gray matter reductions over time (Borgwardt et al., 2007; Pantelis et al., 2003). However, in young high-risk siblings who did not develop serious psychopathology, gray matter deficits normalize by late adolescence, suggesting that normal plasticity is associated with resilience (Gogtay et al., 2007; Mattai et al., 2011). Genetic and environmental factors may determine variation in trajectories of high-risk individuals (Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007). For example, more severe gray matter loss over time is seen in FHR subjects exposed to cannabis compared with those without such exposure (Welch et al., 2013). Interaction between cortical thickness and the well-studied cathechol-*O*-methyltransferase (*COMT*) val158met polymorphism provides another example of differential susceptibility: while valine/valine homozygosity was related to steeper gray matter loss in adolescence in probands and their siblings, it *attenuated* cortical thinning in healthy controls (Raznahan et al., 2011).

Alterations in functional connectivity. FMRI studies in FHR subjects using nonlinear dynamic causal modelling have shown reduced thalamocortical connectivity (Dauvermann et al., 2013). In a recent fMRI study using an emotion recognition paradigm, Gee et al. (2012) demonstrated that relative to controls, CHR subjects showed increased amygdala and decreased ventral prefrontal cortex activation with age. This suggests that a failure of the prefrontal cortex to regulate amygdala reactivity emerges during adolescence and young adulthood.

Altered glutamatergic neurotransmission. Altered glutamatergic function implicated in impaired brain development (Keshavan, 1999) may be related to aberrant neuroplasticity in schizophrenia. Neuronal "dysconnectivity," in this model, may be mediated by abnormal NMDA receptor function. Evidence for this model stems from structural and functional neuroimaging, electroencephalography, neurophysiology, neuropharmacology, genetics, network modeling, neuropathology, and postmortem studies of patients with schizophrenia (Stephan et al., 2009). However, direct evidence of premorbid glutamatergic abnormalities is sparse. Of interest, recent magnetic resonance spectroscopy reports have found abnormal glutamine/glutamate levels in FHR and CHR subjects (de la Fuente-Sandoval et al., 2011; Fusar-Poli et al., 2011; Stone et al., 2009, 2010; Tandon et al., 2013).

Mismatch negativity, a promising biomarker in schizophrenia (Javitt et al., 1996), is significantly reduced in CHR subjects compared to healthy control subjects and in those who convert to psychotic disorders (Perez et al., 2014). The mismatch negativity effect has been thought to reflect abnormal modulation of NMDA receptor-dependent plasticity (Baldeweg & Hirsch, 2014). Another physiological measure thought to reflect integrity of GABAergic circuits is that of gamma synchrony, known to be abnormal in schizophrenia. Recent evidence suggests abnormalities in gamma band

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responses to auditory stimuli in CHR subjects (Perez et al., 2014). These observations support the view that impaired NMDA/GABA mediated plasticity may underlie the risk for schizophrenia.

BDNF. As discussed earlier, neurotrophins such as BDNF appear to be altered in schizophrenia (Buckley, Pillai, & Howell, 2011). In FHR groups, a verbal memory task undertaken during fMRI found decreased activation during encoding and retrieval in multiple corticolimbic regions for valine/valine BDNF homozygotes at the rs6265 polymorphism (Baig et al., 2010). It is interesting that this risk allele does not suppress task-related frontal activation per se, because the same risk allele *increased* activation at the anterior cingulate cortex during a sentence completion task (Whalley et al., 2010). Altogether, these variable findings suggest impaired neuroplasticity in frontal brain functions depending on region and/or task.

