Synaptic Plasticity and Dysconnection in Schizophrenia

Klaas E. Stephan, Torsten Baldeweg, and Karl J. Friston

Current pathophysiological theories of schizophrenia highlight the role of altered brain connectivity. This dysconnectivity could manifest 1) anatomically, through structural changes of association fibers at the cellular level, and/or 2) functionally, through aberrant control of synaptic plasticity at the synaptic level. In this article, we review the evidence for these theories, focusing on the modulation of synaptic plasticity. In particular, we discuss how dysconnectivity, observed between brain regions in schizophrenic patients, could result from abnormal modulation of N-methyl-D-aspartate (NMDA)-dependent plasticity by other neurotransmitter systems. We focus on the implication of the dysconnection hypothesis for functional imaging at the systems level. In particular, we review recent advances in measuring plasticity in the human brain using functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) that can be used to address dysconnectivity in schizophrenia. Promising experimental paradigms include perceptual and reinforcement learning. We describe how theoretical and causal models of brain responses might contribute to a mechanistic understanding of synaptic plasticity in schizophrenia.

Key Words: Dynamic causal models, mismatch negativity, NMDA, glutamate, acetylcholine, dopamine

The notion that schizophrenia is not caused by focal brain abnormalities, but results from pathological connectivity between brain regions, has been an influential idea in schizophrenia research. This idea was initially proposed by Wernicke (1906), who postulated that psychosis arises from anatomical disruption of association fiber tracts, and reformulated later in terms of psychopathology by Bleuler (1911), who coined the term schizophrenia to denote the "splitting" of different mental domains. More recently, this theme re-emerged in neurophysiologic and neuroimaging experiments showing abnormal distributed activity and functional connectivity in schizophrenia (Volkow et al 1988; Hoffman et al 1991; Weinberger et al 1992; Friston and Frith 1995). In an attempt to explain these observations, the disconnection hypothesis (Friston 1998) suggested that the core pathology of schizophrenia is an impaired control of synaptic plasticity that manifests as abnormal functional integration of neural systems, i.e., dysconnectivity.[1]

In this article, we review evidence for the dysconnection hypothesis and its convergence with recent genetic studies. We use this to motivate studies of plasticity in schizophrenic patients using noninvasive techniques like functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). Following a brief and selective review of synaptic plasticity, we look at some theoretical models that may constrain psychopharmacological neuroimaging paradigms. The aim of this approach is to establish models of synaptic plasticity that can be evaluated at the systems level using functional imaging of individual patients. This approach may eventually furnish surrogates for diagnostic classification, facilitate genetic studies, and have predictive validity for pharmacotherapy.

Abnormal Anatomical Connections, Abnormal Synaptic Plasticity, or Both?

There is wide-ranging evidence for dysconnection in schizophrenia (Andreasen et al 1999; Hoffman and McGlashan 2001; Friston, 2005b). For example, in terms of functional connectivity, neuroimaging studies of language have shown consistently reduced frontotemporal coupling in schizophrenia relative to control subjects. Similarly, patients show abnormal electrophysiological measures of functional connectivity, e.g., reduced interregional gamma-band synchrony during sensory processing (Table 1).

The question is how dysconnectivity is caused. Functional coupling between brain areas might be abnormal because their anatomical connections are altered, e.g., due to a "miswiring" of association fibers. Alternatively, functional coupling could be disturbed due to impairments in synaptic transmission and plasticity.[2] These mechanisms are not necessarily exclusive but could coexist, because they have a common cause or because one causes the other. For example, several genes linked to schizophrenia are involved in both establishing long-range connections during development and in regulating synaptic plasticity (e.g., NRG1 or dysbindin) (Harrison and Weinberger 2005). Conversely, any impairment in synaptic plasticity would affect the way long-range connections are established in the developing brain. This is because the strength of functional coupling between two neurons determines whether their connection survives developmental pruning (Hua and Smith 2004). Furthermore, functional coupling is a function of experience-dependent synaptic plasticity (Zhang and Poo 2001). Dysconnectivity due to impaired experience-dependent synaptic plasticity is consistent with the observation that schizophrenia cannot be explained by

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[1]Because of the original meaning of the Latin prefix "dis" (= apart), the term disconnection might suggest connectivity in schizophrenia is reduced, leading to less interaction between neural units. This is not what the original disconnection hypothesis implies (Friston 1998). To avoid confusion and emphasize the notion of abnormal synaptic plasticity in schizophrenia, we use the term dysconnection (the Greek prefix "dys" meaning bad or ill).

[2]Of course, functional dysconnections due to abnormal synaptic plasticity must also have microstructural correlates, e.g., changes in the morphology of dendritic spines and/or the number or structure of receptors. Here, we restrict impaired structural connectivity to the level of cellular processes such as axonal fiber bundles.

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Table 1. Evidence for Abnormal Functional Connectivity in Schizophrenia

Experimental Finding	References (Selection)	Comments
Abnormal Functional Connectivity Between Temporal and Frontal Regions as Measured by PET and fMRI	Friston and Frith 1995 Friston et al 1996 Lawrie et al 2002 Meyer-Lindenberg et al 2005	Replicated finding
Abnormal Gamma Synchrony During Sensory Processing (as measured by MEG/EEG)	Lee et al 2003 (review) Spencer et al 2004 Symond et al 2005	Replicated finding
Abnormal Patterns of Functional Interactions as Measured by EEG	Breakspear et al 2003 Koukkou et al 1993 Saito et al 1998	Agreement that abnormalities exist, but differences in the nature of abnormalities reported

This table lists some experimental findings related to abnormal functional connectivity in schizophrenia. *Replicated finding* means that, to our knowledge, the large majority of studies have found the same abnormality in schizophrenic patients. Note that due to editorial space constraints, we can only provide a selected and representative subset of publications for each finding; for most points, additional studies exist that are not cited here.

