Schizophrenia Bulletin vol. 36 no. 2 pp. 289–300, 2010
doi:10.1093/schbul/sbp153
Advance Access publication on December 21, 2009

Cognition in Mouse Models of Schizophrenia Susceptibility Genes

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Cognitive deficits are core features of psychiatric disorders and contribute substantially to functional outcome. It is still unclear, however, how cognitive deficits are related to underlying genetic liability and overt clinical symptoms. Fortunately, animal models of susceptibility genes can illuminate how the products of disease-associated genetic variants affect brain function and ultimately alter behavior. Using as a reference findings from the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia program and the SchizophreniaGene database, we review cognitive data from mutant models of rare and common genetic variants associated with schizophrenia.

Key words: CNTRICS/MATRICS/executive control/working memory/22q11/*DISC1*

Introduction

Psychiatric disorders are heterogeneous behavioral syndromes marked by significant cognitive impairments. These deficits are particularly prominent in psychotic disorders and are especially severe in schizophrenia. Given that cognitive capacity largely influences functional outcome, improving cognition is currently a major focus of schizophrenia research. It is clear that model systems will be instrumental in developing targeted treatments toward this end. As such, defining the proper role for and utilizing the full potential of animal models is of utmost importance. In this review, we discuss insights from mutant animal models and what they reveal about the cognitive architecture related to genetic risk for schizophrenia.

As our guide, we use suggestions from the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) program.[1] Recent comprehensive reviews on animal models have focused on the various behavioral paradigms available, their ability to measure specific cognitive constructs, and their potential use in drug development.[2,3] These reviews are largely based on suggestions from the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative.[4] In order to achieve rapid utility, the cognitive test battery that emerged from this collaboration is based on well-characterized, classical neuropsychological instruments. CNTRICS emerged in recognition that these tests are rather imprecise and now dated and identified 7 cognitive domains for more refined characterization in schizophrenia.[5] We therefore discuss findings from mutant animal models in light of these cognitive domains.

Carving up and Comparing Cognition

It is still not clear whether cognitive dysfunction in schizophrenia reflects discrete independent deficits or a generalized functional impairment. This ambiguity is due to the current statistical methods used for identifying different cognitive domains, the rather blunt neuropsychological instruments used for cognitive profiling, and/or the limitations of classifying cognitive processes based on folk psychology.[6,7] For example, MATRICS identified independent cognitive domains based on analytic methods that a priori orthogonalize different factors.[8] Performances on tests measuring these cognitive processes, however, are significantly correlated with each other, and these processes are not necessarily independent at the level of common genetic influence.[9,10] While schizophrenia patients show cognitive deficits across a range of neuropsychological tests, when modern cognitive neuroscience tasks are used, deficits within a given task can be highly specific.[11] For now, resolving the specificity vs generality of cognitive deficits awaits profiling the cognitive architecture of both healthy and clinical populations using more refined cognitive neuroscience tools.

Regardless of the exact architecture of cognitive deficits, measuring relevant cognitive processes in model animals usually relies on the neuronal and psychological homology of these processes. Thus, tasks that are dependent on the same neural systems as those in humans and thought to measure the same psychological constructs are usually the most relevant. Using these criteria alone, however, may be problematic. For example, although

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prefrontal cortical (PFC) dysfunction contributes to cognitive deficits in schizophrenia, not all PFC-dependent processes are affected in patients,[11] and PFC dysfunction is implicated in most, if not all, psychiatric disorders. Moreover, this poor specificity also applies to the psychological constructs themselves, such as working memory (WM), which is impaired across a variety of disorders.[12–14] As such, a given PFC-dependent, WM task used in animal models may be relevant to autism or attention deficit/hyperactivity disorder in addition to schizophrenia. This implies that, because of the poor specificity of any particular, or even set of, cognitive deficits, behavioral tests alone cannot be used to validate an animal model. Additional support, like a solid genetic foundation, is needed for animal models to provide reliable insight into a disease process.

Varieties of Mutant Animal Models

Model systems can be used for various means including mimicking an etiological factor, inducing a pathogenetic cascade, or recapitulating a final pathophysiological state. Here, we focus on mutant models of schizophrenia susceptibility genes and thus do not discuss all animal models that may be relevant for understanding schizophrenia neurobiology and cognition. Importantly, mutant animal models themselves are only as reliable as the genetic and clinical data upon which they are based, and choosing wisely among genetic findings is the first step in creating etiologically valid models. Although the genetic architecture of psychiatric disorders, as for other complex disorders, is still unknown, it likely consists of both highly penetrant rare alleles and common alleles of small effect. The potential, however, to translate genetic findings into etiologically valid animal models varies greatly for rare vs common risk alleles.

It is unclear to what extent or in what manner common genetic variants contribute to the etiology of psychiatric disorders, whether it is by incrementally increasing disease risk, through strong epistatic interactions, and/or by modifying the penetrance of rare variants. Even so, for most candidate genes with putative common risk variants, there is inconsistent statistical support, little consensus on the exact risk alleles, or scarce information on the alleles' functional effects.[15–19] This makes modeling efforts problematic, and, although models based on these genes may provide important insight into the biological functions of a particular gene, they do not identify which of these functions are relevant to disease pathogenesis.[20,21] In light of the large number of potential schizophrenia susceptibility genes with common risk alleles,[15] none of which have been unequivocally identified, we only discuss models available from the "top 30" candidates genes of the SchizophreniaGene database (http://www.szgene.org). This is an impartially compiled database of risk genes based on meta-analyses of genetic association studies (table 1). The list is by no means definitive and is constantly evolving, and we use it only to avoid a biased representation of genes. Critically, because most mutant models based on these genes do not recapitulate specific risk alleles, their relevance to disease pathogenesis remains unknown.