Increased stress reactivity and emergent symptoms may be related to aberrant plasticity

Adolescence denotes a period of increasing physiologic response to stress, which, if dysregulated, can alter the long-term set point of neurobiologic pathways (Walker, Sabuwalla, & Huot, 2004). One mechanism invoked to explain the linkage between stress and psychotic symptoms is that of sensitization, the notion that repeated exposures to stress will produce successively larger physiologic responses over time, in some cases becoming aberrant, particularly in those at risk (Collip et al., 2008). First, recurrent administration and withdrawal of amphetamine in peripubertal mice leads to long-lasting alterations in neuroplasticity-related genes, which then may increase dopamine-dependent behaviors (Calabrese et al., 2013). Support for this theory is found in experiments in which dopamine response following amphetamine challenge is associated with psychotic symptoms; in time, exposure to even attenuated stressors can lead to excessive dopamine release (Laruelle & Abi-Dargham, 1999; Lieberman, Sheitman, & Kinon, 1997). Second, dynamic changes in the hypothalamic–pituitary–adrenal (HPA) axis are believed to occur in response to internal and external stimuli and demands, whether adaptive or pathologic (Pariante, 2008). The number and significance of stressful life events increases as children enter adolescence (Gunnar & Quevedo, 2007; Gunnar & Talge, 2011); with this comes HPA axis alterations, including higher basal cortisol levels and more robust acute responses to stress (Lupien, McEwen, Gunnar, & Heim, 2009; Walker et al., 2013). Pituitary volume is elevated in the early phases of the illness (first episode and high-risk subjects who later convert; Nordholm et al., 2013). Cortisol has also been repeatedly found to be elevated in psychosis (Borges, Gayer-Anderson, & Mondelli, 2013) and in CHR subjects, particularly those who will later convert to psychosis (Sugranyes, Thompson, & Corcoran, 2012; Walker et al., 2010). Third, prevailing theories regard dopaminergic hyperactivity as a "final common pathway" by which attenuated and (later) full-blown symptoms emerge in psychosis. It has been postulated that dopaminergic dysregulation in psychosis is sensitized (influenced by stress) through the HPA axis, because mesolimbic dopamine activity is known to be associated with cortisol release, symptom appearance, and relapse. Positron emission tomography studies link psychosocial stress with dopamine release abnormalities in healthy individuals (Pruessner, Champagne, Meaney, & Dagher, 2004; Wand et al., 2007), patients with schizophrenia, CHR, and first-degree relatives (Brunelin et al., 2010; Lataster et al., 2014; Mizrahi et al., 2012).

Social deafferentation may predispose to plastic brain reorganization, leading to psychosis

Observations of social withdrawal long preceding psychotic symptoms, in the premorbid and prodromal phases of schizophrenia, is consistent with Hoffman's model (2007, 2008), discussed earlier, which posits that the plastic brain reorganizes neural pathways following isolation to "produce spurious social meaning . . . in the form of complex, emotionally compelling hallucinations and delusions" (Hoffman, 2008) Social deafferentation suggests a chain of causation, beginning with the effect of environment on neurobiology, followed by the impact of neurobiological changes and plasticity on experience. This concept also identifies a critical period during which both social withdrawal and deafferentation might result in psychotic symptoms. Initial, although only preliminary, evidence for the hypothesis has been obtained in CHR patients (Hoffman, 2007).

Summary

The aberrant plasticity model and critical period concepts, as they relate to the premorbid and onset periods prior to psychosis, allow for the suggestion of an evolution of risk states that brings together various hypotheses of reduced plasticity predisposing to aberrant plastic reorganization of neural circuits. Early brain insults due to prenatal or early life adversity may lead to reduced cortical glutamatergic function and impaired experience-dependent neuroplasticity. This fits with the picture of early cognitive and learning deficits, and social withdrawal and deafferentation seen in premorbid studies of adolescents at risk for schizophrenia. In turn, reduced glutamatergic tone would result in decreased synaptic and gray matter density by the time of early adolescence. Combined with increased exposure to stressful situations and decreased cognitive adaptive capacity to them, these alterations would lead to a maladaptive plasticity cascade, that is, overactivation of the HPA axis (even beyond the normal HPA changes expected during adolescence) and dopaminergic stress responses that underlie affective dysregulation, risk for substance abuse, and eventually psychosis. This integrative pathophysiologic model might explain the "classic" trajectory of phenomena and symptomatology in high-risk populations.

