

Dysconnection in Schizophrenia: From Abnormal Synaptic Plasticity to Failures of Self-monitoring

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Over the last 2 decades, a large number of neurophysiological and neuroimaging studies of patients with schizophrenia have furnished in vivo evidence for dysconnectivity, ie, abnormal functional integration of brain processes. While the evidence for dysconnectivity in schizophrenia is strong, its etiology, pathophysiological mechanisms, and significance for clinical symptoms are unclear. First, dysconnectivity could result from aberrant wiring of connections during development, from aberrant synaptic plasticity, or from both. Second, it is not clear how schizophrenic symptoms can be understood mechanistically as a consequence of dysconnectivity. Third, if dysconnectivity is the primary pathophysiology, and not just an epiphenomenon, then it should provide a mechanistic explanation for known empirical facts about schizophrenia. This article addresses these 3 issues in the framework of the dysconnection hypothesis. This theory postulates that the core pathology in schizophrenia resides in aberrant *N*-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity due to abnormal regulation of NMDARs by neuromodulatory transmitters like dopamine, serotonin, or acetylcholine. We argue that this neurobiological mechanism can explain failures of self-monitoring, leading to a mechanistic explanation for first-rank symptoms as pathognomonic features of schizophrenia, and may provide a basis for future diagnostic classifications with physiologically defined patient subgroups. Finally, we test the explanatory power of our theory against a list of empirical facts about schizophrenia.

Key words: dysconnectivity/corollary discharge/psychosis/hallucinations/delusions/NMDA/dopamine/

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Introduction

Schizophrenia has largely remained an enigma. Despite all research efforts, there is still no consensus about its exact pathophysiological mechanisms. Over the last 2 centuries, a large number of competing hypotheses have been put forward, ranging from theories originating in genetics and molecular biology to those formulated in terms of social psychology. This special issue of *Schizophrenia Bulletin* challenges several scientists with somewhat different views on schizophrenia. The task is to defend one's favorite theory and state to what degree it can explain a set of "established facts" about schizophrenia. These were selected by the editors as facts that any decent theory should explain. One can argue whether all the statements provided are really established facts or not. However, fact 1 is paradigmatic: schizophrenia has "a heterogeneous presentation, with disorganized, positive, and negative symptoms" (fact 1, see below). Within the positive symptoms, it is sometimes characterized by rather specific and extraordinarily bizarre symptoms,¹ in particular the first-rank symptoms of Schneider² (eg, delusions of control). Although many patients currently classified as being schizophrenic do not show first-rank symptoms, these symptoms provide the toughest test for any account of schizophrenia because they are completely outside our normal experience. Any comprehensive theory of schizophrenia should therefore be able to explain why these particular symptoms frequently occur. In this article, we defend the theory that schizophrenia results from dysconnection and describe in detail how the dysconnection hypothesis can explain first-rank (and other) symptoms observed in schizophrenia and account for the remaining facts compiled by the editors.

The notion that schizophrenia is not caused by focal brain abnormalities, but results from pathological interactions between brain regions, is an old and influential idea in schizophrenia research. Wernicke³ was the first to propose this hypothesis. He postulated that psychosis arises from anatomical disruption of association fiber

tracts and referred to this disruption as “sejunction.” Subsequently, a similar notion, but formulated in terms of psychopathology, was expressed by Bleuler⁴ who coined the term “schizophrenia” to denote the “splitting” of different mental domains. With the advent of noninvasive neuroimaging techniques in the 1980s (positron emission tomography, PET) and 1990s (functional magnetic resonance imaging, fMRI), this theme re-emerged in experiments that showed abnormally distributed activity and functional connectivity in schizophrenia.^{5–7} For example, a PET study by Volkow *et al.*⁸ found that “schizophrenic subjects showed derangements in the pattern of interactions among brain areas.” Similar conclusions emerged from cognitive activation studies, based on PET, whose findings were “consistent with the notion that schizophrenia involves pathology of and dysfunction within a widely distributed neocortical-limbic neural network.”⁹ Similarly, analyses of cross-sectional studies suggested “disinhibition of left medial temporal lobe activity mediated by fronto-limbic connections.”¹⁰ Following these initial studies, further evidence for dysconnectivity comes from at least 3 independent lines of research. First, many studies have found abnormal functional connectivity between temporal and frontal regions as measured by PET and fMRI.^{11–13} Second, magnetoencephalography/electroencephalogram (MEG/EEG) studies have indicated abnormal beta and gamma band synchrony during sensory processing and cognitive tasks.^{14–18} Third, EEG studies have found abnormal functional connectivity patterns both during rest and during performance of various tasks.^{19–22} In an attempt to provide a unifying neurobiological explanation for these empirical observations, the “disconnection hypothesis” suggested that the core pathology of schizophrenia is an impaired neuromodulation of synaptic plasticity, leading to abnormal functional integration of neural systems, *ie*, dysconnectivity.^{6,23,24} Recently, this hypothesis was updated in the light of new experimental findings, particularly from genetic studies.²⁵

This article is structured as follows. After defining what we mean by dysconnectivity, we suggest a specific pathophysiological mechanism that underlies its occurrence in schizophrenia. Briefly, we postulate that the central pathomechanism in schizophrenia is aberrant *N*-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity due to abnormal regulation of NMDARs by neuromodulatory transmitters like dopamine (DA), acetylcholine (ACh), or serotonin (5-HT). We then discuss how dysconnectivity resulting from abnormal NMDAR-dependent synaptic plasticity could lead to a fundamental failure of self-monitoring (or corollary discharge) and how the latter could explain the positive symptoms of schizophrenia. Subsequently, we address how dysconnectivity speaks to the empirical facts compiled by the editors. We conclude with a summary of a scientific strategy, combining experimental and computational approaches, by which critical predictions of the disconnection hy-

pothesis can be tested and underline the importance of having a theory.

What Do We Mean by “Dysconnectivity”?

The 2 most frequently used terms in the schizophrenia literature to describe abnormal brain connectivity are disconnection (or disconnection) and dysconnectivity (or dysconnection). These terms are frequently used as if they were identical in meaning and interchangeable. Etymologically, however, they are quite different. Whereas the Latin prefix “dis” means “apart,” the Greek prefix “dys” means “bad” or “ill.” Thus, “disconnection” refers to the disintegration of cognitive functions in schizophrenia. This term might suggest that connectivity in schizophrenia is necessarily reduced, leading to less interaction between neural units. This is not what the original disconnection hypothesis meant to imply; instead, while some functional interactions appear to be reduced (eg, functional coupling between temporal and prefrontal regions in language tasks),⁶ other functional interactions may be abnormally increased.²⁴ To avoid this confusion, we use “dysconnectivity.”²⁵ This term emphasizes the notion that there is *abnormal* (rather than decreased) functional integration among brain regions in schizophrenia.

In concrete neurobiological terms, we suggest that dysconnectivity results from abnormal regulation of NMDAR-dependent synaptic plasticity by modulatory transmitters like DA, ACh, or 5-HT. NMDAR activation can change the strength of glutamatergic synapses by altering the functional state and/or number of α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptors (AMPA); this is achieved by NMDAR-initiated phosphorylation of AMPAR subunits or by trafficking of AMPARs into/out of the postsynaptic density.^{26–28} Importantly, NMDAR-dependent plasticity can be controlled by modulatory transmitters through various mechanisms.²⁹ For example, DA and ACh receptors regulate the trafficking and insertion of NMDARs in the cell membrane as well as their endocytosis, and these mechanisms are known to be highly relevant for pathophysiological processes in several brain diseases.³⁰ Furthermore, the conductance properties of NMDARs depend on their phosphorylation status, and this is under strong control by DA and 5-HT receptors.^{31–34} Finally, ACh and 5-HT also impact on the relative expression of different NMDAR subunits, leading to NMDARs of different molecular structure and electrophysiological properties.^{35–39} It is this regulatory effect of modulatory transmitters on NMDAR-dependent synaptic plasticity that is central to the disconnection hypothesis and that distinguishes it from other pathophysiological theories of schizophrenia that postulate impaired NMDAR function alone.^{40–44}

What Causes Disconnection?

