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Mutant Mouse Models: Genotype-Phenotype Relationships to Negative Symptoms in Schizophrenia

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Negative symptoms encompass diminution in emotional expression and motivation, some of which relate to human attributes that may not be accessible readily in animals. Additionally, their refractoriness to treatment precludes therapeutic validation of putative models. This review considers critically the application of mutant mouse models to the study of the pathobiology of negative symptoms. It focuses on 4 main approaches: genes related to the pathobiology of schizophrenia, genes associated with risk for schizophrenia, neurodevelopmental-synaptic genes, and variant approaches from other areas of neurobiology. Despite rapid advances over the past several years, it is clear that we continue to face substantive challenges in applying mutant models to better understand the pathobiology of negative symptoms: the majority of evidence relates to impairments in social behavior, with only limited data relating to anhedonia and negligible data concerning avolition and other features; even for the most widely examined feature, social behavior, studies have used diverse assessments thereof; modelling must proceed in cognizance of increasing evidence that genes and pathobiologies implicated in schizophrenia overlap with other psychotic disorders, particularly bipolar disorder. Despite the caveats and challenges, several mutant lines evidence a phenotype for at least one index of social behavior. Though this may suggest superficially some shared relationship to negative symptoms, it is not yet possible to specify either the scope or the pathobiology of that relationship for any given gene. The breadth and depth of ongoing studies in mutants hold the prospect of addressing these shortcomings.

Key words: psychosis/psychopathology/pathobiology/social behavior/anhedonia/avolition

Introduction

While it is widely accepted that negative symptoms in schizophrenia constitute a major, pernicious cause of functional debility, and impaired quality of life, there is considerably less agreement on a number of related challenges that impact directly on attempts to model such psychopathology in rodents in general and in genetically modified mice in particular; eg, clinical debates endure as to the nature of "primary" vs "secondary" negative symptoms and the relationship between negative symptoms and a putative "deficit syndrome."[1–3] Until such clinical debates are resolved, it will not be possible to seek fully homologous or isomorphic models of these or, indeed, any other domains of psychopathology in schizophrenia.

In general terms, negative symptoms encompass diminution in emotional expression and motivation, some of which relate to human attributes that may not be accessible readily in animals; this has long been recognized as highly problematic.[4,5] Additionally, uncertainty as to the pathophysiological basis of negative symptoms, together with their essential refractoriness to any treatment modality,[2,6] impedes "proxy" approaches and precludes therapeutic validation of putative models. The difficulties for mutant mouse studies created by such general issues are exacerbated on considering more specific challenges.

The Negative Symptom Challenge

Scope of Negative Symptoms

The domain of negative symptoms is widely held to encompass features such as anhedonia, avolition, blunted affect, poverty of speech [alogia], and social withdrawal [asociality] and to be distinguishable both phenomenologically and psychometrically from their positive symptom counterparts.[2,3] However, while factor analytic studies consistently resolve such negative symptoms into a domain of *psychomotor poverty* that is distinct from the positive symptom domains of *reality distortion* and *disorganization*, there is less clarity as to whether *psychomotor poverty* is itself a unitary or polydimensional domain; there is some evidence to suggest at least 2 negative symptom domains: diminished expression (blunted

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affect and poverty of speech) and anhedonia-asociality.[1,7] Thus, the challenge posed is whether mutant studies are seeking to illuminate the basis of a single construct or the bases of diverse constructs.

Relationship to Cognitive Dysfunction

An associated challenge is the relationship of negative symptoms to cognitive dysfunction. While evidence indicates that both constructs contribute importantly to functional impairment and may bear some psychometric relationship to each other, this relationship is weak and varies with the domain of cognition at issue.[1,8] Thus, the challenge posed is the extent to which mutant studies relating to cognition (see Arguello and Gogos, this issue) inform on processes bearing some relationship to negative symptoms and their putative pathophysiology, perhaps, in terms of some shared involvement of cortico-striato-pallido-thalamo-cortical network dysfunction/dysconnectivity[9–12] or on an independent process in schizophrenia that is unrelated to negative symptoms.

Specificity of Negative Symptoms

Another fundamental challenge is whether the concept of negative symptoms, however defined, is specific to schizophrenia or applies also to other neuropsychiatric disorders. There is evidence for the identification of negative symptoms, or at least negative symptom-like features, also in depression and Parkinson disease.[13] Thus, as above, the challenge posed is the extent to which mutant studies relating to disorders such as depression and Parkinson disease may inform on processes bearing some relationship to negative symptoms in schizophrenia and their putative pathophysiology, perhaps, in terms of some shared involvement of cortico-striato-pallido-thalamo-cortical network dysfunction[11,13,14] or on independent processes unrelated to negative symptoms in schizophrenia.

It is on this complex and uncertain clinical background that molecular genetics, neurobiology, and behavioral neuroscience converge. Their conjoint purpose is the phenotypic study of mice mutant for genes associated with aspects of the putative pathophysiology of or risk for schizophrenia that may inform on the basis of negative symptoms and indicate novel therapeutic targets.

Modelling Negative Symptoms in Animals

Certain negative symptoms, such as poverty of speech, are extremely difficult to model in animals; indeed, they may be uniquely human conditions.[15,16] In contrast, anhedonia, asociality, and avolition represent constructs that, at least theoretically, apply to and are accessible in both humans and animals. However, while many such behaviors in rodents may possess superficial similarity to those observed in patients, whether a given model system is homologous to or isomorphic with the human condition is dependent primarily on our understanding of (1) the underlying taxonomy of "core emotional tendencies," (2) their molecular/cellular bases, and (3) the extent to which these processes are conserved across species and then expressed across a diversity of species-specific behaviors.[17,18]

Social Behavior

Deficits in social functioning represent a core negative symptom in schizophrenia[2,3] and constitute perhaps primary focus, as disturbances in social behavior, particularly social withdrawal, provide a quantifiable "negative symptom" readily amenable to modelling in animals. However, where a given animal model indicates impairment in social interaction, this may confer the model with face validity only for this symptom type because these deficits may alternatively reflect changes across several emotional and cognitive domains in both human and rodents. The latter consideration may be addressed, at least partly, by employing a comprehensive phenotyping strategy capable of capturing and assessing multiple domains and several aspects within each domain, eg, social approach behavior, aggression, and social cognition.[19]

Social Approach-Avoidance

Social approach-avoidance behaviors of putative relevance to schizophrenia are typically measured in rodents by distance between 2 unfamiliar animals placed in a novel environment or the time a pair spend engaged in a defined species-specific element of "active" social interaction. Such assessments of social interaction in a novel environment have generally been conducted across studies using established protocols[20,21]; these typically involve use of automated analysis with appropriate object tracking software to provide indices such as inter-animal distance and contact time, with complementary analysis using a time-sampling procedure to score social behaviors according to the presence or absence of a set of species-typical affiliative (eg, investigative sniffing) or agonistic (eg, biting, pinning) behaviors.