Although individual rare alleles (even recurrent ones) are so far associated with only a small fraction of cases,[22,23] their statistical associations with disease status are robust and their functional effects clear. Due to the limited resolution of available genotyping platforms, most rare alleles identified thus far are large structural variants.[24] These include a balanced chromosomal translocation (1;11)(q42.1;q14.3)[25] and copy number variants (CNVs) at 22q11.2 as well as possibly at 1q21.1, 2p16.3, 15q13.3, 16p11.2, and 17p12.[22,23,26–30] The ability to model these genetic lesions accurately makes models of rare alleles etiologically valid and more likely to identify disease-relevant biological pathways.[31] As of yet, there are few animal models of CNVs, although some of them encompass or disrupt promising candidate genes. Two examples are the neurexin 1 gene (*NRXN1*) within the 2p16.3 locus and the α7 cholinergic nicotinic receptor gene (*CHRNA7*) within the 15q13.3 locus. Mutant *NRXN1* mice have not been extensively characterized cognitively.[32] Mice missing a single copy of *CHRNA7* do not have robust cognitive deficits,[33] and in the absence of a model of the entire 15q13.3 microdeletion it remains unclear how *CHRNA7* deficiency may contribute to the diverse phenotypes associated with this CNV. We thus primarily focus on available mutant models from 2 of the few structural variants to be unequivocally associated with schizophrenia, t(1;11) and 22q11.2 microdeletion.

Different methodological approaches have been used to model the t(1;11) translocation that disrupts the *DISC1* and *DISC2* (Disrupted-In-Schizophrenia-1 and -2) genes and segregates with psychiatric disorders in a large Scottish family. Most models assume that the translocation produces a truncated DISC1 protein that interferes with the intact copy's function and thus overexpresses a truncated form of human DISC1 (figure 1). These include mice expressing an N-terminal fragment under the *αCAMKII* promoter (*Tg(Camk2a-DISC1)10Asaw*),[34] tet-off double transgenic mice expressing human DISC1 under the *CMV* promoter with tetracycline under the *αCAMKII* promoter (*Tg(tetO/CMV-DISC1*)1001Plet* × *Tg(Camk2a-tTA)1Mmay*),[35] and mice expressing a C-terminal fragment of DISC1 under the *αCAMKII* promoter using a single transgenic inducible and reversible system (*Tg(Camk2a-ESR1/DISC1*)2698.1Sva*).[36] Another set of models was generated using an N-ethyl-N-nitrosourea-induced mutagenesis screen that uncovered 2 lines of mice carrying missense mutations in exon 2 of *Disc1*.[37] Only one model (*Disc1*^{tm1Kara}) directly targeted the endogenous murine *Disc1* ortholog in a way that mimics the effect of the

Table 1. Rare and Common Alleles Associated With Schizophrenia and Related Mutant Models[a]

Locus	Gene Function	Top Risk Allele	Functional Effect	Related Mouse Alleles
Rare variants				
DISC1	Found in the nucleus, cytoplasm, and mitochondria, the encoded scaffolding protein is involved in cellular proliferation and migration as well as intracellular signaling and transport	t(1;11) (q42.1;q14.3)	Truncating mutation	*Disc1*^{tm1Kara}, *Tg(Camk2a-DISC1*)10Asaw*, *Tg(tetO/CMV-DISC1*)1001Plet*, *Tg(Camk2a-ESR1/DISC1*)2698.1Sva*
22q11.2	This locus contains ~30 genes influencing neuronal development, synaptogenesis, dendritic growth, neuromodulation, and microRNA biogenesis	Δ22q11.2	Hemizygous deletion	*Del(Dgcr2-Hira)2Aam*, *Del(Dgcr2-Hira)1Rak*, *Del(16Es2el-Ufd11)217Bld*, *Del(16Zpf520-Slc25a1)1Awb*
Common variants				
1. *DISC1*	Found in the nucleus, cytoplasm, and mitochondria, the encoded scaffolding protein is involved in cellular proliferation and migration as well as intracellular signaling and transport	*rs3737597(A)*	3′UTR, unknown	*Disc1*^{tm1Kara}, *Tg(Camk2a-DISC1*)10Asaw*, *Tg(tetO/CMV-DISC1*)1001Plet*, *Tg(Camk2a-ESR1/DISC1*)2698.1Sva*
2. *SLC18A1*	Encodes the vesicular monoamine transporter that acts to accumulate cytosolic monoamines into vesicles	*rs2270641(C)*	Missense, unknown	*Slc18a1*^{tm1Dgen}
3. *GABRB2*	Encodes the β2 subunit of the γ-aminobutyric acid A receptor mediating fast inhibitory synaptic transmission	*rs6556547(G)*	Intronic, unknown	*Gabrb2*^{tm1Kwa}, *Gabrb2*^{tm1Twr}
4. *DRD2*	Encodes the D2 subtype of DA receptors, a G-protein–coupled receptor that inhibits adenylyl cyclase activity	*rs6277(C)*	Synonymous, unknown	*Drd2*^{tm1Schm}
5. *10q26.13*	Unknown	*rs17101921(A)*	Noncoding, unknown	N/A
6. *AKT1*	Encodes a serine-threonine protein kinase involved in cellular survival, signaling, and neuromodulation	*rs3803300(A)*	5′UTR, unknown	*Akt1*^{tm1Mbb}
7. *GRIN2B*	Encodes the NR2B subunit of the NMDA receptor mediating fast excitatory synaptic transmission	*rs1019385(G)*	Noncoding, unknown	*Grin2b*^{2lo}, *Tg(Camk2a-Grin2b)1Jzt*
8. *DGCR2*	Encodes a novel putative adhesion receptor protein, which could play a role in neural crest cells migration.	*rs807759(G)*	Unknown	*Dgcr2*^{tm1Ais}
9. *PLXNA2*	Encodes a plexin A family of semaphorin coreceptors mediating axonal growth	*rs1327175(C)*	Intronic, unknown	*Plxna2*^{nmf454}, *Plxna2*^{tm1Hfu}
10. *RPGRIP1L*	Encoded protein localizes to the basal body-centrosome complex or to primary cilia and centrosomes in ciliated cells	*rs9922369(A)*	Intronic, unknown	*Rpgrip1l*^{tm1Urt}
11. *TPH1*	Encodes tryptophan hydroxylase 1, which catalyzes the first and rate-limiting step in the biosynthesis of serotonin	*rs1800532(A)*	Intronic, unknown	*Tph1*^{tm1Bdr}, *Tph1*^{tm1Kry}, *Tph1*^{tm1Lex}, *Tph1*^{tm1Mlt}
12. *DRD4*	Encodes the D4 subtype of DA receptors, a G-protein–coupled receptor that inhibits adenylyl cyclase activity	*rs4646984(Long)*	5′UTR 120-bp INDEL	*Drd4*^{tm1Dkg}
13. *DAOA*	Encodes G72, a protein involved in mitochondria function	*rs3916971(C)*	Unknown	N/A
14. *11p14.1*	Unknown	*rs1602565(C)*	Unknown	N/A

