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A *Perspective* on the history of the concept of "disconnectivity" in schizophrenia

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Abstract

Nearly sixty years ago Seymour Kety proposed that research on genetics and brain pathology but not on neurochemistry would ultimately lead to an understanding of the pathophysiology of schizophrenia. This *Perspective* will demonstrate how prescient Kety's proposal was as advances in research on brain structure and on genetics have shaped our current understanding of the pathophysiology of schizophrenia. Brain imaging techniques have shown that schizophrenia is associated with cortical atrophy and ventricular enlargement, which progresses for at least a decade after the onset of psychosis. Cortical atrophy correlates with negative symptoms and cognitive impairment but not with psychosis in schizophrenia. Studies with the Golgi staining technique that illuminates the entire neuron indicate that cortical atrophy was due to reduced synaptic connectivity on the pyramidal neurons and not due to actual loss of neurons. Results of recent genetic studies indicate that several risk genes for schizophrenia are within two degrees of separation from the N-methy-D-aspartate (NMDA) receptor, a subtype of glutamate receptor that is critical to synapse formation and synaptic plasticity. Inactivation of one of these risk genes encoding serine racemase, which synthesizes D-serine, a co-agonist of the NMDA receptor, reproduces the synaptic pathology of schizophrenia. Thus, widespread loss of cortical synaptic connectivity appears to be the primary pathology in schizophrenia that is driven by multiple risk genes that adversely affect synaptogenesis and maintenance as hypothesized by Kety.

Introduction

It may be useful to reflect on the origins of the concepts that implicitly guide scientific enquiry as they are often obscured by the slow, incremental nature of scientific advances, especially in the realm of neuroscience. Nearly sixty years ago, Seymour Kety published back-to-back lead review articles in *Science* on the "Biochemical Theories of Schizophrenia" (1, 2). In spite of the title, his interpretation of the impact of biochemical research was quite pessimistic,, noting that because of the likely heterogeneity of the schizophrenia, the impact of nutritional deficiencies and the effects of drugs, the findings were neither coherent nor convincing. Rather, he focused on the promise of genetic approaches and presented a meta-analysis of twin studies published thus far, which revealed a concordance rate for schizophrenia in identical twins with one affected twin being 86% whereas the concordance rate in fraternal twins being equivalent to that observed in siblings, approximately 12–18%. Suggesting that the likely consequence of genetic risk factors was to "determine inappropriate connections", he concluded that "the physiologic psychologist, the neuropsychologist or the anatomist is likely to find meaningful information long before the biochemist does." Thus, he was prescient in proposing a "connectionist" theory of schizophrenia.

Given the dominance of the psychoanalytic paradigm In American Psychiatry at that time, considerable reservations were expressed about the heritability of schizophrenia, particularly based on studies utilizing the twin study design: identical twins would be expected to be subject to serious problems with personal identity, a core psychoanalytic feature of schizophrenia (3). Kety rose to this challenge and carried out an heroic "cross-fostering study", considered to be *de riguer* in animal studies for disentangling gene-environmental interactions. Exploiting the Danish medical registry, which maintained detailed medical records of the diagnoses and treatment of all residents of Denmark, he and his colleagues compared the diagnoses of offspring of schizophrenics adopted into homes of "normal" parents to offspring of "normal" parents adopted into homes with a schizophrenic parent in the city of Copenhagen (4). Chi square analysis revealed a significantly greater prevalence of psychopathology (schizophrenia and latent schizophrenia) in the adoptees born of a schizophrenic parent but raised by "normal" parents. A follow-up study carried out two decades later that used the entire Danish population confirmed the results of the prior smaller Copenhagen study in showing a 10-fold greater prevalence of chronic schizophrenia in biologic relatives of the adoptees from a schizophrenic parent than from "normal" biologic parents (5).

