NMDA Receptor Delayed Maturation and Schizophrenia

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Abstract

This paper presents the hypothesis that NMDA receptor delayed maturation (NRDM) may lead to the pathogenesis of schizophrenic psychotic symptoms. This hypothesis is further analyzed in the language of a neural modeling formulation. This formulation points to a possible chain of pathological events, leading from molecular-level NRDM to over-increased synaptic plasticity, and to the formation of pathological attractors, a putative macroscopic-level correlate of schizophrenic positive symptoms. The relations of the NRDM hypothesis to other alterations which are assumed to take place in schizophrenia are discussed, together with possible ways to test this hypothesis.

1 The *NRDM* Hypothesis

NMDA receptor antagonist drugs exacerbate schizophrenic symptoms and, in animals, produce neurodegenerative effects in brain areas thought be to involved in the pathogenesis of this disorder. Consequently, it has been proposed that spontaneously occurring NMDA receptor hypofunction causes schizophrenia [1]. This paper describes a related but distinct hypothesis, namely that *NMDA Receptor Delayed Maturation (NRDM)* plays an important role in the pathogenesis of schizophrenia.

Molecular studies have identified several NMDA receptor subtypes in the brain which are likely to regulate neural learning and plasticity [2]. NMDA receptors are mainly composed of an NR1 subunit together with different NR2 subunits. The specificity of NMDA receptor subtypes arises from the NR2 subunit, which displays different regional expression patterns [3, 4]. These receptor types differ in their time of appearance in the developing brain, in their binding affinities for NMDA agonists and antagonists, in their conductance properties and in their threshold of voltage-dependent Mg^{++} blockade. NMDA receptor currents are of longer duration and have a weaker Mg^{++} block in young neurons compared with adult neurons [4, 5]. This has raised the suggestion that during normal development NMDA receptors undergo a process of maturation, where earlier subtypes which provide greater plasticity are replaced by less malleable forms, thereby stabilizing the mature synaptic connections [6].

A recent study measuring the mRNA levels of NMDA receptor subtypes in schizophrenic and normal brains had two main findings [7]: First, NMDA receptors are present in high levels in the prefrontal cortex, a primary pathological site in schizophrenia. Second, the prefrontal cortex of schizophrenic brains manifests a shift in the relative proportions of mRNAs for the NR2 subunit family, with a 53% relative increase in the expression of the "immature" NR2D receptor subtype, compared with to controls. This finding strongly supports the possibility that delayed maturation of NMDA receptors occurs in schizophrenia.

Delayed maturation of NMDA receptors does have the potential to disrupt behavior, as shown recently in animal studies [8, 9]. These studies tested the effects of expressing an embryonic NR2 subunit in mature forebrain neurons by creating transgenic mice overexpressing the NR2D subunit. Interestingly, while the transgenic mice expressed normal memory acquisition and retention they showed altered exploratory behavior, moving less than control mice (with intact motor systems).

Based on recent neural network simulations summarized below, we propose that the increased synaptic plasticity that results from the existence of high levels of immature NR2D receptors causes maladaptive synaptic alterations. These alterations serve to harbor 'pathological attractors', a possible neural correlate of schizophrenic symptoms. The next section discusses the NRDM hypothesis in the realm of neural network models. It describes the implications of a recent computational study in such networks to the NRDM hypothesis, offering a a way to understand how delayed receptor maturation may set up a pathological synaptic process that can eventually end in forming psychotic symptoms. Section 3 discusses how NRDM may interact with other pathological processes that are assumed to take place in forming psychotic symptoms in schizophrenia. Finally, several potential ways to test the NRDM hypothesis which may become feasible in the near future are discussed in section 4.