Two possible explanations for how disconnection arises are currently being discussed, a cellular and a synaptic

one. Interregional functional coupling might be abnormal in schizophrenia because of impairments of structural (anatomical) connectivity, eg, due to aberrant wiring of association fibers during brain development.⁴⁵ This explanation rests on the abnormal deployment of cellular processes like axons. Alternatively, functional coupling could be disturbed due to impairments in synaptic plasticity.²⁴ (Of course, dysconnectivity resulting from abnormal synaptic plasticity must also have structural correlates, eg, changes in the morphology or distribution of dendritic spines, the numbers of transmitter receptors, their composition out of different subunits, or their phosphorylation status. Here, we restrict the term “impaired structural connectivity” to the level of cellular processes such as axonal fiber bundles.) Importantly, however, aberrant wiring of connections and impaired synaptic plasticity are not necessarily exclusive but could coexist because they have a common (genetic) cause or because one causes the other.²⁵ For example, some candidate genes for schizophrenia play a role in establishing long-range connections during development as well as in the regulation of synaptic plasticity (eg, neuregulin 1, NRG1⁴⁶). Furthermore, any impairment in synaptic plasticity would affect the survival of long-range connections in the developing brain and thus the resulting pattern of anatomical connectivity in later life. This is because the strength of functional coupling between neurons, which depends on experience-dependent synaptic plasticity mediated by NMDARs,⁴⁷ determines whether their connection survives developmental pruning.⁴⁸ Dysconnectivity due to impaired modulation of NMDAR-dependent synaptic plasticity is consistent with the fact that schizophrenia cannot be explained by genetics alone but only by interactions between genes and environment.⁴⁹

In a recent article,²⁵ we assessed the relative evidence for these 2 mechanisms and concluded that while there is so far inconclusive data on alterations of anatomical connectivity, the notion of abnormal modulation of NMDAR-dependent synaptic plasticity in schizophrenia is supported by converging evidence from multiple lines of research. In the following, we review this evidence briefly.

Neurophysiology

One of the most robust findings in schizophrenia research is that patients show a significant reduction of the “mismatch negativity” (MMN) event-related potential.⁵⁰ According to a recent meta-analysis,⁵¹ this finding has been replicated by more than 30 studies. There is strong evidence that the MMN represents a prediction error signal during implicit perceptual learning and depends critically on synaptic plasticity.^{25,52,53} For example, the NMDA antagonist ketamine reduces the MMN in healthy volunteers, rendering it very similar to that of

patients.^{54,55} Furthermore, invasive recording studies in monkeys with local infusion of ketamine have demonstrated the dependence of the MMN on NMDAR-mediated synaptic plasticity;⁵⁶ in humans, this plasticity is modulated by ACh and 5-HT, both of which alter the MMN.^{57,58} A recent electrophysiological study has also provided evidence for impairment of synaptic plasticity during procedural (motor) learning in schizophrenic patients. Daskalakis et al⁵⁹ used a well-established, pharmacologically validated transcranial magnetic stimulation paradigm⁶⁰ to demonstrate impaired synaptic plasticity in the motor cortex of schizophrenic patients: both medicated and unmedicated patients demonstrated significantly reduced posttreatment motor reorganization compared with healthy subjects. Finally, there is increasing evidence that delusions in schizophrenia are a likely result of abnormal reinforcement learning,^{61–64} a process that depends on DAergic modulation of NMDAR-mediated synaptic plasticity.^{65,66}

Neuropharmacology

Various drugs that impact on synaptic plasticity (eg, NMDA antagonists, DA agonists (D2), and 5-HT agonists) can induce psychotic symptoms in healthy subjects, following chronic use or high single doses.^{40,67–69} In particular, the psychotic symptoms and cognitive deficits induced by NMDA antagonists overlap with those of schizophrenia.⁷⁰ Notably, NMDAR-dependent plasticity can occur very quickly, ie, from seconds to minutes.^{26–28} However, NMDAR activation also elicits excitatory postsynaptic potentials (EPSPs).^{71,72} Therefore, it is likely that the cognitive effects seen after ketamine administration to healthy volunteers result both from reducing EPSPs and from diminishing NMDAR-dependent synaptic plasticity.

Neuropathology

Reductions in dendritic field size and dendritic spines of cortical neurons have been reported consistently in post-mortem studies of schizophrenia.^{73–76} This microstructural deficit might be a consequence of impaired synaptic plasticity: one of the most important promoters of dendritic growth and dendritic spine formation is activation of NMDARs.^{77–79} In contrast, blocking NMDARs decreases dendritic length and spine density.^{80–82}

Genetics

A majority of the currently strongest candidate genes for schizophrenia, as determined by linkage and association studies, play an important role in NMDAR-dependent signaling and plasticity and its regulation by DA and ACh.^{25,83} Additionally, a recent genetic study that found a strong increase in structural variants (ie, chromosomal microduplications and microdeletions) in the genome of schizophrenic subjects highlighted that many of these

mutations affected genes involved in NMDAR-dependent plasticity of glutamatergic synapses.⁸⁴ The genetic findings on schizophrenia and their relation to the dysconnection hypothesis are reviewed in more detail below (fact 3).

Interactions Among Different Neurotransmitter Systems

There is a growing body of evidence that documented abnormalities of γ -aminobutyric acid-mediated (GABAergic) and DAergic function in schizophrenia may result from NMDAR dysfunction.^{85,86} For example, glutamatergic projections from prefrontal cortex and various subcortical regions regulate the activity of DAergic neurons in the ventral tegmental area (VTA).^{87,88} Importantly, the strength of these projections is controlled by NMDAR-dependent synaptic plasticity^{89–91} and targets 2 different neuronal populations in the VTA: (1) DAergic neurons that project to the DLPFC (where their effects are mainly mediated by D1 receptors) and (2) GABAergic neurons that project to the nucleus accumbens and (probably) also dampen DAergic mesostriatal projections.^{88,92,93} (So far, there is no anatomical but only indirect neurophysiological evidence that mesostriatal DA neurons in VTA are inhibited locally by those GABAergic neurons that receive direct input from prefrontal cortex.^{88,93}) From this, one can predict that hypofunction of NMDARs decreases prefrontal input to VTA, resulting in reduced activity of GABAergic interneurons in VTA and thus in increased activity of DAergic cells projecting to the striatum via D2 receptors; at the same time, reduced prefrontal input to VTA decreases activity of DAergic neurons projecting back to the DLPFC via D1 receptors.⁸⁶ Indeed, NMDAR blockade mimics the amphetamine-induced abnormalities of DA release in the striatum (presumably through disinhibition of the DAergic mesostriatal projections) that are seen in schizophrenic patients.^{94–99} It is thus conceivable that, at least in some patients, DAergic dysfunction is a consequence of primary NMDAR dysfunction. However, it must also be considered that the NMDAR-dependent plasticity of prefrontal projections to VTA is modulated by DA itself.^{100–102} It is thus likely that the prefrontal hypo-DAergic and striatal hyper-DAergic effects resulting from NMDAR blockade as described above can also be achieved by aberrant modulation of NMDARs by DA. Crucially, these lines of evidence point to the importance of interactions among NMDAR-dependent plasticity and DAergic modulation,¹⁰³ as opposed to an isolated NMDAR dysfunction. Moreover, the NMDAR-dependent plasticity of prefrontal projections to VTA is also regulated by nicotinic receptors⁹⁰ and 5-HT receptors.⁸⁹ Therefore, similar considerations as for DA apply to the role of interactions between NMDARs and ACh/5-HT for the pathophysiology of schizophrenia.²⁵ The putative mechanisms behind this interaction, which are central to the dysconnection hypothesis, are reviewed in more detail below.