PET, positron-emission tomography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalogram; EEG, electroencephalogram.

genetics alone but only by interactions between genes and environment (Sullivan et al 2003).

Several studies have reported abnormalities in intra-areal connectivity in schizophrenia, demonstrating area- and lamina-specific reductions in dendritic field size and dendritic spines (Table 2). Although this could be interpreted as a developmental disturbance of microcircuit formation, it may also reflect abnormal synaptic plasticity: long-term potentiation (LTP) induces growth of dendrites and upregulation of dendritic spines (Monfils et al 2004; Engert and Bonhoeffer 1999), whereas blocking LTP or inducing long-term depression (LTD) decreases dendritic length and spine density (Monfils and Teskey 2004). There is less convincing evidence, so far, that long-range anatomical connections are compromised in schizophrenia (Harrison 1999; Table 3). This may be due to a lack of sensitive postmortem methods for studying anatomical connectivity in the human brain. However, diffusion weighted imaging (DWI) studies have delivered negative results or widely varying findings (Table 3).

In contrast to the sparse evidence for abnormal connectivity at the level of cellular processes, pharmacological studies of healthy volunteers show that impairments of synaptic plasticity are consistent with schizophrenic symptoms (Table 2). It is well known that N-methyl-D-aspartate (NMDA) antagonists, dopamine (D2) agonists, amphetamines, and serotonin agonists can induce psychotic symptoms in healthy subjects (Allen and Young 1978; Javitt and Zukin 1991; Kapur 2003). Additionally, psychotic symptoms and cognitive deficits induced by NMDA antagonists are similar to those of schizophrenia (Domino et al 2004 list similarities and differences).[3] Finally, and perhaps even more intriguing, electrophysiological signatures of impaired sensory learning are found consistently in schizophrenic patients and can be induced pharmacologically in healthy volunteers. As described below, schizophrenic patients show a significant reduction in an event-related potential (ERP), the "mismatch negativity" (MMN). The MMN has been interpreted as an error signal, elicited during sensory learning (Friston, 2005a). A replicated finding is that the NMDA antagonist ketamine reduces the MMN, rendering it very similar to that of patients (Table 2).

Indirect, but important, support for abnormal synaptic plasticity in schizophrenia is additionally provided by recent genome-wide linkage and allelic association studies. Reviewing the current findings, Harrison and Weinberger (2005) identified seven candidate genes for schizophrenia for which at least three studies provided positive evidence. Remarkably, six of these genes are intimately related to glutamatergic synapses, notably NMDA receptor (NMDAR)-dependent signaling, and/or to neuromodulatory transmitters (Figure 1). Harrison and Weinberger (2005) 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 NMDA receptor (NMDAR)-mediated glutamatergic transmission. . . ."

In conclusion, even though one cannot exclude cellular dysconnectivity (along with or as a consequence of impaired synaptic plasticity), it seems more promising to pursue the notion that schizophrenia is caused by abnormal synaptic regulation. This is fortuitous, because in the human brain, synaptic plasticity is more amenable to experimental study. Measuring the effects of reversible pharmacological manipulations of synaptic plasticity with in vivo imaging techniques is feasible in humans, whereas experimental manipulations of structural connectivity would require developmental perturbations.

Neurotransmitter Modulation of Synaptic Plasticity

Although the concept of impaired synaptic plasticity is, on its own, too broad to be useful for clinical research, it provides a framework for developing testable pathophysiological models in schizophrenia research. While it is beyond the scope of this article to review synaptic plasticity in depth, this section reviews selectively some aspects that are useful to guide the rest of the article. For details, the reader is referred to comprehensive reviews on synaptic plasticity cited below.

Synaptic plasticity can be defined as a state- and history-dependent change in synaptic strength (Zucker and Regehr

[3] N-methyl-D-aspartate (NMDA) receptors (NMDARs) also play a role in synaptic transmission of sensory information (Fox et al 1990; Kelly and Zhang 2002). It is therefore likely that NMDA antagonists also diminish the strength of glutamatergic synapses directly by blocking NMDAR-dependent excitatory postsynaptic currents (EPSCs). However, (in)activation of NMDARs leads to various intracellular processes that change α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)-mediated EPSCs as well, e.g., through phosphorylation of AMPAR subunits or rapid trafficking of AMPARs from intracellular sites into the postsynaptic density or vice versa. These processes operate at fast time scales, i.e., from seconds to minutes (Montgomery and Madison 2004; Passafaro et al 2001; Bagal et al 2005). Therefore, it is likely that the cognitive effects seen after ketamine administration to healthy volunteers result both from reducing NMDAR EPSCs and from NMDA-dependent synaptic plasticity, i.e., changes in the functional state and number of AMPARs.

Table 2. Evidence for Abnormal Synaptic Plasticity in Schizophrenia

Experimental Finding	References (Selection)	Comments
Pharmacologically Induced Symptoms of Psychosis and Schizophrenia- like Cognitive Deficits in Healthy Volunteers	Allen and Young 1978 Javitt and Zukin 1991 (review) Kapur 2003 (review)	Replicated finding
Abnormal ERPs of Sensory Learning in Patients can be Mimicked by Pharmacological NMDA Blockage in Healthy Controls Subjects	Kreitschmann-Andermahr et al 2001 Umbricht et al 2000	Replicated finding
Candidate Genes Identified in Genetic Studies	Harrison and Weinberger 2005 (review)	Almost all genes are implicated in synaptic plasticity (see main text)
Reduction in Dendritic Field Size and Spine Density	Black et al 2004 Garey et al 1998 Glantz and Lewis 2000 Rosoklija et al 2000	Replicated finding; although structural changes, these are likely consequences of impaired synaptic plasticity (see main text)
Onset in Adulthood		Speaks to learning-dependent processes and against abnormal structural connectivity as the main cause of schizophrenia

This table lists some experimental findings related to abnormal synaptic plasticity in schizophrenia. See legend to Table 1 for further explanations. ERP, event-related potentials; NMDA, *N*-methyl-*D*-aspartate.

