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Electrophysiological endophenotypes in rodent models of schizophrenia and psychosis

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Abstract

Schizophrenia is caused by a diverse array of risk factors, and results in a similarly diverse set of symptoms. Electrophysiological endophenotypes lie between risks and symptoms, and have the potential to link the two. Electrophysiological studies in rodent models, described here, demonstrate that widely differing risk factors result in a similar set of core electrophysiological endophenotypes, suggesting the possibility of a shared neurobiological substrate.

Keywords

schizophrenia; EEG; local field potentials; oscillations; excitation/inhibition balance; synaptic plasticity

Introduction

Research into the etiology of schizophrenia (SCZ) is complicated by the diversity of both symptoms and risk factors. Factors that predispose to schizophrenia range from parental age (1) to single nucleotide polymorphisms (2), and clinical presentation is similarly diverse. Bridging risk factors and clinical presentation requires an understanding of the physiological disruptions that occur at the intervening cellular and circuit levels. Patient studies have revealed electrophysiological abnormalities associated with schizophrenia that may play important causal roles in symptomatology (3, 4). However, studies with human subjects are limited in temporal and spatial resolution, and the ability to induce and thus causally model

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disease-associated changes. Meanwhile, recent advances in technology have greatly enhanced the ability to interrogate circuits in rodent models. In this context, characterizing electrophysiological endophenotypes in rodent models of schizophrenia can be seen as an important step in the effort to understand the neurobiology underlying this devastating disorder.

This review will focus on electrophysiological findings from a variety of rodent, classified here into three categories: genetic models that recapitulate some of the diverse mutations associated with predisposition and heritability of the disease, pharmacologically-based models that mimic known neurochemical abnormalities, and neurodevelopmental models that explore the impact of stress, infection and injury in the developing brain. Though they vary in ontogeny, molecular targets and causal processes, these models tend to elicit a convergent set of physiological endophenotypes, including: 1) altered excitatory/inhibitory balance, 2) disrupted functional and synaptic connectivity, 3) impaired synaptic plasticity, and 4) abnormal oscillatory and evoked potentials. This review focuses on findings that best illustrate these core phenotypes and how they manifest orthogonally across models of disparate etiology. This convergence suggests that SCZ results from a common core of physiological disruptions at the level of neural activity.

Characterizing electrophysiological endophenotypes in rodents

Electrophysiological investigations of SCZ models leverage an array of experimental methods, each designed to elucidate specific pathophysiological properties. The techniques include both *in vitro* and *in vivo* approaches.

In vitro electrophysiological studies of SCZ are performed with cultured cells or slices of prepared brain tissue. The advantages of *in vitro* recording include the ability to target individual cells using techniques such as patch clamping that elucidate biophysical properties. For example, *in vitro* recording techniques may find a shift in the cellular resting membrane potential or a difference in the current threshold necessary to generate an action potential, either of which would suggest changes in excitatory/inhibitory balance. *In vitro* recording techniques are also useful for investigating disruptions in synaptic plasticity. The ability to precisely stimulate specific pathways, enhanced recently through the use of optogenetics, is one key advantage in this regard. Moreover, variability due to differences in behavioral state is minimized.

In vivo experiments allow for multisite electrophysiological recordings of the activity of multiple single neurons as well as local field potentials (LFPs), which reflect the ongoing population activity thought to be predominantly synaptic in nature. Extracranial electroencephalography (EEG) also takes advantage of the intact preparation, and permits direct translation to human studies. Studies of ongoing “spontaneous” and stimulus-locked “evoked” activity have proven useful in studying neural circuits in schizophrenia models. A principle advantage of *in vivo* recordings is the opportunity to explicitly link patterns of activity with behavior: neuronal and LFP activity is frequently modulated by behavioral state. Correlations between behavior and physiology give rise to hypotheses regarding how circuit-level changes might account for behavioral effects of a given model; these hypotheses can then be tested using a variety of techniques. The ability to perform

simultaneous recordings from multiple, distant brain regions also permits evaluation of functional connectivity – the degree to which activity in one brain region influences activity in another – typically assessed by measuring synchrony between regions.