2 Delayed NMDA Maturation in Neural Network Terms

There has been a growing interest in the development and study of 'connectionist' neural network models of cognition and memory [10] in the brain (see [11, 12] for reviews). One class of models are associative memory networks [13] where several neural firing patterns, representing items or concepts, are stored via changes in the 'weights' of synaptic projections. After storage, a memorized pattern is retrieved by the network in an associative-like manner if it is cued by an input pattern that is sufficiently similar to it. The stored patterns are therefore called "attractors." Such associative neural models have been shown to provide interesting insights both to normal human memory function and to its degradation (e.g., [14, 15, 16, 17, 18]). These models have also received biological support from electrophysiological studies showing delayed, sustained activity in the brain during memory-related tasks [19, 20].

In a recent study [21], we have modeled voltage-dependence of NMDA receptors as a learning threshold. The functional effects of NMDA receptor maturation failure described above, i.e., decreased $Mg^{+}+$ block and prolonged NMDA currents, were modeled as a continuing low membrane voltage threshold for Hebbian synaptic modification. In these conditions, we have found that NRDM leads to erroneous, excessive growth of synapses and to the formation of "pathological attractors", where a few stored patterns, or distorted mixtures of such patterns, turn to dominate the retrieval scene and are spontaneously activated. Such pathological attractors may take part in the generation of schizophrenic positive

symptoms [22, 23, 24, 18, 25]. Like schizophrenic positive symptoms, pathological attractors can activate in the absence of apparent external cues and intrude into other network processes. Their recurrent content accounts for the concentration of actual delusions and hallucinations on a few pervasive themes [26, 27].

The relation between such pathological attractor states and schizophrenic positive symptoms has been recently discussed in detail in [24]. Pathological attractors could, for instance, co-opt a cortical speech production region. The result could be inner speech or 'thoughts' which are experienced as out of the control of the subject, who might then conclude that an alien or non-self force is inserting thoughts into his head. In a similar fashion, a pathological attractor involving speech perception may produce a fictitious voice percept or mold ambiguous acoustic stimuli into its own verbal output, resulting in the production of auditory hallucinations.

As shown in [25], some characteristics of the formation and the dynamics of pathological attractors may shed light on the evolution of schizophrenic positive symptoms. The schizophrenic symptoms evolve in a almost deterministic sequence from positive to negative symptoms, in parallel with the clinical observation that as schizophrenia progresses positive symptoms tend to wane, while the negative symptoms are enhanced [28, 29]. Interestingly, recent cognitive studies show that delusional and hallucinatory themes may be elucidated by a wide range of environmental cues [24], supporting the notion that schizophrenic pathological attractors should have large basins of attraction, as observed in [25].

Having discussed the possible causal role of NRDM in the formation of pathological attractors, let us revisit the studies of [8, 9]. Interestingly, while long term potentiation was only partially decreased compared with control animal slices, long term depression was completely abolished in the transgenic mice investigated in the latter studies. This complete shutdown of long-term depression brings additional support to the possibility that "synaptic runaway" and pathological attractors are likely to follow NRDM.

3 NRDM and Other Alterations in Schizophrenia

Dopaminergic overactivity has been classically thought to be the primary alteration underlying psychotic symptoms in schizophrenia, in light of the strong correlation between the therapeutic efficacy of antipsychotic drugs and their dopaminergic-blocking activity (e.g., [29]). NRDM pathological effects are likely to work synergistically with such increased

dopaminergic activity, as dopamine is thought to enhance synaptic plasticity and hence exacerbate the effects of NMDA dysfunction: dopaminergic influences during and immediately after long-term potentiation tetanization contribute to long-lasting maintenance of synaptic potentiation [30]. In addition, haloperidol can block both the induction and expression of amphetamine-induced sensitization, which may be a behavioral manifestation of long-term potentiation [31]. Finally, dopamine antagonists can block long-term depression, whose induction can be restored by applying exogenous dopamine [32]. That is, at least part of the therapeutic effect of dopaminergic-blocking agents in the reduction of schizophrenic positive symptoms may be due to the attenuation of the pathological Hebbian activity-dependent synaptic changes that follow NRDM. This hypothesized role of dopamine in the NRDM hypothesis may also explain why dopamine-blocking agents take weeks to exert their therapeutic effects; after the reenforcement of pathological attractors is blocked with these agents, it is likely to take weeks (the typical estimation of synaptic turnover period in mammals [33, 34, 35]) for these pathological attractors to attenuate. In addition to dopamine, other neurotransmitter alterations may play a similar role in augmenting the increased synaptic plasticity induced by NRDM; e.g., the NMDA-associated glycine binding site was recently found to be elevated in schizophrenics [36, 37], and increase the activity of the NMDA receptors [38].