Analysis of free social interaction in a novel environment is subject to certain caveats and methodological considerations. First, in a dyadic paradigm, the social encounter can be initiated by either mouse, while in a social choice paradigm (see "Social Choice" section) the experimental mouse initiates the social encounter. Second, when social interaction tasks are conducted in a novel environment an effect of treatment or genotype on response to novelty may modulate social behavior. Third, it has been argued that impairment in social functioning in schizophrenia may reflect several other factors, including anhedonia, anxiety, or deficits in social

cognition.[19] Finally, as many rodent models of social withdrawal were developed as screens for anxiogenic/anxiolytic drug activity,[22] genotype- or treatment-related effects on social behavior may also reflect a change in anxiety, emphasizing a requirement for multiple construct measures and/or manipulation of experimental parameters known to alter the anxiety component in such tasks.[23]

Social Choice

Choice paradigms for affiliative behaviors are now commonly used to test interest to engage in social interaction in mouse mutant models related to schizophrenia and other psychiatric disorders that are characterized by profound impairment in social interaction.[24,25] Social choice tasks have the advantage that they rely upon spontaneous behaviors, thereby requiring no previous training. Social affiliative behavior is typically assessed in an apparatus with 3 interconnected chambers, with 2 dividing walls containing doors allowing access to each of the side chambers. Sequentially, the test mouse is allowed to freely explore (1) a chamber containing an unfamiliar conspecific vs an empty chamber (ie, to study sociability), then (2) a chamber containing an unfamiliar conspecific vs a chamber containing a familiar conspecific (ie, to study preference for social novelty). The sociability phase reflects social approach-avoidance behavior, while the social novelty phase assesses social recognition memory and the ability to discriminate and respond appropriately to a socially novel stimulus.

This task has now been well characterized in terms of mouse strain differences.[26,27] It has also been shown that sociability in this task correlates well with frequency of social investigative behaviors in free social interaction assays.[24] A number of factors have been identified which may influence the behavior of the test mouse in a social choice paradigm. As social recognition in mice is highly dependent upon olfactory sensory control, it is important to control for phenotypic or treatment effects on olfaction. Social approach behavior in these paradigms may also be influenced by the test animal's appraisal of each conspecific, eg, in terms of social status or aggression.

Social Discrimination-Recognition

It has been suggested that impaired social functioning in schizophrenia involves impaired interplay between different dysfunctional cognitive domains relating to processing and interpreting social cues, ie, social cognition.[28] Social memory or social recognition has also been typically assessed in a 2-stage procedure: the test animal is first introduced to an unfamiliar (usually juvenile) conspecific for a brief period, during which social behaviors are scored, followed 30 min later by a second stage, during which both animals are reintroduced and social behaviors again recorded; a reduction in social exploration following the interval reflects integrity of social memory.[29,30] Assessment of recognition memory using social recognition-discrimination paradigms provides a parsimonious index of memory because the task relies on spontaneous exploratory behavior and does not require additional stimuli; this avoids the complication of interpreting data involving conditional and unconditional stimuli.

Social Dominance-Aggression

When aggression is present in schizophrenia, the nature of its relationship to psychopathology and cognitive dysfunction is unclear.[31,32] In rodents, 5 varieties of behavior have been studied under the rubric of aggression: (*a*) play fighting, (*b*) offensive aggression, (*c*) defensive aggression, (*d*) maternal aggression, and (*e*) predatory aggression.[33] Although numerous procedures have been offered for assessing offensive and defensive aggression in rodents,[33–35] few of these paradigms or the investigators employing them distinguish between the varieties of aggressive behavior outlined above.

Typically, aggressive behavior in rodents is assessed via dyadic interaction where the test animal is confronted with an unfamiliar conspecific. Two situations commonly used involve a neutral setting (ie, a clean, unfamiliar cage) or the home cage (ie, a ''resident-intruder'' procedure). Factors which influence the display of offensive or defensive aggression include strain of the test subject, size of the area used in the encounter, duration of isolation of test subject and rearing conditions,[36] social status of conspecific, and age and sex of both parties.[37] Assessment of aggressive behavior is now commonly employed as part of a central nervous system (CNS) phenotyping screen for mutant mice, although some have questioned the extent to which differing studies purporting to measure aggressivity are in fact examining the same construct.[36]

Long-term exposure to ''social defeat'' has been proposed as an environmental factor relevant to the development of schizophrenia.[38,39] In this context, dominance status and complexity of social structure have been shown to modify behavior in rodents across a variety of domains.[40] Social dominance is usually assessed in the tube test,[41] whereby 2 chambers each containing an unfamiliar mouse are connected by a narrow cylindrical tube which does not allow mice to pass within the tube. A subject is considered dominant when it remains in the tube while its opponent has retreated.

Social Play

Other indices of social behavior in rodents include social play, which involves patterns relevant to the development of agonistic, sexual, and social behavior in adulthood.[42] Play behavior in mice includes play soliciting behavior (push under, crawl below, push past between cage

wall, and cage mate) and social grooming; it occurs mainly between weaning and puberty.[43,44]

Anhedonia

On moving beyond social behavior to other domains, mouse models for negative symptoms of schizophrenia enter yet more difficult terrain. In relation to anhedonia, decrease in sucrose consumption has been commonly interpreted as evidence of reduction in reward function in rodents.[45,46] However, using sucrose volume intake as an index of anhedonia is problematic, given alternative explanations for changes in this measure; in particular, during long-term consumption analysis of intake may be confounded by extraneous factors such as conditioned taste aversion, presence of competing behaviors such as locomotion or stereotypies, or visceral malaise.[47] A further level of complication is that, as for social behavior, voluntary sucrose consumption has been used also to model anhedonia in relation to depression[13,45]; indeed, stress-induced anhedonia in this task has been shown to be sensitive to antidepressant treatment.[48,49]

Avolition

A large psychological and neurobiological literature on motivation has yet to inform substantively on models of avolition in schizophrenia.