Neuropathology

If schizophrenia is indeed a brain disorder with substantial genetic influences, studies should focus on the brain itself to determine how the brains of individuals with schizophrenia differ from those without psychopathology or comparable psychopathology. However, after nearly a century of studies since Kreapelin first proposed schizophrenia (*dementia praecox*) to be a brain disorder (6), the results of neuropathologic studies, so revealing in Alzheimer's 's dementia and Parkinson's Disease, were contradictory, inconsistent or unremarkable (7), leading the eminent neurologist Fredrick Plum (8) to opine that schizophrenia was the "graveyard of neuropathology". The failure to identify a consistent pathology could have stemmed from the inability of vital stains, which are most effective in illuminating the nucleus and cell body of neurons, to reveal alterations in synaptic structure. Other limitations of neuropathologic studies include selection bias of subjects with schizophrenia at end of their lives with confounding substance abuse, poor hygiene and dietary deficiencies common to the severely mentally ill and the small number of subjects in individual studies, which precluded statistical comparisons.

The development of brain imaging technology provided a way forward for non-invasive visualization of the brain in living subjects, thus dramatically enlarging the number of subjects able to be studied and permitting careful patient selection that reduced the confounds from which post-mortem studies suffered. These methods included structural [computer assisted tomography (CAT) and magnetic resonance imaging (MRI)], functional brain imaging with Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI) and brain chemical analysis with Magnetic Resonance Spectroscopy (MRS). The path-breaking CAT scanning study of Johnstone et al (8) revealed significant ventricular enlargement in a cohort of subjects with schizophrenia as compared to controls. This finding confirmed the results of prior pneumoencephologographic studies, in which the ventricles are drained of cerebrospinal fluid and filled with air in order to visualize them with a standard x-ray of the brain, thereby revealing the enlarged ventricles in schizophrenia. (9,10). Subsequently, van Horn and McManus (11) carried out a multivariant meta-analysis of 39 MRI studies of ventricular size, which used ventricular brain ratio (VBR) as the measure. While the average VBR declined with later studies of schizophrenia, they confirmed that VBR enlargement is an “indisputable characteristic of schizophrenia”; however, the difference from that of controls is sufficiently small so as preclude its diagnostic utility in individual subjects.

Given the fixed volume of the cranium, it is logical that increased VBR in schizophrenia would be associated with comparable volume reduction in some components of the brain. Numerous studies utilizing quantitative MRI reported loss of volume of cortical sub-regions such as the temporal and prefrontal cortices in schizophrenia (12). Kuperberg et al. (13) used high resolution MRI to show that cortical thinning was not restricted to these two regions but rather was widespread. Furthermore, comparisons of patients early in the course of schizophrenia to those late in the course as well as prospective studies involving repeated MRIs demonstrated that ventricular enlargement and cortical atrophy are progressive, at least during the first ten years after onset of psychosis (14). Severity of cortical atrophy at the onset of psychosis as assessed by reduced gyrification predicts poor response to antipsychotic treatment (15). Evidence accumulated that antipsychotic treatment itself may contribute to the loss of grey matter over and above that which is part of the underlying pathology of schizophrenia (15).

The compelling evidence that brain volume is already significantly reduced at the onset of psychosis (16) as well as the progressive loss of grey and white matter after onset of psychosis in schizophrenia (14) raises the question whether schizophrenia is a neurodegenerative disorder. Stereologic cell counting techniques as well other assessments of neuronal loss have not demonstrated neuronal loss in the cortex or hippocampus in schizophrenia, at least not commensurate with the degrees of atrophy (17, 18). Rather, increased cell packing density, reduced neuronal somal size and, in the case of Golgi studies, reduced dendritic complexity and reduced spine density have been documented in diverse cortical areas including prefrontal cortex, auditory cortex and hippocampus (21–23). Consistent with the inference that the onset of atrophy commences in the mature brain is the observation that skull size does not differ between adult controls and subjects with schizophrenia (24). In contrast, the mediodorsal nucleus of the thalamus, which projects to the frontal cortex, and anteroventral-anteromedial nuclei of the thalamus, which project to the cingulate and entorhinal cortices, both exhibit substantial neuronal loss in schizophrenia (24, 25). Since an absolute reduction in dendritic spines has been described in the prefrontal cortex, the question remains open as to whether this spine loss is secondary to the loss of projecting thalamic neurons or whether the thalamic neurons die as a consequence reduced post-synaptic access.