Collectively, the experimental evidence summarized above indicates that schizophrenia is a spectrum disease that may be caused by different genetic mechanisms and pathophysiological processes; these processes, however, appear to converge onto the same functional pathway, ie, the regulation of NMDAR-controlled plasticity of glutamatergic synapses by neuromodulatory transmitters like DA, 5-HT, and ACh. In contrast to this converging evidence for impaired regulation of plasticity of glutamatergic synapses as a cause of dysconnectivity in schizophrenia, it is not clear yet whether altered patterns of anatomical long-range connections coexist. Given the evidence summarized above that impaired experience-dependent plasticity due to NMDAR dysfunction impacts on selection and pruning of axonal connections during neurodevelopment,^{47,48} the dysconnection hypothesis would predict that such structural alterations of connectivity exist. So far, the only available technique for *in vivo* measurements of human brain connectivity, diffusion-weighted imaging, has yielded inconsistent results.^{104–106} However, this may be due to an immature state of this technique, and it is possible that technological refinements, enhanced spatial resolution, and improved analysis techniques might lead to more consistent results in the future. Alternative approaches that allow for indirect assessments of structural connectivity changes, eg, multivariate analyses of covariations in regional brain volume or morphometric analyses of white matter maps, have indicated that disturbances of anatomical connectivity may exist in schizophrenia.^{107–110} From a mechanistic perspective, however, the issue is not so much whether one would expect to see disrupted axonal connectivity or not but whether this alteration is secondary to or independent from abnormal synaptic plasticity. This is an important question for future research.

How Does Dysconnectivity Relate to the Clinical First-Rank Symptoms of Schizophrenia?

It is currently fashionable to explain a wide range of clinical disorders, such as dyslexia or autism, in terms of dysconnectivity.^{111,112} Any serious pathophysiological theory based on dysconnectivity should fulfill at least 2 criteria. First, it should provide a neurobiologically precise explanation of what causes the dysconnection. The dysconnection hypothesis, for which the evidence is summarized above, provides such an explanation: it suggests that the underlying cause of dysconnectivity in schizophrenia is a specific impairment of synaptic plasticity, which results from aberrant modulation of NMDAR function by DA, ACh, and 5-HT. This abnormal modulation can be described in neurobiologically precise terms; eg, DA, ACh, and 5-HT receptor activation initiates intracellular cascades that lead to alterations in the conductance properties of NMDARs due to changes in phosphorylation status or receptor subunit expression

and to alterations of NMDAR receptor trafficking (for details, see above and Stephan et al²⁵). Second, any dysconnection theory should provide a mechanistic explanation for the cognitive symptoms that are specific to the particular disease. In this section, we provide such an explanation for schizophrenia. We will focus on how first-rank symptoms,² such as delusions of control, may be explained as the failure of self-monitoring mechanisms,^{113–116} also referred to as “corollary discharge” mechanisms. In the following section, we link all levels—synaptic plasticity, corollary discharge, and clinical symptoms—by summarizing recent evidence that corollary discharge mechanisms depend on synaptic plasticity.

First-rank symptoms, which were initially defined by Schneider in an attempt to isolate those symptoms that are pathognomonic of schizophrenia,² continue to have major importance in clinical classifications of schizophrenia. First-rank symptoms are essentially experiences of “passivity,” ie, patients report that their actions, thoughts, or emotions are no longer caused by themselves but are imposed upon them by external forces or agents. For example, schizophrenic patients may report that their thoughts are being “inserted” or “broadcast,” that alien voices may tell them what to do or comment on their actions, or that some external force or agent is controlling their movements. While many patients who fulfill current diagnostic criteria for schizophrenia do not have first-rank symptoms, these are the symptoms that are the most difficult to understand because they are so far outside our normal experience. These symptoms, therefore, provide the toughest test for any account of schizophrenia.

First-rank symptoms may result from a diminished ability to distinguish between events that we control (eg, self-generated inner speech or limb movements) and those that occur independently of us in the external world (eg, someone else speaking or some external force moving our limbs). Normally, we can differentiate between these events depending on how well we can predict the sensory input they evoke. For example, regardless of whether we actively move our arm or whether our arm is moved by someone else, somatosensory areas of our brain receive input from peripheral proprioceptors. However, when the movement is self-generated, the sensory areas also receive a signal from motor areas, informing them about the intended movement and thus allowing them to predict the proprioceptive input they should be receiving. This signal has been called a “corollary discharge,”¹¹⁷ or “efference copy.”¹¹⁸ The prediction conveyed by corollary discharge from motor areas may be used to cancel or explain away the sensation that is normally associated with proprioceptive input and the associated activation of sensory areas. A corresponding corollary discharge mechanism is used to deal with changes in visual perception induced by self-generated eye movements. Neurophysiological studies in primates suggest that during self-generated saccades the frontal eye field receives a corollary

discharge signal from the superior colliculus that may be used for coordinating sequential saccades and for stabilizing vision across saccades.^{119,120} Similarly, there is evidence from human fMRI studies that during eye blinks frontal oculomotor regions send a corollary discharge signal to visual areas, probably to ensure a stable visual percept across blinks.¹²¹

In essence, the notion that the first-rank symptoms of schizophrenia result from a failure of self-monitoring, or corollary discharge refers to a dysconnection between a motor act (which may or may not be conscious) and its sensory consequences. Several studies have provided evidence for this type of dysconnection in schizophrenia and demonstrated that self-monitoring is indeed abnormal in patients. In a series of EEG studies, Ford, Mathalon, and colleagues have demonstrated a reduction in functional connectivity between areas that initiate an action and areas that mediate the perception of the sensory consequences of that action.^{122–124} For example, they examined the hypothesis that both before and during talking a corollary discharge mechanism, expressed through functional frontotemporal connectivity, may act to prepare temporal auditory areas for the sounds generated by frontal areas. They argue that a disruption of this functional connectivity would lead to mismatch between the expected auditory consequences of self-generated speech and the actual auditory experience.^{122,123} Ford et al¹²² found that whereas frontotemporal delta and theta band coherence was enhanced during talking (compared with listening) in healthy volunteers, schizophrenic patients failed to show this correlate of corollary discharge; this failure was particularly pronounced in patients with auditory hallucinations. These results suggest that in schizophrenia an impairment of corollary discharge may prevent frontal areas generating thoughts (inner speech) from informing auditory areas that this inner speech is self-generated. This could lead to a misattribution of inner speech to external sources and thus produce auditory hallucinations.¹²⁵ These conclusions were supported by an independent fMRI study of a sentence completion task (the Hayling Test) in schizophrenic patients.¹² Compared with healthy controls, patients showed reduced functional connectivity between prefrontal and temporal regions; furthermore, the degree of dysconnection was inversely correlated with the severity of their hallucinations.