It has been proposed that progressive ratio schedule procedures, ie, operant task variants whereby response demands for reward increase across a series of trials, may provide a useful model of reduced motivation in schizophrenia.[50] However, when employing a progressive ratio schedule, it is important to distinguish phenotypically between a high "breaking point," which may be attributable to the level of motivation the animal is willing to transfer to work for reward, and "perseveration," which may be attributable to enhanced impulsivity or disinhibition of a conditioned response.[51,52] Others have considered assessment of motivation using operant paradigms where rats are offered a choice between lever pressing for a preferred reward food or ad libitum access to a less-preferred food.[53] However, it should be noted that adapting specific, often complex operant paradigms established in rats to measure motivational and effort-based processes in mutant mice can prove difficult because stable performance in these types of tasks is generally more difficult to achieve in mice.

Rodent paradigms used to assess antidepressant drug action have also been applied to assess avolition and anhedonia in experimental models of schizophrenia, in terms of behavioral features commonly interpreted as relating to depression; these include tests such as the forced swim task and tail suspension test, which purport to assess "behavioral despair" in rats and mice. However, there endure the conceptual challenges of (1) the extent to which negative symptom–like features in depression might be related psychopathologically and pathophysiologically to negative symptoms in schizophrenia[13] and (2) the lack of sufficient sensitivity of behavioral measures in small rodents to effect the necessary distinctions between features related to clinically similar symptoms in schizophrenia and depression.[54]

Blunted Affect

Modelling restriction in range of affect in schizophrenia is predicated on having some rodent index of affect. This has long-challenged research into affective disorders, from which there has been little cross-fertilization to research into schizophrenia: models of depressed mood are often validated in terms of antidepressant response, when antidepressants are without material effect on negative symptoms in schizophrenia; conversely, models of elevated mood are few, with antipsychotics being more effective in treating manic symptoms in bipolar disorder than negative symptoms in schizophrenia. As modelling reduced emotional expression in rodents clearly represents a general challenge, some investigators have interpreted decreases in tests of anxiety, such as the elevated plus maze and the open field test, as a measure of blunted affect.[55] However, such interpretations remain conjectural and have yet to be substantiated.

Criteria for Validating Rodent Models of Negative Symptoms

The paucity of preclinical assays that provide rodent analogues of the negative symptom domain has disrupted progress in establishing criteria for their validation. Aside from face validity, rodent models of negative symptoms fare even less well with respect to construct and predictive validity.

In contrast to their positive counterparts, uncertainty as to the pathophysiological basis of negative symptoms and their lack of response to treatment with antipsychotic drugs impedes both "proxy" approaches and psychopharmacological validation. Negative symptoms respond poorly, if at all, to essentially all first- and second-generation antipsychotic drugs, with even clozapine exerting at best modest therapeutic efficacy[2,6]; thus, it is not clear whether, in addition to nonresponsivity to other antipsychotics, responsivity or nonresponsivity to clozapine should be considered a validating criterion for rodent models. It has been suggested that, when of any effectiveness, a longer duration of antipsychotic treatment may necessary to see significant reduction in negative relative to positive symptoms.[56,57] However, this lacks the substance for even pragmatic model validation. Furthermore, because D2 dopamine (DA) receptor antagonism endures as the primary mechanism of antipsychotic activity, and because the dopaminergic (DAergic) system

plays an important role in motivation and emotion, antagonism of D2-mediated reward and reinforcement might be expected to induce or exacerbate anhedonia and avolition.[58]

It is on this chastening background that we review phenotypic studies relating to negative symptoms in mice mutant for genes associated with aspects of the putative pathophysiology of schizophrenia or with risk for schizophrenia (see table 1 for summary of evidence for negative symptom phenotypes in mutant models).

Genes Related to DAergic Neurotransmission

Over recent years, the long-standing DAergic hyperfunction hypothesis of schizophrenia has been subjected to a series of elaborations: while positive symptoms appear to be related to increased release of DA onto subcortical D2 receptors that may be attenuated by D2 antagonist antipsychotics, negative symptoms may reflect associated reduction in cortical release of DA, particularly onto D1 receptors in prefrontal cortex.[9,10,59]

In contrast to positive symptoms, few studies have explicitly applied mutant mice approach to understand putative DAergic underpinnings to negative symptomatology in schizophrenia. One of the limitations to the application of constitutive gene deletion studies to this symptom domain is regional selectivity; in prevailing constitutive mutants, DA receptor subtypes and associated entities are deleted over the entire brain, when the prevailing hypothesis posits the differential involvement of cortical as opposed to subcortical brain regions. While the necessary studies with conditional mutants are awaited, there are to date a range of constitutive mutant studies that have sought to understand the independent roles of DA receptor subtypes and associated entities in processes of putative relationship to negative symptoms.

DA Receptor Subtypes

While polymorphisms in *D1*, *D2*, and *D4* receptor genes may be associated with risk for schizophrenia,[60] reports of associations with domains of psychopathology are limited; eg, variants in the *D1* gene have been associated with responsivity to clozapine[61] and variants in the *D2* gene have been associated with negative symptoms[62] and their limited responsivity to antipsychotics.[63] In parallel, extensive phenotypic studies in mutants with knockout (KO) of each of the 5 DA receptor subtypes[64,65] include aspects of behavior such as emotionality, reward, and social interaction that, in broad terms, may relate to negative symptomatology.

Evidence from studies in *D1* and *D2* KOs indicate that *D1* and particularly *D2* receptors play roles in diverse aspects of emotional behavior such as novelty seeking/detection, emotional arousal, retrieval of fear memory, limbic aspects of behavioral responses leading to the drive of action, and reward.[65,66] More specifically, *D2* KOs display a marked reduction in responding for rewarding lateral hypothalamic stimulation,[67] suggesting a role for the D2 receptor in hedonic responses and, by inference, in anhedonia.