Table 1. Continued

Locus	Gene Function	Top Risk Allele	Functional Effect	Related Mouse Alleles
15. *DRD1*	Encodes the D1 subtype of DA receptors, a G-protein–coupled receptor that activates adenylyl cyclase activity	*rs4532(G)*	5′UTR, unknown	*Drd1a*^{tm1Jcd}
16. *HTR2A*	Encodes the serotonin 2A receptor, a G-protein–coupled receptor that activate phospholipase C	*rs6311(A)*	Noncoding, unknown	*Htr2a*^{tm1Grch}, *Htr2a*^{tm2Grch}, *Htr2a*^{tm1Rhn}
17. *RELN*	Encodes an extracellular matrix protein controlling cell-cell interactions critical for cell positioning and neuronal migration during development	*rs7341475(G)*	Intronic, unknown	*Reln*^{rl}
18. *APOE*	Encodes an essential protein for the normal catabolism of triglyceride-rich lipoprotein constituents	*rs429358(C)* + *rs7412(C)*	Missense, alters binding to LDLR	*Tg(GFAP-APOE*4)Hol*, *Apoe*^{tm1Unc}
19. *NRG1*	Encodes a signaling protein that mediates cell-cell interactions and plays critical roles in the growth and development of multiple organ systems	*rs10503929(T)*	Missesne, unknown	*Nrg1*^{tm2Zhou}, *Nrg1*^{tm1Leth}, *Nrg1*^{tm1Lwr}
20. *IL1B*	Encodes an interleukin 1 cytokine family protein that mediates the inflammatory response, cellular proliferation, differentiation, and apoptosis	*rs16944(C)*	Noncoding, unknown	*Il1b*^{tm1Dch}, *Il1b*^{tm1Lvp}, *Il1b*^{tm1Yiw}
21. *MTHFR*	Encodes the methylenetetrahydrofolate reductase protein involved in homocysteine remethylation	*rs1801133(T)*	Missense, unknown	*Mthfr*^{tm1Rzn}
22. *COMT*	Encodes a protein involved in the degradation of catecholamine neurotransmitters	*rs4818(C)*	Synonymous, unknown	*Comt1*^{tm1Kara}, *Tg(tetO-COMT*Val)*
23. *HP*	Encodes haptoglobin, which allows degradative enzymes to gain access to hemoglobin	*HP(2)*	Reduces binding to Hgb	*Hp*^{tm1Alev}, *Hp*^{tm1Skl}
24. *DAO*	Encodes a flavoprotein enzyme that degrades the NMDA coagonist D-serine	*rs4623951(T)*	Noncoding, unknown	*Dao*^{G181R}
25. *TP53*	Encodes for the tumor suppressor, p53, involved in cell cycle arrest, apoptosis, senescence, and DNA repair	*rs1042522(C)*	Missense, unknown	Numerous
26. *ZNF804A*	Encodes a zinc finger protein of unknown function	*rs1344706(T)*	Unknown	N/A
27. *16p13.12*	Unknown	*rs7192086(T)*	Unknown	N/A
28. *DTNBP1*	Encodes a protein involved in organelle biogenesis associated with melanosomes, platelet dense granules, and lysosomes	*rs3213207(A)*	Intronic, unknown	*Dtnbp1*^{sd}
29. *OPCML*	Encodes an immunoglobulin protein that may have an accessory role in opioid receptor function	*rs3016384(C)*	Intronic, unknown	*Opcml*^{m1}
30. *RGS4*	Encodes a regulator of G-protein signaling family member, which regulates molecules that act as GTPase activating proteins.	*rs2661319(G)*	Intronic, unknown	*Rgs4*$^{tm1.1Jbr}$

[a]Data in the table are compiled from the SZGene database (www.szgene.org) (updated May 7, 2009), the Gene and SNP databases of National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/sites/entrez), and the Mouse Genome Informatics database from the Jackson Laboratory (www.informatics.jax.org) (accessed July 19, 2009). Shaded rows reflect that no animal models are available or there are no data relevant to the cognitive domains highlighted and therefore are not discussed in the main text. UTR, untranslated region; DA, dopamine; NMDA, *N*-methyl-D-aspartic acid; N/A, not applicable; bp, base pair; LDLR, low-density lipoprotein receptor; Hgb, hemoglobin; GTPase, guanosine triphosphate hydrolase.