There are many further studies that have provided evidence for dysconnection between prefrontal and temporal regions^{11,19,126,127} (note, however, that for some language tasks, temporal regions exhibited dysconnectivity not with prefrontal but with other brain regions¹²⁸). Space constraints prevent us from discussing all these studies in detail. Finally, it should be noted that evidence for impaired corollary discharge mechanisms is not restricted to speech generation. Other studies have obtained equivalent evidence concerning the somatosensory

perception of the consequences of limb movements,^{129,130} of self-generated sensory stimuli,¹³¹ the visual consequences of limb movements,¹³² and the visual consequences of eye movements.¹³³

Our hypothesis does not provide a precise explanation of the exact content of hallucinations and delusions. One likely possibility is that this content is determined by prior individual differences in brain physiology, experience, culture, etc, which are not in themselves part of the psychotic process. Empirical evidence for this notion was obtained recently by an fMRI study of healthy volunteers showing that the individual predisposition to developing psychotic symptoms under ketamine was predicted by regional brain responses during cognitive tasks under placebo.¹³⁴

Can Dysconnection Also Explain Negative and Cognitive Symptoms of Schizophrenia?

The focus of this article is on explaining how positive symptoms in schizophrenia result from impaired perceptual *inference*, caused by aberrant corollary discharge, which, as explained, results from abnormal regulation of NMDA-dependent synaptic plasticity by modulatory transmitters like DA, ACh, and 5HT. Nevertheless, we would like to comment briefly on how other symptoms of schizophrenia, ie, negative and cognitive symptoms, could also be explained by abnormal modulation of synaptic plasticity and understood as instances of dysfunctional perceptual *learning*. Negative symptoms, eg, blunted affect and social withdrawal, can be understood as resulting from a failure of operant and emotional learning during social interactions. In other words, if abnormal synaptic plasticity renders the patient incapable of learning from social experiences and thus from adaptive changes in the cognitive and motor processes required for successful social exchange, he/she will experience the world as frustrating and unpredictable, which is likely to trigger social withdrawal and apathy. Concerning the various cognitive symptoms frequently seen in schizophrenia, many, if not all, of them can also be understood as a consequence of aberrant modulation of synaptic plasticity, eg, deficits in (various types of) learning and memory, which are prominent cognitive symptoms in schizophrenia.¹³⁵ These general impairments in learning are likely to have profound downstream effects on other cognitive processes: eg, impaired regulation of synaptic plasticity by DA is known to disturb associative learning processes,^{63,64,136} and the resulting “loosening” of associations may cause thought disorder, altered speech, and deficits in reasoning.

How Does Synaptic Plasticity Relate to Corollary Discharge Mechanisms?

The problem of distinguishing between self-generated and externally generated actions, which was initially

described by von Helmholtz,¹³⁷ is an evolutionary very old one and faces any creature that is able to perform limb or eye movements. It is therefore not surprising that corollary discharge mechanisms have been described in a large range of organisms, including insects,^{138,139} fish,^{140–142} bats,¹⁴³ birds,¹⁴⁴ rodents,¹⁴⁵ cats,¹⁴⁶ and primates.^{119,120} Self-monitoring relies on forming a prediction about the expected sensory consequences of one’s action, triggered by a corollary discharge, and then subtracting this prediction from the actual sensory input. Importantly, the sensory input associated with a given action can change due to contextual or environmental factors. As an example, the dynamics of proprioceptive input following a particular arm movement differ depending whether this movement is performed in air or in water during swimming. Also, predictions about proprioceptive input have to be updated rapidly and continuously when performing movements in the presence of additional external forces (eg, strong wind or water currents) or when being exposed to novel mappings between motor actions and sensory outcome. This means that at the neuronal level, self-monitoring must be implemented by a system that is capable of rapid adaptation and plasticity.

Indeed, elegant neurophysiological studies in fish have demonstrated that there are at least 2 separate subsystems for corollary discharge: one system that deals with situations where the relation between motor action and sensory input is invariant and one where this relation changes due to contextual or environmental factors.¹⁴⁰ In the former case, the canceling out of sensory inputs is implemented through temporally highly precise inhibitory postsynaptic potentials that are triggered by corollary discharge^{138,140}; for this mechanism, no synaptic plasticity is needed. In the latter case, however, corollary discharge mechanisms depend critically on spike-timing-dependent plasticity (STDP), a form of short-term synaptic plasticity that critically relies on NMDARs^{147–151} and is regulated by DA, ACh, and 5-HT.^{152–154} In brief, Bell and colleagues^{140–142} showed that cerebellum-like structures in electric fish act as adaptive sensory processors, in which learned predictions about sensory input are subtracted from actual sensory input; notably, there is recent evidence that the cerebellum has a similar role in humans.¹⁵⁵ In their experiments, responses of Purkinje-like medium ganglion (MG) cells to central corollary discharge signals were “negative images” of responses to previously paired sensory inputs; adding these to concurrent sensory input suppressed MG cells responses.¹⁴¹ Neuroanatomically, sensory inputs are relayed to basal dendrites of MG cells, whereas predictive corollary discharge signals are transmitted by parallel fibers to the apical dendrites of MG cells. Bell and colleagues^{141,142,156} showed in several studies that the mechanism generating negative images of predicted inputs relied on NMDAR-mediated plasticity of parallel fiber synapses. This

plasticity was of an anti-Hebbian nature (ie, EPSPs were depressed after pairing with a postsynaptic spike) and strongly spike-timing dependent, with depression occurring only if the postsynaptic spike followed EPSP onset within a narrow time window of 60 milliseconds. A next step will be to demonstrate directly that corollary discharge depends on neuromodulatory regulation of NMDAR-dependent plasticity; this dependence is very likely given that STDP relies on this mechanism (see above). While functional data are lacking so far, neuro-anatomical studies indeed indicate a role of modulation by DA and 5-HT in corollary discharge.^{157,158}

Altogether, the experimental results discussed in this and the previous sections provide a framework for understanding some of the symptoms in schizophrenia, namely, first-rank symptoms including delusions of control and hallucinations. This framework explains how first-rank symptoms can be understood as an impairment of corollary discharge and thus as a dysconnection between a motor act and its sensory consequences and how such failures of corollary discharge can be linked to neurobiological mechanisms (ie, synaptic plasticity) that are known to be disturbed in schizophrenia.

It is interesting to note that corollary discharge is implicit in “predictive coding.” Predictive coding is a general framework that, put simply, requires the brain to minimize prediction error. It suggests that hierarchically arranged neural systems optimize their functional interactions, through message passing (inference) and short- and long-term synaptic plasticity, such that the difference between the sensory inputs, conveyed by bottom-up inputs and a prediction about this input, mediated by top-down projections, is minimized or “explained away.”^{53,159} This framework includes corollary discharge as a special case, where predictions are generated by motor structures and prediction error is minimized in sensory areas (cf Figure 3 in Kilner et al¹⁶⁰). This perspective might be useful for explaining symptoms of schizophrenia beyond delusions of control. For example, Friston⁵³ outlined how hallucinations (in any modality) could be explained as a failure of predictive coding, where the precision (encoded in the postsynaptic sensitivity of units encoding prediction error) of prior expectations is abnormally high. This produces a suboptimal balance between sensory inputs and prior expectations leading to distorted predictions of what caused a particular sensation. In other words, if too much weight is afforded to prior expectations, false inferences about the cause of a perceptual state may ensue. This will lead to a failure of explaining away prediction error and increased activity in subordinate levels of processing hierarchies; this is exactly what has been seen by fMRI measurements of auditory hallucinations in patients.^{161–163} Similarly, delusions, including the delusions of persecution (that are among the most frequent symptom associated with schizophrenia), can be explained as failure of hierarchical

inference, leading to an imbalance between new evidence and prior beliefs.