Mutants with selective overexpression of subcortical D2 receptors evidence deficits that include reduced incentive motivation, as indexed by reduced lever pressing for food reward in both an operant timing task and under a progressive ratio schedule of reinforcement.[68] It remains to be determined whether this constitutes a model of anhedonia or alternatively involves the interplay of learning processes and cognitive mechanisms.

While *D3*, *D4*, and *D5* KOs indicate subtle roles in several domains of behavior,[65,66] there is little evidence for a role in processes related more directly to negative symptoms.

Dopamine Transporter

Evidence that variation in the *dopamine transporter* (DAT) gene may be associated with negative symptoms[69] is complemented by the finding that *DAT* KOs with heightened DAergic function[70] show impairments in social interaction,[71,72] including disruption to social hierarchies under conditions where wild types (WTs) showed stable hierarchies. Under both group- and isolation-housed conditions, *DAT* KOs exhibited increased reactivity and aggression in the course of social contact, while during isolation, exposure to a novel environment exacerbated these social deficits. Stereotyped and perseverative patterns of social responses were a common feature of the *DAT* KO repertoire and abnormal social behavior coincided with the emergence and predominance of these inflexible behaviors.[72] Importantly, these data suggest that social interaction may be disrupted under conditions of chronic DAergic hyperfunction. It should be noted that *DAT* KOs evidence impaired olfactory discrimination in the relative absence of impairment in odor detection.[73] Thus, as noted previously, olfactory deficits might contribute to and confound the interpretation of changes in social functioning.

In contrast, tests assessing the rewarding values of tastants or food indicate *DAT* KOs to develop a more positive bias toward a hedonically positive tastant[74] and enhanced resistance to extinction of food-reinforced operant behavior[75]; this would reflect the role of DA in updating rewarding values, habit learning, and memory. Increased sucrose consumption in *DAT* KOs would be further consistent with disruption to hedonic processes.[76] In a sucrose-motivated runway task, mutants with *DAT* knockdown, to 10% of the complement in WT, showed greater motivation for the task (wanting) without influencing responsivity for sucrose reward (liking). These findings differ from those in *DAT* KOs; while they indicate that chronic DAergic hyperfunction produces changes in incentive motivation, they are in the opposite

direction to what might be expected as part of a negative symptom profile[77] and must be juxtaposed with the above findings on social behavior.

Catechol-O-methyltransferase

The enzyme catechol-*O*-methyltransferase (COMT) is involved in the catabolism of DA, with functional polymorphisms in the *COMT* gene indicated to exert differential regulation of DA metabolism in the prefrontal cortex and related cognitive processes, particularly working memory.[78] While the *COMT* gene lies within a chromosomal region (22q11) of interest for psychosis, associations with risk for schizophrenia[60,79] and dysfunction in cognitive processes mediated by the prefrontal cortex[78,80] remain uncertain; *COMT* genotype has been associated with aggression in schizophrenia.[81,82] While sociability and social novelty preference are unaltered in both heterozygous and homozygous *COMT* Kos,[83] heterozygous *COMT* mutants evidence increased aggression in the resident-intruder test.[84]

The Chakragati Mouse

The Chakragati mouse is a serendipitously discovered, insertional transgenic mutant characterized by DAergic dysfunction, including increased D2 receptor density; such mutants display reduced social interaction, including decreased proximity during a dyadic test and reduced social approach behaviors.[85,86]

Other Mutants

Mutants for components of several related aspects of DAergic neuronal development, morphology, and signal transduction have been constructed (eg, AKT1, FGFR1, GSK3β, Nurr1). However, their phenotypic evaluation in the context of schizophrenia does not yet extend systematically to models of negative symptoms.[87,88]

Preliminary Overview

Renewed interest in the DA hypothesis of schizophrenia points evidentially to subcortical D2 hyperfunction in relation to positive symptoms and their attenuation by antipsychotic drugs; this is supported by some mutant studies. A postulated role also for cortical D1 hypofunction in negative symptoms is less well supported but remains heuristic. Mutant studies paint a complex picture where it proves difficult to specify the relative roles of D1 and D2 receptors in relation to individual domains of behavior that might relate to clinical psychopathology. For example, there endures the paradox that in animals antipsychotic (D2 antagonist) drugs acutely attenuate the effects of reward normally associated with "pleasure," whereas in patients, antipsychotics act incrementally against positive symptoms with negligible effect on negative symptoms such as anhedonia.[89]

Genes Related to Glutamatergic Neurotransmission

Glutamate receptors have been suggested to play an important role in the pathogenesis of schizophrenia. In addition to subcortical D2-mediated hyperfunction and putative cortical D1-mediated hypofunction in schizophrenia (see "Genes Related to DAergic Neurotransmission" section), there is evidence for glutamatergic hypofunction. Alongside the well-characterized psychotomimetic properties of phencyclidine (PCP) and other *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists, NMDA deficits in the brain have been described in schizophrenia[90–92] and antipsychotic activity has been reported for a metabotropic glutamate receptor agonist.[93] While much clinical genetic data have focused on genes encoding the NMDA receptor and interacting signaling components as susceptibility candidates, there is also a growing body of evidence linking schizophrenia susceptibility with genetic variance in other glutamate receptor classes, including metabotropic receptor subtypes as well as non-NMDA ionotropic receptors, namely x-amino-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and, to a lesser extent, kainate receptors.[94]

NMDA Receptors

Mice expressing reduced levels of the NR1 subunit of the NMDA receptor display abnormalities across several negative symptom–related domains, including social behavior. These include greater distance from unfamiliar mice during free social interaction in a novel environment, together with reduced social investigative and aggressive behaviors when acting as the resident in the resident-intruder paradigm; interestingly, these deficits showed little sensitivity to amelioration by clozapine.[95,96] Decreased sociability, as assessed in the sociability and preference for social novelty test, has also been observed in NR1 hypomorphs.[25,96,97] However, modest impairment in olfactory function may contribute to these social deficits.[25,96]

Grin1 (D481N) mutants, having reduced NMDA glycine site occupancy, display a decrease in sociability but not in social novelty preference; this deficit in sociability showed limited sensitivity to amelioration by clozapine.[98] Interestingly, treatment with the selective glycine transporter 1 inhibitor SSR103800 attenuated deficits in social recognition in adult rats induced by neonatal injections of PCP.[99] Additionally, agonists at the glycine site of the NMDA receptor may have some efficacy as adjunctive therapies for the negative symptoms of schizophrenia.[100–102] Overall, studies in both rodents and humans would indicate therapeutic potential for glycine agonism in the treatment of negative symptoms.