Two recent technical and conceptual advances in magnetic resonance imaging that together shed light on reduced synaptic connectivity in schizophrenia are diffusion tensor imaging

(DTI) and default mode imaging. DTI is based upon fractional anisotropy (FA), a measure of the degree to which water diffusion is directionally hindered in white matter tracts as a measure myelin integrity (26). Although there is some variation among studies, significant FA reductions are widespread in cortex including the cingulate bundle, the corpus callosum, the frontal cortex and the temporal cortex (27). FA reductions are present at first episode of psychosis but appear to progress over the course of the disorder (28).

Default mode imaging refers to an fMRI method according to which regional brain activity is correlated when the subject is conscious but at rest, there by revealing “default” networks (29). Regional correlations can be generated by selecting a reference region (“seed”-based) or in an unbiased manner by using principal component analysis. There is general agreement that individuals with schizophrenia have impairments in deactivating the default mode network when performing mental tasks (30). Altered patterns of network connectivity in schizophrenia have been demonstrated, although the results remain inconsistent. But, the application of graph theoretical analysis to structural network data in schizophrenia has revealed broad network inefficiency, pointing to disturbed integration among brain regions (31).

Neurochemistry

Studies of the neurochemistry of the post-mortem brain in schizophrenia began over forty years ago as this approach successfully illuminated the selective neuropathology of Parkinson’s disease and Huntington’s Disease (32). Early on, deficits in pre-synaptic GABAergic markers were reported although it was unclear if this was the result of the disease itself or agonal processes (33). Similarly, one of the most replicable findings was the up-regulation of dopamine D2-receptors although this was likely the consequence of treatment with antipsychotic drugs (34). By the end of the 20^{th} century, as reviewed in detail by Harrison (35), there was of paucity replicable neurochemical findings in schizophrenia, consistent with Kety’s concern.

With development of multiple methods for measuring gene expression and the expansion of brain banks with standardized collection techniques, the last 15 years have yielded a body of consistent results that exhibit agreement across modes of analysis including quantitative neurochemistry, *in situ* hybridization, immunocytochemistry and DNA chip array. For example, several groups have developed internally consistent evidence of a down-regulation of pre-synaptic markers for the fast-firing parvalbumin expressing GABAergic neurons and up-regulation of its post-synaptic $GABA_A$ receptors indicative of reduced GABAergic recurrent inhibition of pyramidal neurons (36). With the appreciation of the spine loss in schizophrenia, studies have begun to focus on components of the glutamatergic synapse in cortico-limbic regions of the schizophrenic brain. In their comprehensive and critical review, McCullumsmith et al. (37) point-out the inconsistent data in the assessment of AMPA receptor trafficking, NMDA receptors subunit levels and PSD-95 and associated proteins of the glutamatergic synapse in contrast to the above described pathology of the parvalbumin-positive GABAergic neurons.

Genetics

Most of the early studies of the genetics of schizophrenia focused on putative risk genes identified by post-mortem neurochemical findings or pathways related to the dominant hypothesis of pathophysiology based on D2-dopamine receptor blocking action of antipsychotic drugs. For example, using the case control method, several studies involving at most hundreds of subjects implicated dopamine receptors D2, D3 and D4 as risk genes for schizophrenia while others contradicted these results (38–41). The contradictory results emanating from these early studies stemmed from multiple problems: biased selection of genes, underpowered studies leading to type 1 errors and publication bias where negative findings were either not submitted to journals or were denied publication.

With the completion of the sequencing of the human genome in 2001, the ability to carryout molecular genetic studies to identify genes that confer risk for disorders such as schizophrenia in an unbiased fashion was greatly facilitated (42). Initial studies exploited linkage analysis, looking for significant associations of identifiable markers located randomly on the genome with the disorder in multi-generational families having several affected individuals (for example, 43). As the sequence variation of the human genome became better characterized, the distribution single nucleotide polymorphisms (SNPs) and microsatellites (short repeated DNA sequences) were mapped on the chromosomes. However, the much greater frequency of SNPs, which occur at the rate of one in every 1,000 base pairs, and the lower risk of mutation because SNPs involve a single base substitution, led to SNP dominance over microsatellites for association studies (44).