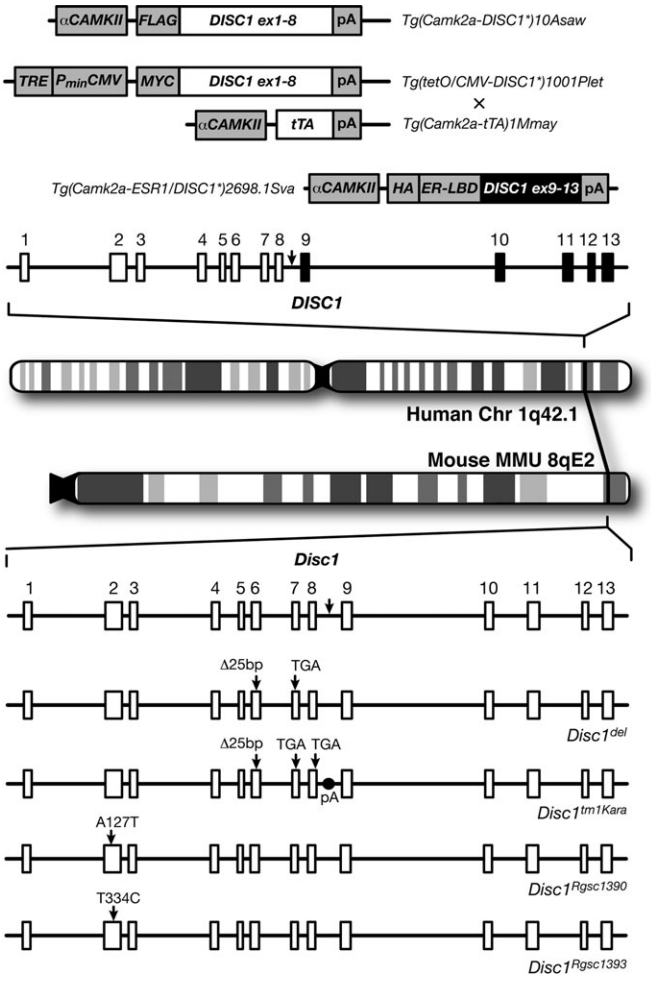

Fig. 1. Animal Models of the *DISC1* Locus. *Top*: chromosomal location and genetic structure of the human *DISC1* locus. The t(1;11) translocation break point occurs between exons 8 and 9 (arrow) with exons 9–13 (black) relocated to chromosome 11. Above it are the allele symbols and transgenic constructs based on the human *DISC1* gene used to model the functional effects of the translocation. These models interfere with endogenous mouse *Disc1* function in a dominant negative manner. *Bottom*: syntenic chromosomal location and genetic structure of the mouse *Disc1* locus and the corresponding break point location (arrow). Below it are 5 of the *Disc1* alleles so far described in mice. $Disc1^{del}$ arose from a spontaneous 25–base pair (bp) deletion within exon 6 that introduces a premature stop codon in exon 7 (TGA) of 129 and related strains of mice. $Disc1^{tm1Kara}$ was engineered to carry a premature stop codon at the end of exon 8 (TGA) followed by a polyadenylation signal in an attempt to recapitulate the translocation, but because this was created in a 129S6/SveV background the allele also carries the endogenous 25–bp deletion. $Disc1^{Rgsc1390}$ and $Disc1^{Rgsc1393}$ carry missense mutations in exon 2.

Scottish mutation (figure 1).[38] These mice carry a truncating lesion in *Disc1* that abolishes expression of the major Disc1 isoforms and, despite an artificial polyadenylation signal, causes low expression of the truncated protein indicating its potential instability under physiological conditions.[39]

22q11.2 microdeletions were the first recurrent genetic lesion unequivocally associated with increased risk for schizophrenia.[26] Carriers of these microdeletions, which occur predominantly de novo, are at inordinately high risk of developing schizophrenia.[22,23,26,27] Fortunately, the human 22q11.2 locus is conserved within the syntenic region of mouse chromosome 16 and harbors nearly all orthologs of the human genes. There are now various single-gene and multigene deletions of this locus as well as mice hemizygous for all genes within the minimal 1.5-Mb region associated with schizophrenia (figure 2; *Lgdel*, *Del(Dgcr2-Hira)1Rak*, and *Df(16)A*, *Del(Dgcr2-Hira)2Aam*).[40,41] Given the close similarity of the lesion in these mice to that occurring in humans, they afford an unprecedented opportunity for characterizing the cognitive consequences and underlying neural correlates associated with genetic risk for the disease.

Findings Across Cognitive Domains

Perception

Patients with schizophrenia show deficits even at the lowest levels of sensory function. This is evident across all sensory modalities and can detrimentally impact downstream cortical processing. Consequently, many deficits in higher order cognitive operations may result from primary sensory deficits.[42] Although this area of research has a long history in animal models,[43,44] few mutant models of putative risk genes have directly assessed perceptual disturbances.