NMDA Receptor–Related Processes

Abnormalities in various components of the NMDA receptor signaling complex have been implicated in

schizophrenia.[87,103] In particular, preclinical studies have implicated several such regulatory components, including the glial glutamate and aspartate transporter (GLAST) and the postsynaptic density-enriched scaffold and signaling molecule SynGAP.[104,105] A rare genetic variant in the human gene encoding GLAST has been reported in schizophrenia,[106] and postmortem brain studies have demonstrated altered GLAST expression in the dorsolateral prefrontal cortex, anterior cingulate cortex, and thalamus in schizophrenia.[107,108]

Heterozygous *SynGAP* mutant mice evidence intact sociability but impaired social novelty preference.[104] Conversely, when assessed in the same paradigm *GLAST* KOs evidence a marked reduction in sociability, with intact social novelty preference and dyadic social interaction in a novel environment; there was no effect on sucrose preference as a putative index of anhedonia.[105]

Mutants with heterozygous deletion of *glutamate carboxypeptidase II*, a signaling component implicated in NMDAR activation, evidenced reduced sociability in a social choice paradigm.[109]

Non-NMDA Ionotropic Glutamate Receptors

Mutants with KO of the AMPA GluR1 receptor subunit fail to show the increase in aggression toward a conspecific that normally follows social isolation, in a manner similar to the effects of treatment with an AMPA/kainate antagonist,[110] and display reduced social behavior as measured by anogenital-directed social investigation.[111]

Metabotropic Glutamate Receptors

Recent studies have suggested alleles of several metabotropic receptor subtypes to be associated with increased risk for schizophrenia.[112,113] Pharmacological modulation of activity at mGluR3 or mGluR5 receptor subtypes may ameliorate social interaction deficits in pharmacological or environmentally based models for negative symptoms in mice (PCP treatment and isolation rearing, respectively).[114,115] However, metabotropic receptor mutants have yet to receive systematic investigation in relation to social or other behaviors relevant to negative symptoms.

Other Glutamate-Related Processes

Vesicular glutamate transporters (VGluTs) 1 and 2 are recognized markers of glutamatergic neurons that are responsible for the vesicular packaging of glutamate in the presynaptic axon terminal.[116–118] Abnormal VGluT1 expression in schizophrenia has been reported in the striatum and hippocampus[119] and in the anterior cingulated.[120]

Mutants with heterozygous deletion of *VGluT1* exhibited reduced sucrose consumption consequent to chronic mild stress.[121] Mutants with conditional, heterozygous deletion of VGluT2 in the cortex, hippocampus, and amygdala during the third postnatal week evidence reduced social dominance in the tube test and spend more time interacting with unfamiliar conspecifics in a novel environment.[55] These data would suggest that reduced expression of VGluTs is associated with an array of social and anhedonic phenotypes.

Other Mutants

Mutants for components of several related aspects of glutamatergic transmission have been constructed (eg, D-serine, mGluR1-8, NR2A [GluRϵ1]). However, their phenotypic evaluation in the context of schizophrenia does not yet extend systematically to models of negative symptoms.[87,88]

Preliminary Overview

Enduring interest in glutamatergic hypotheses of schizophrenia points evidentially to NMDA hypofunction in relation to both positive and negative symptoms. This is supported and elaborated by mutant studies that indicate, with some consistency, disruption to a number of social and hedonic processes. Therapeutically, studies in mutants have contributed to interest in glycine transporter inhibitors, as indirect facilitators of glutamatergic transmission, for the treatment of negative symptoms. The incisiveness and specificity of mutants have the potential to illuminate the development of glutamatergic neuronal (dys)function because it might relate to the pathobiology of schizophrenia and, particularly, to delineate more optimal therapeutic targets in the glutamatergic transmission-signaling cascade.

Genes Associated With Risk for Schizophrenia

Over the past several years, molecular genetics has identified a number of candidate risk genes, using both association and linkage studies, as documented and synthesized in recent systematic reviews and meta-analyses.[60,122–126] Inconsistency between studies and a continually evolving tableau in ongoing, ''real-time'' meta-analyses[60,127] may reflect: (a) a putative polygenic basis to schizophrenia, with several genes of small effect contributing to overall liability; (b) that implicated genes confer risk not for schizophrenia per se but, rather, for psychosis as a dimensional construct that transcends any unitary diagnostic category; (c) a diversity of genetic loci associated with different domains of psychopathology; (d) as a variant of the above, that individual genes or combinations of genes are associated with endophenotypes within the overall schizophrenia syndrome; and (e) that genetic risk may depend upon interactions between individual susceptibility genes (epistasis) and/or interaction between susceptibility genes and exposure to one or more environmental adversities.[123,128] Most recently, there has been intense interest in multiple copy number

variations each conferring risk for schizophrenia in relatively small numbers of cases.[106,129] It remains to be determined whether a plethora of genome-wide association studies will clarify or further confound these issues.

Although relatively few studies have sought to delineate the relationship between schizophrenia risk genes and domains of psychopathology, this approach has the potential to provide an important conceptual link toward understanding the genetics of schizophrenia. The construction of mice mutant for genes either implicated in CNS processes relevant to putative pathophysiologies of the disorder or associated directly with risk for schizophrenia has provided an important translational stimulus to addressing these questions.