2002). For glutamatergic synapses, on which we focus here, synaptic strength depends on presynaptic transmitter release and the number and functional states of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs). Synaptic plasticity therefore results from changing any of these factors (Montogomery and Madison 2004; Perez-Otano and Ehlers 2005). A key distinction is between short-term plasticity (STSP) and long-term plasticity (LTSP). Short-term plasticity comprises short-lived phenomena, e.g., rapid synaptic facilitation or depression with time constants around 100 ms, that do not require a remodeling of the synapse (Zucker and Regehr 2002). In contrast, LTSP includes enduring changes that last hours and possibly years (long-term potentiation and long-term depression) and depend on lasting structural alterations of the synapse. Clearly, this classification is oversimplified; there are intermediate processes like "early LTP" that have a rapid onset due to phosphorylation and rapid trafficking of AMPARs (Frey and Morris 1998; Malinow and Malenka 2002).

The NMDARs play a central role in plasticity at glutamatergic synapses where the number and functional states of postsynaptic AMPARs are controlled primarily through NMDAR-dependent mechanisms (Malinow and Malenka 2002; Montgomery and Madison 2004; Perez-Otano and Ehlers 2005) (Figure 1). Modulatory transmitters affect synaptic plasticity mainly through changes in NMDAR function (Gu 2002).[4] Given the induction of psychotic symptoms by NMDA antagonists and the genetic studies described above, the relationship between AMPARs (synaptic strength), NMDARs (synaptic plasticity), and modulatory neurotransmitters (modulation of plasticity) is of great interest in schizophrenia research. Here, we list just a few examples of neurotransmitter effects on NMDARs that are related to candidate genes for schizophrenia described above. For example, metabotropic glutamate receptors (mGluR), particularly mGluR3 (one of the candidate genes highlighted by Harrison and Weinberger 2005) and mGluR5, interact strongly with NMDARs. Metabotropic glutamate receptor agonists lead to potentiation of NMDAR-mediated responses and can even reverse the effects of NMDAR antagonists (Moghaddam 2003). Dopamine receptors also strongly alter NMDAR function: D1 agonists and D2 antagonists increase NMDAR-dependent LTP, whereas D2 agonists decrease it (Centonze et al 2004; Tseng and O'Donnell 2004). Cholinergic mechanisms greatly modulate NMDA-dependent LTP and LTD in visual cortex (Brocher et al 1992; Kirkwood et al 1999) and hippocampus (Yun et al 2000). Furthermore, the nicotinergic α7 nicotinic receptor, a putative candidate gene for schizophrenia (Martin et al 2004), is expressed abundantly on glutamatergic synapses in cortex and hippocampus both presynaptically and postsynaptically (Fabian-Fine et al 2001).

Given the "bottleneck" role of NMDARs for synaptic plasticity, it seems likely that whatever neurotransmitter systems are affected in schizophrenia, the ensuing abnormal plasticity might be dependent, at least partially, on dysfunctional modulation of NMDAR-dependent processes. The next section considers the practical implications of this observation for research at the systems level.

Investigating Synaptic Plasticity in a Clinical Context

In this section, we consider how noninvasive functional neuroimaging techniques might afford clinical tests of synaptic plasticity in schizophrenia. The notion that synaptic plasticity is impaired in schizophrenic patients is not sufficient to specify useful tests (cf. the discussion by Harrison and Weinberger 2005). The dysconnection hypothesis is more specific and says that it is not plasticity per se that is abnormal but its modulation during reinforcement and perceptual learning (Friston, 2005b). This raises the possibility that the interaction of NMDAR function and modulatory neurotransmitter systems lies at the heat of the pathophysiology. However, given the polygenetic nature of schizophrenia and evidence from gene expression studies (Mirnics et al 2000), it is likely that mechanisms of abnormal modulation of plasticity differ across patients. For example, in some patients dysfunctional modulation of NMDAR-dependent synaptic plasticity might be due primarily to changes in dopaminergic function, whereas in others it might be caused through abnormal modulation by acetylcholine. The challenge is to develop suitable psychopharmacological paradigms and data analyses by which one could possibly distinguish among these possibilities.

The selective dependence of different forms of learning on different neurotransmitter systems speaks to psychopharmaco-

[4]Some neurotransmitters like acetylcholine (Massey et al 2001) or dopamine (Wolf et al 2003) can affect synaptic plasticity independently of NMDARs.