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Harnessing Neuroplasticity for Therapeutic (and Prophylactic) Gains

It is clear that observations of diminished as well as aberrant excessive plasticity motivate novel therapeutic as well as prophylactic therapeutic strategies in schizophrenia and the at-risk states for this illness. We herein provide examples of such emerging approaches.

Cognitive training

Cognitive training or cognitive remediation is an evolving form of intervention that allows us to intentionally harness neuroplastic processes related to learning for therapeutic purposes that target the disabling cognitive deficits of schizophrenia (Keshavan, Vinogradov, Rumsey, Sherill, & Wagner, 2014). A recent meta-analysis suggested that cognitive training resulted in modest gains on cognition and socio-occupational functioning with mean effect sizes of 0.45 and 0.42, respectively (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Besides, the benefits of some of these interventions are likely to last beyond treatment cessation (Eack, Greenwald, Hogarty, & Keshavan, 2010; Subramaniam et al., 2012; Wykes et al., 2003).

The underlying plastic changes with cognitive training have been explored by neuroimaging studies. Patients who received cognitive training showed less gray matter loss in the left parahippocampal and fusiform gyrus and greater gray matter increases in the left amygdala after 2 years of cognitive enhancement therapy, as compared to a nonspecific supportive therapy (Eack, Hogarty, et al., 2010). It is interesting that patients with larger cortical thickness at baseline (higher cortical "reserve") improved faster (Keshavan, Eack, et al., 2011). Computer-based cognitive training (a reality-monitoring task) has been shown to normalize the task-based activation of the prefrontal regions (Subramaniam et al., 2012), emotional-task based neural activations in the postcentral gyrus (Hooker et al., 2012), and attention/executive task based activations of the dorsolateral prefrontal cortex, anterior cingulate, and frontopolar cortex (Haut, Lim & MacDonald, 2010). In addition, specific training of auditory discrimination and verbal memory and not a broadly administered cognitive training showed normalization of abnormally reduced sensory gating in schizophrenia patients as measured using magnetoencephalography (Popov et al., 2011). Diffusion tensor imaging studies provide additional evidence by revealing normalization of the interhemispheric connectivity between the bilateral prefrontal cortices via the corpus callosum in patients who received cognitive remediation (Penades et al., 2013). While structural and functional cortical plasticity changes have been demonstrated with cognitive training, one study also showed an increase in serum BDNF levels (Vinogradov et al., 2009).

Brain stimulation approaches to improve symptoms by targeting cortical plasticity

Noninvasive brain stimulation strategies have been increasingly used to target specific regions of the brain, guided by existing neurobiological evidence of impaired (either reduced or excessive) activity in specific neural systems (Hasan, Wobrock, Rajji, Malchow, & Daskalakis, 2013; Rajji, Rogasch, Daskalakis, & Fitzgerald, 2013). Two symptom dimensions that have been commonly studied are negative symptoms, where high-frequency TMS pulses are applied to activate the left dorsolateral prefrontal cortex, and auditory hallucinations, where low-frequency TMS pulses are applied to inhibit the left temporoparietal cortex (Hoffman et al., 1999). In a meta-analysis of studies on high-frequency rTMS delivered to the left dorsolateral prefrontal cortex, it was shown that the rTMS improved negative symptoms of schizophrenia with a modest effect size of 0.43 (Dlabac-de Lange, Knegtering, & Aleman, 2010). Similar findings were also replicated in a larger, more recent meta-analysis (Shi, Yu, Cheung, Shum, & Chan, 2014). This is still an evolving treatment modality, and one of the means to optimize the therapeutic benefit is by targeting different sites like deeper prefrontal cortices (Levkovitz, Rabany, Harel, & Zangen, 2011) or even the cerebellar vermis (Demirtas-Tatlidede et al., 2010).