Disrupted-in-schizophrenia 1

A study in a Scottish pedigree demonstrated that a familial mutation in the *disrupted-in-schizophrenia-1 (DISC1)* gene, due to a balanced chromosomal translocation at 1q42.1–1q42.3, segregated with several psychiatric disorders, including schizophrenia; this association between *DISC1* and schizophrenia has been replicated across diverse populations.[124,125] During embryonic development, *DISC1* appears to play an important role in neurodevelopment and structural plasticity via interaction with several proteins, including phosphodiesterase-4B, Fez1, NudEL, and LIS1.[130] While there is little clinical evidence for any specific relationship between *DISC1* and negative symptoms, a relationship with social anhedonia in a large population cohort has been reported.[131]

Among several mutant lines with disruption to *DISC1*,[132] a *DISC1* mutation (Q31L) generated using chemical mutagenesis demonstrated disruption to both sociability and preference for social novelty; additionally, this line evidenced decreased sucrose consumption.[133] In a conditional transgenic line with inducible expression of a DISC1 C-terminal fragment, early postnatal (day 7) induction was associated with reduced sociability.[134] Conversely, expression of a dominant-negative truncated form of DISC1 under the CaMKII promoter did not disrupt social interaction.[135] A conditional transgenic line with forebrain-specific expression of mutant human DISC1 was associated with a sex-specific decrease in social investigation in males, with increased aggressivity in a dyadic test of social interaction but no effect on sociability or social novelty preference.[136]

DTNBP1 (dysbindin)

Dystrobrevin-binding protein 1 (DTNBP1; dysbindin) was initially identified as a schizophrenia susceptibility gene after fine mapping of a linkage region on chromosome 6p22 in Irish multiplex families; this has since been replicated across diverse populations.[60] DTNBP1 expression is decreased in schizophrenia in the dorsolateral prefrontal cortex and hippocampus.[137,138] Clinical genetic studies in schizophrenia have indicated associations between *DTNBP1* and negative symptoms.[139]

The *sdy* mouse, a spontaneous mutation constituting a murine model of Hermansky-Pudlak syndrome,[140] is characterized by a large deletion encompassing 2 exons of the *DTNBP1* gene and shows no expression of dysbindin protein. In a test of dyadic social interactions, *dysbindin* (*sdy*) mutants evidence a reduction in social contact time.[141]

G72/G30

Following an initial report in 2 independent samples, the *G72/G30* gene complex has been associated with risk for schizophrenia across numerous populations[60,142]; this gene regulates the activity of D-amino acid oxidase (DAO); hence, the alternative nomenclature D-amino acid oxidase activator.

In transgenic mutants carrying the human *G72/G30* genomic region, nonaggressive social interaction is intact, while male mutants show a reduction in aggressive behaviors; there were also deficits in olfactory function.[143]

Neuregulin-1

Following an initial report in an Icelandic sample, the identification of *neuregulin-1 (NRG1)* as a putative risk gene for schizophrenia has been replicated across many populations[127,144]; furthermore, studies in postmortem brain tissue support a role for *NRG1* and associated signaling through ErbB receptors in the pathobiology of schizophrenia.[145–147] Distinct targeted mutations of various *NRG1* isoforms have made it possible to delineate some of their specific functions, including some that relate to negative symptoms.

Mutants with heterozygous deletion of transmembrane (TM) domain (pan-isoform) *NRG1* display selective impairment in response to social novelty, as demonstrated by intact sociability but absence of preference to investigate a novel over a familiar conspecific.[148] In contrast, heterozygous *epidermal growth factor (EGF)*-like domain (pan-isoform) *NRG1* KO mice display reduced sociability as measured in a social choice paradigm,[149] the differences between these findings and those reported in TM domain *NRG1* mutants may relate to the mutation or several important procedural differences (type of social stimulus used, lighting conditions). Mutants with loss of ErbB signaling in oligodendrocytes also show impaired social interaction in a dyadic paradigm.[150] TM-*NRG1* mutants,[148,151] but not EGF-like domain[149] or type III isoform-specific *NRG1* mutants,[152] also display enhanced aggression in social encounters, while mutants with conditional KO of the ErbB2/B4 receptor show increased aggression in the resident intruder paradigm; this deficit was reversible by treatment with clozapine.[153]

B-site amyloid precursor protein-cleaving enzyme 1 (BACE1) has been implicated in *NRG1* signaling.[154] Its function has been studied using a social choice task variant, the social habituation-dishabituation paradigm, to assess response to social novelty. In this task, the test mouse is repeatedly exposed to a juvenile conspecific and social behaviors are then recorded across sessions (habituation); a novel social stimulus is then added and response to the new stimulus is examined (dishabituation); *BACE1* KOs evidenced reduced dishabituation, suggesting decreased behavioral response to social novelty.[155]

PPP3CC

Calcineurin is a calcium- and calmodulin-dependent protein phosphatase composed of 2 subunits, a regulatory subunit of calcineurin B and a catalytic subunit of calcineurin A (CNA) that has been implicated in downstream regulation of DAergic signal transduction and in NMDA receptor–dependent synaptic plasticity; PPP3CC is the gamma isoform of CNA. Variation in the *PPP3CC* gene has been associated with risk for schizophrenia.[122,126]

Mutants with conditional, forebrain-specific *calcineurin* KO display a sustained decrease in social contacts with an unfamiliar mouse in a home cage environment.[156] KO of *ryanodine receptor 3*, an interacting partner alongside calcineurin, results in a decrease in social contacts in both home cage and novel environments; there were no effects in the test of sociability and preference for social novelty.[157]

Regulator of G-Protein Signaling-4

Regulator of G-protein signaling-4 (RGS4) was initially identified as a putative risk gene for schizophrenia in a multinational sample and reported to show reduced expression in postmortem brain; however, subsequent meta-analyses across numerous samples and further studies in postmortem brain have indicated these issues to be less clear.[60,158] *RGS4* polymorphisms have been associated with poorer social function in schizophrenia and greater amelioration of that dysfunction by risperidone.[159]

Mutants with *RGS4* KO (cre-deleted $RGS4_{lacZ/lacZ}$) have yet to be examined for behaviors related to negative symptoms.[160] However, mutants deficient in phospholipase C-β1, a signaling molecule that mediates activity within several neurotransmitter pathways and with which RGS4 interacts,[161] display reduced social dominance, as measured in the tube test; they also evidence reduced whisker trimming, a form of mutual grooming related to social dominance.[162]

Other Mutants

Mutants for additional genes, either implicated in risk for schizophrenia or interacting with those above, have been constructed (eg, *DAO, FEZ1, Nogo receptor 1 [RTN4R], PRODH, ZDHHC8*). However, their phenotypic evaluation in the context of schizophrenia does not yet extend systematically to models of negative symptoms.[87,88]

Preliminary Overview

Advances in the molecular genetics of schizophrenia can, in a "top-down" manner, prompt construction of a line of mutants for each risk gene as it is identified; the purpose is then to investigate phenotypically the functional role of that gene because it might relate, in the present context, to negative symptoms. However, studies can also proceed also in a "bottom-up" manner; eg, is intact sociability but impaired social novelty preference in *NRG1* mutants[18,148] related to a particular pattern of social deficit in patients carrying a given *NRG1* risk polymorphism?

