Schizophrenia Bulletin vol. 35 no. 3 pp. 509–527, 2009
doi:10.1093/schbul/sbn176
Advance Access publication on January 20, 2009

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

Klaas E. Stephan[1–3], Karl J. Friston[2], and Chris D. Frith[2,4]

[2]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, 12 Queen Square, London WC1N 3BG, UK; [3]Laboratory for Social and Neural Systems Research, Institute for Empirical Research in Economics, University of Zurich, Zurich, Switzerland; [4]Centre of Functionally Integrative Neuroscience (CFIN), Aarhus University Hospital, 8000-Aarhus, Denmark

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/acetylcholine/serotonin/effective connectivity/dynamic causal modeling/DCM/predictive coding

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 Schneider[2] (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. Wernicke[3] was the first to propose this hypothesis. He postulated that psychosis arises from anatomical disruption of association fiber

[1]To whom correspondence should be addressed; tel: +44-207-8337472, fax: +44-207-8131420, e-mail: k.stephan@fil.ion.ucl.ac.uk.

tracts and referred to this disruption as "sejunction." Subsequently, a similar notion, but formulated in terms of psychopathology, was expressed by Bleuler[4] 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 dysconnection hypothesis 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 disconnectivity (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 (AMPARs); 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 dysconnection hypothesis and that distinguishes it from other pathophysiological theories of schizophrenia that postulate impaired NMDAR function alone.[40–44]

What Causes Dysconnection?

Two possible explanations for how dysconnection 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, NRG1[46]). 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 al[59] used a well-established, pharmacologically validated transcranial magnetic stimulation paradigm[60] 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 postmortem 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 receptors[90] 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 al[25]). 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 al[122] 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 regions[128]). 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, neuroanatomical 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 al[160]). This perspective might be useful for explaining symptoms of schizophrenia beyond delusions of control. For example, Friston[53] 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 cortisol[169] 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 glutamatergic 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 LTP[182] 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 polygenetic 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 studies[186] 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 Weinberger[83] 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 al[84] 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 endocytosis[188]). Furthermore, a study of high-risk subjects reported that the risk allele in the NRG1 promotor 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 environmental 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 al[25]), this finding is perfectly consistent with chronic NMDA hypoactivation: NMDAR activation is a potent promotor 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 dysconnection 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-Burgos[86] 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 al[212]). 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 explaining 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 DA[59]), 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 dysconnection 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.

Funding

Wellcome Trust (to K.E.S., K.J.F., C.D.F.); University Research Priority Program "Foundations of Human Social Behaviour" at the University of Zurich (to K.E.S.); Danish National Research Foundation (to C.D.F.); Arts and Humanities Research Council (to C.D.F.).

Acknowledgments

We are grateful to Eve C. Johnstone for her comments on an earlier version of this article.

References

1. Frith CD. *The Cognitive Neuropsychology of Schizophrenia.* Hove, Germany: Lawrence Earlbaum Associates; 1992.
2. Schneider K. *Klinische Psychopathologie.* Stuttgart, Germany: Thieme; 1950.
3. Wernicke C. *Grundrisse der Psychiatrie.* Leipzig, Germany: Thieme; 1906.
4. Bleuler E. *Dementia Praecox or the Group of Schizophrenias.* [in German]. New York, NY: International Universities Press; 1911.
5. Andreasen NC, O'Leary DS, Cizadlo T, et al. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci USA*. 1996;93:9985–9990.
6. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci*. 1995;3:89–97.
7. McGuire PK, Frith CD. Disordered functional connectivity in schizophrenia. *Psychol Med*. 1996;26:663–667.
8. Volkow ND, Wolf AP, Brodie JD, et al. Brain interactions in chronic schizophrenics under resting and activation conditions. *Schizophr Res*. 1988;1:47–53.
9. Weinberger DR, Berman KF, Suddath R, Torrey EF. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry*. 1992;149:890–897.

10. Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RS. The left medial temporal region and schizophrenia. A PET study. *Brain*. 1992;115:367–382.
11. Friston KJ, Frith CD, Fletcher P, Liddle PF, Frackowiak RS. Functional topography: multidimensional scaling and functional connectivity in the brain. *Cereb Cortex*. 1996;6:156–164.
12. Lawrie SM, Buechel C, Whalley HC, Frith CD, Friston KJ, Johnstone EC. Reduced frontotemporal functional connectivity in schizophrenia associated with auditory hallucinations. *Biol Psychiatry*. 2002;51:1008–1011.
13. Meyer-Lindenberg AS, Olsen RK, Kohn PD, et al. Regionally specific disturbance of dorsolateral prefrontal-hippocampal functional connectivity in schizophrenia. *Arch Gen Psychiatry*. 2005;62:379–386.
14. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci USA*. 2006;103:19878–19883.
15. Lee KH, Williams LM, Breakspear M, Gordon E. Synchronous gamma activity: a review and contribution to an integrative neuroscience model of schizophrenia. *Brain Res Rev*. 2003;41:57–78.
16. Spencer KM, Nestor PG, Perlmutter R, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci USA*. 2004;101:17288–17293.
17. Symond MP, Harris AW, Gordon E, Williams LM. . "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry*. 2005;162:459–465.
18. Uhlhaas PJ, Linden DE, Singer W, et al. Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci*. 2006;26:8168–8175.
19. Breakspear M, Terry JR, Friston KJ, et al. A disturbance of nonlinear interdependence in scalp EEG of subjects with first episode schizophrenia. *Neuroimage*. 2003;20:466–478.
20. Hoffman RE, Buchsbaum MS, Escobar MD, Makuch RW, Nuechterlein KH, Guich SM. EEG coherence of prefrontal areas in normal and schizophrenic males during perceptual activation. *J Neuropsichiatry Clin Neurosci*. 1991;3:169–175.
21. Koukkou M, Lehmann D, Wackermann J, Dvorak I, Henggeler B. Dimensional complexity of EEG brain mechanisms in untreated schizophrenia. *Biol Psychiatry*. 1993;33:397–407.
22. Saito N, Kuginuki T, Yagyu T, et al. Global, regional, and local measures of complexity of multichannel electroencephalography in acute, neuroleptic-naive, first-break schizophrenics. *Biol Psychiatry*. 1998;43:794–802.
23. Friston KJ. Theoretical neurobiology and schizophrenia. *Br Med Bull.* 1996;52:644–655.
24. Friston KJ. The disconnection hypothesis. *Schizophr Res*. 1998;30:115–125.
25. Stephan KE, Baldeweg T, Friston KJ. Synaptic plasticity and dysconnection in schizophrenia. *Biol Psychiatry*. 2006; 59:929–939.
26. Bagal AA, Kao JP, Tang CM, Thompson SM. Long-term potentiation of exogenous glutamate responses at single dendritic spines. *Proc Natl Acad Sci USA*. 2005;102:14434–14439.
27. Montgomery JM, Madison DV. Discrete synaptic states define a major mechanism of synapse plasticity. *Trends Neurosci*. 2004;27:744–750.
28. Passafaro M, Piech V, Sheng M. Subunit-specific temporal and spatial patterns of AMPA receptor exocytosis in hippocampal neurons. *Nat Neurosci*. 2001;4:917–926.
29. Gu Q. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. *Neuroscience*. 2002;111:815–835.
30. Lau CG, Zukin RS. NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nat Rev Neurosci*. 2007;8:413–426.
31. Jiao H, Zhang L, Gao F, Lou D, Zhang J, Xu M. Dopamine D(1) and D(3) receptors oppositely regulate NMDA- and cocaine-induced MAPK signaling via NMDA receptor phosphorylation. *J Neurochem*. 2007;103:840–848.
32. Missale C, Fiorentini C, Busi C, Collo G, Spano PF. The NMDA/D1 receptor complex as a new target in drug development. *Curr Top Med Chem*. 2006;6:801–808.
33. Salazar-Colocho P, Del Río J, Frechilla D. Serotonin 5-hT1A receptor activation prevents phosphorylation of NMDA receptor NR1 subunit in cerebral ischemia. *J Physiol Biochem*. 2007;63:203–211.
34. Wolf ME, Mangiavacchi S, Sun X. Mechanisms by which dopamine receptors may influence synaptic plasticity. *Ann N Y Acad Sci*. 2003;1003:241–249.
35. Delibas N, Doguc DK, Sutcu R, Eroglu E, Gökalp O. Effect of nicotine on hippocampal nicotinic acetylcholine alpha7 receptor and NMDA receptor subunits 2A and 2B expression in young and old rats. *Int J Neurosci*. 2005;115:1151–1163.
36. Hsieh CY, Leslie FM, Metherate R. Nicotine exposure during a postnatal critical period alters NR2A and NR2B mRNA expression in rat auditory forebrain. *Brain Res Dev Brain Res*. 2002;133:19–25.
37. Moyano S, Frechilla D, Del Río J. NMDA receptor subunit and CaMKII changes in rat hippocampus induced by acute MDMA treatment: a mechanism for learning impairment. *Psychopharmacology (Berl)*. 2004;173:337–345.
38. Wang F, Chen H, Steketee JD, Sharp BM. Upregulation of ionotropic glutamate receptor subunits within specific mesocorticolimbic regions during chronic nicotine self-administration. *Neuropsychopharmacology*. 2007;32:103–109.
39. Yuen EY, Jiang Q, Chen P, Gu Z, Feng J, Yan Z. Serotonin 5-HT1A receptors regulate NMDA receptor channels through a microtubule-dependent mechanism. *J Neurosci*. 2005;25:5488–5501.
40. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*. 1991;148:1301–1308.
41. Phillips WA, Silverstein SM. Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behav Brain Sci*. 2003;26:65–82.
42. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry*. 1995;52:998–1007.
43. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry*. 2001;158:1367–1377.
44. Abi-Saab WM, D'Souza DC, Moghaddam B, Krystal JH. The NMDA antagonist model for schizophrenia: promise and pitfalls. *Pharmacopsychiatry*. 1998;31:104–109.
45. Bullmore ET, Frangou S, Murray RM. The dysplastic net hypothesis: an integration of developmental and dysconnectivity theories of schizophrenia. *Schizophr Res*. 1997;28:143–156.
46. Mei L, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci*. 2008; 9:437–452.
47. Zhang LI, Poo MM. Electrical activity and development of neural circuits. *Nat Neurosci*. 2001;4(suppl):1207–1214.
48. Hua JY, Smith SJ. Neural activity and the dynamics of central nervous system development. *Nat Neurosci*. 2004;7:327–332.
49. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003;60:1187–1192.

