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PERSPECTIVE

Modeling psychiatric disorders for developing effective treatments

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Recent advances in identifying risk-associated genes have provided unprecedented opportunities for developing animal models for psychiatric disease research with the goal of attaining translational utility to ultimately develop novel treatments. However, at this early stage, successful translation has yet to be achieved. Here we review recent advances in modeling psychiatric disease, discuss the utility and limitations of animal models, and emphasize the importance of shifting from behavioral analysis to identifying neurophysiological abnormalities, which are likely to be more conserved across species and thus may increase translatability. Looking forward, we envision that preclinical research will align with clinical research to build a common framework of comparable neurobiological abnormalities and to help form subgroups of patients on the basis of similar pathophysiology. Experimental neuroscience can then use animal models to discover mechanisms underlying distinct abnormalities and develop strategies for effective treatments.

According to the latest US National Institute for Mental Health (NIMH) estimates from 2006, more than three times as many people in the US paid expenses for care related to psychiatric disorders as compared to those requiring cancer treatments (cost statistics on http://www.nimh.nih.gov/index.shtml). Strikingly, most of the drug treatments these patients receive were discovered serendipitously decades ago and are often unspecific and ineffective. The current outlook for developing novel compounds is also bleak, given consistently lower clinical approval success rates of central nervous system (CNS)-related compounds compared to their non-CNS counterparts (**Fig. 1**), as well as a general lack of mechanistic understanding that indicates no clear path to success. Consequently, pharmaceutical companies have drastically reduced R&D expenditures related to psychiatric disorders. This is in stark contrast to a comparatively growing number of treatments that are being developed and approved in the US for other non-CNS diseases with increasingly understood pathophysiological mechanisms, such as neoplastic diseases (**Fig. 1**).

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To set the stage for a similar development in psychiatric disease research, we must gain a better understanding of the pathophysiology of these disorders, including improving our understanding of the heterogeneity of the disorders. First, we must advance our knowledge regarding disease etiology. Because most psychiatric disorders are highly heritable, identifying genetic factors conveying risk is a crucial step. Current large-scale genetic studies are already taking this step by discovering numerous risk-associated genes for various psychiatric diseases[1–5]. Second, owing to a lack of access to brain tissue *in vivo*, we must use model systems to investigate neurophysiological abnormalities that may be caused by genetic variants and mutations. Although no model systems will ever perfectly phenocopy human disease, we can use cellular models for the interrogation of conserved molecular pathways or animal models to dissect complex neural circuit defects that may underlie particular phenotypic abnormalities found in humans. Third, beyond the assessment of observable signs in disease-affected individuals, we need to identify clusters of affected individuals with similar neurophysiological abnormalities that have been studied on a molecular basis and targeted for treatment development in model systems. Eventually, we will be able to give these more homogeneous clusters of patients interventions developed for their specific pathophysiological mechanisms (personalized medicine).

The past decade has seen a large increase in the number of rodent models generated for mechanistic research and treatment development. However, many of the early studies using these models have focused on behavioral characterizations. Only recently, animal-model studies are starting to reveal mutation-specific neural circuit defects that might be relevant to human disease pathology (see review in refs. 6,7). The lack of a deep understanding of disease-relevant cellular and circuit mechanisms is a bottleneck for successful translation in psychiatry research.

In this perspective, we discuss the utility and limitations of animal models. We emphasize the importance of using animal models that are based on disease etiology, the difficulties and approaches in modeling polygenic disorders, the necessity to shift emphasis from behavioral studies to neurophysiological characterization with a focus on translatable molecular and neural circuit mechanisms that are evolutionarily conserved. Finally, we envision an integrated path forward that may enable us to better translate preclinical findings into effective treatments for psychiatric diseases.

Animal models and disease etiology

During the last decade, a host of animal models for psychiatric disease research have been developed. Generally, neuroscientists evaluate these models in terms of construct validity, face validity and predictive validity[8,9]. Construct validity in the context of animal models for