A particular complication is that for any given risk gene of interest, several mutants may be available. Diverse mutants for *DISC1* and *NRG1* illustrate the dilemma in determining which may be the most informative on the psychopathology and pathobiology of schizophrenia. These decisions will only be clarified by greater understanding of the neurobiology of such entities in the context of the neurobiology of schizophrenia itself.

It must be considered also whether negative symptoms can be modeled, in any simple way, by a single-gene manipulation. If schizophrenia reflects the operation of several risk genes of small effect that act in a complex environmental milieu, negative (and indeed other) domains of psychopathology may involve gene × gene interactions (epistasis) and gene × environment interactions.[123,163] To the extent that this is sustained, progress may require generation of mutants with concurrent disruption to 2 or more risk genes of interest and assessment of mutant phenotypes in relation to external biological and psychosocial adversities.[87,88]

Neurodevelopmental-Synaptic Genes

In addition to the above genes associated with specific DAergic and glutamatergic pathophysiologies or with risk for schizophrenia, other genes regulate more general synaptic processes implicated in schizophrenia, particularly in the context of developmental disruption to neuronal connectivity.[11,12,123,164]

Complexin 1

Complexins are small presynaptic proteins that bind to the soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) assembly and stabilize the SNARE complex for fast calcium-mediated exocytosis[165]; complexin 1 (Cplx1) expression is decreased in the postmortem brain in schizophrenia.[166] Mutants with *Cplx1* KO show disruption in preference for social

novelty in the absence of any effect on sociability or olfactory function; in a resident-intruder paradigm, male *Cplx1* KO showed reduced aggression toward an unfamiliar intruder.[165]

Reelin

Reelin is a neuronal glycoprotein involved in CNS development and expressed in γ-aminobutyric acid (GABA)–containing cells of the cortex, hippocampus, and cerebellum. In schizophrenia, reelin and the GABA synthesizing enzyme glutamic acid decarboxylase (GAD67) are downregulated in cortical GABAergic interneurons, such that partial deletion of reelin has been offered as a pathophysiological model of schizophrenia.[167] Mutation of one allele encoding the reelin protein (the heterozygous reeler mouse) results in higher levels of social dominance in the tube test[167] but does not otherwise disrupt social interaction.[169]

Mutation in the neuronal PAS domain protein 1/3 (NPAS1/NPAS3) transcription factors resulted in reduced expression of reelin in various brain areas that was accompanied by impaired social recognition.[170] Methionine-induced epigenetic reelin promoter hypermethylation in mice resulted in deficits in aggression and habituation in the resident intrude test and reduced social interaction in a novel environment.[167,171]

Stable Tubule–Only Polypeptide

The stable tubule–only polypeptide (STOP) proteins are involved in the cold stability of microtubules, brain development and connectivity, synaptic plasticity, and neurotransmission.

Mutants with *STOP* KO evidence reduced sniffing of a conspecific introduced into the home cage, together with reduction in aggressive responses, in the absence of any substantive disruption to olfaction; these social deficits were poorly sensitive to amelioration by chlorpromazine and haloperidol.[172] Provocatively, while other behavioral, synaptic vesicular, and electrophysiological abnormalities described also in *STOP* mutants appear to be ameliorated by treatment with the microtubule stabilizer epothilone D,[173] any effects on these recently reported social deficits are yet to be reported.

Synapsin II

Synapsins are a family of neuron-specific, vesicle-associated phosphoproteins involved in the regulation of neural development and transmitter release; synapsin II mRNA is reduced in the medial prefrontal cortex in schizophrenia, while chronic treatment with haloperidol increases synapsin II mRNA in rats.[174] Mutants with *synapsin II* KO demonstrate a marked reduction in social interaction.[175]

Preliminary Overview

Rather than deriving in a "top-down" manner from clinical molecular genetic studies, these mutants are of considerable value via their relationship to mechanisms of synapse formation, plasticity, and connectivity that are posited to be disrupted in schizophrenia. Importantly, they can be related phenotypically, here in the context of negative symptoms, to pathobiology via psychopathological neuroimaging and postmortem studies in patients. Thus, on a long-term basis, such mutant studies may contribute importantly to clarifying the pathobiology of negative symptoms, at a more fundamental level than is apparent for approaches based on current neurochemically based hypotheses or individual risk genes.

Variant Approaches

A variant approach is to consider the neurobiology of behavioral processes that could relate to negative symptoms, with a view to their study in schizophrenia-related mutants with putative negative symptom phenotypes. Several molecules have been show to play a critical role in such behaviors. Several examples, involving mutant studies of social behavior, are outlined in the subsequent paragraphs.