Table 3. Evidence for Abnormal Structural Connectivity in Schizophrenia

Experimental Finding	References (Selection)	Comments
Aberrantly Located Neurons in White Matter, Implying Disturbances in Neuronal Migration and Formations of Connections	Akbarian et al 1996 Eastwood and Harrison 2003	Agreement that abnormalities exist, but differences in the nature of abnormalities reported
Abnormal Cytoarchitecture of Entorhinal Cortex, Implying Aberrant Formation of Microcircuits	Jakob and Beckmann 1986 Arnold et al 1991	Agreement that abnormalities exist, but differences in the nature of abnormalities reported
White Matter Abnormalities Observed with Diffusion Weighted Imaging	Foong et al 2002 Steel et al 2001 Hulshoff Pol et al 2004 Kubicki et al 2002 Szeszko et al 2005	Inconsistent findings across studies, several negative results
Changes in Morphology of the Corpus Callosum	Woodruff et al 1995 (meta-analysis) Woodruff et al 1997 Highley et al 1999	Inconsistent findings across studies

This table lists some experimental findings related to abnormal structural connectivity in schizophrenia. See legend to Table 1 for further explanations.

logical studies of healthy volunteers using paradigms that induce different types of learning (e.g., perceptual, associative, reinforcement, or procedural learning) and have different time courses (i.e., STSP vs. LTSP). For example, there is good evidence that dopamine is crucial for reinforcement and other forms of emotional learning, whereas acetylcholine is important for perceptual learning (Friston, 2005b). One could argue that many of the disintegrative and autistic aspects of schizophrenic symptoms can be viewed as a failure of emotional learning that is secondary to a fundamental failure of reinforcement learning (Friston 1998); this view points to reinforcement learning as a useful paradigm. On the other hand, hallucinations could be interpreted as resulting from problems with perceptual learning and inference and a role for sensory paradigms (Friston, in press).

Many schizophrenic patients are unable to perform well on complex cognitive tasks. More attractive are tasks that are not confounded by patient performance or effort and are relatively independent of strategy and attentional set. Arguably, the most promising paradigm that meets these constraints is implicit learning.[5] Implicit learning is "non-episodic learning of complex information in an incidental manner, without awareness of what has been learned" (Seger 1994) and independent of the subject's strategy of learning (Chun and Jiang 1998). Some forms of implicit learning can take place in the absence of attention to the relevant stimuli and can progress quickly. This has been observed particularly in the sensory domain, e.g., audio-visual associative learning (McIntosh et al 1998) and learning of stimulus probabilities (e.g., MMN paradigms; see below).

In the next section, we review recent developments in modeling that are especially relevant to the neurobiological considerations above. These developments enable plasticity to be measured noninvasively using fMRI and EEG. We then turn to more theoretical models of how the brain actually learns. These link dysconnection theories of schizophrenia to empirical analysis and may provide a mechanistic framework in which to understand how abnormal plasticity might be expressed functionally.

[5]Several studies focusing on priming effects in language have shown that, behaviorally, schizophrenic patients are not impaired in implicit learning (Danion et al 2001). Neurophysiological studies have shown, however, that even in the absence of behavioral differences, the neural dynamics during implicit learning are different in schizophrenic patients relative to control subjects (Mathalon et al 2002). Furthermore, implicit learning in other domains shows clear impairments in schizophrenia (Schwartz et al 2003).

Modeling Synaptic Plasticity

There are many approaches to modeling learning-related synaptic plasticity at the systems level. Here, we review two approaches that may be particularly useful in the present context.

Dynamic Causal Modeling

Dynamic causal modeling (DCM) is a generic approach to describing the dynamics of interacting neural systems. It combines a model of neural population dynamics, which entails perturbations (e.g., sensory inputs), intrinsic connections, and contextual modulations of these connections, with a modality-specific forward model (fMRI: Friston et al 2003; EEG/magnetoencephalography [MEG]: David et al 2005, in submission). Using a Bayesian approach, with priors that constrain the values parameters can assume, DCMs are fitted such that the predicted data are as similar as possible to the measured responses. This allows one to quantify and make statistical inferences about regional responses in terms of the connectivity at the neural level and, critically, how this connectivity changes as a function of experimental context (e.g., time or drug effect). For example, DCM for fMRI is based on the following bilinear model of neural population dynamics

$$\frac{dz}{dt} = Az + \sum_{j=1}^{m} u_j B^{(j)} z + Cu \qquad (1)$$

where z is the state vector (with one state variable per brain region), t is time, and u_j is the j-th input to the system (i.e., some experimentally controlled manipulation). This state equation represents the strengths of direct inputs to the modeled system (sensory stimuli; C matrix), the strength of connections between regions (A matrix), and the modulation of these connections ($B^{(1)} \ldots B^{(m)}$ matrices) as a function of cognitive set (e.g., task, attention), time (e.g., learning), or drug (e.g., ketamine). These parameters correspond to rate constants of the modeled neurophysiologic processes and serve as an index of connection strength. The modulation of connections with time allows one to estimate and quantify plasticity on a macroscopic scale.

This state equation only describes the behavior of large neuronal populations, without reference to any specific neurophysiologic mechanism by which connection strengths