In bringing these approaches to bear on rodent models of schizophrenia, one goal has been to identify and explore rodent analogues of pathophysiological findings seen in human studies. Indeed, such studies led directly to the ideas underlying each of the core physiological endophenotypes. For example, the notion that a disturbance in the balance between excitation and inhibition might play a role in schizophrenia rests on the original, oft-confirmed findings of decreases in inhibitory markers such as GAT-1 (a GABA transporter) and GAD67 (an enzyme responsible for GABA synthesis) in post-mortem tissue from SCZ patients (5-7). Similarly, evidence for decreased connectivity, both anatomical and functional, is seen in brain imaging studies (8); altered strength and patterns of oscillatory activity (whether stimulus-evoked, “spontaneous” or “task-related”) are found in EEG and MEG studies (9, 10); and deficits in plasticity have been demonstrated both directly (using transcranial magnetic stimulation) (4, 11) and indirectly (inferred from behavioral memory deficits) in patients. These phenotypes provide a window into neurobiology, provided they can be identified in neurobiologically tractable models.

Genetic susceptibility models of schizophrenia

The genetic basis for schizophrenia is complex. A well-established literature supports the idea that the disease is between 60% and 80% inheritable (12); however, *de novo* (sporadic) cases are prevalent, though many of these are also attributable to a number of known susceptibility genes (13, 14). Risk genes come from both rare, high penetrance and common, low penetrance mutations. Rare, high penetrance alleles have been identified by analysis of copy number variations (CNVs) (15, 16) and translocations (17); common, low penetrance alleles have emerged more recently from genome-wide association studies (2, 12, 18, 19). Modeling the genetic roots of schizophrenia in rodents has been a successful means of relating specific molecular abnormalities with neural and behavioral impairments. Here we will describe select molecular models of SCZ with relevant physiological impairments.

CNVs entail pathological deletion or duplication of entire chromosomal loci inclusive of multiple genes (15). CNVs occurring at loci such as 22q11.2, 16p11.2 and 15q13.3 precipitate many *de novo* incidences of schizophrenia and have been modeled and characterized electrophysiologically in the rodent. The most common schizophrenia-associated CNV is a microdeletion on chromosome 22q11.2 known as DiGeorge's or Velocardiofacial syndrome (20-22). The 22q11.2 microdeletion imparts an approximate thirty-fold increase in risk of developing schizophrenia (16, 22). Mouse models of this deletion have been engineered to be haploinsufficient for the corresponding region of chromosome 16 (22-24). One of these, the *Df16(A)*^{+/-} mouse, is broadly impaired in schizophrenia-associated cognitive skills such as sensorimotor gating, fear conditioning and spatial working memory (SWM) (23, 25). Several key physiological endophenotypes were observed in the *Df16(A)*^{+/-} mouse model, including alterations in excitatory/inhibitory balance, synaptic plasticity and functional connectivity. In slices from the hippocampus of *Df16(A)*^{+/-} mice, Drew et al. (26) found evidence of reduced inhibition with preserved

excitation onto CA1 neurons; they also found mild deficits in long-term potentiation. Recording *in vivo* during the performance of a spatial working memory task, Sigurdsson et al. (25) found a decrease in the degree of synchrony between activity in the hippocampus and the medial prefrontal cortex, two regions that normally must work together to carry out the task (25, 27, 28). Importantly, the deficits in synchrony correlate with deficits in behavioral performance in the mutants (25). In a very similar 22q11 deletion model, thalamic input to the auditory cortex is similarly reduced, likely due to the aberrant expression of the dopamine D2 receptor (24). This latter effect seems to be attributable to a single gene within the microdeletion, as haploinsufficiency of *Dgcr8*, a gene responsible for microRNA processing, replicates the phenotype (24). Notably, *Dgcr8* deficiency on its own also alters excitatory/inhibitory balance (29, 30). Additional studies of single genes from within the 22q11.2 locus have implicated molecular targets such as, *PRODH*, *Zdhhc8* and *Dgcr8* in several of the physiological and behavioral phenotypes of the complete microdeletion (31-35).

These results from the 22q11 model studies illustrate the many advantages of studying electrophysiological endophenotypes in genetic models. First, there is the definitive demonstration that a single genetic risk factor can result in multiple electrophysiological endophenotypes. Second, by dissecting the specific genes within the region that are responsible for specific deficits, a pathway towards elucidating the cellular and molecular mechanisms underlying these endophenotypes emerges. Here, the effect of *Dgcr8* haploinsufficiency suggests the involvement of microRNAs. Finally, the correlation between physiological (hippocampal-prefrontal synchrony) and behavioral (working memory) deficits suggests the possibility that the endophenotypes may be related to the debilitating symptoms of the disorder. Experiments testing the causal connection between these endophenotypes and behavioral symptoms can then be designed with these correlations in mind.