We recognize that hallucinations and delusions can be observed in diagnostic categories other than schizophrenia. Even first-rank symptoms are sometimes observed in bipolar patients, and other forms of hallucination and delusion are associated with disorders such as Charles Bonnet syndrome, Capgras syndrome, and anosognosia. We suggest that all these phenomena reflect an imbalance between evidence (sensory inputs) and prior beliefs (expectations). However, this imbalance may have different causes at the physiological level. For example, in Charles Bonnet syndrome, the cause is the random visual input consequent upon retinal degeneration. As a result, visual hallucinations are created by unconstrained operation of learned expectations about visual inputs.

In theoretical treatments of learning and prediction, like predictive coding, uncertainty or the amplitude of prediction error is often thought of as being encoded by DA and other neuromodulators,^{164–166} which play a central role in optimizing synaptic connection strengths.^{29–39,152–154} This is one important reason why the dysconnection hypothesis focuses on the role of neuromodulators in synaptic plasticity.

Can the Dysconnection Hypothesis Explain Established Facts About Schizophrenia?

In the following, we consider the list of established facts about schizophrenia (in italics) that were selected by the editors and examine whether and how precisely they can be explained by the dysconnection hypothesis.

1. *Schizophrenia has a heterogeneous presentation, with disorganized, positive, and negative symptoms having different levels of prominence across time and across individuals.*

The clinical heterogeneity of schizophrenia has long given rise to the notion that it is not a single disease but a spectrum of diseases.¹⁶⁷ This could be explained independently by 2 principles: (1) different pathophysiological processes may underlie schizophrenia but converge onto the same, or similar, functional pathways and (2) a particular pathophysiological process may be strongly modulated by factors that differ across patients and change over time within a given patient. The dysconnection hypothesis, as outlined above, accommodates both principles.

Concerning the first principle, we postulate that NMDAR-dependent synaptic plasticity is impaired due to an abnormality of the regulation of NMDARs by neuromodulatory transmitters like DA, ACh, and 5-HT (which control, eg, phosphorylation, subunit composition, and trafficking of NMDARs).^{30–39} This means that a patient in whom the dominant abnormality is

a DAergic dysregulation of NMDARs is likely to show different symptoms (eg, a predominance of delusions resulting from impaired reinforcement learning)^{61–64} than a patient in whom the primary abnormality is a cholinergic dysregulation of NMDARs (where symptoms might be dominated by perceptual abnormalities like hallucinations and impaired attention).^{24,168} In other words, from the perspective of the dysconnection hypothesis, the diversity of clinical symptoms is due to differences in where dysfunctional experience-dependent plasticity is expressed in the brain. These (between-subject) differences may be at the level of the molecular biology mediating the effect of different modulator neurotransmitters on NMDAR plasticity or (within-subject) differences in the sensory experience or environmental influence (see below) inducing plasticity.

With regard to the second principle, NMDA-dependent synaptic plasticity is a process that is strongly modulated by hormonal,^{169–171} immunological,^{172–175} and metabolic factors.¹⁷⁶ Similarly, DAergic, cholinergic, and 5-HTergic transmission (and thus their regulation of NMDA-dependent synaptic plasticity) are subject to developmental changes throughout life and modulation by nonneuronal factors.^{177,178} Together, these changes in synaptic plasticity over the life span of an individual patient may contribute to fluctuations of clinical symptoms over time.

2. *Schizophrenia has a peak of onset in young adulthood and is rare before adolescence or after middle age. Onset also interacts with sex, such that men are likely to become ill earlier in life than women. Prevalence is greater in men throughout most of adulthood but is equal by the end of the risk period.*

The peak of onset of schizophrenia and the strong sex differences suggest a hormonal influence that changes markedly during neurodevelopment, eg, steroidal hormones like cortisol, estrogens, or androgens. Sensitivity to developmental factors and gender are inevitable under the dysconnection hypothesis because NMDAR-dependent synaptic plasticity is profoundly altered by both cortisol¹⁶⁹ and estrogens.^{170,171} As noted earlier,²⁴ “the fact that schizophrenia is expressed symptomatically in adulthood points to an abnormal modulation of experience-dependent plasticity, as distinct from the induction and maintenance of synaptic connections through epigenetic mechanisms or indeed activity-dependent plasticity in utero: for example, there is no evidence to suggest that the ocular dominance columns in the striate cortex of schizophrenics are abnormal.”

The sex difference in onset is simply explained by hormonal mechanisms that exert a protective effect on synaptic plasticity in females but less so in males. Such a mechanism exists: it has been shown that estrogens markedly enhance NMDAR-dependent plasticity of glu-

tamatergic synapses, leading to increased postsynaptic efficacy of NMDARs, enhanced long-term potentiation (LTP), and also behavioral improvements, eg, in memory tasks.^{170,171,179} Estrogens also prevent stress-induced loss of LTP in the hippocampus.¹⁸⁰ In contrast, the effects of androgens on synaptic plasticity in general, and NMDAR-dependent plasticity in particular, are much less well documented. While some studies reported beneficial effects of androgens, ie, maintaining dendritic spines of hippocampal CA1 pyramidal neurons,¹⁸¹ other studies demonstrated detrimental effects of androgens on NMDAR-dependent synaptic plasticity, namely, a decrease in LTP¹⁸² and a reduction of the expression of specific NMDAR subunits.¹⁸³ Furthermore, animal studies have demonstrated that androgen-mediated regulation of spine density is found in both sexes, whereas plasticity-enhancing effects of estrogens are observed in females only.¹⁸¹ These neurophysiological findings are complemented by endocrine measurements in drug-free first-episode patients, which found decreased estrogen levels in females.¹⁸⁴ Altogether, the currently available experimental data imply that estrogens may exert a protective effect on NMDAR-dependent synaptic plasticity that may delay the onset of schizophrenia in genetically predisposed females. In contrast, such a protective effect does not appear to exist in males, which explains the earlier onset of schizophrenia in men.

3. *Liability to schizophrenia is highly heritable (about 0.81), and concordance between identical twins is almost 50%, suggesting a role for environmental or stochastic influences as well.*

The interaction between genetic and environmental factors is an inevitable and necessary consequence of the dysconnection hypothesis. This is because the molecular mechanisms underlying the control of synaptic plasticity are specified genetically and epigenetically, whereas the functional expression of synaptic plasticity rests explicitly on the exchange with the environment and the resulting sensory experience and changes in internal milieu.

It has long been known that schizophrenia is a polygenic disease that is strongly modulated by environmental factors.¹⁶⁷ Over the last few years, a large number of genetic linkage and association studies have been conducted which, despite considerable inconsistency across studies, have led to 3 major provisional conclusions. First, it is likely that schizophrenia is caused by a combination of common alleles, each of which contributes a small increase in the risk for illness.¹⁸⁵ Second, given the clinical heterogeneity of schizophrenia, it has long been suspected that what we call schizophrenia is not a single disease but a spectrum of diseases caused by different pathophysiological processes.¹⁶⁷ This notion is compatible with the variability across genetic linkage studies¹⁸⁶ and the variability in patient-specific profiles