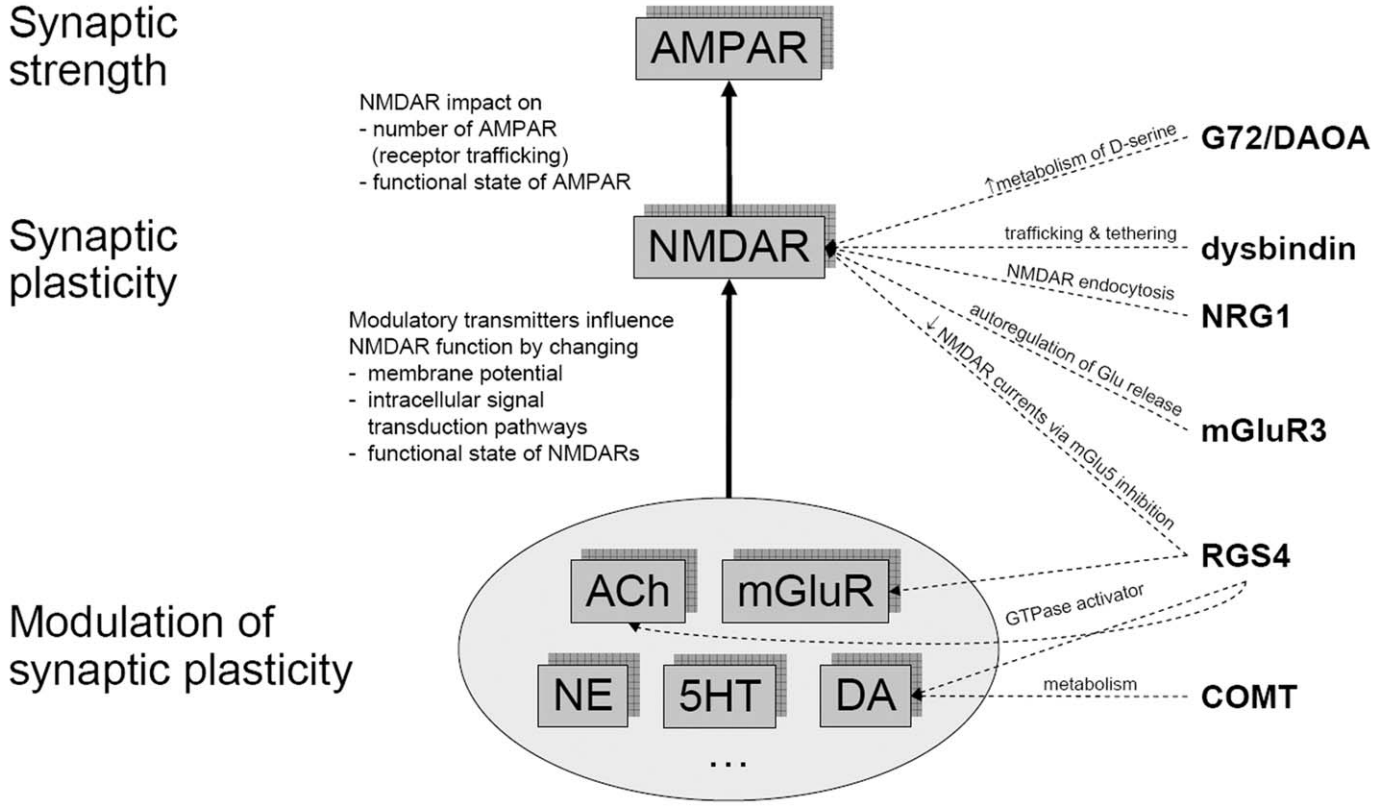

Figure 1. Strongly simplified schema of the hierarchical relation among synaptic strength, synaptic plasticity, and its modulation at glutamatergic synapses. Leaving presynaptic mechanisms aside, the efficacy or strength of a glutamatergic synapse depends largely on the number and functional state of postsynaptic AMPA receptors (AMPARs). The AMPARs are rapidly inserted into and removed from the cell membrane and have discrete electrophysiological states (Montgomery and Madison 2004; Malinow and Malenka 2002). Both the trafficking and state-dynamics of AMPARs are mainly under the control of NMDA receptors (NMDARs). The function of NMDARs is influenced by mGluRs as well as by a variety of neuromodulatory transmitters, including acetylcholine (ACh), norepinephrine (NE), serotonin (5HT), and dopamine (DA) (Gu 2002). Note that some of these neuromodulators, e.g., dopamine (Wolf et al 2003) and acetylcholine (Massey et al 2001), can also affect AMPAR function independently of NMDARs. Out of seven candidate genes for schizophrenia identified by Harrison and Weinberger (2005), six genes (right part of figure) encode proteins known to be involved in synaptic plasticity and its modulation (dashed arrows). The majority of these genes affect NMDAR function directly. A few examples of their functions are listed; note that all genes are involved in other processes as well. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AMPAR, AMPA receptors; NMDA, N-methyl-D-aspartate ; NMDAR, NMDA receptors; mGluRs, metabotropic glutamate receptors; ACh, acetylcholine; NE, norepinephrine; 5HT, serotonin; DA, dopamine.

change (cf. Stephan 2004). Dynamic causal models for ERPs are based on a much more realistic neural model and account, for example, for the influences of different neurotransmitters on connection strengths (David et al 2005, in submission). Dynamic causal models may be very useful in studying changes in connectivity during learning, particularly in combination with pharmacological paradigms that target different neurotransmitters. For example, dopamine has been implicated in reinforcement (emotional) learning, while acetylcholine may be important for perceptual learning (Friston, 2005b). A dichotomy among schizophrenic subgroups with regard to differential impairments in dopaminergic and cholinergic modulation of NMDA-dependent plasticity might be expressed as differences in plasticity when tested with emotional and perceptual learning paradigms, respectively. Furthermore, by combining learning paradigms with pharmacological interventions, the neurotransmitter specificity of learning-related differences could be established.

Having introduced causal models to assess connections empirically, we now consider theoretical models of learning that may constrain the search for changes in connectivity during perceptual learning.

Hierarchical Empirical Bayesian Models of Perceptual Inference

Over the last years, perceptual inference has been increasingly understood from the perspective of hierarchically organized cortical systems that implement "predictive coding" based on Empirical Bayes (Rao and Ballard 1999; Friston 2003). Here, each level of the hierarchy strives to attain a compromise between bottom-up information about sensory inputs provided by the level below and top-down predictions (or priors) provided by the level above. We describe briefly how this perspective may prove useful for understanding aberrant learning and hallucinations in schizophrenia (see Friston 2005a for details).