Electrophysiological endophenotypes have also been demonstrated in a model of the 15q13.3 deletion, a CNV that imparts high susceptibility for SCZ and epilepsy (36). The deletion comprises six genes including two genes for receptors, *TRPM1* and *CHRNA7* (37), and has been functionally implicated in the expression of inhibitory markers (38). A mouse model of this mutation recapitulates abnormalities in oscillatory and evoked activity seen in EEG studies of SCZ patients. These mice have reduced magnitude of auditory evoked potentials (averaged LFP responses to auditory stimuli) in various cortical regions (39). In the hippocampus and medial prefrontal cortex, LFPs have increased gamma power at rest (baseline), but decreased gamma power when stimulated (39), a profile seen in SCZ patients that suggests a decreased signal-to-noise ratio (40).

In addition to CNVs there are a number of single gene mutations that impart increased risk for SCZ. The chromosomal translocation mutation *Disc1* (Disrupted-In-Schizophrenia-1) is a susceptibility gene for SCZ (41) as well as other psychiatric disorders (42,44). The gene is functionally implicated in cyclic AMP signaling, neuronal migration and neurite outgrowth and as such, plays an important role in neurotransmitter signaling (45, 46). Mice engineered to model this mutation exhibit a number of anatomical and physiological impairments, particularly in the HPC and mPFC (47-49). Short-term plasticity is disrupted in the HPC of

Disc1 deficient mice (47-50). This synaptic deficit was very similar to that observed in other genetic models of SCZ including *Dgcr8*^{+/-} and *Df16A*^{+/-} (51, 52). In the mPFC, the *Disc1* protein is localized in dendritic spines and likely plays a role in regulating synaptic efficacy (53).

Another prominent SCZ susceptibility gene is *DTNBP1*, which encodes for dystrobrevin binding protein 1 or dysbindin. Dysbindin is found in high concentrations in glutamatergic vesicles and postsynaptic densities (54) and has been shown to be necessary for both glutamatergic and dopaminergic neurotransmission in the HPC (55-57). Knockout mice lacking the dysbindin have reduced auditory evoked potentials and disturbed gamma-frequency oscillations; inhibition onto cortical neurons is also reduced in these mice, as is parvalbumin immunoreactivity (58). Decreases in excitatory evoked and miniature postsynaptic potentials suggest similar reductions in excitation in these mutants; short-term plasticity is also reduced (56), as is a form of long-term potentiation in the hippocampus (59).

Several other schizophrenia risk genes have been linked to deficits in synaptic plasticity and connectivity. These include Neuregulin-1 (NRG-1) and ERBB4 (60, 61), membrane-bound proteins which bind each other, facilitating bidirectional signaling between synaptically paired neurons (62). Neuregulin is present in many isoforms, the loss of any of which can result in schizophrenia-related phenotypes (61, 63). Mice deficient for the type III isoform exhibit altered plasticity (61, 64) and reduced functional connectivity between the vHPC and nucleus accumbens (nACC) (65). Altering NRG-1/ERBB4 signaling alters gamma oscillations, perhaps by disrupting signaling between pyramidal neurons and interneurons (66, 67).

Pharmacologically-based models of schizophrenia and psychosis

Models based on pharmacological challenges and molecular pharmacology can recapitulate schizophrenia symptomology and induce neurophysiological phenotypes. In particular, dopaminergic and glutamatergic manipulations have been used to test specific hypotheses regarding the neurochemistry and neurobiology of SCZ.

The predominant neurochemical theory regarding SCZ was, historically, the dopamine hypothesis (68). Based primarily on the recognition that antipsychotic efficacy correlates strongly with the ability of a drug to block D2-type dopamine receptors, the dopamine hypothesis posited that hyperactivity of the dopamine system underlies the psychotic symptoms of schizophrenia. Recently, there has been a resurgence of interest in this hypothesis, spurred by the observation that D2 receptors are indeed overexpressed in the striatum of schizophrenia patients (70, 71). Subsequent efforts to model these findings in mice have shown that striatal D2 overexpression can cause impairments in SCZ-related cognitive tasks, including working memory and behavioral flexibility (72). These deficits are accompanied by an increase in excitatory synaptic transmission and decreased inhibition onto layer 5 pyramidal neurons in the mPFC (73), demonstrative of disturbances in excitatory/inhibitory balance.