While recognizing the widespread perceptual deficits in schizophrenia,[45] CNTRICS prioritized 2 constructs within visual perception for further clinical investigation: (1) visual gain control and (2) visual integration. The nominated tasks within these domains do not have clear rodent analogs, but CNTRICS recognized that prepulse inhibition (PPI) and mismatch negativity (MMN) might serve as a useful measures of gain control.[46]

PPI is a relatively robust preattentive assay with great translational potential that is well characterized at the neural circuit level. Its sensitivity and specificity, however, are rather low. Moreover, drugs that are not clinically effective cognitive enhancers nonetheless improve PPI suggesting that it has low discriminatory power for novel therapeutic agents. PPI in the context of mutant animal models has been recently reviewed,[47] and thus, we do not review it further here.

MMN is another preattentive measure that is well characterized and reflects early stages of auditory processing. Similar to perceptual deficits in other domains, levels of MMN are directly related to overall functional ability in patients.[48] Only one mutant strain of a "top 30" candidate gene has assessed MMN. These mice lack functional isoforms of Nrg1 due to a targeted mutation of the EGF domain ($Nrg1^{tm1Cbm}$).[49] When presented with novel auditory stimuli following a stream of familiar stimuli, $Nrg1^{+/-}$ mice do not show the characteristic negative deflection in the event-related potential indicating changes

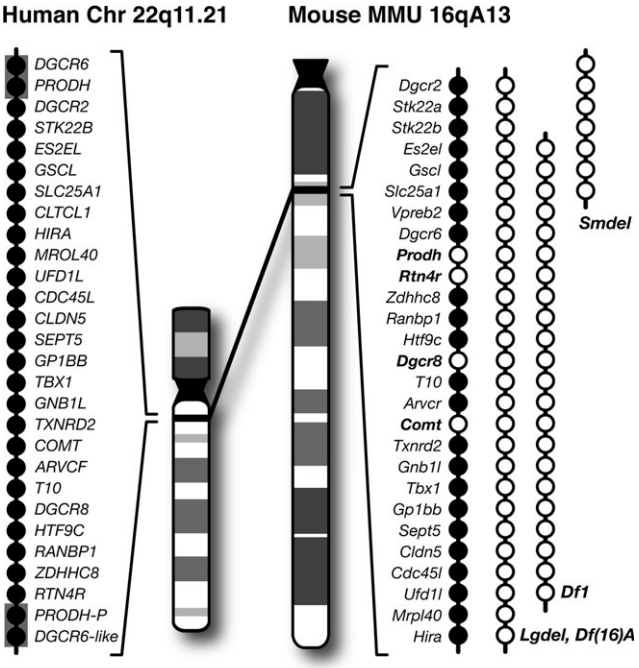

Fig. 2. Animal Models of the 22q11.2 Locus. Left: chromosomal location and genetic organization of the 22q11.2 locus. Each closed circle represents one gene. This 1.5-megabase critical region is flanked by low-copy repeat sequences (gray boxes) making it prone to nonhomologous recombination. *PRODH-P* and *DGCR6-like* are pseudogenes. Right: syntenic region of mouse chromosome 16 and the genetic organization of the corresponding orthologs. Single-gene deletion models that have been analyzed within the relevant CNTRICS cognitive domains are indicated with open circles. Various multigene deletion models that have been cognitively characterized and are discussed in the main text are also shown. The official allele symbols for the models are *Lgdel*, *Del(Dgcr2-Hira)1Ra*; *Df(16)A*, *Del(Dgcr2-Hira)2Aam*; *Df1*, *Del(16Es2el-Ufd1l)217Bld*; and *Smdel*, *Del(16Zpf520-Slc25a1)1Awb*.

in sensory integration.[50] In order to compare these findings with human studies, it will be important to know if and how the early perceptual changes in these mutants, and potentially other models, are related to higher order cognitive function.

Social and Affective Regulation

Directly relating social behavior in nonhuman animals to human social cognition is inherently problematic. Like for other domain-specific operations, it is uncertain what gives social cognition its uniqueness, whether it is specialization at the level of information processing or information selectivity.[51] In fact, in humans, developmentally early changes in perceptual biases[52] and faulty perceptual processing in the adult[53,54] can be responsible for higher order social cognitive dysfunction making directly modeling social deficits in animals difficult. CNTRICS chose to focus on 2 constructs within social cognition: (1) emotional identification and (2) emotional responding.[55] While there are rodent social interaction tasks that may, at face value, seem similar to these constructs, whether the relevant underlying mechanisms are the same is unknown. Nevertheless, social behavior in mutant animal models is commonly assessed and is discussed further in the accompanying review of negative symptoms.

Executive Control

Executive control encompasses an array of higher order cognitive processes. It is broadly defined as the ability to coordinate thoughts and actions in accordance with changing external demands or internal goals.[56] Achieving this requires dynamically updating, manipulating, selecting, retrieving, and integrating information across sensory and motor modalities. Executive control is thus a domain-general process influencing various other cognitive operations. Deficits in executive control can potentially explain patients' poor performance in a variety of cognitive tasks including those measuring attention,[57] long-term memory (LTM),[58] and WM.[59] CNTRICS selected 2 constructs within executive control for further clinical development: (1) rule generation and selection and (2) dynamic adjustments in control.[60]