Although there was little evidence for Mendelian inheritance of schizophrenia, it became apparent that on rare occasions highly penetrant mutations, often *de novo*, were associated with schizophrenia (45). These mutations are the result of deletion or replication of kilobases of DNA including multiple genes. This type of mutation has been designated a “copy number variant” (CNV). The same CNV has been associated with autism and schizophrenia as indicated by studies of carriers of the 22q11.2 deletion (46). Kirov et al. (45) sequenced the CNVs involving nearly eight thousand subjects with schizophrenia. They found that the CNVs were highly significantly enriched with genes encoding proteins localized to the glutamatergic synapse and its post-synaptic density.

One study reported a much lower prevalence of CNVs in bipolar disorder as compared to schizophrenia. (47). Green et al. (48) reported that three large CNVs associated with schizophrenia were also found in a sample of 2591 bipolar subjects although their analysis supported the prior finding of a substantially reduced prevalence of large CNVs in bipolar disorder. This evidence of shared mutations between schizophrenia and bipolar disorder is consistent with evidence of increased risk for either disorder in probands diagnosed with either disorder (49). Furthermore, a recent Golgi staining study has shown that schizophrenia and bipolar disorder share virtually the same dendritic spine pathology in the dorsal lateral prefrontal cortex (50). Consistent with this evidence of pyramidal neuronal atrophy in both bipolar disorder and schizophrenia, Pearlson et al. showed that enlargement of the lateral ventricles also occurred in bipolar disorder and was associated with frequent hospitalizations and persistent unemployment. (51).

To avoid the biases of candidate gene studies, the hazards of false positives and publication bias of under-powered studies (meta-analyses of underpowered studies can yield spuriously highly significant results because of non-inclusion of unpublished negative studies), geneticists interested in psychiatric disorders have advocated for sufficiently powered genome-wide association studies so that risk genes could achieve the high statistical threshold required: $5X10^{-8}$. The Schizophrenia Working Group of the Psychiatric Genomics Consortium carried out a genome-wide association study (GWAS) comprised of nearly 37,000 cases and over 110,000 controls and identified 108 loci that met genome-wide significance (51). Associations were enriched with genes expressed primarily in the brain, especially those associated with NMDA receptor neurotransmission or its down-stream mediators. Thus, the findings from the GWAS are consistent with the gene analysis of the CNVs associated with schizophrenia. In addition, the locus with the most robust association with schizophrenia is situated in genes encoding the major histocompatibility complex.

The question then arises as to how these risk genes for schizophrenia might be related to the dendritic pathology and reduced cortical connectivity characteristic of schizophrenia. Studies have been carried out in mice in which individual genes have been inactivated to document their roles in glutamatergic synapse formation and their use-dependent modification. It should be emphasized that glutamatergic synapses are structurally quite dynamic as a reflection of their activity, which has been elegantly demonstrated *in vivo* with two-photon confocal microscopy in transgenic mice expressing green fluorescent in pyramidal neurons (52, 53).

Balu et al. (54) showed that genetically silencing in mice the gene encoding serine racemase (SR), a risk gene identified in the large GWAS (50), results in a phenotype that closely replicates many aspects of schizophrenia including reduced dendritic length, reduced spine density, ventricular enlargement, cortical atrophy, down regulation of the cortical fast-firing parvalbumin-postive GABAergic interneurons and cognitive impairments. In mice with SR constitutively silenced, sub-chronic treatment of adult SR−/− mice with doses of D-serine that normalize their cortico-hippocampal D-serine levels restores trophic factor markers and transcriptional down-stream to the NMDA receptor corrects cognitive deficits and partially restores spine density (55). The dendritic deficits are also observed in mice in which SR is conditionally silenced in glutamateric neurons in forebrain in late adolescence (56). Thus, NMDA receptor hypofunction in cortico-limbic brain regions caused by the lack of D-serine replicates those aspects of schizophrenia associated with negative symptoms and cognitive impairments (57). Furthermore, these seemingly irreversible structural brain changes due to congenital NMDA receptor hypofunction may be corrected with restoration NMDA receptor function in adulthood (55).

SR stands at the apex of a family of risk genes for schizophrenia that are within two degrees of separation from the NMDA receptor (Figure 1). For example, the kinase, Akt3 is a major regulator in the class I PI3 kinase pathway, and is activated in neurons by phosphorylation as a consequence of NMDA receptor activity. Silencing Akt3 expression in neurons adversely affects neuronal survival and axon extension (58). Notably, the activation of Akt, a risk gene for schizophrenia, is reduced in SR knockout mice, pointing to potential of epistatic interactions of two risk genes (55).