A more traditional pharmacological challenge approach has proven fruitful in the exploration of the glutamate hypothesis. This hypothesis grew out of the recognition that sub-anesthetic doses of ketamine and other NMDA receptor antagonists produce psychomimetic effects in healthy human subjects (74) and psychotic episodes in patients with SCZ (75). In rodents, NMDA receptor antagonists result in SCZ-like behavioral impairments, among other findings (76-78). Subsequent neurophysiological studies have revealed strong effects on oscillations, functional connectivity, and neural plasticity. NMDA receptor antagonists diminish spontaneous and stimulus-evoked theta-frequency activity in the HPC, while concurrently enhancing the power of gamma frequency oscillations (79)(80, 81). Ketamine administration administered locally in the thalamus of rats elicits delta oscillations similar to those observed in slow wave sleep in healthy humans (82); intriguingly, delta oscillations have been reported during wakefulness in some patients with SCZ (83). Ketamine administration also disrupts functional connectivity between the HPC and PFC (78). Finally, deficits in long term potentiation (LTP) seen with NMDA receptor antagonism may have behavioral relevance; Manahan-Vaughan and colleagues (84) showed that a single administration of MK801 was sufficient to cause significant impairments in spatial memory, sensory gating and synaptic plasticity.

NMDA hypofunction models have also been useful in the identification of phenotypes at the level of EEG. Disruption in auditory gating is a prominent schizophrenia endophenotype that is seen in patients and several animal models of the disorder. Ketamine administration in mice impairs the latency, amplitude and gating of auditory evoked-potentials (85). SCZ phenomenology may relate in part to disruption in the signal-to-noise ratio of stimulus-evoked electrophysiological responses. Such are the findings of Saunders, Gandal and Siegel (86), in an investigation of NMDA receptor antagonism via ketamine and MK801 on the constitutive properties of both evoked and resting-state potentials in mice. NMDA receptor hypofunction was shown to result in diminished power and coherence of evoked and steady-state signals in a dose-dependent fashion across a range of frequencies.

Neurodevelopmental models

Epidemiological evidence shows that environmental insults to the developing fetus or pregnant mother significantly increase the risk of schizophrenia in the child (87, 88). Several neurodevelopmental models have been studied in order to further understanding of the effects of these insults on the developing brain, and their subsequent effects on function in the adult. Although prenatal infection is a well-established risk factor for SCZ, no specific infectious agent has been definitively linked to the disorder. The maternal immune response to infection has therefore come under suspicion. In rodents, this is typically modeled by using synthetic immune activators to mimic this response. Intriguingly, rat pups born to dams subjected to maternal immune activation go on to demonstrate a range of SCZ-related behavioral phenotypes as adults (89). While relatively few studies have explored the neurophysiological manifestations of this manipulation, adult offspring of immune activated dams have decreased hippocampal-prefrontal synchrony (90), similar to that seen in the genetic models described above. They also have alterations in hippocampal oscillations (91). Maternal immune activation has also been shown to reduce expression of the inhibitory markers (92) and increase neuronal excitability (93), suggestive of altered excitation/

inhibition balance; subtle abnormalities in long-term potentiation in the hippocampus were also reported (93). Intriguingly, some of the effects of maternal immune activation are exacerbated by combining the manipulation with deletion of the *NRG-1* gene, providing a powerful model of a gene-by-environment interaction in SCZ risk (94).