Put simply, the challenge of perceptual inference is to determine the most likely cause, in the external world, of sensory data. One can frame the problem of representing causes in terms of a deterministic nonlinear function

$$u = g(v, \theta) \quad (2)$$

where v is a vector of causes (e.g., properties of a physical object), u represents sensory input, and θ are parameters. $g(v,\theta)$ is a generative model, i.e., a function that generates data from the

causes. The problem the brain has to contend with is to find a function of the inputs that recognizes the underlying causes, i.e., to invert g in Equation 2 and to learn the parameters (which correspond to connection strengths in the brain's generative model of how inputs are caused). In general, this is a difficult problem because of nonlinear interactions among the causes.

Generative models are specified in terms of a prior distribution over the causes $p(v;\theta)$ and the generative distribution or likelihood of the inputs given the causes $p(u|v;\theta)$. Importantly, in the framework of Empirical Bayes, cortical hierarchies construct their own priors. At each level of the hierarchy, the conditional density of the causes, i.e., the compromise between priors from the level above and the likelihood (sensory evidence) from the level below, represents the prior for the level below in the hierarchy. Thus, throughout the hierarchy, priors depend on the sensory input at the lowest level and the priors at the highest level:

$$\begin{aligned} u &= g_1(v_2, \theta_1) + \varepsilon_1 \\ v_2 &= g_2(v_3, \theta_2) + \varepsilon_2 \\ v_3 &= \ldots \end{aligned} \tag{3}$$

with $u = v_1$. At each level, the conditional density of the causes, given the inputs, is given by the recognition model

$$p(v|u;\theta) = \frac{p(u|v;\theta)\, p(v;\theta)}{p(u;\theta)} \tag{4}$$

where the numerator corresponds to the marginal distribution of the sensory inputs

$$p(u;\theta) = \int p(u|v;\theta)\, p(v;\theta)\, dv \tag{5}$$

Recognition corresponds to inversion of the generative model. However, the generative model may not be inverted easily, e.g., it may not be possible to parameterize this recognition distribution. This is crucial because the end point of learning is the acquisition of a useful recognition model that the brain can apply to sensory inputs. One solution is to posit an approximate recognition model $q(v)$ that is consistent with the generative model and that can be parameterized. Estimating the moments of this density corresponds to inference. Estimating the parameters of the underlying generative model corresponds to learning.

Let us take a brief look at how this could be implemented in the brain. Mathematically, neuronal dynamics can be considered to minimize the so-called free energy (F), a concept from statistical physics (Neal and Hinton 1998). The free energy depends on the conditional density of the causes given the inputs, or its approximation $q(v)$, and some hyperparameters λ encoding the uncertainty of this approximation. These two quantities can be updated iteratively using expectation maximization (EM). The E-step decreases F with respect to the expected cause, ensuring a good approximation to the recognition distribution implied by the parameters θ. This is inference. The M-step changes θ (the synaptic efficacies of forward and backward connections between levels), enabling the generative model to match the input density. This corresponds to learning:

$$\text{Inference E-step: } q(v) = \min_q F \tag{6}$$

$$\text{Learning M-step: } \begin{aligned} \theta &= \min_\theta F \\ \lambda &= \min_\lambda F \end{aligned} \tag{7}$$

This can be implemented in a simple neuronal architecture as shown in Figure 2.

Perceptual inference in such a hierarchical system would fail when either the parameters or hyperparameters were not estimated correctly in the M-step. This would happen with abnormal modulation of synaptic plasticity, because adjusting parameters and hyperparameters corresponds to adjusting synaptic efficacies between and within neural levels, respectively (see Figure 2). What would be the consequences? In both cases, prediction error (conveyed by forward projections) and priors (provided by backward projections) would be wrong. This would result in aberrant learning. An interesting case is where the hyperparameters, encoding the relative uncertainty about bottom-up and top-down information, are learned improperly. If too much weight is afforded to the prior expectation from supraordinate cortical levels, hallucinations may result (Friston, in press).

In this section, we have focused on models of perceptual learning. Similar themes arise in theoretical models of reinforcement learning that were the original motivation for the dysconnection hypothesis. These models of value-dependent learning also rely on prediction error, pertaining not to the sensory input but to the prospective value of a particular action (Friston et al 1994). The strength of hierarchical Empirical Bayes models is that they provide a mechanistic understanding of perception and learning. They furnish the principles behind the neuronal infrastructure that encodes statistical properties of complex environmental input, while accounting for learned regularities. This speaks to one of the most attractive paradigms for studying synaptic plasticity, i.e., implicit learning, as described above. The MMN is a particularly promising example of implicit perceptual learning and is reviewed in the next section.

MMN as a Paradigmatic Example of Synaptic Plasticity During Perceptual Learning

Although MMN can be observed in various sensory domains, our review will be restricted to the auditory system where it is most pronounced and where abnormalities in schizophrenia have been described. Classically, a MMN potential is elicited when a sequence of repeated stimuli (standards) is interrupted by a stimulus that differs in intensity, frequency, or duration (deviant). It is also elicited when temporal (interstimulus intervals) or higher-order features (patterns) are changed, suggesting that memory traces about regularities of stimulus-to-stimulus relationships are encoded (Näätänen et al 2001). Although MMN potentials can be affected by attention under some conditions (Arnott and Alain 2002), attentional effects on MMN are usually minor or absent (Näätänen et al 1993a, 2001). Moreover, MMN is elicited in the absence of attention (and even during sleep and light coma) (Atienza et al 2002a; Fischer et al 1999), implying that a preattentive echoic memory trace of the preceding standards is used as a template against which incoming sounds are compared.