of gene expression.¹⁸⁷ The final and perhaps most important conclusion is that, although patients may differ in their genetic risk profile, the resulting pathophysiological processes ultimately leading to schizophrenia may nevertheless converge onto the same functional pathway. Indeed, a unifying theme of the available genetic studies is that many, if not most, candidate genes for schizophrenia are intimately related to some aspect of glutamatergic synaptic signaling,²⁵ notably NMDAR-dependent plasticity and/or to neuromodulatory transmitters like DA, 5-HT, and ACh that exert strong control over NMDAR function. In a recent review on the genetics of schizophrenia, Harrison and Weinberger⁸³ identified 7 candidate genes for schizophrenia for which at least 3 studies provided positive evidence; 6 of these genes are related, directly or indirectly, to NMDAR function. They concluded that these candidate genes "... predispose, in various ways but in a convergent fashion, to the central pathophysiological process: an alteration in synaptic plasticity, especially affecting NMDAR-mediated glutamatergic transmission" It is remarkable that a recent study that was based on a completely different working hypothesis about the genetics of schizophrenia came to the same conclusion. Walsh et al⁸⁴ postulated that schizophrenia may not only be caused by a combination of risk-enhancing alleles but may also, and possibly more frequently, be caused by microduplications and microdeletions, ie, individually specific chromosomal mutations, also known as structural variants. In their genome-wide scans, they found structural variants in only 5% of control subjects, but in 15% of adult schizophrenic patients and 20% of young-onset patients, both highly significant differences. Most importantly, these mutations affected, to a large degree, genes that are involved in signaling and plasticity of glutamatergic synapses, eg, erbB4 and NRG1 signaling (NRG1 is a potent regulator of NMDAR function, reducing its synaptic currents and increasing its endocytosis¹⁸⁸). Furthermore, a study of high-risk subjects reported that the risk allele in the NRG1 promoter region was associated with the development of psychotic symptoms.¹⁸⁹ These genetic findings are complemented by results from recent gene expression studies using a new postmortem tissue stimulation approach, which found that in schizophrenic patients NRG1-induced suppression of NMDAR function was considerably higher than in controls subjects.¹⁹⁰

It is important to note that under the dysconnection hypothesis the phenotypic expression of abnormal experience-dependent plasticity is limited to those plastic mechanisms that are sensitive to neuromodulatory regulation. This is particularly relevant for DA that has been clearly implicated in value and emotional learning,^{164,165} that is central for predicting not only one's own behavior (eg, through corollary discharges) but also the behavior of others (eg, theory of mind). Furthermore, NMDAR-dependent synaptic plasticity can be modulated by envi-

ronmental factors, often via the internal milieu of the body. For example, increased cortisol levels, eg, induced by psychosocial stress, inhibit NMDAR currents and LTP.¹⁶⁹ Similarly, some proinflammatory cytokines, eg, interleukin-1 and interleukin-18, attenuate NMDAR-dependent LTP,^{172,173,175} while other cytokines activate enzymatic pathways that lead to an accumulation of kynurenic acid, an endogenous NMDAR antagonist.¹⁷⁴ These examples demonstrate how a genetically encoded basic mechanism of brain function, ie, NMDA-dependent plasticity and its regulation by modulatory transmitters, can be altered by humoral factors whose expression depend on environmental influences.

4. *All drugs with established antipsychotic effects block DA D2-like receptors, but antipsychotic drugs are not effective for all schizophrenia symptoms. Among available agents, the atypical antipsychotic Clozaril is the most effective; however, it carries unique risks for some.*

This is a complex point with several aspects, which we address one by one. First, the fact that all antipsychotic drugs block DA D2 receptors is a cornerstone of the dysconnection hypothesis. There is much experimental evidence on bidirectional interactions between NMDAR and DA receptor signaling that explains the beneficial effects of D2 blockade in schizophrenia. On the one hand, glutamatergic afferents from prefrontal cortex project to VTA, regulating the activity of DAergic midbrain neurons and their projections to the striatum.^{87,88,92} Critically, the strength of these prefrontal projections to VTA is regulated through NMDAR-dependent plasticity,⁸⁹⁻⁹¹ which, in turn, is modulated by DA.¹⁰⁰⁻¹⁰² This provides a mechanism for the DA system to regulate its own inputs and endow these inputs with acquired value.¹⁶⁴ A failure of DA-modulated NMDAR plasticity would lead to dysfunctional DA release from midbrain projections in the striatum and severely impaired value learning. Indeed, both human PET and rodent microdialysis studies have demonstrated that acute NMDA blockade by ketamine led to a massive enhancement of amphetamine-induced DA release in the striatum,^{96,99} similar to what is seen in schizophrenic patients.^{94,95,97,98} Generally, DA exerts strong control over NMDAR-mediated plasticity. Briefly, D1 receptor activation increases NMDAR transmission and LTP, whereas D2 receptor activation decreases it.^{85,191} This depressive effect of D2 receptors on LTP is reversed by antipsychotic medication.¹⁹² Heuristically, NMDAR hypofunction and excessive D2 receptor activation mutually reinforce each other; enhancing the former and inhibiting the latter may break this pathological impasse.⁸⁵

Second, the fact that antipsychotic drugs are not effective for all schizophrenia symptoms, or indeed for all patients, fits well with the notion that different subgroups

of patients show distinct neuromodulator-specific impairments in NMDAR-dependent plasticity. From this perspective, no single drug will work equally effectively for all patients (see also point 6 below). One critical future challenge is to devise methods for delineating patient subgroups that are physiologically defined through one or several specific impairments in NMDAR-dependent plasticity;²⁵ see “From Dysconnectivity to Model-Based Diagnostics” of this article for more details.

Third, the fact that atypical antipsychotic Clozaril (clozapine) is the most effective of currently available drugs may be due to its unique efficacy in promoting synaptic plasticity. For example, there is some evidence that clozapine might not only antagonize D2 receptors but at the same time might also act as a partial agonist at D1 receptors, thus promoting NMDAR-dependent synaptic plasticity in 2 independent ways.^{193,194} Furthermore, *in vitro* studies of rat hippocampal neurons demonstrated that haloperidol decreased dendritic spine numbers and the expression of proteins in the postsynaptic density of NMDARs, whereas these critical components of glutamatergic plasticity were strongly enhanced (up to 70%) by clozapine.¹⁹⁵

5. *Several early neurological insults, later life stressors and nonhereditary genetic risk factors confer additional risk. These include (in order of impact) migrant status, older fathers, Toxoplasmosis gondii antibodies, prenatal famine, lifetime cannabis use, obstetrical complications, urban rearing, and winter or spring birth.*

This wide range of risk factor can only be explained in terms of a fundamental aspect of brain function, which is affected by experience-dependent, humoral, and developmental factors. NMDAR-dependent synaptic plasticity and its regulation by neuromodulatory systems represent such a fundamental mechanism that is affected by immunological, metabolic, and hormonal factors.^{169,174,176} For example, both migrant status and urban rearing are associated with increased psychosocial stress, leading to higher cortisol plasma levels,^{196,197} which are known to diminish NMDAR-mediated synaptic plasticity.¹⁶⁹ Similarly, perinatal exposure to *T. gondii* and viral agents, which are more prevalent during winter and spring, might trigger a shift in the balance of type I/type II immunological responses with an increase in proinflammatory cytokines (eg, interleukin-1 and interleukin-18) that are known to reduce NMDAR-dependent LTP.^{172,173,175} Importantly, even a transient diminution of NMDAR function during early development can lead to various and lasting cognitive deficits such as those seen in schizophrenia.¹⁹⁸ Finally, in relation to cannabis use, there is strong experimental evidence that endocannabinoids produced by neurons or glia interact with NMDARs to mediate several forms of transient and persistent synaptic plasticity.^{199,200} “Given the widespread role of CB1 receptors

and endocannabinoids in eliciting or shaping neuronal plasticity, it is reasonable to speculate that THC and other cannabinoids produce their psychoactive effects by perturbing endocannabinoid-mediated plasticity.”²⁰¹