For rule generation and selection, CNTRICS nominated an intra/extradimensional set-shifting task that has been recently adapted for use in rodents and is based on the Wisconsin card sorting test. Mice lacking dopamine (DA) D2 receptors ($Drd2^{tm1Schm}$) have selective deficits in this task. Under some conditions, these mice show deficits in early discrimination stages but not later rule abstraction or set-shifting stages.[61] Using a different testing procedure that produces the expected performance profile in control animals, mutant mice exhibit selective deficits during the rule reversal phase.[62] This later result is consistent with other work showing that D2 knockout (KO) mice have robust reversal learning deficits.[63,64] In contrast, transgenic mice overexpressing the high-activity, human catechol-O-methyl transferase *(COMT) Val* allele (*Tg(tetO –COMT-Val) × Tg(Eno2tTA)*) seem to show selective impairments in the set-shifting phase of this task and perform normally at all other stages.[65] Interestingly, while patient performance in this task varies according to clinical status, the most consistent impairments are during the reversal and set-shifting phases.[66]

Although there is a rodent analog to the task recommended by CNTRICS for dynamic adjustments in control, there is, as of yet, no data for mutant animal models. Other findings that may be relevant to executive control deficits in schizophrenia are from tasks looking at other forms of behavioral flexibility. In an operant-based reversal learning task and an inhibitory control task, mice carrying a spontaneous null allele of the reelin gene ($Reln^{rl}$, reeler mice) learn and perform these tasks normally.[67] For the related construct of impulsivity, as measured with a delayed discounting and a go/no-go task, mice lacking D4 receptors ($Drd4^{tm1Dkg}$) also perform normally.[68] Given

the central role executive control deficits may play in schizophrenia in particular and in psychiatric disorders in general, the further development and use of tasks measuring these various cognitive processes are critically needed to behaviorally characterize mutant models.

Control of Attention

As for many psychological terms, the precise meaning of attention varies and spans basic bottom-up, exogenously driven, and top-down, endogenously driven, modulation of processing within other cognitive or perceptual domains. Attention is closely related to and often intimately involved in executive control and WM.[57] CNTRICS focused on the single construct of attentional control because other basic forms of attention seem to be intact in patients. Although there are several rodent paradigms for measuring attentional control,[69,70] there are no findings from models based on the "top 30" gene list or from models of the *DISC1* or 22q11 rare alleles. Considering the central importance of attentional function to cognition and its impairment in schizophrenia, there is an obvious dearth of studies measuring attention in mutant models of candidate genes.

Long-term Memory

Learning and memory deficits are well known in schizophrenia and are one of the strongest predictors of functional outcome. As mentioned earlier, executive control deficits may account for many aspects of memory impairments in patients including LTM deficits.[71] CNTRICS focused on 3 constructs within learning and memory for further development: (1) relational encoding and retrieval, (2) item encoding and retrieval, and (3) reinforcement learning.[58] There are several animal behavioral paradigms for each of these constructs, although there are few direct analogs to the specific tests recommended by CNTRICS. We nonetheless summarize some findings in mutant animals that may be relevant to learning and memory deficits in schizophrenia.

There are many classical learning and memory paradigms that are widely used to characterize genetically modified mice. As such, there is a rich literature for mutant models with potential relevance to schizophrenia and other psychiatric disorders. Transgenic mice overexpressing the *N*-methyl-D-aspartic acid receptor NR2B subunit (*Tg(Camk2a-Grin2b)1Jzt*), encoded by the *Grin2B* gene, show enhancements in novel object recognition, conditioned fear and extinction, and spatial reference memory in the Morris water maze (MWM).[72] Not surprisingly, postnatal deletion of NR2B from principle forebrain neurons (*Grin2b*^{2lox} × *Tg(Camk2a-cre)1Gsc*) produces not only widespread deficits in learning and memory including impaired spatial reference memory in the MWM and elevated Y-maze but also deficits in spatial navigation and visual discrimination.[73] Homozygous DA D1A receptor KO mice (*Drd1a*^{tm1Jcd}) are consistently impaired in the spatial reference memory version of the MWM, and, while they learn conditioned fear normally, they retain fear memory for longer and show delayed extinction.[74–76] Reeler mice show normal acquisition and retention of spatial reference memory in the MWM but show less consistent retention of conditioned fear.[67,77] *Sdy* mice (*Dtnbp1*^{sdy}) carry a spontaneous null mutation of *Dtnbp1*, the dysbindin gene, and have impaired spatial reference memory and object recognition memory but enhanced conditioned fear.[78–80] In contrast, mice carrying a spontaneous null mutation of DAO (*Dao*^{G181R}) perform better in the spatial reference memory version of the MWM.[81] Finally, heterozygous *Nrg1* mutant animals (*Nrg1*^{tm1Cbm}) have impaired conditioned fear but normal object recognition memory.[50]

Only a few of the mutant *DISC1* mice so far described have been assessed in LTM tests. Transgenic *DISC1* mice (*Tg(Camk2a-DISC1)10Asaw*) have normal spatial reference memory in the MWM,[34] but double transgenic (*Tg(tetO/CMV-DISC1*)1001Plet* × *Tg(Camk2a-tTA)1Mmay*) female mice are impaired in this same task.[35] Mice carrying the truncated *Disc1* allele (*Disc1*^{tm1Kara}) have intact spatial reference memory in the MWM and also express normal conditioned fear and object recognition memory.[39] Thus, despite varying genetic approaches, *DISC1* mutant mice seem to have essentially normal LTM using traditional learning and memory paradigms.