Other neurodevelopmental models have focused on brain regions, such as the hippocampus, implicated in SCZ by other models. Neonatal ventral hippocampal-lesioned (NVHL) rats have been extensively studied as a model of SCZ. These animals develop SCZ-related deficits in cognition, dopamine function, and interneuron dysfunction in adulthood that mimic those seen in patients (95-97); many of these deficits are ameliorated by treatment with antipsychotic agents (98). NVHL rats have a reduction in hippocampal interneurons and disrupted expression of *GAD67* (99), as well as a disruption of mPFC interneurons and hyper-excitability of mPFC neurons (100, 101). Administration of quinpirole, a dopamine D2 receptor agonist, in NVHL rats did not increase excitation of mPFC interneurons as observed in control rats (102), potentially relating the hyperexcitability and dopamine dysfunction phenotypes. Auditory evoked responses were more variable in NVHL rats, demonstrating less reliability across trials (103). Thus, NVHL rats demonstrate several of the core neurophysiological endophenotypes seen in other rodent models of schizophrenia: dysconnectivity; hyperexcitability; and disturbances in evoked potentials.

Another developmental manipulation that targets the hippocampus is prenatal exposure methylazoxymethanol acetate (MAM), a teratogen that impairs DNA replication. MAM exposure at specific ages disrupts the development of relatively specific structures (104). Exposure on embryonic day 17 preferentially affects hippocampal development and results in physiological and behavioral disruptions that recapitulate those observed in schizophrenia patients (105, 106). Neurophysiological phenotypes observed in MAM-treated rats including abnormal evoked and spontaneous oscillatory signals. Goto and Grace (107) found that MAM treated rats showed a reduction in delta and low gamma oscillations recorded from the mPFC. In addition, Lodge and colleagues (108) recorded during a latent inhibition task and found reduced conditioned tone-evoked gamma. Within the hippocampus of MAM-treated rats, neuronal excitability is enhanced, and, although long-term potentiation is normal, subsequent reversal through depotentiation is impaired (109). MAM-treated rats also have abnormalities in plasticity and hippocampal-prefrontal synaptic connectivity (110, 111).

Etiological models converge in core pathophysiology

Reviewing the findings discussed above, it is clear that multiple neurophysiological endophenotypes can be identified in rodent models of SCZ. The purpose, however, behind characterizing electrophysiological endophenotypes in rodents is not to identify them. This has been done from human studies. Rather, the goal of studying these endophenotypes in rodents is to determine whether and how they relate to the underlying causal neurobiology. Encompassed by this goal are several more specific questions. Can multiple endophenotypes result from the same underlying causal risk factor? Do different risk factors result in common endophenotypes? How do these various endophenotypes relate to each other? What are their underlying molecular and cellular mechanisms? How do they relate to the

symptoms of the disorder? These are the primary motivating factors behind examining patterns of neural activity, plasticity and connectivity in diverse models of schizophrenia. Above are described the answers to the first two questions: multiple neurophysiological endophenotypes can clearly result from a single risk factor, and different risk factors can clearly result in common endophenotypes (see Table 1). The remaining questions remain open, for each of the four endophenotypes highlighted here – altered excitatory/inhibitory balance, dysconnectivity, altered synaptic plasticity, and altered oscillatory activity.

Neural excitability refers both to spontaneous activity of neurons and their sensitivity to afferent stimulation. A precise balance between excitatory and inhibitory neural activity is necessary for maintaining adaptive function in neural circuits. As noted above, decreased inhibition and/or elevated excitation has been demonstrated in a range of different rodent models. This commonality suggests the possibility of a mutual cellular site of action; a promising candidate is the glutamatergic synapses of GABAergic interneurons. A number of SCZ-related genes such as DISC1, dysbindin and NRG-1 co-localize to the glutamatergic synapse (112). There are also convergent links between the glutamatergic and dopaminergic systems which are consistent with a role in the balance of excitation and inhibition. Dopamine D4 receptors, for example, have been implicated in SCZ due to their relatively high density on prefrontal cortical GABAergic interneurons (113) and affinity for the antipsychotic drug clozapine (114). These receptors down-regulate the activity of AMPA receptors on, and thus glutamatergic activation of, GABAergic interneurons in the prefrontal cortex (115). Conversely, there is also evidence that disruption of prefrontal NMDA receptors results in brain-wide dopamine malfunction (116). Thus, the balance between excitation and inhibition can be conceived of as causally related to dopaminergic function, though the directionality of this relationship is unclear.