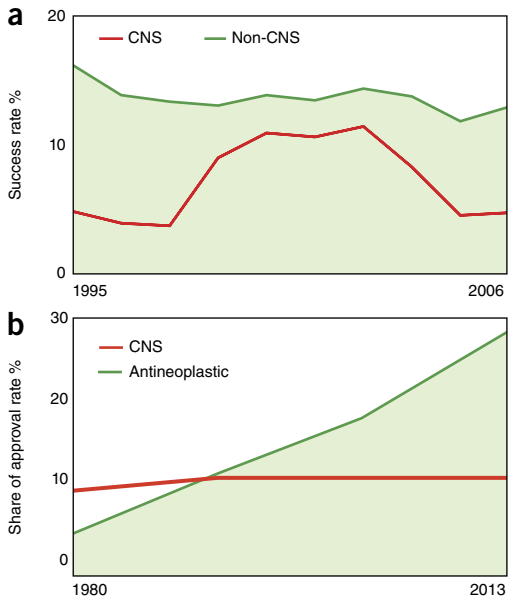

Figure 1 Clinical approval of CNS-drugs. (**a**) The clinical approval success rates for CNS-related drugs fall far below drugs for non-CNS disorders between 1995 and 2006. Except for a period of increased approvals of so-called 'me-too' drugs, which are improved variants of existing drugs, the approval rates were consistently low, with about 5 in 100 compounds receiving approval. (**b**) In contrast to compounds for CNS disorders, the share of the US Food and Drug Administration approval rate for antineoplastic drugs increased substantially between 1995 and 2006, probably because therapy evolved from unspecific cytotoxic compounds to highly cancer subtype–specific compounds. Source: Tufts Center for the Study of Drug Development[92].

psychiatric disease research refers to the degree to which the model is based on disease etiology, such as environmental or genetic risk conditions for developing the disease. An animal model's face validity is its phenotypic resemblance to the human disease, whereas its predictive validity describes the similarities in treatment response between the animal model and human patients.

Construct validity is impossible to achieve in an animal model if we do not understand the etiology. Little is known about etiology of psychiatric disease and no biomarkers are available, except in a few syndromic disorders such as Rett syndrome and Fragile X syndrome, in which genetic lesions are known and used for diagnosis. Thus, clinicians assess patients on the basis of phenotypic presentation and observable signs of disease. For example, by using guidelines in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), a person with impaired reciprocal social interactions combined with restricted, repetitive behaviors manifesting in early childhood would be diagnosed with autism spectrum disorder (ASD). Such heavily phenotype-based diagnoses in psychiatric diseases have inspired similar phenotypic assessment in animal models, particularly mice. For instance, comparison of the inbred mouse strain BTBR T+tf/J with the inbred mouse strain C57BL/6 reveals that these mice show relatively less reciprocal social interaction, more grooming and different ultrasonic vocalizations[10]. Thus, the BTBR T+tf/J mice have been proposed to be used as an autism model with high face validity, and they are used for ongoing preclinical drug testing[11,12].

Similarly, it has been suggested that a mouse in which hyperlocomotion has been induced by amphetamine, a psychostimulant that causes psychosis-like episodes in humans, is a predictively valid model for schizophrenia, given that treatment with approved antipsychotic drugs normalizes locomotion in these mice[13]. This hypothesis is supported by findings showing that schizophrenia is associated with increased amphetamine-induced synaptic dopamine concentrations[14] and that there is a genetic association of the dopamine receptor *DRD2* with schizophrenia[4]. At the same time, animal models centered on face and predictive validity have substantial drawbacks. First, behaviors have considerably diverged during the 80 million years since the last common ancestor of humans and mice, and should only be interpreted as a correlate of neural circuit function, and ideally only in models based on an evolutionarily proximal species. Second, approaches focused on predictive validity with the ultimate goal of discovering new therapeutic targets for the development of new compounds are inherently flawed, because they are biased toward the same molecular pathways that have been targeted, with limited success, in the past. Third, making inferences regarding human pathophysiology from these models is substantially complicated by the fact that they do not reflect the etiology of ASD or schizophrenia in human patients on the basis of current knowledge. An alternative approach is to deemphasize face and predictive validity and only consider them in models with high construct validity[15].

How can we generate animal models that do not merely mirror phenotypic presentation, but that are built on disease etiology? High heritability indicates that genetics is among the most important contributors to the development of psychiatric disease[16,17].

In fact, it is widely assumed that genetic and environmental factors interact and converge on the same molecular pathways and, in combination, exert either protective or adverse effects[17]. In other words, the consequence of an environmental experience such as stress depends on the presence or absence of certain genetic variants within an individual. To date, reported environmental influences on psychiatric disease include (but are not limited to) maternal stress or infection during pregnancy, birth complications, infections, stressful life events, and drug abuse. Although the field of modeling gene and environment interactions in animals is still in its infancy and facing challenges related to uncertainties regarding nature and quantitative parameters of environmental factors, several studies have already shown promising results, and excellent reviews on this exciting topic can be found elsewhere[17–19]. In the future, it may be crucial to explore and define standardized paradigms mimicking the exact time course and nature of gene-environment interplay in humans to determine how and to what extent such interplay might affect developmental trajectories and neurophysiology.