LTM function in models of the 22q11.2 microdeletion are just beginning to be characterized despite the prominent learning and memory deficits in human deletion carriers. Mice hemizygous for 18 orthologs within the 1.5-Mb region associated with schizophrenia risk (figure 2, *Df1*) have impaired conditioned fear memory,[82] but mice hemizygous for just 7 of the orthologs do not (figure 2, *Smdel*).[83] Depending on the exact behavioral protocol, mice with a hemizygous deletion spanning all the orthologous genes within the 1.5-Mb region either exhibit (*Df(16)A*)[41] or do not exhibit (*Lgdel*)[40] impaired conditioned fear (figure 2).

Importantly, the tasks mentioned above do not directly assess the aspects of executive control that may contribute to LTM impairments in patients. Additionally, it is likely that the neural mechanisms underlying the executive control of LTM differ from those underlying the actual encoding and consolidation of memories. Although some models show clear LTM deficits, other models such as *DISC1* mutants do not. It remains to be seen how these mutant mice and others perform in tasks more closely measuring the LTM constructs identified by CNTRICS.

Working Memory

WM is probably the best characterized cognitive domain in those with schizophrenia. It is also a constantly

evolving construct in cognitive neuroscience making it extremely difficult to model in animals.[84,85] Modern cognitive neuroscience definitions of WM emphasize executive control as a central feature and disagree mostly about the structure and localization of the memory stores or "slave systems."[86] Here, we distinguish WM from simple short-term memory (STM). While STM is a limited capacity system for transiently holding readily accessible information, WM is the manipulation and use of this information in accordance with internal goals. Thus, WM can be understood as the specific implementation of executive control over STM. In fact, CNTRICS has prioritized the translation of 2 executive components of WM: (1) goal maintenance and (2) interference control.[87] Thus, in order to be clinically meaningful, it is critical that studies of mutant and other types of models examine the executive components of WM.

Unfortunately, many commonly used rodent tasks lack explicit executive demands and thus likely confound STM and WM. These demands for executive control recruit various processes including the manipulation and updating of information held in STM in addition to goal maintenance and interference resolution. Importantly, for a given task, animals, including humans, may use several cognitive processes in conjunction with different memory systems. This can make a behavioral test an imprecise measure of any particular psychological construct like WM. The exact load, however, placed on executive control, and thus WM, can be influenced by the number of trials per day, the intertrial interval, and the delay across which information is held active in memory. These parameters vary greatly across tasks, and while spontaneous alternation tasks likely measure simple STM, the extent that delayed alternation and delayed nonmatch to place (DNMTP) tasks measure WM depends on the exact task parameters influencing executive control as outlined above. It should be noted that the fact that these latter tasks may depend on the integrity of functionally homologous neural regions and are similarly neuromodulated as human WM tasks[88] suggests that they may tap into related cognitive and physiological processes. Nevertheless, the need to model executive processes explicitly should not be overlooked because they largely determine WM capacity in general[89] and disproportionately contribute to WM deficits in schizophrenia patients.[90]

Given that WM deficits have long played a central role in the neuropsychology of schizophrenia, many mutant models have been tested in putative WM tasks, although, for reasons mentioned above, the extent to which this is true depends on specific task parameters. Conditional NR2B KO mice (*Grin2b*^{2lox} × *Tg(Camk2a-cre)1Gsc*) are severely impaired and show chance performance in a simple spontaneous alternation task[73] as do mice lacking *Rgs4* (*Rgs4*$^{tm1.1Jbr}$).[91] In contrast, mice heterozygous for a deletion of the transmembrane (*Nrg1*^{tm2Zhou}) or immunoglobulin-like domain (*Nrg1*^{tm1Leth}) of *Nrg1* perform normally in this task.[92,93] However, mice with decreased expression of the type III *Nrg1* isoform (*Nrg1*^{tm1Lwr}) are impaired in a delayed alternation task that included nonrandomly introduced delay periods and extensive training.[94] *Akt1*-deficient mice (*Akt1*^{tm1Mbb}) are impaired under various pharmacological challenges in a delayed alternation task with only a single delay period.[95] Both D2 KO mice and *COMT-Val* transgenic mice show delay-dependent impairments during a delayed alternation and DNMTP task, respectively.[65,96] Conditional NR2B KO mice are impaired in a DNMTP task with a single delay period and with relatively long intertrial intervals.[73] Transgenic *ApoE* learn a delayed spatial win-shift task more slowly than wild-type controls[97] and *Sdy* mice learn a DNMTP task more slowly than wild-type controls but then perform normally when the delay period is lengthened in an unpredictable manner.[67] Finally, reeler mice perform normally in an operant-based delayed *matching* to place task with short intertrial intervals and parametrically varied delay periods.[67]

It is possible that some *DISC1* mutant mice may have actual deficits in WM attributable to deficits in executive control in the context of normal STM. Transgenic *DISC1* mice (*Tg(Camk2a-DISC1)10Asaw*) perform normally in a spontaneous alternation task,[34] while mice transiently expressing the truncated C-terminal *DISC1* protein (*Tg(Camk2a-ESR1/DISC1*)2698.1Sva*) have delay-dependent impairments in a DNMTP task.[36] Mutant mice carrying missense mutations in *Disc1* (*Disc1*^{Rgsc1390} and *Disc1*^{Rgsc1393}) also show deficits in a DNMTP task, but they are impaired only at the briefest delay periods where STM load is the lowest suggesting that nonmnemonic processes may be at play. Interestingly, mice with the targeted disruption of *Disc1* (*Disc1*^{tm1Kara}) are not impaired in STM tasks but display deficits in 2 independent DNMTP tasks with pseudorandomly introduced delay periods.[38,39] In these studies, one task is prone to proactive interference due to short intertrial intervals, and the other task requires the successful updating of information in order to concurrently remember 2 independent spatial locations. Thus, both implementations of these DNMTP tasks likely require some type of executive control. It is important to note, however, that these studies, like others, did not explicitly manipulate variables associated with executive control.