50. Näätänen R, Gaillard AWK, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. *Acta Psychol*. 1978;42:313–329.
51. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res*. 2005;76:1–23.
52. Baldeweg T. Repetition effects to sounds: evidence for predictive coding in the auditory system. *Trends Cogn Sci*. 2006;10:93–94.
53. Friston KJ. A theory of cortical responses. *Proc R Soc Lond B Biol Sci*. 2005;360:815–836.
54. Kreitschmann-Andermahr I, Rosburg T, Demme U, Gaser E, Nowak H, Sauer H. Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Cogn Brain Res*. 2001;12:109–116.
55. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000;57:1139–1147.
56. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci USA*. 1996;93:11962–11967.
57. Baldeweg T, Wong D, Stephan KE. Nicotinic modulation of human auditory sensory memory: evidence from mismatch negativity potentials. *Int J Psychophysiol*. 2006;59:49–58.
58. Kähkönen S, Mäkinen V, Jääskeläinen IP, Pennanen S, Liesivuori J, Ahveninen J. Serotonergic modulation of mismatch negativity. *Psychiatry Res*. 2005;138:61–74.
59. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Chen R. Dysfunctional neural plasticity in patients with schizophrenia. *Arch Gen Psychiatry*. 2008;65:378–385.
60. Bütefisch CM, Davis BC, Wise SP, et al. Mechanisms of use-dependent plasticity in the human motor cortex. *Proc Natl Acad Sci USA*. 2000;97:3661–3665.
61. Corlett PR, Murray GK, Honey GD, et al. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*. 2007;130:2387–2400.
62. Jensen J, Willeit M, Zipursky RB, et al. The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology*. 2008;33:473–479.
63. Murray GK, Corlett PR, Clark L, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 2008;13:267–276.
64. Roiser JP, Stephan KE, den Ouden HEM, Barnes TRE, Friston KJ, Joyce EM. Do patients with schizophrenia exhibit aberrant salience? *Psychol Med*. 2008; In press.
65. Baldwin AE, Sadeghian K, Kelley AE. Appetitive instrumental learning requires coincident activation of NMDA and dopamine D1 receptors within the medial prefrontal cortex. *J Neurosci*. 2002;22:1063–1071.
66. Smith-Roe SL, Kelley AE. Coincident activation of NMDA and dopamine D1 receptors within the nucleus accumbens core is required for appetitive instrumental learning. *J Neurosci*. 2000;20:7737–7742.
67. Allen RM, Young SJ. Phencyclidine-induced psychosis. *Am J Psychiatry*. 1978;135:1081–1083.
68. Featherstone RE, Kapur S, Fletcher PJ. The amphetamine-induced sensitized state as a model of schizophrenia. *Prog-Neuropsychopharmacol Biol Psychiatry*. 2007;31:1556–1571.
69. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160:13–23.
70. Domino EF, Mirzoyan D, Tsukada H. N-methyl-D-aspartate antagonists as drug models of schizophrenia: a surprising link to tobacco smoking. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:801–811.
71. Fox K, Sato H, Daw N. The effect of varying stimulus intensity on NMDA receptor activity in cat visual cortex. *J Neurophysiol*. 1990;64:1413–1428.
72. Kelly JB, Zhang H. Contribution of AMPA and NMDA receptors to excitatory responses in the inferior colliculus. *Hear Res*. 2002;168:35–42.
73. Black JE, Kodish IM, Grossman AW, et al. Pathology of layer V pyramidal neurons in the prefrontal cortex of patients with schizophrenia. *Am J Psychiatry*. 2004;161:742–744.
74. Garey LJ, Ong WY, Patel TS, et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry*. 1998;65:446–453.
75. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry*. 2000;57:65–73.
76. Rosoklija G, Toomayan G, Ellis SP, et al. Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: preliminary findings. *Arch Gen Psychiatry*. 2000;57:349–356.
77. Cline H, Haas K. The regulation of dendritic arbor development and plasticity by glutamatergic synaptic input: a review of the synaptotrophic hypothesis. *J Physiol*. 2008;586:1509–1517.
78. Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature*. 1999;399:66–70.
79. Monfils MH, VandenBerg PM, Kleim JA, Teskey GC. Long-term potentiation induces expanded movement representations and dendritic hypertrophy in layer V of rat sensorimotor neocortex. *Cereb Cortex*. 2004;14:586–593.
80. Monfils MH, Teskey GC. Induction of long-term depression is associated with decreased dendritic length and spine density in layers III and V of sensorimotor neocortex. *Synapse*. 2004;53:114–121.
81. Rajan I, Cline HT. Glutamate receptor activity is required for normal development of tectal cell dendrites in vivo. *J Neurosci*. 1998;18:7836–7846.
82. Sin WC, Haas K, Ruthazer ES, Cline HT. Dendrite growth increased by visual activity requires NMDA receptor and Rho GTPases. *Nature*. 2002;419:475–480.
83. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005;10:40–68.
84. Walsh T, McClellan JM, McCarthy SE, et al. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*. 2008;320:539–543.
85. Laruelle M, Frankle WG, Narendran R, Kegeles LS, Abi-Dargham A. Mechanism of action of antipsychotic drugs: from dopamine D(2) receptor antagonism to glutamate NMDA facilitation. *Clin Ther*. 2005;27(suppl A):S16–S24.
86. Lewis DA, Gonzalez-Burgos G. Pathophysiologically based treatment interventions in schizophrenia. *Nat Med*. 2006;12:1016–1022.
87. Jackson ME, Frost AS, Moghaddam B. Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits

dopamine release in the nucleus accumbens. *J Neurochem*. 2001;78:920–923.
88. Sesack SR, Carr DB. Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. *Physiol Behav*. 2002;77:513–517.
89. Bonci A, Malenka RC. Properties and plasticity of excitatory synapses on dopaminergic and GABAergic cells in the ventral tegmental area. *J Neurosci*. 1999;19:3723–3730.
90. Mansvelder HD, McGehee DS. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. *Neuron*. 2000;27:349–357.
91. Overton PG, Richards CD, Berry MS, Clark D. Long-term potentiation at excitatory amino acid synapses on midbrain dopamine neurons. *Neuroreport*. 1999;10:221–226.
92. Carr DB, Sesack SR. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci*. 2000;20:3864–3873.
93. Gao M, Liu CL, Yang S, Jin GZ, Bunney BS, Shi WX. Functional coupling between the prefrontal cortex and dopamine neurons in the ventral tegmental area. *J Neurosci*. 2007;27:5414–5421.
94. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry*. 1998;155:761–767.
95. Breier A, Su TP, Saunders R, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA*. 1997;94:2569–2574.
96. Kegeles LS, Abi-Dargham A, Zea-Ponce Y, et al. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry*. 2000;48:627–640.
97. Laruelle M, Abi-Dargham A, van Dyck CH, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci USA*. 1996;93:9235–9240.
98. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry*. 1999;46:56–72.
99. Miller DW, Abercrombie ED. Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. *Brain Res Bull*. 1996;40:57–62.
100. Kalivas PW, Alesdatter JE. Involvement of N-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. *J Pharmacol Exp Ther*. 1993;267:486–495.
101. Schilström B, Yaka R, Argilli E, et al. Cocaine enhances NMDA receptor-mediated currents in ventral tegmental area cells via dopamine D5 receptor-dependent redistribution of NMDA receptors. *J Neurosci*. 2006;26:8549–8558.
102. Ungless MA, Whistler JL, Malenka RC, Bonci A. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature*. 2001;411:583–587.
103. Sesack SR, Carr DB, Omelchenko N, Pinto A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. *Ann N Y Acad Sci*. 2003;1003:36–52.
104. Kanaan RA, Kim JS, Kaufmann WE, Pearlson GD, Barker GJ, McGuire PK. Diffusion tensor imaging in schizophrenia. *Biol Psychiatry*. 2005;58:921–929.
105. Konrad A, Winterer G. Disturbed structural connectivity in schizophrenia primary factor in pathology or epiphenomenon? *Schizophr Bull*. 2008;34:72–92.
106. Kubicki M, McCarley R, Westin CF, et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res*. 2007;41:15–30.
107. Wright IC, Sharma T, Ellison ZR, et al. Supra-regional brain systems and the neuropathology of schizophrenia. *Cereb Cortex*. 1999;9:366–378.
108. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. Hierarchical organization of human cortical networks in health and schizophrenia. *J Neurosci*. 2008;28:9239–948.
109. Sigmundsson T, Suckling J, Maier M, et al. Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. *Am J Psychiatry*. 2001;158:234–243.
110. McDonald C, Bullmore ET, Sham PC, et al. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry*. 2004;61:974–984.
111. Minshew NJ, Williams DL. The new neurobiology of autism: cortex, connectivity, and neuronal organization. *Arch Neurol*. 2007;64:945–950.
112. Temple E. Brain mechanisms in normal and dyslexic readers. *Curr Opin Neurobiol*. 2002;12:178–183.
113. Feinberg I. Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophr Bull*. 1978;4:636–640.
114. Frith CD. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychol Med*. 1987;17:631–648.
115. Frith CD, Done DJ. Towards a neuropsychology of schizophrenia. *Br J Psychiatry*. 1988;153:437–443.
116. Frith CD. The cognitive abnormalities underlying the symptomatology and the disability of patients with schizophrenia. *Int Clin Psychopharmacol*. 1995;10(suppl 3):87–98.
117. Sperry RW. Neural basis of the spontaneous optokinetic response produced by visual inversion. *J Comp Physiol Psychol*. 1950;43:482–489.
118. von Holst E, Mittelstaedt H. Das Reafferenzprinzip. *Naturwissenschaften*. 1950;37:464–476.
119. Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. *J Neurophysiol*. 2004;91:1381–1402.
120. Sommer MA, Wurtz RH. What the brain stem tells the frontal cortex. II. Role of the SC-MD-FEF pathway in corollary discharge. *J Neurophysiol*. 2004;91:1403–1423.
121. Bristow D, Haynes JD, Sylvester R, Frith CD, Rees G. Blinking suppresses the neural response to unchanging retinal stimulation. *Curr Biol*. 2005;15:1296–1300.
122. Ford JM, Mathalon DH, Whitfield S, Faustman WO, Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol Psychiatry*. 2002;51:485–492.
123. Ford JM, Gray M, Faustman WO, Heinks TH, Mathalon DH. Reduced gamma-band coherence to distorted feedback during speech when what you say is not what you hear. *Int J Psychophysiol*. 2005;57:143–150.
124. Ford JM, Roach BJ, Faustman WO, Mathalon DH. Out-of-synch and out-of-sorts: dysfunction of motor-sensory