Mice, in which the gene encoding the NR2A subunit, GluN2A, another risk gene, was silenced, exhibited reduced LTP and impaired spatial learning (59). Silencing the gene encoding PSD-93 (DLG1) elevates the threshold for LTP (60) whereas silencing DLG2, which encodes synapse-associated protein with a molecular weight of 97 kDa (SAP-97), has negligible effects on glutamatergic neurotransmission or LTP (61). Interestingly, SAP-97 plays an important role in the trafficking to the synaptic membrane the AMPA receptor subunit, GlurR1, which is encoded by the schizophrenia risk gene, GRAI1. Silencing GRAI1 itself causes a profound deficit in spatial memory and impaired LTP at the CA3-CA1 synapse (62). Thus, the products of two schizophrenia risk genes directly interact. Although mice with GRM3 silenced exhibited profound memory impairments including spatial, contextual and working memory, there was no abnormality in LTP at the CA2-CA1 synapse (63).

Except for CNVs, there is little evidence of Mendelian-type risk genes that alone are causative of schizophrenia. Rather, multiple genes of modest effect interact with the environment to produce the schizophrenia phenotype; and no risk gene accounts for more than 5 percent of imputed risk (51). However, it is likely that epistasis, gene-gene interactions, plays an important role with regard to the 108 risk sites for schizophrenia on the human genome. For example, Huang et al. (64) found that mice heterozygous for two schizophrenia risk genes, Akt1 and NRG, exhibited social impairments whereas mice heterozygous for either null mutation did not exhibit such a phenotype. In this context, it is noteworthy that the most robust phenotype resembling schizophrenia in those genes clustered around the NMDA receptor results from silencing SR (55). So, even though glycine can substitute for D-serine at the GMS on the NMDA receptor, it appears that such a “work around” is not particularly effective in the cortex and hippocampus. But, the SR−/− phenotype underlines the likely substantial impact of epistasis of allelic variants of risk genes surrounding the NMDA receptor.

Conclusion

Seymour Kety (1, 2) was prescient in proposing nearly 60 years ago that studies of brain structural pathology and genetics together would provide the most productive way forward in understanding the cause of schizophrenia. Not surprisingly, many of the risk genes for schizophrenia play a critical role in glutamatergic synaptogenesis and neuroplasticity (65), thereby affecting cortical connectivity. Inactivation of one of these genes, SR, causes an ~35 percent reduction in cortical glutamatergic synapses similar to what is inferred from the results of Golgi staining studies of schizophrenia (19–21). Since cortical atrophy and ventricular enlargement in schizophrenia correlate significantly with negative symptoms and cognitive deficits but not with psychosis (66, 67), these cognitive and motivational symptoms appear to be much more central to the cause of schizophrenia than psychosis. Thus, the dopamine hypothesis of schizophrenia, which is directly linked to the antipsychotic effects of dopamine D-2 antagonists, has lost salience as primary explanatory etiology of schizophrenia. Pharmacologic interventions targeted at modifying glutamatergic neurotransmission now represent prominent strategies for developing treatments that would address the cognitive and negative symptoms of schizophrenia (68). Given the fact that psychosis is a “down-stream” consequence of cortical dysfunction in schizophrenia, it is likely that such treatments would also have antipsychotic effects. Thus, there is hope that glutamatergic treatments, likely coupled with cognitive interventions, may prove to be not simply symptomatic but rather truly restorative of cortical connectivity.