Schizophrenia has long been considered a “dysconnection syndrome” as deficits in functional connectivity between brain regions have been observed clinically and experimentally, and have been implicated in both cognitive deficits and positive symptoms of SCZ (8, 117, 118). Disruptions of functional connectivity were evident in a wide range of models. It is tempting to consider deficits in connectivity as synaptic or anatomical, as deficits in either of these cellular processes might be expected to reduce the ability of far-flung brain regions to communicate with each other. Considered in this way, it is not surprising that genetic models such as NRG-1 and ERBB4 would disrupt long-range connectivity, as they have the potential to directly effect the development and stability of synapses. The absence of axonal pathfinding genes as risk factors for SCZ might argue against a primary anatomic basis for these deficits. It is also possible that deficits in inhibition contribute to dysconnectivity, functional connectivity as reported here relies on synchronous oscillations in the theta and gamma ranges; GABAergic neurons have important roles to play in the generation of both types of oscillations (119, 120).

Abnormal synaptic plasticity has been observed in many of the SCZ models described here and could also play a role in each of the three other physiological phenotypes we have discussed. Several SCZ susceptibility genes were implicated in impaired synaptic plasticity including Dgcr8 (31, 51), NRG-1 (64) and Dysbindin (56, 59). Disrupted synaptic plasticity mechanisms could cause a range of downstream, secondary neurophysiological

effects. For example, inappropriately weakened synapses could reduce long-range functional connectivity; locally, the same weakened synapses could degrade the precise timing required for normal oscillatory activity, whether spontaneous or evoked. And deficits in, for example, potentiation of glutamatergic synapses onto inhibitory interneurons could impair inhibition, disturbing the balance between excitation and inhibition.

Within a given brain region, abnormal activity patterns can be classified as disruptions in resting-state oscillations, induced and evoked oscillations, and evoked potentials. Abnormal neural oscillations have been shown to occur during a number of SCZ-related cognitive and behavioral deficits (121), including working memory (122, 123), attention (124), and sleep (125, 126). Here the connection to deficits in the balance between excitation and inhibition are clearest, since this balance is critical to the generation of oscillatory signals. What is less clear is whether abnormal patterns of oscillatory activity play a causal role in behavioral deficits, or whether they simply reflect abnormal activation secondary to the behavioral differences.

Indeed, the issue of causality is a crucial one if endophenotypes are to be used to clarify the neurobiological mechanisms of psychiatric disease rather than simply be a marker thereof. Do the various electrophysiological findings described here actually cause the debilitating symptoms of schizophrenia? Emerging tools such as opto- and pharmacogenetics are beginning to permit one to ask such questions; in this way, for example, gamma oscillations have been causally linked to cortical function and cognition (127-130). These tools might be used to explore the relationship between specific neurophysiological endophenotypes, neural circuits, and behavior.

Conclusions

As described herein, a core set of neurophysiological endophenotypes, identified through human studies, can also be found in a wide range of rodent models. These endophenotypes are present in models based on a variety of causal risk factors, perhaps through perturbation of common neurobiological substrates. Uncovering such substrates promises to aid in the development of interventions that might have more comprehensive outcomes, in contrast to current medications, which predominantly treat only psychotic symptoms. Delivering on the promise of this pathway to better treatments will require a greater understanding of how divergent risk factors may lead to convergent neurophysiological endophenotypes, and in turn, how these endophenotypes lead to symptoms.

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Table 1

Diversity of electrophysiological endophenotypes by model.

	E/I Balance	Synaptic Plasticity	Oscillations/Potentials	Connectivity
Molecular				
22q11.2	[26]	[26, 31, 52]	[24, 31, 52]	[24, 25]
Dgcr8	[29,30]	[31,51]	[24,51]	[24]
15q13.3	[39]	- - -	[39]	- - -
Disc1	- - -	[47, 49, 50]	- - -	- - -
Dybindin1	[55, 56, 57, 58]	[56, 59]	[58]	- - -
Neuregulin1	[67]	[61]	[66, 67]	[61, 65, 67]
Pharmacological				
NMDAR Ant.	[78]	[84]	[80, 81, 82]	[78]
D2 Overexpr.	[71]	- - -	- - -	- - -
Neurodevelopmental				
NVHL	[97, 98, 99]	- - -	[98]	- - -
Immune	[88, 89, 90]	[90]	[89]	[88]
MAM	[106]	[109]	[105, 106]	[108]

References for each known phenotype are listed. NMDAR Ant., NMDA receptor antagonism. D2 Overexpr, D2 receptor overexpression. Dashed lines indicate untested or unknown phenotypes. Other abbreviations as in text.