A recent meta-analysis of five randomized, double blind, sham-controlled studies reported that low-frequency rTMS delivered to the left temporoparietal cortex improved auditory hallucinations with a modest effect size of 0.44 (Slotema, Aleman, Daskalakis, & Sommer, 2012). Furthermore, another study using the same investigation demonstrated a reduction in cerebral blood flow in the primary auditory cortex, left Broca's area, and cingulate gyrus in patients who received 10-day rTMS sessions for auditory hallucinations (Kindler et al., 2013). Recently, tDCS has been shown to be beneficial in treating medication-resistant auditory hallucinations in schizophrenia (Brunelin et al., 2012).

A third application of brain stimulation in schizophrenia that is gaining preliminary empirical support is in treating cognitive deficits (Guse, Falkai, & Wobrock, 2010). A single session of 20-Hz rTMS delivered to the bilateral dorsolateral prefrontal cortex resulted in a potentiation of the frontal gamma oscillatory activity during a working-memory task in healthy individuals (Barr et al., 2009). This sequence of bilateral rTMS administered in schizophrenia patients for 4 weeks, was compared to stimulation using sham rTMS in a randomized controlled trial. It was found that the group receiving true rTMS performed significantly better on a working-memory task at the end of the 4-week trial (Barr et al., 2013). However, another study using unilateral (left) 10-Hz rTMS did not find similar benefits (Guse et al., 2013). Application of rTMS for cognitive enhancement is still in its infancy and requires more studies to standardize and optimize the treatment protocols. One way ahead may be to target modulation of mirror neuron regions to enhance social cognitive performance (Mehta, Thirthalli, et al., 2013).

Medications

Antipsychotic medications are the most common form of therapeutic intervention in schizophrenia. Multiple studies have demonstrated that antipsychotic medications induce

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both anatomical- and molecular-level neuroplastic changes in the brain (Konradi & Heckers, 2001). Studies using rat hippocampal neuronal cultures have revealed adaptive changes in postsynaptic density proteins, dendritic spine morphology, BDNF expression, and excitatory postsynaptic potentials (Critchlow, Maycox, Skepper, & Krylova, 2006; Pandya, Kutiyanawalla, & Pillai, 2013; Park et al., 2013; Shim, Hammonds, Tatsuoka, & Feng, 2012). It is interesting that typical and atypical antipsychotics have a differential regulation of synaptic plasticity by modulating activity of different postsynaptic proteins (Critchlow et al., 2006). At a molecular level, typical antipsychotic medication-induced plasticity changes are largely observed in the striatum and nucleus accumbens, whereas atypical antipsychotic drugs have a subtler and more widespread impact (Konradi & Heckers, 2001).

Such a pattern is partially corroborated by structural neuroimaging studies. Treatment with typical antipsychotic medications is associated with enlargement of the striatum and other structures in the basal ganglia and reduction in frontal, temporal, and parietal cortical gray matter volume (Dazzan et al., 2005; Lieberman et al., 2005; Smieskova et al., 2009). Atypical antipsychotic medications are associated with enlargement of thalamus and cortical gray matter volumes (Dazzan et al., 2005; Deng et al., 2009; Scherk & Falkai, 2006), as well as, reduction in other cortical (medial frontal gyrus) volumes (Deng et al., 2009). It is intriguing that potential neuroplastic changes are seen considerably early. A pharmacological-MRI investigation in humans reported striatal volume changes and structural–functional decoupling in motor circuits within hours of administering D2-receptor blockers (Tost et al., 2010). It is however important to note that it is still unclear as to whether long-term cortical volume change is a function of antipsychotic medications or of disease progression (Andreasen, Liu, Ziebell, Vora, & Ho, 2013).

The therapeutic efficacy of lithium may also be explained based on its ability to modulate synaptic plasticity. Chronic lithium treatment increases dendritic branching in hippocampal neurons, and also enhances LTP-like plasticity (Shim et al., 2012). Lithium in humans can cause a switch from LTD- to LTP-like plasticity using TMS (Voytovych, Krivanekova, & Ziemann, 2012). Lithium's effects on BDNF (Voytovych et al., 2012; Yasuda, Liang, Marinova, Yahyavi, & Chuang, 2009) and on the B-cell lymphoma 2 (*BCL2*) family of genes that regulate apoptosis (Beech et al., 2014; Lowthert et al., 2012) may explain these observed effects.