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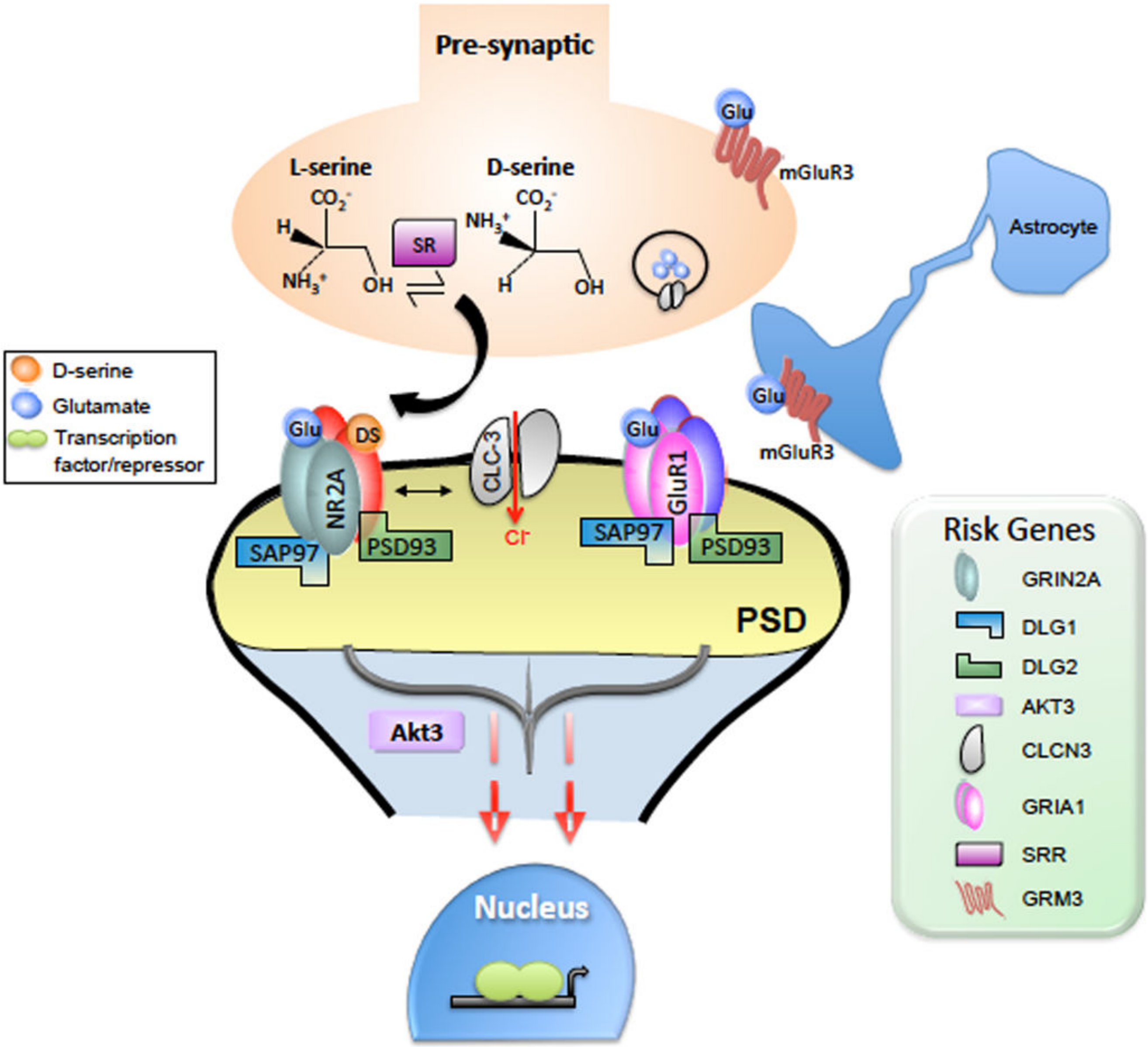

Figure 1. Schematic representation of the synaptic localization of eight risk genes for schizophrenia that are within two degrees of the NMDA receptor

A recent large scale genome wide association study (GWAS) comprising nearly 150,000 subjects including nearly 40,000 subjects with schizophrenia revealed 108 loci on the human genome that achieved genome wide significance ($<5X10^{-8}$) for association with schizophrenia (51). Eight of these genes encode proteins associated with glutamatergic neurotransmission, especially that component mediated by the NMDA receptor. These genes include SRR for serine racemase; GRIN2A for the NMDA receptor subunit 2A; GRIA1 for the AMPA receptor subunit, GluR1; DLG1 and DLG2 for synapse-associated protein-97 and post-synaptic density protein-93, respectively, which are scaffolding proteins on the interior surface of the glutamatergic synapse: GRM3 for mGluR3, a metabotrophic glutamate receptor that regulates glutamate release; CLCN3 for a voltage gated chloride channel that regulates glutamatergic spine excitability. (Adapted from Balu and Coyle (68).