How can the NRDM hypothesis be reconciled with the exacerbating effect of NMDA blockers on schizophrenic positive symptomatology? An important distinction should be made between the *formation* of pathological attractors, and their *activation* (after they have already been formed). While we hypothesize that NRDM is a primary factor in the formation of pathological attractors, it is highly likely that a few other factors may enhance the activation of pathological attractors (once they have been formed) and generate the resulting psychotic symptoms. NMDA receptor hypofunction may well do just that, as increased excitation in the network (for instance, via inhibition of GABA interneurons) is a strong inducer of pathological attractor activation [18, 25, 21]. In addition, a functional loss of connections due to NMDA blockers could cause portions of the network to function "autonomously" and thereby produce psychotic symptoms [23].

4 Discussion

Obviously, the primary task required to test the NRDM hypothesis experimentally is a search for evidence supporting a delay in NMDA receptor maturation in schizophrenia. An obvious approach would be further postmortem studies of the sort reported by [7]. But the limitation of postmortem studies, however, is that most of these subjects are older. Thus, these data reveal only the end stage of what is potentially a life-long neuromaturatioal process. Therefore other experimental tests should also be sought to test this model. One could use neural models to specifically predict catabolic and anabolic processes which accompany synaptic changes and pathological attractor formation. These theoretical predictions can then be compared with experimental results in schizophrenics. Such data has recently become available, even if only indirectly, by utilizing P-31 magnetic resonance spectroscopy to trace the breakdown products of membrane phospholipids in the early stages of schizophrenia [39, 40, 41]. But other investigations may also be undertaken: Another possible strategy is to perform perceptual and cognitive studies searching for evidence of pathological attractors corresponding to schizophrenic delusions and hallucinations. A preliminary study shows that hallucinated "voices" express highly constrained verbal content as would be expected from a pathological attractor model [42].

The NRDM hypothesis is consistent with the intriguing findings of [43], which have studied conscious recollection of studied words in schizophrenic patients. Their observation of a broad activation of several prefrontal areas during memory retrieval in schizophrenics, may well be a manifestation of the development of pathological attractors, resulting from a partial unification and broadening of the stored memories' basins of attraction [25]. This increase in the size of basins of attraction also provides a simple explanation of the surprising finding of [43] that schizophrenics performed better than controls in low-recall conditions. Indeed, our analysis shows that compensatory synaptic changes necessarily lead to heightened retrieval by strengthening the neurons' total synaptic efficacies beyond their normal, premorbid baseline [18, 25].

Interestingly, delayed maturation of NMDA receptors has been recently proposed to contribute to the process of hippocampal epileptogenesis via the promotion of abberant hippocampal axonal sprouting [44]. It should be reemphasized that the increased levels of the NR2D NMDA receptor found in schizophrenics are not diffusely spread over the cortex, but concentrated specifically in prefrontal cortical regions [7]. Hence, NRDM seems to

occur in a region-specific manner that varies in different patient groups, which determines its distinct, specific pathological consequences.

In summary, this paper has presented the possibility that altered NMDA maturation may lead to over-increased synaptic plasticity, which in turn may serve as an important contributing factor to the pathogenesis of schizophrenic positive symptoms. Using a computational neural modeling formulation, this paper points to a possible causal link between molecular-level NRDM and the formation of pathological attractors, a putative macroscopic-level correlate of schizophrenic positive symptoms.

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