Erythropoietin has important neurotrophic and immunomodulatory functions (Rabie & Marti, 2008) and has shown improvement in cognitive performance in a controlled trial in schizophrenia (Ehrenreich et al., 2007). Overall, these novel treatment strategies provide broader therapeutic avenues for clinicians to harness neuroplasticity in aiding patients with schizophrenia.

Other approaches

Physical exercise (wheel running) in mice has shown to increase neurogenesis, dendritic proliferation, and LTP in the dentate gyrus of the hippocampus (van Praag, Kempermann, & Gage, 1999). In humans, regular aerobic exercise increases hippocampal and cortical volumes and improves cognitive performance in the elderly (Erickson et al., 2011), as well as in early middle adulthood (Killgore, Olson, & Weber, 2013). Plausible mechanisms include increased blood flow and oxygenation to the hippocampus (Pereira et al., 2007) and greater production of BDNF (Vaynman, Ying, & Gomez-Pinilla, 2004). Pajonk et al. (2010) have extended this work in patients with chronic schizophrenia. They found that 3 months of aerobic exercise, as opposed to control condition (playing table football), not only increased hippocampal volumes but also resulted in greater *N*-acetylaspartate to creatine ratio in the hippocampus, and improved short-term memory of these patients.

Other novel therapeutic options that can enhance synaptic plasticity include enriched environment. Providing an enriched environment comprising novel and complex sensory, cognitive, social, and motor stimuli can boost key neural circuits to bring about adaptive behavioral change. This has been demonstrated in rodents, where enriched environments have resulted in neuroplasticity-driven molecular, cellular, and behavioral changes. These plasticity-harnessing benefits have been demonstrated in rodent models of Alzheimer dementia, schizophrenia, and autism spectrum disorders (Hannan, 2014; Pang & Hannan, 2013). Integrating specific dimensions of environmental enrichment in rehabilitation programs for schizophrenia patients needs further study.

Conclusion

We have outlined evidence that the core manifestations of schizophrenia (positive, negative, and cognitive symptoms) may be understood as resulting from aberrant neuroplasticity. As shown in patients with schizophrenia as well as at-risk populations, this dysplasticity may involve both hypoplasticity in key brain systems serving cognitive functions and goal-directed behavior, and hyperplasticity in neural systems governing salience detection, emotion processing, and regulation as well as default mode systems. It is possible that the hyperplasticity is a maladaptive response in an effort to compensate for a primary impairment in plasticity, though the converse is also possible (Figure 3). Preventive and therapeutic interventions with medications, neuromodulation, and psychosocial treatments may be directed both at reversing plasticity deficits as well as harnessing compensatory neuroplasticity in more adaptive channels. The conceptual model we have developed herein has heuristic value, and suggests several testable questions for future research. The increasing understanding of brain mechanisms underlying plasticity may suggest new ways of detecting preclinical disease, better biomarkers to guide treatment selection, and novel therapeutic targets.

A number of essential questions remain to be examined and answered by future generations of basic and clinical research: (a) What specific mechanisms of altered plasticity contribute to schizophrenia? Are they primary rather than

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secondary to other pathophysiological processes, and what gene–environment interactions underlie such mechanisms? (b) What underlies the variable trajectories among high-risk individuals, for example, between those who to convert to psychosis versus nonconverters, and (in nonconverters) between those who develop cognitive versus affective, anxiety, or substance misuse disorders? (c) Among proband groups, do differences in plasticity capacities predict differential outcome trajectories? (d) What are the best ways to noninvasively harness plasticity in the service of prevention and early intervention? (e) Are the plasticity alterations unique to specific diagnoses, or do they vary dimensionally across a broad spectrum of major psychiatric disorders? (f) Can critical windows of neuroplasticity be reopened in patients who are already on a trajectory to major mental illness or who have an already-evident disorder?

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