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Primate models of schizophrenia: future possibilities

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Abstract

Schizophrenia is a disorder of the association cortices, with especially prominent structural and functional deficiencies in the dorsolateral prefrontal cortex (PFC). True dorsolateral PFC is found only in higher primates, and is characterized by highly elaborate pyramidal cells with extensive recurrent connections. The development of the primate PFC also involves distinct developmental and genetic pathways. Thus, primate models may be particularly important in determining the functional impact of genetic changes in patients with schizophrenia. Genes involved with pyramidal cell network connectivity may be especially important to study in primates, as their effects may be magnified in the extensively connected primate neurons. Adeno-associated virus technology appears particularly promising for studying the impact of genetic insults on the structure and function of the primate association cortex.

Keywords

Primate; prefrontal cortex; DISC1; evolution; working memory

Schizophrenia is a profound cognitive disorder with established neuropathological insults to the high-order association cortices that subserve thought. As the association cortices expand tremendously from rodents to monkeys to humans, nonhuman primate (NHP) models may be particularly important for understanding the impact of genetic insults on higher cortical circuitry, and their relevance to symptoms of schizophrenia. Recent advances in viral technologies may be especially useful in determining how genetic variants associated with schizophrenia alter higher-order cortical structure and function.

Schizophrenia as an affliction of the association cortices

Schizophrenia is characterized by fundamental cognitive deficits that significantly impede daily life and social relationships (Barch, 2005). Neuropathological and imaging studies have shown deficits in the structural integrity and functional activity of the frontal and temporal association cortices in patients with schizophrenia, particularly in the dorsolateral prefrontal cortex (PFC) (Lewis and Gonzalez-Burgos, 2006; Ragland et al., 2007). Neuropathological studies have revealed loss of dendritic spines (Selemon et al., 1995; Glantz and Lewis, 2000) from the layer III pyramidal cells in dorsolateral PFC that form the recurrent excitatory networks which subserve representational knowledge, our “mental sketchpad” (Goldman-Rakic, 1995).

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Conflicts of interest

Dr. Arnsten and Yale University have a license agreement with Shire Pharmaceuticals for the development of guanfacine for the treatment of ADHD. Dr Arnsten receives research funding, and consults, speaks, and teaches for Shire as well.

Recent studies suggest that many of the so-called positive symptoms of schizophrenia such as hallucinations and delusions likely involve disruption of association cortical processing as well. For example, auditory hallucinations may arise from impaired communication between the PFC and temporal association cortices involved in language production and interpretation; specifically, weakened corollary discharge from the PFC to Wernicke's area to indicate that inner speech is self-generated (Ford et al., 2002). This idea has received experimental support from studies that used transcranial magnetic stimulation to weaken Wernicke's area that found a reduction in auditory hallucinations in patients with schizophrenia (Hoffman et al., 2005). Disruptions in PFC and temporal association cortices have also been associated with formal thought disorder, e.g. Perlstein et al. (2001). Most recently, the rostral dorsomedial PFC has been linked to reality testing and psychosis (Simons et al., 2008), while disturbances in the right dorsolateral PFC underlie delusional thinking (Corlett et al., 2007; Sun et al., 2008). Thus, disruptions in the higher association cortices are key to schizophrenia symptomatology. Altered cortical processing may be magnified by excessive dopamine (DA) D2 receptor signaling in the caudate, while medications with DA D2 blocking properties may diminish this amplification, but not solve the underlying cause of the illness. Thus, understanding genetic impacts on cortical circuitry is of highest priority in revealing the underlying etiology of schizophrenia.

The vast evolution of the association cortices from rodents to primates

The great, areal expansion of the association cortices

The association cortices expand greatly from rodents to monkeys to humans. As shown in Fig. 1, the cortex expands 100 times from mouse to monkey, and 1000 times from mouse to human, with the vast majority of this increase comprised of association cortex (Rakic, 2009). In contrast, the hippocampus has become relatively smaller in primates, as rodents and primates have taken differing and distant evolutionary paths (Fig. 1D). Indeed, there are types of neurons that are unique to primate and/or human cortex, and developmental trajectories unique to primate cortices (Rakic, 2009).

The development of the immensely convoluted human cortex begins in the second trimester of pregnancy, and is mediated by extraordinarily complex, yet precise, molecular events (for a recent review, see Rakic (2009)). Recent whole-genome, exon-level expression characterization of the developing human brain has revealed molecules that are differentially expressed in the developing primate and/or human association cortices (Johnson et al., 2009). The wealth of genes identified by this and similar studies will likely guide many future explorations of molecules mediating cortical development. Importantly, differential gene expression was prevalent even *within* the developing PFC.