Mice hemizygous for the orthologous 22q11.2 deletion also have deficits in delayed response tasks in addition to the learning and memory deficits described above. These mice (*Del(Dgcr2-Hira)2Aam*) are impaired in the acquisition of a delayed alternation T-maze task but perform normally once the task is acquired and delay periods are increased.[41] Interestingly, this deficit may arise in part from impaired microRNA production due to deficiency of one gene within the deletion, *Dgcr8*, a microRNA processor; heterozygous deletion of *Dgcr8* alone (*Dgcr8*$^{Gt(xH157)Byg}$) similarly impairs acquisition of

a DNMTP task.[41] In contrast, haploinsufficiency of other examined genes within the deletion on their own do not cause robust deficits. Heterozygous and homozygous mice lacking the Nogo receptor (*Rtn4r*^{tm1Gogo}) perform normally in a delayed alternation task,[98] but homozygous animals of a different KO strain (*Rtn4r*^{tm1Stmr}) are impaired in a delayed alternation task using a longer training schedule and with no manipulation of memory delay periods.[99] This study, however, did not assess performance of heterozygous animals, and these are the most relevant to understanding how haploinsufficiency of individual genes contribute to the entire microdeletion syndrome. Heterozygous *Comt* KO mice show improvements in a DNMTP task, albeit at delays outside the range of immediate STM.[65] Mice carrying a hypomorphic allele of *Prodh* (*Prodh*^{m1Kara}) acquire a delayed alternation task as well as controls and perform normally when the memory delay is pseudorandomly lengthened.[100] In *Prodh* mutant mice, however, there is an epistatic interaction between *Prodh* and *Comt*, such that *Prodh* deficiency causes a compensatory increase in Comt expression. Pharmacologically inhibiting this genetic feedback loop unmasks underlying DA dysfunction and reveals delayed alternation deficits in *Prodh* mutant mice using a single delay period.[100] Taken together, this suggests that cognitive deficits associated with the 22q11.2 microdeletion result from the combined effects of genes acting individually and interactively.

Overall, it is clear that in order to better understand the neural and psychological constructs related to WM dysfunction and genetic risk for schizophrenia, novel rodent WM tasks are needed that parametrically vary the demand for executive control and thus isolate and specifically measure executive processes.

Cognition and Genetic Liability to Psychosis

Cognitive deficits are common to psychiatric disorders, but their exact relationship to the clinical syndromes is unclear. They are prominent in psychotic disorders, but psychosis is not a feature of all disorders with cognitive deficits, and within individuals, there is little relationship between cognition and psychotic symptoms. There is strong evidence that many cognitive deficits are mediated by the same genetic risk factors that lead to the overt disease. First-degree, unaffected relatives of those with schizophrenia, bipolar disorder, attention deficit/hyperactivity disorder, obsessive compulsive disorder, and autism, among others, show cognitive deficits, especially in executive control.[12,101–103] This implies that genetic variants generally influencing cognition may also influence risk for psychiatric disorders.

The question remains, however, whether cognitive deficits lie along a disease pathway from genetic risk to clinical syndrome or arise independently due to genetic pleiotropy. Although cognitive deficits are common among psychiatric disorders, it is unclear if these are due to shared genetic liability across disorders. Given our limited understanding of the neural bases of cognitive processes and the exact nature of cognitive deficits across diagnostic groups, it is unknown whether deficits within a given domain, although superficially similar across different syndromes, result from the same abnormal physiological processes. The study of the mutant models reviewed above afford the opportunity to identify whether deficits within a cognitive domain converge merely at the behavioral level or whether there are common underlying neural correlates, and if so, how this may be related to diverse clinical phenotypes.

Conclusions

The focus on cognitive function in schizophrenia and other psychiatric disorders has grown tremendously. This is reflected by the recent establishment of both the MATRICS and CNTRICS programs and the subsequent basic science gap that animal models now need to fill. Although we have been critical of many current cognitive tasks used in animals, we do not suggest that all behavioral paradigms will have to necessarily mirror human tasks to be clinically relevant. A behavioral task may be extremely useful, regardless of its resemblance to any clinical test, if it is sensitive to and specific for some underlying disease process and predicts the clinical efficacy of therapeutic interventions. We speculate, however, that highly precise tools for probing cognition will be indispensable for identifying relevant disease processes. The fact that schizophrenia patients have executive control deficits across cognitive domains,[104] are impaired even at the lowest levels of sensory perception,[42] and have the most severe deficits in basic processing speed[105] suggests a fundamental difference in some elementary and ubiquitous mechanism of cortical computation. Thus, carefully designed tasks for animal models are needed that dissect out and identify specific neural mechanisms underlying cognitive dysfunction. Ultimately, the integration of new cognitive neuroscience tools with those of new mutant animal models has the potential to clarify the relationships among genetic variation, cognition, and the psychopathology observed in those afflicted with mental illnesses.

Funding

National Institute of Mental Health (R01 MH077235, MH080234-01A1 to J.A.G.) National Alliance for Research on Schizophrenia and Depression (young investigator award); Simons Foundation.

Acknowledgments

We thank David Jentsch and Rebecca Levy for helpful comments and critical insights on an earlier draft of

the manuscript. We apologize to our colleagues whose work we did not cite due to space limitations.

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