6. *While antipsychotics can lead to immediate improvement for some individuals, the time course of medication effects varies widely with some patients showing responses to medication more than a month after beginning treatment.*

This point is related to the interpatient variability in treatment response described by point 4 above. Both points are consistent with the notion embodied by the dysconnection hypothesis that distinct impairments in the modulation of NMDAR-mediated synaptic plasticity define distinct subgroups of patients. From this view, different time courses of the therapeutic response could be explained by pathophysiology differences across patients. Such differences could occur along various dimensions. One example is that the time scale of plasticity required to achieve therapeutic changes may differ across patients. The early and late improvement seen with antipsychotics speaks to the dual role of neuromodulatory transmitters in terms of shaping (1) short-term synaptic plasticity resulting in fast changes in postsynaptic responses and (2) long-term synaptic plasticity leading to a lasting reconfiguration of neuronal connections. Symptom improvement will therefore depend on whether immediate changes in synaptic efficacy are sufficient (fast responders) or whether a lasting reshaping of neuronal circuitry by experience-dependent plasticity is necessary to suppress symptoms (slow responders). An alternative view is that different neuromodulatory actions may be impaired across patients. For example, *in vivo* receptor PET studies showed that the level of striatal D2 receptor occupancy predicted how quickly positive symptoms responded to treatment with conventional antipsychotic treatment by D2 antagonists: patients with high levels of D2 receptor occupancy responded much more rapidly to treatment than patients with normal levels of D2 receptor occupancy.²⁰² Based on these (and other) findings, Laruelle *et al.*⁸⁵ hypothesized that in the former group of schizophrenic patients the primary deficit might be D2 receptor-induced NMDA hypofunction, whereas in the latter group the positive symptoms might be driven by an NMDA deficiency that was unrelated to DAergic modulation. They argued that the therapeutic effect in the latter group consists of setting D2 receptor stimulation to below-normal levels and thus shifting the D1/D2 receptor ratio in favor of D1 receptors that promote NMDAR-dependent signaling and plasticity.

7. *Exposure to amphetamine, a DA agonist, can result in schizophrenia-like symptoms in some individuals. This effect may interact with liability, such that a single dose*

can trigger relapse in patients, but more chronic use is usually needed to induce psychosis in low-risk populations.

And

8. *A single exposure to phencycline and other NMDA receptor antagonists (such as ketamine) can result in schizophrenia-like symptoms in some individuals.*

Above, we have explained the occurrence of psychotic experiences through a failure of self-monitoring, or corollary discharge, which results from a disturbance of NMDA-dependent plasticity. Experimentally, psychotic symptoms can be induced reliably by acute administration of NMDA antagonists in both healthy controls and medication-free schizophrenic patients.^{40,67,203} Presumably, a certain threshold of NMDA dysfunction must be reached before symptoms are manifest. Indeed, previous experiments demonstrated that there is a buildup of cognitive deficits with increasing ketamine dose, with psychotic symptoms only being observed at higher doses.²⁰⁴ Alternative, an indirect, and probably slower, way of reaching a critical threshold of NMDA dysfunction would be through changing neuromodulatory influences on NMDA-dependent synaptic plasticity. For example, shifting the D1/D2 receptor activation balance toward D2 receptor activation (eg, by amphetamine-induced hyperrelease of DA from midbrain projections to the striatum),^{94,95,97,98} could reach the critical threshold of NMDAR hypofunction over time due to D2-evoked dampening of NMDAR-dependent plasticity.^{191,192}

9. *In postmortem studies, pyramidal neurons in input layers of prefrontal cortex have a reduced dendritic spine density, whereas hippocampal neurons appear to be abnormally oriented with signs of arrested migration.*

The postmortem finding of reduced spine density has been experimentally replicated across multiple studies and various brain regions, including prefrontal cortex, hippocampus, and sensorimotor cortex.^{73–76} As discussed above (see also Stephan et al²⁵), this finding is perfectly consistent with chronic NMDA hypoactivation: NMDAR activation is a potent promoter of dendritic spine formation and dendritic growth.^{77–79} In contrast, NMDAR blockade reduces spine density and dendritic length.^{80–82} It is precisely this sort of change in spine density that is the consequence of abnormal synaptic plasticity and speaks to disconnection at a synaptic as opposed to a cellular level (eg, due to a leukodystrophy or abnormal cell migration).

An abnormal orientation of neurons in the hippocampal formation (particularly the entorhinal cortex) and occurrence of heterotopic cell clusters have also been described by more than one study, although with some inconsistencies with regard to the nature of the abnormality.^{205–207} In our opinion, it is therefore a less well-

established finding than the reduction of dendritic spine density. Nevertheless, such an abnormal orientation due to a presumed disturbance of neuronal migration during development could also be explained by NMDA dysfunction. This is because NMDARs play an important role during neuronal migration. In rodent studies, pharmacological blockade of NMDARs during development strongly impairs neuronal migration, leading to abnormally oriented pyramidal neurons and formation of heterotopic cell clusters in the cortex,^{208,209} ie, cytoarchitectonic abnormalities that are similar to the postmortem findings in schizophrenia described above.

10. *GAD65 and 67, the rate-limiting enzymes that convert glutamate to GABA, are reduced in schizophrenia patients. Reelin, an important factor involved in synaptic plasticity that colocalizes to GABAergic interneurons, is also reduced.*

There are theoretical accounts, most eloquently formulated by Lewis and colleagues, which link the idea of NMDAR-dependent dysconnectivity to empirically observed pathologies of GABAergic neurons in schizophrenia. In particular, Lewis and Gonzalez-Burgos⁸⁶ suggest an elegant pathophysiological model of working memory dysfunction in schizophrenia, explaining how a primary NMDAR abnormality in the DLPFC can cause changes in both GABAergic and DAergic function. Summarized briefly, this model starts from the results of basic neuroanatomical and neurophysiological studies, which, as explained above, show that the activity of DAergic midbrain neurons is controlled by glutamatergic projections from prefrontal cortex.^{87,88,92} These prefrontal projections are regulated in strength through NMDAR-dependent plasticity^{89–91} and target 2 different neuronal populations in the midbrain: DAergic neurons that project to the DLPFC (where their effects are mainly mediated by D1 receptors) and GABAergic neurons in VTA. Assuming that these interneurons dampen DAergic mesostriatal projections,^{88,93} one can predict that hypofunction of NMDARs decreases prefrontal input to VTA, resulting in reduced activity of GABAergic interneurons in VTA and thus in increased activity of DAergic cells projecting to the striatum (via D2 receptors); at the same time, reduced prefrontal input to VTA decreases activity of DAergic neurons projecting back to the DLPFC (via D1 receptors). Both NMDA hypofunction and reduced D1-mediated signaling in DLPFC diminishes the activity of (parvalbumin-positive) GABAergic neurons. Because the expression of GAD65 and GAD67 is activity dependent,^{210,211} this decrease in prefrontal GABAergic activity may explain the reduced levels of GAD65 and GAD67 messenger RNA levels that have been demonstrated in postmortem studies in the DLPFC of schizophrenic patients (for review, see Lewis et al²¹²). Supportive evidence for this comes from a recent rodent

study by Homayoun and Moghaddam,²¹³ which found that NMDARs preferentially drive the activity of GABAergic interneurons in PFC, rather than that of excitatory pyramidal cells.