communication in schizophrenia. *Biol Psychiatry*. 2008;63: 736–743.

125. Feinberg I, Guazzelli M. Schizophrenia—a disorder of the corollary discharge systems that integrate the motor systems of thought with the sensory systems of consciousness. *Br J Psychiatry*. 1999;174:196–204.
126. Fletcher PC, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. *J Neurosci*. 1996;16:7055–7062.
127. Fletcher PC, McKenna PJ, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Arch Gen Psychiatry*. 1998;55:1001–1008.
128. Spence SA, Liddle PF, Stefan MD, et al. Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *Br J Psychiatry*. 2000;176:52–60.
129. Spence SA, Brooks DJ, Hirsch SR, Liddle PF, Meehan J, Grasby PM. A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). *Brain*. 1997;120:1997–2011.
130. Shergill SS, Samson G, Bays PM, Frith CD, Wolpert DM. Evidence for sensory prediction deficits in schizophrenia. *Am J Psychiatry*. 2005;162:2384–2386.
131. Blakemore SJ, Smith J, Steel R, Johnstone CE, Frith CD. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychol Med*. 2000;3:1131–1139.
132. Farrer C, Franck N, Frith CD, et al. Neural correlates of action attribution in schizophrenia. *Psychiatry Res*. 2004;131:31–44.
133. Lindner A, Thier P, Kircher TT, Haarmeier T, Leube DT. Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. *Curr Biol*. 2005;15:1119–1124.
134. Honey GD, Corlett PR, Absalom AR, et al. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. *J Neurosci*. 2008;28:6295–6303.
135. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165:203–213.
136. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*. 2006;442:1042–1045.
137. von Helmholtz H. *Handbuch der physiologischen Optik*. Leipzig, Germany: Voss; 1867.
138. Poulet JF, Hedwig B. The cellular basis of a corollary discharge. *Science*. 2006;311:518–522.
139. Zaretsky M, Rowell HF. Saccadic suppression by corollary discharge in the locust. *Nature*. 1979;280:583–585.
140. Bell CC. Sensory coding and corollary discharge effects in mormyrid electric fish. *J Exp Biol*. 1989;146:229–253.
141. Bell CC, Han VZ, Sugawara Y, Grant K. Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature*. 1997;387:278–281.
142. Sawtell NB, Williams A, Bell CC. Central control of dendritic spikes shapes the responses of Purkinje-like cells through spike timing-dependent synaptic plasticity. *J Neurosci*. 2007;27:1552–1565.
143. Neuweiler G. Evolutionary aspects of bat echolocation. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*. 2003;189:245–256.
144. Yang Y, Cao P, Yang Y, Wang SR. Corollary discharge circuits for saccadic modulation of the pigeon visual system. *Nat Neurosci*. 2008;11:595–602.
145. Fee MS, Mitra PP, Kleinfeld D. Central versus peripheral determinants of patterned spike activity in rat vibrissa cortex during whisking. *J Neurophysiol*. 1997;78:1144–1149.
146. Peck CK. Saccade-related neurons in cat superior colliculus: pandirectional movement cells with postsaccadic responses. *J Neurophysiol*. 1984;52:1154–1168.
147. Campanac E, Debanne D. Spike timing-dependent plasticity: a learning rule for dendritic integration in rat CA1 pyramidal neurons. *J Physiol*. 2008;586:779–793.
148. Kampa BM, Letzkus JJ, Stuart GJ. Requirement of dendritic calcium spikes for induction of spike-timing-dependent synaptic plasticity. *J Physiol*. 2006;574:283–290.
149. Letzkus JJ, Kampa BM, Stuart GJ. Learning rules for spike timing-dependent plasticity depend on dendritic synapse location. *J Neurosci*. 2006;26:10420–10429.
150. Urakubo H, Honda M, Froemke RC, Kuroda S. Requirement of an allosteric kinetics of NMDA receptors for spike timing-dependent plasticity. *J Neurosci*. 2008;28:3310–3323.
151. Zhou YD, Acker CD, Netoff TI, Sen K, White JA. Increasing Ca2+ transients by broadening postsynaptic action potentials enhances timing-dependent synaptic depression. *Proc Natl Acad Sci USA*. 2005;102:19121–19125.
152. Pawlak V, Kerr JN. Dopamine receptor activation is required for corticostriatal spike-timing-dependent plasticity. *J Neurosci*. 2008;28:2435–2446.
153. Sakurai A, Katz PS. Spike timing-dependent serotonergic neuromodulation of synaptic strength intrinsic to a central pattern generator circuit. *J Neurosci*. 2003;23:10745–10755.
154. Seol GH, Ziburkus J, Huang S, et al. Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. *Neuron*. 2007;55:919–929.
155. Synofzik M, Lindner A, Thier P. The cerebellum updates predictions about the visual consequences of one's behavior. *Curr Biol*. 2008;18:814–818.
156. Han VZ, Grant K, Bell CC. Reversible associative depression and nonassociative potentiation at a parallel fiber synapse. *Neuron*. 2000;27:611–622.
157. Denizot JP, Clausse S, Elekes K, et al. Convergence of electrotonic club endings, GABA- and serotoninergic terminals on second order neurons of the electrosensory pathway in mormyrid fish, Gnathonemus petersii and Brienomyrus niger (Teleostei). *Cell Tissue Res*. 1987;249:301–309.
158. Wang M, Vijayraghavan S, Goldman-Rakic PS. Selective D2 receptor actions on the functional circuitry of working memory. *Science*. 2004;303:853–856.
159. Rao RP, Ballard DH. Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. *Nat Neurosci*. 1999;2:79–87.
160. Kilner JM, Friston KJ, Frith CD. Predictive coding: an account of the mirror neuron system. *Cogn Process*. 2007;18:159–166.
161. Dierks T, Linden DE, Jandl M, et al. Activation of Heschl's gyrus during auditory hallucinations. *Neuron*. 1999;22:615–621.
162. Bentaleb LA, Beauregard M, Liddle P, Stip E. Cerebral activity associated with auditory verbal hallucinations: a functional magnetic resonance imaging case study. *J Psychiatry Neurosci*. 2002;27:110–115.
163. van de Ven VG, Formisano E, Röder CH, et al. The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *NeuroImage*. 2005;27:644–655.