The most notable advances in understanding etiology of psychiatric disorders in the past decade have come from genetic studies. Recent genome-wide association studies, copy number variation studies and whole-exome sequencing studies have identified a large number of genetic risk factors for the development of psychiatric disease (see ref. 20 and references therein). Here we outline how such genetic findings provide neuroscientists with the unprecedented opportunity to generate animal models that are similar in etiology to human disease and hence may prove to be more valid tools for the dissection of disease-associated pathways and circuits.

Utility and limitations of current animal models

A range of model organisms from fruit flies to zebrafish to mice has been successfully used to investigate gene to phenotype relationships and discover relevant molecular mechanisms underlying disease[15,21,22]. Because the etiology and clinical expression of psychiatric disease is complex and related to the unique biology of humans, genetic findings

will by no means enable researchers to generate animal models that recapitulate all phenotypic features of any one DSM-defined disorder. However, simpler units of intermediate disease phenotypes associated with genetic variants, called endophenotypes, are amenable to interrogation[23,24]. Compared to a disorder classified by a combination of complex symptoms, these quantifiable endophenotypes are thought to arise from the interaction of fewer gene products, and they can be neurophysiological, biochemical, neuroanatomical or behavioral. By using this approach, one hope in the field is to deconstruct complex traits into fewer distinct cellular and circuit mechanisms and subsequently to reconstruct a general neurobiological logic, which will help explain and better predict consequences of similar genetic variants, acting singularly or in combination with non-genetic factors.

Both common and rare genetic variants have been used to model gene-endophenotype relationships in animals. Common variants are polymorphisms that occur in more than 5% of the human population. In animal models, such variants have been used to generate useful models that display endophenotypes, some of which have also been observed in humans[25–27]. The advantage of this approach is that investigators can study the relevance and endophenotypic impact of polymorphisms of interest in fairly large cohorts of human subjects and animal models in parallel using comparable experimental paradigms in both species[25]. Although this approach has yet to be taken one step further to the demonstration of causality through circuit manipulation, the adoption of robust methodology and the focus on comparable endophenotypes hold great promise for translation.

Modeling neural circuit abnormalities in autism spectrum disorder

Currently, most animal disease-modeling studies focus on highly penetrant rare mutations. Specifically, we highlight genetic mouse models for the interrogation of neural circuit abnormalities in ASD, a psychiatric disease in which the discovery of highly penetrant variants in affected individuals has enabled the study of monogenic models. Many such genetic models have been developed in the past decade, a few of which are shown in **Table 1**.

These monogenic models have collectively revealed several cellular and neurophysiological abnormalities that may be related to autism pathology, encompassing synaptic dysfunction and abnormal dendritic spine morphology, excitation-inhibition imbalance, and glia cell dysfunction. First, excitatory synaptic dysfunction in the hippocampus or the striatum is a consistent defect found in mutant mice lacking synaptic organizing proteins such as neurexin-1α, SHANK2 or SHANK3 (refs. 28–30). In addition, both SHANK2- and SHANK3-deficient mice display altered expression of synaptic proteins, as well as reduced density and abnormal shape of dendritic spines. Second, excitation-inhibition imbalance is implicated in a range of monogenic ASD models including homozygous deletion of *Cntnap2* in mice, a gene important for neurodevelopment and clustering of potassium channels; mice heterozygous for *Syngap1*, a gene involved in dendritic spine development; and mice with the ASD-associated R451C missense mutation in the synaptic organizing gene encoding neuroligin-3 (*Nlgn3*) (refs. 31–33). Third, studies of mice with knocked-out *Mecp2*, a gene transcription regulator, suggest that distinct cellular entities, particularly astroglia[34] and microglia[35] (but also see ref. 36) may have a substantial role in the neurobiology of Rett syndrome.