The neuropeptide oxytocin is a modulator of animal[176,177] and human[178,179] social functioning. Central administration of oxytocin to rodents improves social interaction, [180,181] and exogenous *oxytocin* reverses deficits in social behavior following prenatal exposure to a stressor.[182] Conditional oxytocin KOs show deficits in social recognition[183] and in intrastrain but not interstrain social recognition,[184] indicating a more specific role for oxytocin in social discrimination. Interestingly, clozapine but not haloperidol has been shown to increase plasma concentrations of oxytocin.[185]

The antidiuretic hormone arginine-vasopressin (AVP) is known to play an important role in social and emotional behavior[176]: *AVP-V1aR* KOs display impaired social recognition memory and social interaction that can be rescued by reexpression of AVP-V1aR in the lateral septum[186–188]; *AVP-V1bR* KOs display impaired social recognition and conspecific aggression,[189,190] with disruption to sociability and preference for social novelty.[191]

Mutants with KO of *neuronal nitric oxide synthase* show impaired social recognition.[192] Pretreatment with an NOS inhibitor reverses deficits in social interaction induced by PCP,[193] a treatment that increases NO in prefrontal cortex.[194]

A related variant approach involves inbred strains of mice with neurodevelopmental phenotypes that may inform on schizophrenia. For example, the BTBR *T+tf*/J inbred strain displays impairment in dyadic social interactions, reduced social transmission of food preference, disrupted sociability, and reduced social play.[195]

Table 1. Negative symptom models in mice mutant for candidate genes. +, evidence for effect of mutation; 0, evidence for no effect of mutation; ?, no or insufficient evidence. There is little or no systematic evidence relating to the negative symptoms of blunted affect and poverty of speech

		Negative symptom		
Candidate gene		Asociality	Anhedonia	Avolition
Altered DA neurotransmission	D2 over expression	?	?	+
	Dopamine transporter	+	0	0
	COMT	+	?	?
	Chakragati	+	?	?
Altered glutamatergic neurotransmission	NMDAR dysregulation	+	?	?
	SynGAP	+	?	?
	GLAST	+	0	?
	Glutamate carboxypeptidase	+	?	?
	VGluT1	?	+	?
	VGluT2	+	?	?
Schizophrenia risk genes	*DISC1*	+	+	?
	Dysbindin	+	?	?
	NRG1	+	?	?
	G72/G30	+	?	?
	PPP3CC	+	?	?
	RGS4	?	?	?
Neurodevelopmental-synaptic genes	*Complexin 1*	+	?	?
	Reelin	+	?	?
	STOP	+	?	?
	Synapsin II	+	?	?

Accessing "Inaccessible" Negative Symptom Constructs?

In contrast to asociality, anhedonia and to some extent avolition, in animals blunted affect is confounded with our concepts and measures of either polarity of "affect," while poverty of speech may be uniquely human. However, some researchers have sought to meet the challenge of these "inaccessible" constructs and have offered novel behavioral indices and end points for their assessment.

In relation to impaired processing of emotions in humans, a recent animal model has been offered[196]; using fear processing and ketamine-induced glutamatergic hypofunction, impaired amygdala-based fear processing was reversed by clozapine but not by haloperidol. This paradigm has yet to be applied to mutant models relating to schizophrenia.

In relation to poverty of speech, reduction in stress-induced vocalization has been offered as an animal model. Specifically, isolation-induced ultrasonic vocalizations in neonates, which are produced to elicit maternal approach and/or retrieval, are increasingly used in the phenotypic study of mice mutant for genes associated with neurodevelopmental disorders, in particular those characterized by communicative/social deficits.[197] Reductions in ultrasonic vocalizations in separated pups have been observed in several mutant models of schizophrenia, including the reeler mouse[198] and *DISC1* mutants.[199] While investigation of adult mouse vocalizations has proved more difficult, abnormalities in vocalizations signaling male-female recognition have been observed in *D2* KOs.[200] However, just as olfactory deficits may confound the investigation of social behavior in mutants, it is important to assess potentially confounding factors such as lung function or larynx morphology on vocalization.[201]

An ethological approach affirms that characterisation of the species-specific behavioral repertoire takes precedence in any analysis of the clinical relevance of behavioral changes encountered in experimental models. This approach has been used extensively in systematic investigation of the phenotype of mutants with KO of each of the 5 individual DA receptor subtypes.[64] Among other naturalistic behaviors, disturbance in nest building has been offered as a murine measure of the negative symptom of self-neglect in *Dvl1* KOs[41] and *NMDA NR1* hypomorphic mutants.[97] However, disruption of nest building is likely to be multifactorial and may be subject to other interpretations.

Overview

Despite rapid advances over the past several years,[18,19,87,88,123,202,203] it is clear that we continue to face substantive challenges in applying mutant models to better understand the pathobiology of negative symptoms (and other domains of psychopathology) in schizophrenia.

First, the majority of evidence relates to impairments in social behavior, with only limited data relating to

anhedonia and negligible data concerning avolition and other aspects of negative symptoms.

Second, even for the most widely examined behavior, studies in the various mutant lines have used diverse tests of sociability and aggression. While the test of sociability and social novelty preference is, perhaps, emerging as the most widely applied paradigm, this currently allows meaningful comparisons between only a minority of studies. In this regard, there endures also the problem that the ''same'' test applied in different laboratories to the ''same'' subjects may, for poorly understood reasons,[204] generate different results.

Third, in the absence of validating pharmacology, other than perhaps nonresponse, to what extent should the dearth of systematic psychopharmacological studies be understood as rational conservation of resources or negligence in not confirming such nonresponse. There endures the challenge of how to interpret the few but potentially important findings with clozapine vis-à-vis the clinical debate as to its clinical efficacy for negative symptoms.

Fourth, modelling must proceed in cognizance of increasing evidence that genes and pathobiologies implicated in schizophrenia overlap with other psychotic disorders, particularly bipolar disorder, in which negative symptoms may be less evident.

Despite the caveats and challenges considered above, it should not be overlooked that several mutant lines evidence a phenotype for at least one index of social behavior, independent of whether the gene at issue relates to a putative pathophysiological processes or to risk for schizophrenia. Though this may suggest superficially some shared relationship to negative symptoms, it is not yet possible to specify either the scope or the pathobiology of that relationship for a given gene. Furthermore, whether each mutant line indicates the same or a different phenotypic relationship to the individual components of negative symptoms is poorly understood. Conditional mutants, where expression of a gene at issue can be controlled in space (ie, differentially across brain regions) and/or temporally (ie, differentially over stages of development), have the potential to markedly increase the yield from mutant studies.

As an essential context, it must be emphasized that (1) our knowledge of the psychopathological boundaries and pathophysiology of negative symptoms in patients is also far from clear, and (2) these uncertainties derive, at least in part, from the diversity of clinical psychopathology, treatment response, and outcome. Thus, it could be argued that the diversity of findings from putative mutant models is actually reflective of clinical reality.

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