164. Friston KJ, Tononi G, Reeke GN, Jr, Sporns O, Edelman GM. Value-dependent selection in the brain: simulation in a synthetic neural model. *Neuroscience*. 1994;59:229–243.
165. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275:1593–1599.
166. Yu AJ, Dayan P. Uncertainty, neuromodulation, and attention. *Neuron*. 2005;46:681–692.
167. Kinney DK, Matthysse S. Genetic transmission of schizophrenia. *Annu Rev Med*. 1978;29:459–473.
168. Friston KJ. Hallucinations and perceptual inference. *Behav Brain Sci*. 2005;28:764–766.
169. Setiawan E, Jackson MF, MacDonald JF, Matthews SG. Effects of repeated prenatal glucocorticoid exposure on long-term potentiation in the juvenile guinea-pig hippocampus. *J Physiol*. 2007;581:1033–1042.
170. Smith CC, McMahon LL. Estradiol-induced increase in the magnitude of long-term potentiation is prevented by blocking NR2B-containing receptors. *J Neurosci*. 2006;26: 8517–8522.
171. Woolley CS, Weiland NG, McEwen BS, Schwartzkroin PA. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor–mediated synaptic input: correlation with dendritic spine density. *J Neurosci*. 1997; 17:1848–1859.
172. Coogan A, O'Connor JJ. Inhibition of NMDA receptor-mediated synaptic transmission in the rat dentate gyrus in vitro by IL-1 beta. *Neuroreport*. 1997;8:2107–2110.
173. Curran B, O'Connor JJ. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. *Neuroscience*. 2001;108:83–90.
174. Müller N, Schwarz MJ. The immunological basis of glutamatergic disturbance in schizophrenia: towards an integrated view. *J Neural Transm Suppl*. 2007;72:269–280.
175. Spedding M, Gressens P. Neurotrophins and cytokines in neuronal plasticity. *Novartis Found Symp*. 2008;289: 222–233.
176. Martineau M, Baux G, Mothet JP. D-serine signalling in the brain: friend and foe. *Trends Neurosci*. 2006;29:481–491.
177. Thompson JL, Pogue-Geile MF, Grace AA. Developmental pathology, dopamine, and stress: a model for the age of onset of schizophrenia symptoms. *Schizophr Bull*. 2004;30: 875–900.
178. Walker EF. Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophr Bull*. 1994;20:453–480.
179. Liu F, Day M, Muñiz LC, et al. Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. *Nat Neurosci*. 2008;11:334–343.
180. Foy MR, Baudry M, Foy JG, Thompson RF. 17ss-estradiol modifies stress-induced and age-related changes in hippocampal synaptic plasticity. *Behav Neurosci*. 2008;122: 301–309.
181. MacLusky NJ, Hajszan T, Prange-Kiel J, Leranth C. Androgen modulation of hippocampal synaptic plasticity. *Neuroscience*. 2006;138:957–965.
182. Harley CW, Malsbury CW, Squires A, Brown RA. Testosterone decreases CA1 plasticity in vivo in gonadectomized male rats. *Hippocampus*. 2000;10:693–697.
183. Heinrich JE, Singh TD, Nordeen KW, Nordeen EJ. NR2B downregulation in a forebrain region required for avian vocal learning is not sufficient to close the sensitive period for song learning. *Neurobiol Learn Mem*. 2003;79:99–108.
184. Oades RD, Schepker R. Serum gonadal steroids in young schizophrenic patients. *Psychoneuroendochrinology*. 1994;19:373–385.