As can be seen in Figs. 1 and 2, the PFC expands tremendously from rodents to primates, even on the medial surface (Fig. 2) where rodent PFC is concentrated. The region of PFC most afflicted in schizophrenia — the granular dorsolateral PFC — does not exist in rodents, or even in some lower primates (Preuss, 1995). Instead, the medial PFC in rodents shares greatest anatomical and functional homology with some medial PFC areas in monkey (Preuss, 1995).

The greatly increased complexity of primate PFC neurons

The pyramidal cells of the PFC also have an expanded dendritic architecture to support their numerous connections, and have about 70% more spines than the pyramidal cells of the primary sensory or motor cortices (Jacobs et al., 2001). Elston et al. (2006) have written that “the highly branched, spinous neurons in the human granular PFC may be a key component of human intelligence”. Similarly, the pyramidal neurons in monkey dorsolateral PFC, which subserve recurrent network connections, have extensive dendritic arborization, with especially elaborate

basal dendrites (e.g. Fig. 3). Careful measurements show that the basal dendrites of layer III pyramidal cells in monkey dorsolateral PFC are more than 3 times the length, and have more than 6 times the complexity of basal dendrites of layer III pyramidal cells in rat medial PFC (Radley et al., 2005; Hao et al., 2007). Thus, developmental and/or genetic insults to synaptic connections may have particular impact on the function of dorsolateral PFC, and other high-order association cortex with elaborated dendritic complexity.

Pyramidal cell network connections as a key site of vulnerability in schizophrenia

Representational knowledge — our “mental sketchpad” — arises from recurrent excitation between PFC pyramidal neurons whose activity is sculpted by GABAergic interneurons (Goldman-Rakic, 1995). The interconnection of precise microcircuits is a fragile process, and many of the genetic alterations associated with schizophrenia appear to impact these network connections. These include genes key to the development of dendritic architecture (Lewis and Levitt, 2002), but also gene products needed for appropriate activity of the established circuit. For example, physiological studies in monkeys indicate that recurrent excitation between PFC pyramidal cells depends on *N*-methyl-D aspartate (NMDA) receptors (M. Wang and A. Arnsten, unpublished), and several genes associated with NMDA transmission have been linked to schizophrenia (Coyle et al., 2003). Disrupted In Schizophrenia (DISC1) and nicotinic $\alpha 7$ receptors have also been localized in PFC spines, and both have strong links to schizophrenia (Kirkpatrick et al., 2006; Duffy et al., 2009). DISC1 is thought to regulate cAMP levels, by activating PDE4 under conditions of high cAMP concentration (Millar et al., 2007). We have shown that excessive cAMP levels, e.g. during stress exposure, cause PFC network disconnection through opening of ion channels on dendritic spines (Wang et al., 2007). In this context it is of interest that chronic stress exposure leads to spine loss in the PFC (Radley et al., 2005), especially in layer III, the layer harboring the recurrent microcircuits (Goldman-Rakic, 1995), that are most afflicted in schizophrenia (Glantz and Lewis, 2000). Future studies will uncover how genetic insults lead to the impaired development and/or degeneration of PFC microcircuitry.

The need for NHP models

Molecules involved in the development, maintenance, and physiology of dendrites and spines may have an especially large impact in primates compared to lower species, and have more effect on the association cortices than on sensorimotor functions. Thus, it will be important to study the impact of genetic alterations linked to mental illness in primate models. Indeed, evidence shows evolution of the molecules as well as the cortical circuitry, e.g. DISC1 is highly conserved between humans and monkeys but differs markedly from rodents (Bord et al., 2006). However, as transgenic approaches do not seem feasible in monkeys, alternative technologies will be needed. A promising direction for primate work is RNA interference through viral vectors.