From a theoretical perspective, the projections from prefrontal cortex to DAergic midbrain neurons are central to the dysconnection hypothesis: “The ability of events to elicit activity in ascending modulatory systems will be determined by the inputs (afferents) to the cells of origin of these systems (e.g., the VTA for DA or the nucleus basalis for ACh). These afferents therefore determine what is valuable. How that valuable state is achieved depends on selective consolidation of adaptive responses to salient stimuli (e.g., conditioned responses to appetitive stimuli) dictated by discharges in the ascending systems.”²⁴ This means that if NMDAR-dependent plasticity of projections to DA neurons is under dysfunctional DA control, the schizophrenic brain may not be able to represent salient or valuable stimuli, let alone respond to them adaptively.

Concerning the second aspect of this point, reelin is a signaling protein that was originally described as an important regulator of neuronal migration in the cortex during development.²¹⁴ More recently, it has become clear that reelin also has important functions in the adult brain where it takes part in the regulation of synaptic plasticity.²¹⁵ In particular, reelin is a potent enhancer of NMDAR-dependent synaptic plasticity.²¹⁶ A reduced expression of reelin, as found in postmortem studies of schizophrenia,^{217,218} would therefore lead to reduced NMDAR-mediated synaptic plasticity.

From Dysconnectivity to Model-Based Diagnostics

In this article, we have described a pathophysiological framework for schizophrenia, which explains both the neurobiological causes of dysconnection, ie, abnormal functional integration, and how dysconnectivity gives rise to pathognomonic symptoms of schizophrenia. At the neurophysiological level, we have reviewed evidence that dysconnectivity results from a disturbance of NMDAR-dependent synaptic plasticity due to abnormal regulation by neuromodulatory transmitters. In an attempt to bridge neurophysiological and cognitive levels, we have described how this could lead to a fundamental failure of self-monitoring (or corollary discharge) and how the latter could explain some key clinical symptoms of schizophrenia. Finally, we have demonstrated, point by point, that our pathophysiological model of schizophrenia has good explanatory power, accounting for the majority of the empirical facts compiled by the editors of this special issue.

The model of schizophrenia that is most closely related to ours is probably that of Lewis and Gonzalez-Burgos.⁸⁶ Anatomically, this model is concerned principally with the DLPFC and, at a cognitive level, focuses on explain-

ing working memory dysfunction in schizophrenia. The strength of this model is that by proposing a single primary mechanism, ie, hypofunction of NMDARs in the DLPFC, it can account for a large range of empirically established abnormalities of DAergic and GABAergic function in the DLPFC. This model gives a precise account of the downstream effects that NMDAR dysfunction in prefrontal cortex can be expected to have on other transmitter systems. However, it overlooks the fact that a primary deficit in NMDAR-dependent plasticity would not be limited to the DLPFC working memory system. In contrast, the dysconnection hypothesis proposes that the pathophysiological mechanism is not an isolated impairment of NMDAR-dependent plasticity per se but an impairment of NMDAR interaction with and regulation by modulatory neurotransmitters like DA, ACh, and 5-HT. This is a subtle but important difference: while it is possible that the etiological basis of this abnormal interaction may reside in a genetically predetermined (and environmentally unmasked) dysfunction of (1) the NMDAR, (2) the receptor(s) of neuromodulatory transmitter(s), or (3) the multiple signal transduction pathways that link the former 2, the pathophysiological mechanism proposed by the dysconnection hypothesis is a selective expression of NMDAR dysfunction in situations that require regulation of NMDAR-dependent plasticity by neuromodulatory transmitters. This notion distinguishes it from other pathophysiological theories of schizophrenia that focus on impairments in NMDAR function per se.^{40–44} Furthermore, the dysconnection hypothesis is a functional hypothesis, formulated under specific theories of perceptual inference and learning. This is important because it ties putative pathophysiological mechanisms to the symptoms and signs of schizophrenia. Finally, it is noteworthy that the notion of dysfunctional interactions between NMDARs and neuromodulatory receptors increasingly moves into the focus of current pathophysiological theories and drug development strategies.^{32,191,219–221}

A specific prediction of the dysconnection hypothesis is that perceptual, procedural (motor), and emotional (reinforcement) learning, all of which are known to require neuromodulation of NMDARs, should induce abnormal synaptic plasticity in schizophrenic patients. This article has described several examples supporting this prediction, eg, impaired perceptual learning in schizophrenia (modulated by ACh and 5-HT^{57,58}), aberrant procedural learning (modulated by DA⁵⁹), and abnormal reinforcement learning (modulated by DA^{62,63,136}). Experimentally, one would test the dysconnection hypothesis by pharmacological challenges that manipulate neuromodulatory influences on NMDAR-mediated plasticity during the above types of learning: if one could establish that these modulatory influences are unimpaired in schizophrenic patients, the dysconnection hypothesis would be refuted.

Another important prediction by the disconnection hypothesis is that subgroups of patients should be distinguished by distinct patterns of impairments in the regulation of NMDAR-dependent plasticity. This perspective accounts for both uniformity and diversity across patients: multiple neuromodulatory processes can, independently or jointly, impact on the same pathophysiological “bottleneck,” the plasticity mediated by NMDARs; and this influence can be modulated by hormonal, metabolic, and immunological factors. In turn, these factors can be induced by environmental influences (eg, psychosocial stress, drugs, and infections). This view is consistent with the facts that (1) the clinical spectrum of schizophrenia is characterized by heterogeneous cognitive symptoms that combine with a core of psychotic symptoms, (2) patients show different therapeutic responses to pharmacological treatment, and (3) genetic studies have demonstrated the polygenetic nature of schizophrenia.

Based on this view, one of the challenges will be to develop methods for delineating patient subgroups that are physiologically defined through one or several specific impairments in NMDAR-dependent plasticity and their regulation by DA, ACh, or 5-HT. As outlined previously,²⁵ our own work aims to establish model-based diagnostic procedures that can provide such classifications. The basic idea is to construct physiologically plausible models of neuronal pathophysiology that can be fitted to noninvasive brain data (eg, fMRI, EEG, and MEG) and then use the estimated model parameters for diagnostic classification. This is not dissimilar to established approaches in internal medicine. For example, decades of research on hypertension have yielded pathophysiological models, which have established diagnostic procedures that are in everyday use for detecting patient-specific causes of high blood pressure (eg, measures of hormone concentrations or renal blood flow). More recently, cardiovascular research progressed toward biophysical and mechanistic models that can be fitted to measurements of individual patients.²²²

Using dynamic causal modeling,^{223–228} we are currently working on models for inferring synaptic plasticity from fMRI and EEG/MEG data, acquired during learning and decision-making tasks. For example, we have recently established a dynamic causal model (DCM) that infers, given measured fMRI data, how prediction errors during incidental learning of audio-visual associations drive plasticity of connections between auditory and visual areas.²²⁹ Similarly, we have established an EEG-based DCM of plasticity during the MMN,²³⁰ which, as described above, can be treated as a prediction error signal during sensory learning that is known to be reduced in schizophrenia. We recently obtained some preliminary construct validation of a DCM for spectral responses using local field potentials recordings in rats and microdialysis measures of extracellular glutamate.²²⁶

Similarly, in ongoing rodent studies using a within-animal pharmacological design (with specific agonists and antagonists of the same receptor), we are currently testing the ability of DCM to detect the functional status of particular neurotransmitter receptors and their involvement in learning-induced plasticity. If successful, such DCMs could then be used in clinical studies (eg, using pharmacological challenges) to subdivide schizophrenic patients into physiologically defined groups on the basis of these receptor function indices. The advantage of this approach is that the grouping of patients is not simply driven by data but is constrained by a principled and carefully specified theory. This model-based approach reduces the effects of sampling variations and other kinds of statistical noise and enhances the chances of identifying the fundamental pathophysiological dimensions of the schizophrenia spectrum.

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