Being able to obtain neural signals not confounded by attention, cooperation, and performance, except perceptual thresholds (Todd et al 2003), makes MMN an interesting candidate for diagnostically useful paradigms in schizophrenia research. A meta-analysis showed that more than 30 studies found significant reductions of MMN amplitude in schizophrenia (Umbricht and Krljes 2005). Moreover, individual MMN correlates well with disease severity and cognitive dysfunction (Baldeweg et al 2004) and functional status (Light and Braff 2005). However, there are conflicting reports about its association with genetic risk for schizophrenia (Michie et al 2002; Bramon et al 2004).

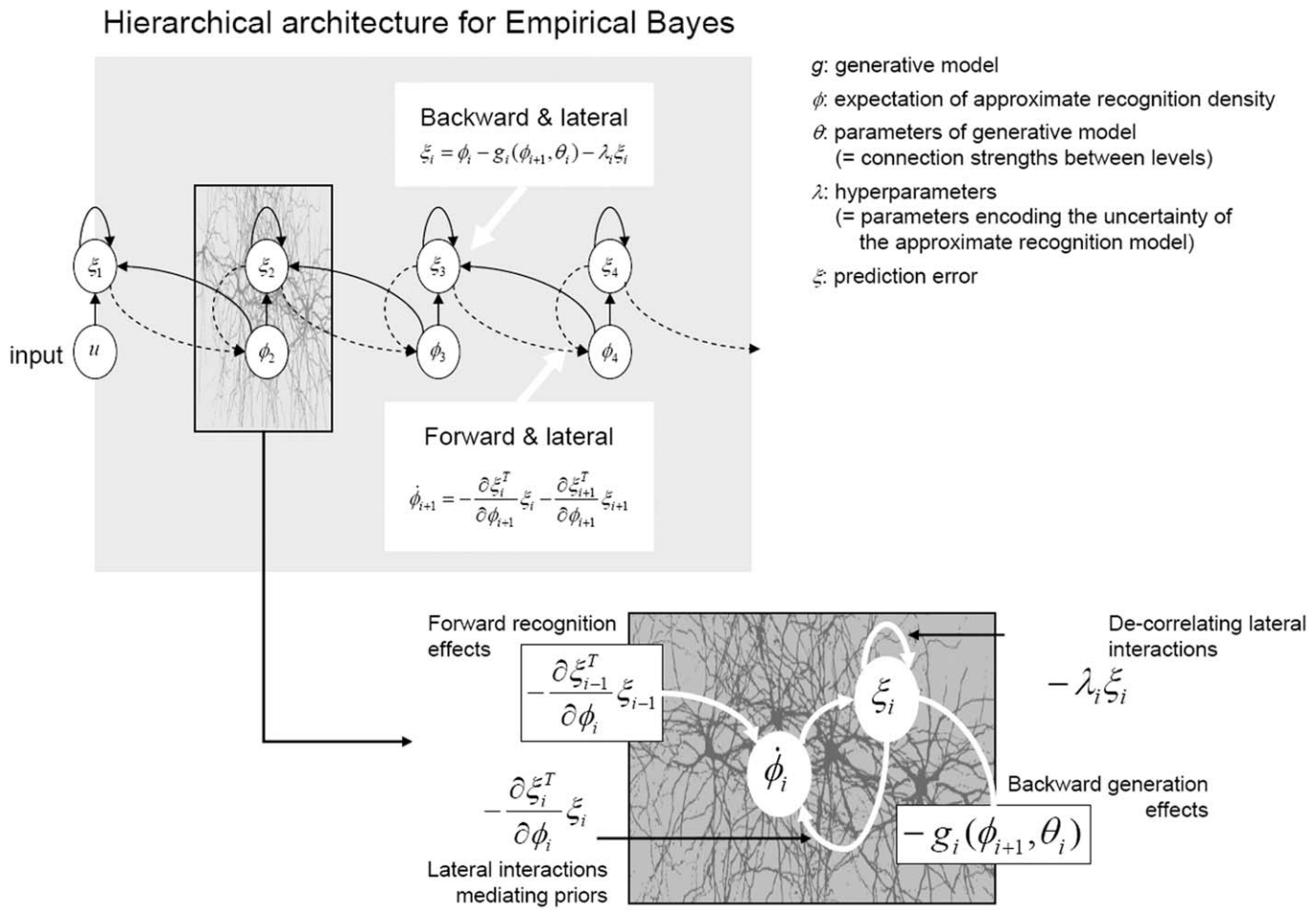

Figure 2. Upper panel: Schematic of a hierarchical neural architecture for implementing predictive coding. Each level in this model provides predictions (priors) to representations in the level below. The upper circles represent neural units encoding prediction error (ξ) and the lower circles represent neural units encoding the conditional expectation of causes (ϕ). At all levels, these expectations change to minimize the prediction error, i.e., the discrepancy between the prediction from the level above and the input from the level below. These two constraints correspond to prior and likelihood terms, respectively (see main text). Lower panel: Details of the influences on representational and error units at a single level in the hierarchy. See Friston (2003, 2005a) for details.

The classical view of the MMN as a fixed cortical response to stimulus change has been challenged by considerable evidence for a role of cortical plasticity in MMN generation. Mismatch negativity amplitude depends on STSP (immediate stimulus past, i.e., at a time scale of seconds) and LTSP (over hundreds and thousands of stimuli, i.e., at a time scale of minutes to hours). Concerning the former, the MMN increases progressively with the number of standard repetitions in the stimulus train (Sams et al 1983; Imada et al 1993; Javitt et al 1998), leading to an increasing strength of the echoic memory trace. Long-term increases in MMN have been related to emergence of memory traces for complex sounds and are correlated to improvements of perceptual performance (Näätänen et al 1993b; Atienza et al 2002b).