Advent of viral technology

Highly efficient gene discovery analyses are revealing gene expression changes associated with PFC function and/or schizophrenia. The challenge that remains is how to most efficiently and effectively manipulate these genes to assess functional consequences in animal models. There are a number of approaches for manipulating gene expression including both transgenic and viral methods. Viral methods allow for efficient testing of gene function with spatial (e.g. specific brain region) and temporal (e.g. during development or in the adult) control. In the case of the PFC and schizophrenia, viral approaches offer the advantage of being effective across species, including NHPs that cannot be manipulated via transgenesis. Viral vectors have been long used to overexpress gene products in animal models, often with the goal of being applied as a gene therapy (Kapli et al., 1994). More recently, the vectors have been used to

create genetic loss of function, or gene knockdown, models in animals. In this approach, the vectors are constructed to express short-hairpin RNA (shRNA) that targets specific genes, and then introduced to specific brain regions via stereotaxic surgery (Hommel et al., 2003). The shRNAs act to reduce mRNA and protein levels via RNA interference, or RNAi (Mello and Conte, 2004). RNAi allows for unprecedented control over specific gene expression. Importantly, RNAi can be used to target specific allelic variants or multiple genes at one time, making it amenable for mimicking human allelic states or evaluating effect of multiple mutations.

The utility of AAV vectors in modeling schizophrenia susceptibility

Understanding the pathophysiology of genetic polymorphisms that effect risk for psychiatric disease is challenging. Although simple model systems play an important role (Reinke and White, 2002; Davis, 2004), psychiatric disorders such as schizophrenia appear to involve complex changes in higher brain circuits (Lewis and Sweet, 2009), necessitating the study of higher mammalian species and NHPs in particular. Unfortunately, NHPs are not easily subject to genetic investigation due to a long generation time and difficulties with the manipulation of NHP embryos.

One technology that circumvents many of these difficulties is the use of recombinant viral vectors, adeno-associated virus (AAV) vectors (Aucoin et al., 2008; Buning et al., 2008). AAV is a single-stranded DNA parvovirus that efficiently targets dividing as well as nondividing cells. The genome consists of two inverted terminal repeats (ITRs) with a *rep* (replication related genes) and *cap* (capsid genes) open reading frame in between and it requires adenoviral genes for replication. The virus is limited to packaging genomes of about 4–5 kb in size. Because of the availability of systems with *rep*, *cap*, and adenoviral genes in *trans* and the fact that the virus is replication defective, the system is safe for laboratory personnel (ibid). AAV vectors have been successfully used in a variety of mammalian species from mice to humans, including NHPs, and can target a variety of cell types (see Table 1, Online Supplement).

A growing number of AAV serotypes have been isolated and characterized, and *cap* genes from one can be combined with *rep* genes from another to make “pseudotyped” viruses with altered properties (Grimm and Kay, 2003; Wu et al., 2006). Table 1 (online) summarizes the properties of various AAV viruses for work in CNS tissue. In addition, recombinant capsid genes have been generated (Girod et al., 1999; Shi et al., 2001; Maheshri et al., 2006; Koerber et al., 2007).

NHP species are a valuable resource and ensuring their safety is very important. AAV2 has been found to be an excellent vector for human gene therapy, and AAV9 also seems to be quite safe, but certain serotypes seem particularly prone to eliciting a strong host immune response, including AAV7 and AAV8 (Broekman et al., 2006; Klein et al., 2006; Howard et al., 2008). Immune reactivity toward the virus may limit the expression of the virus (Mingozzi and High, 2007; Zaiss and Muruve, 2008), and excess gene expression can lead to toxicity as described for AAV8 (Broekman et al., 2006; Klein et al., 2006). The recent development of neuronal cell lines from NHPs (Yasumoto et al., 2008) allows for in vitro testing prior to intracerebral injection.

AAV can mediate strong expression for very long periods of time although this is dependent on the promoter, AAV serotype, and host factors. AAV has been found to express up to 12 months or more after injection (Lo et al., 1999; Feng et al., 2004) based on rodent studies. Important advances in the efficiency of production and purification have been described (Aucoin et al., 2008) and large-scale production as is required for work in NHPs is therefore feasible.

Relevance to DISC1 function

DISC1 has emerged as one of the most important schizophrenia susceptibility genes. DISC1 was initially implicated in risk for schizophrenia when a Scottish family was identified with a translocation between chromosome 1 and chromosome 11 leading to a truncation of the DISC1 gene, reduced DISC1 expression, and strong linkage to schizophrenia and other serious mental illness (Wilson-Annan et al., 1997; Millar et al., 2001; Porteous and Millar, 2006). Single nucleotide polymorphisms in DISC1 were later found to be associated with schizophrenia but with much lower penetrance (Porteous et al., 2006). DISC1 interacts with a great many proteins including NDEL1 and PDE4B, and cAMP regulates some of these associations (Brandon, 2007). DISC1 shows very high conservation between human and rhesus monkey relative to rodent species (Bord et al., 2006), consistent with the need to study NHPs.