185. Lohmueller KE, Pearce CL, Pike M, Lander ES, Hirschhorn JN. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet*. 2003;33:177–182.
186. Mirnics K, Lewis DA. Genes and subtypes of schizophrenia. *Trends Mol Med*. 2001;7:281–283.
187. Mirnics K, Middleton FA, Marquez A, Lewis DA, Levitt P. Molecular characterization of schizophrenia viewed by microarray analysis of gene expression in prefrontal cortex. *Neuron*. 2000;28:53–67.
188. Gu Z, Jiang Q, Fu AK, Ip NY, Yan Z. Regulation of NMDA receptors by neuregulin signaling in prefrontal cortex. *J Neurosci*. 2005;25:4974–4984.
189. Hall J, Whalley HC, Job DE, et al. A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. *Nat Neurosci*. 2006;9:1477–1478.
190. Hahn CG, Wang HY, Cho DS, et al. Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. *Nat Med*. 2006;12:824–828.
191. Tseng KY, O'Donnell P. Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. *J Neurosci*. 2004;24: 5131–5139.
192. Centonze D, Usiello A, Costa C, et al. Chronic haloperidol promotes corticostriatal long-term potentiation by targeting dopamine D2L receptors. *J Neurosci*. 2004;24:8214–8222.
193. Ahlenius S. Clozapine: dopamine D1 receptor agonism in the prefrontal cortex as the code to decipher a Rosetta stone of antipsychotic drugs. *Pharmacol Toxicol*. 1999;84:193–196.
194. Jackson DM, Wikstrom H, Liao Y. Is clozapine an (partial) agonist at both dopamine D1 and D2 receptors? *Psychopharmacology (Berl)*. 1998;138:213–216.
195. Critchlow HM, Maycox PR, Skepper JN, Krylova O. Clozapine and haloperidol differentially regulate dendritic spine formation and synaptogenesis in rat hippocampal neurons. *Mol Cell Neurosci*. 2006;32:356–365.
196. Korenblum W, Barthel A, Licinio J, et al. Elevated cortisol levels and increased rates of diabetes and mood symptoms in Soviet Union-born Jewish immigrants to Germany. *Mol Psychiatry*. 2005;10:974–975.
197. Malan NT, Eloff FC, Pretorius PJ, Van Der Merwe JS, Huisman HW, Laubscher PJ. A comparison of endocrine reactions to different types of acute stressors in rural and urban black populations. *Stress Med*. 1992;8:213–218.
198. Stefani MR, Moghaddam B. Transient N-methyl-d-aspartate receptor blockade in early development causes lasting cognitive deficits relevant to schizophrenia. *Biol Psychiatry*. 2005;57:433–436.
199. Chevaleyre V, Takahashi KA, Castillo PE. Endocannabinoid-mediated synaptic plasticity in the CNS. *Annu Rev Neurosci*. 2006;29:37–76.
200. Sjöström PJ, Turrigiano GG, Nelson SB. Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors. *Neuron*. 2003;39:641–654.
201. Mackie K. Understanding cannabinoid psychoactivity with mouse genetic models. *PLoS Biol*. 2007;5:e280.
202. Abi-Dargham A, Rodenhiser J, Printz D, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA*. 2000;97:8104–8109.
203. Malhotra AK, Pinals DA, Adler CM, et al. Ketamine-induced exacerbation of psychotic symptoms and cognitive

impairment in neuroleptic-free schizophrenics. *Neuropsychopharmacology*. 1997;17:141–150.

204. Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology*. 1999;20:106–118.
205. Arnold SE, Hyman BT, Van Hoesen GW, Damasio AR. Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. *Arch Gen Psychiatry*. 1991;48: 625–632.
206. Jakob H, Beckmann H. Circumscribed malformation and nerve cell alterations in the entorhinal cortex of schizophrenics. Pathogenetic and clinical aspects. *J Neural Transm Gen Sect*. 1994;98:83–106.
207. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm*. 1986;65:303–326.
208. Manent JB, Demarque M, Jorquera I, et al. A noncanonical release of GABA and glutamate modulates neuronal migration. *J Neurosci*. 2005;25:4755–4765.
209. Reiprich P, Kilb W, Luhmann HJ. Neonatal NMDA receptor blockade disturbs neuronal migration in rat somatosensory cortex in vivo. *Cereb Cortex*. 2005;15:349–358.
210. Ramírez M, Gutiérrez R. Activity-dependent expression of GAD67 in the granule cells of the rat hippocampus. *Brain Res*. 2001;917:139–146.
211. Wei J, Lin CH, Wu H, Jin Y, Lee YH, Wu JY. Activity-dependent cleavage of brain glutamic acid decarboxylase 65 by calpain. *J Neurochem*. 2006;98:1688–1695.
212. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci*. 2005;6:312–324.
213. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci*. 2007;27: 11496–11500.
214. D'Arcangelo G, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. *Nature*. 1995;374: 719–723.
215. Weeber EJ, Beffert U, Jones C, et al. Reelin and ApoE receptors cooperate to enhance hippocampal synaptic plasticity and learning. *J Biol Chem*. 2002;277:39944–39952.
216. Chen Y, Beffert U, Ertunc M, et al. Reelin modulates NMDA receptor activity in cortical neurons. *J Neurosci*. 2005;25:8209–8216.
217. Eastwood SL, Harrison PJ. Cellular basis of reduced cortical reelin expression in schizophrenia. *Am J Psychiatry*. 2006; 163:540–542.
218. Guidotti A, Auta J, Davis JM, et al. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry*. 2000;57:1061–1069.
219. Di Pietro NC, Seamans JK. Dopamine and serotonin interactions in the prefrontal cortex: insights on antipsychotic drugs and their mechanism of action. *Pharmacopsychiatry*. 2007;40(suppl 1):S27–S33.
220. Mouri A, Noda Y, Noda A, et al. Involvement of a dysfunctional dopamine-D1/N-methyl-d-aspartate-NR1 and Ca2+/ calmodulin-dependent protein kinase II pathway in the impairment of latent learning in a model of schizophrenia induced by phencyclidine. *Mol Pharmacol*. 2007;71:1598–1609.
221. Yang CR, Chen L. Targeting prefrontal cortical dopamine D1 and N-methyl-D-aspartate receptor interactions in schizophrenia treatment. *Neuroscientist*. 2005;11:452–470.
222. Zenker S, Rubin J, Clermont G. From inverse problems in mathematical physiology to quantitative differential diagnoses. *PLoS Comput Biol*. 2007;3:e204.
223. Friston KJ, Harrison L, Penny W. Dynamic causal modeling. *NeuroImage*. 2003;19:1273–1302.
224. David O, Kiebel SJ, Harrison LM, Mattout J, Kilner JM, Friston KJ. Dynamic causal modelling of evoked responses in EEG and MEG. *NeuroImage*. 2006;30:1255–1272.
225. Moran RJ, Kiebel SJ, Stephan KE, Reilly RB, Daunizeau J, Friston KJ. A neural mass model of spectral responses in electrophysiology. *NeuroImage*. 2007;37:706–720.
226. Moran RJ, Stephan KE, Kiebel SJ, et al. Bayesian estimation of synaptic physiology from the spectral responses of neural masses. *NeuroImage*. 2008;42:272–284.
227. Stephan KE, Harrison LM, Kiebel SJ, David O, Penny WD, Friston KJ. Dynamic causal models of neural system dynamics: current state and future extensions. *J Biosci*. 2007;32:129–144.
228. Stephan KE, Kasper L, Harrison LM, et al. Nonlinear dynamic causal models for fMRI. *NeuroImage*. 2008;42:649–662.
229. den Ouden HE, Friston KJ, Daw ND, McIntosh AR, Stephan KE. A dual role for prediction error in associative learning. *Cereb Cortex*. In press.
230. Garrido MI, Kilner JM, Kiebel SJ, Stephan KE, Friston KJ. Dynamic causal modelling of evoked potentials: a reproducibility study. *NeuroImage*. 2007;36:571–580.