The role of synaptic plasticity in MMN generation has also been established by neuropharmacological studies. There is strong evidence for the role of NMDAR in MMN generation in both monkeys (Javitt et al 1996) and humans (Umbricht et al 2000). Further studies have looked at the effects of neurotransmitters that modulate activity-dependent synaptic modifications mediated by NMDARs. Whereas there is still limited information regarding the modulatory effects of serotonin and dopamine (reviewed in Umbricht and Krljes 2005), converging evidence shows that cholinergic stimulation increases and cholinergic blockage decreases the MMN amplitude (Baldeweg et al, in press; Harkrider and Hedrick 2005; Pekkonen et al 2001).

In terms of the neural mechanisms underlying MMN, some studies have suggested that it could result from stimulus-specific adaptation of neurons in primary auditory cortex (Ulanovsky et al 2003; Jääskeläinen et al 2004), possibly due to neuronal refractoriness and lateral inhibition (May et al 1999). This adaptation theory, however, is challenged by a variety of findings. First of all, there is strong consensus across studies and techniques that MMN responses are not only expressed in primary auditory but also in secondary auditory and prefrontal areas (Brazdil et al 2005; Doeller et al 2003; Liasis et al 2001; Pincze et al 2001). This is compatible with strong and reciprocal anatomical connectivity between auditory and prefrontal areas (Romanski et al 1999). Prefrontal effects on MMN expression are also suggested by studies of patients with prefrontal lesions who exhibit diminished temporal MMN amplitudes (Alain et al 1998). Secondly, invasive recordings from cat auditory cortex demonstrate that MMN amplitude was inversely related to deviant probability (Csepe et al 1987; Pincze et al 2002). Similar findings,

using EEG, have been made in humans (Javitt et al 1998; Winkler et al 1996; Sato et al 2000; Sabri and Campbell 2001). Together, these findings speak to MMN as an example of how the brain encodes the probabilistic structure of sensory input and thus places MMN in the context of perceptual learning. This notion has been formalized by predictive coding models (Friston, 2005a), which, as described above, implicate reciprocal interactions between hierarchical processing levels, where higher levels generate predictions about the sensory input to lower levels. Deviations from that prediction elicit an error (mismatch) signal in lower levels, which then drives modifications of top-down prediction. The learning of relative stimulus probabilities is thought to involve changes in connection strengths between levels (as in the M-step above). This model makes several predictions, all of which are supported by the experimental findings described above: 1) the existence of several, hierarchically arranged, areas that show MMN responses; 2) the central role of synaptic plasticity, expressed by NMDAR-dependent changes in connection strengths between the levels of this hierarchy; 3) the modulation of this plasticity by acetylcholine; and 4) the dependency of MMN amplitude on the probabilistic structure of the stimulus sequence.

Clearly, more work is needed to test detailed predictions with regard to how connection strengths change as a function of the probabilistic structure of the input sequence. However, these predictions can now be tested explicitly in terms of changes in connectivity, using DCM (see David et al, in press, for an example). The key point here is that the combination of paradigms like MMN with causal modeling like DCM provide an opportunity to study, noninvasively and quantitatively, learning-related synaptic plasticity. Combining this with neuropharmacological manipulations may be of great interest for schizophrenia researchers.

Conclusions: Synaptic Plasticity and Schizophrenia

Many questions about the role of synaptic plasticity in the pathophysiology of schizophrenia remain. As pointed out by Harrison and Weinberger (2005, p 56), "... it will not be synapses per se but the neural circuits in which they participate which will prove to be the appropriate explanatory level to understand how the genetic influences operate ... various combinations of susceptibility genes can converge on synaptic processing in these microcircuits to effect a common pattern of dysfunction and emergent symptoms, though the specific combination of genes and possibly alleles can vary across ill individuals." There are two important points here. First, it is not sufficient to identify susceptibility genes. We need to understand the contributions these genes make to the workings of particular brain systems and how changes in the structure and/or the expression of these genes impact mechanistically on these systems. The dysconnection theory is a mechanistic hypothesis that can be formulated in terms of (and indeed arose from) computational models of learning. These models help understand the consequences and loci of abnormal plasticity processes. Second, we need combinations of causal models and paradigms (e.g., DCM and MMN) that can characterize plasticity in individual patients and can help clinical decisions, e.g., diagnostic classification and optimal pharmacotherapy (Stephan 2004). Given some encouraging findings in depression research (Pezawas et al 2005), one may hope that connectivity estimates turn out to be much more sensitive and specific biological markers of disease than local response amplitudes. This article has provided some heuristics for combining functional imaging techniques with computational models to characterize abnormalities in the modulation of learning-related plasticity.

Our own research program is planned in three phases. In the first, we are investigating a variety of perceptual (including MMN) and reinforcement learning paradigms, using fMRI and MEG/EEG in healthy volunteers to establish 1) whether they exhibit robust changes of connectivity and 2) whether they are useful candidates for practical use in a clinical setting. In a second step, we will combine these paradigms with pharmacological manipulations and ensure we can measure the ensuing changes in synaptic plasticity in a dose-dependent fashion. The third step will translate these models into patient studies, looking at predictive validity in relation to diagnosis and treatment response. Hopefully, programs of this nature will provide surrogate markers, based on neuroimaging that can be used in genetic studies (cf. Gottesman and Gould 2003; Egan et al 2004; Baker et al 2005). As noted above, this is important, not only for therapeutics and drug targeting but also for an understanding of abnormal synaptic regulation at the molecular level.

In short, we hope that this sort of work will eventually lead to diagnostic tests for psychiatric diseases that are as useful as biophysical and biochemical tests established in other medical disciplines.

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