One important question with regard to DISC1 is whether the effects of polymorphisms depend on specific developmental periods. Research on children at high risk for schizophrenia has revealed that structural brain changes become evident during childhood and symptoms generally begin to develop in the later teen years (Sporn et al., 2003; Rapoport et al., 2005; Nugent et al., 2007; Arango et al., 2008). AAV expressing shRNAs against DISC1 could be used to model DISC1 loss of function at particular developmental time points to determine the developmental periods that depend most critically on DISC1 function.

DISC1 is ubiquitously expressed in brain tissue (Ma et al., 2002) (<http://mouse.brain-map.org>) as well as in certain peripheral tissues such as lymphocytes, macrophages, liver, and colonic epithelium (<http://www.ncbi.nlm.nih.gov/sites/entrez?db=geo>). Because AAV can be readily targeted to any brain region or peripheral tissue of interest, the technology allows the locus of DISC1 effects on behavioral function to be determined.

Recent work has determined that DISC1 undergoes extensive alternative splicing (Ma et al., 2002) (<http://genome.ucsc.edu/>). The consequence of this molecular diversity is currently not known. AAV technology can readily be used to over-express particular DISC1 isoforms to allow their function to be determined. In addition, AAV technology could be used to express shRNA constructs that target specific DISC1 isoforms to determine which isoforms are most important for proper nervous system development and function.

Disadvantages vs. advantages of NHP model

Although NHP models will likely play a key role in elucidating the impact of genetic insults to higher cortical function, they have many serious disadvantages. NHP research is very expensive, tedious, and requires intensive regulation to maintain the highest ethical standards. It also proceeds very slowly, e.g. requiring 1–2 years to train monkeys to perform tasks required for physiological analyses. Thus, NHP research is not feasible for initial experimentation, and rodents will remain essential for the development of viral technologies or other methods that can be applied to NHP brain.

However, NHP models may be particularly important when weak or negative results are observed in rodent models. A genetic change may have a large impact on complex cortical circuitry in primates, but be scarcely evident in the simpler rodent cortex. Thus, we should always be cautious about negative results in rodent models, and encourage further research in more elaborate models when warranted. NHP models using irradiation (Selemon et al., 2005) or chronic amphetamine exposure (Selemon et al., 2007) have already provided insights regarding circuit changes, and AAV technology promises to further our understanding of genetic insults on PFC structure and function.

Summary

As schizophrenia is a disorder of the association cortices, primate models will be important for understanding the impact of genetic insults on the elaborate neuronal architecture and cortical circuitry distinct to the primate brain. The advent of AAV technology provides the opportunity to study genetic changes in primate brain, and will serve as an important bridge between rodent models and pathological profiles in patients, particularly when there have been negative findings in rodent models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supporting Information

Supplementary data associated with this article can be found in the online version at doi:
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Fig. 1.

Cerebral hemispheres of the mouse (A), macaque monkey (B), and human (C) drawn by Pasko Rakic at approximately the same scale to convey the overall difference in size and elaboration. The pink overlay indicates the area of the PFC that has no counterpart in mouse. The cross sections of the cerebral hemispheres of same species (A', B', C') illustrate the relative small increase in the thickness of the neocortex compared to a large difference in surface of approximately 1:100:1000 X in mouse, macaque monkey, and human, respectively. (D) The timescale of phylogenetic divergence of *Mus musculus*, *Macaca mulatta*, and *Homo sapiens* based on DNA sequencing data. Modified from Rakic (2009); figure courtesy of Dr Pasko Rakic, Department of Neurobiology, Yale Medical School.

Fig. 2. A midsagittal view of the mouse and the monkey brain, with the medial PFC highlighted in red. The medial PFC in rodents is considered to be homologous to the medial PFC in primates, although the primate medial PFC is greatly expanded. Figure courtesy of Dr Nenad Sestan, Department of Neurobiology, Yale Medical School.

Fig. 3.

The architecture of pyramidal cells greatly expands from rodents to primates. The basal dendrites of layer II/III pyramidal cells from rat prelimbic medial PFC (A) are much less extensive than the basal dendrites of dorsolateral PFC (area 46) pyramidal cells in monkeys (B). Neuron A is from Radley et al. (2005); Neuron B is from Hao et al. (2007). Figure courtesy of Dr John Morrison, Mt. Sinai School of Medicine.