Among a host of behavioral abnormalities, several of these studies reported abnormal social interactions and repetitive self-grooming in the mice. When investigators interpret these findings, a prevailing idea is that these behaviors are comparable to DSM-defined symptoms of ASD and causatively related to the cellular and neural

Table 1 Recently developed human genetics–based animal models point toward synaptic mechanisms

Genetic mouse model	Cellular and neurophysiological abnormality	Behavioral abnormality
Shank2 knockout[96,97]	Reduced hippocampal glutamatergic neurotransmission, reduced spine density, increased glutamate receptor expression[96] or reduced *N*-methyl-d-aspartate receptor function[97]	Excessive grooming, increased locomotion, impaired social interaction, abnormal vocalizations
Shank3 knockout, ankyrin repeat[98–100]	Impaired hippocampal synaptic transmission and long-term potentiation (LTP), reduced postsynaptic density (PSD) proteins, reduced activity-dependent α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)[98–100]	Abnormal social behaviors, communication patterns, repetitive behaviors and learning and memory[98–100]
Shank3 knockout, PDZ domain[29]	Reduced cortico-striatal neurotransmission, reduced PSD and PSD proteins, reduced spine density, increased dendritic length, striatal hypertrophy[29]	Excessive grooming, impaired social interaction, increased anxiety[29]
Shank3 knockout, exon 21 (ref. 101)	Hippocampal synaptic defects, increased mGluR5 in PSD[101]	Spatial learning and memory defects, motor-coordination deficits, hypersensitivity to heat, novelty avoidance[101]
Shank3 overexpression[102]	Abnormal EEG, decreased miniature inhibitory postsynaptic current (mIPSC) frequency and increased spontaneous excitatory postsynaptic current (sEPSC) in the hippocampus, increased spine density, increased excitatory synaptic markers and reduced inhibitory markers[102]	Increased locomotor activity, hypersensitivity to amphetamine, abnormal circadian rhythms and seizures[102]
Cntnap2 knockout[31]	Abnormal EEG, cortical neuronal migration abnormalities, reduced cortical neuronal synchrony, reduced number of interneurons in striatum and cortex	Excessive grooming, epileptic seizures, abnormal social behavior, abnormal vocalizations
Nlgn3 R451C knock-in[33]	Increased inhibitory synaptic transmission in somatosensory cortex, increased expression of inhibitory neuron markers in hippocampus and somatosensory cortex	Impaired social interaction, enhanced spatial learning
Syngap1 knockout of one allele[32]	Elevated excitatory synaptic transmission during development, premature spine maturation, abnormal dendritic spine size and shape, abnormal excitatory/inhibitory balance in the hippocampus	Seizures, learning deficit, hyperactivity
Mecp2 knockout[103]; *Mecp2* microglia rescue[34]; *Mecp2* astrocyte rescue[104]	Reduced neuronal cell size, reduced number of dendritic branches, microglia phagocytic activity	Decreased body weight, decreased locomotor activity, shortened lifespan
Nrnx1 knockout[30]	Reduced excitatory synaptic transmission in the hippocampus	Decreased prepulse inhibition, excessive grooming, impaired nest building, improved motor learning

circuit abnormalities observed. Consequently, a common view is that approaches for correcting some circuit defects or abnormal behaviors in animal models could directly translate to treatments in disease-affected humans.

However, this interpretation is problematic for at least three reasons. First, although the cellular and neurophysiological defects reported are likely to be relevant and should thus be studied further, they might neither be necessary nor sufficient to cause a particular abnormal behavior. Thus, it is crucial to establish a causal relationship between an abnormal behavior and a specific cellular or neural circuit defect, the latter of which ideally can also be identified in human patients. For example, decades of clinical research indicated that cortico-striatal-thalamo-cortical circuits are abnormally active in patients with obsessive-compulsive disorder[37,38], but only the experimental optogenetic perturbation in rodent models demonstrated definitively that abnormal activity of this circuit drives compulsive behaviors[39,40].

Second, although exome-sequencing analysis of *de novo* mutations suggest that most mutations associated with ASD are missense mutations, and different mutations in the same gene can either be loss- or gain-of-function mutations[41], animal model studies generally tend to adopt knockout approaches when attempting to understand disease relevance of the gene. The limitations of this approach are exemplified by studies showing that mice deficient for neuroligin-3 and mice carrying the ASD-associated R451C knock-in mutation display different phenotypic and neurobiological abnormalities. The reason may be that unlike neuroligin-3–deficient mice, mice harboring the R451C human mutation express residual amounts of mutant protein, which may result in an unexpected gain of function[33,42]. Thus, inferences made from an animal model carrying a certain mutation may only be valid for that specific mutation or a similar set of mutations. A possible strategy is to exclusively model patient-specific mutations in animals using knock-in approaches. Admittedly, studying the entirety of mutations found in disease-affected individuals is currently unpractical even in rodents, yet screening for loss or gain of function in cell culture and in simple animal models like the zebrafish may help us to group mutations according to their possible mechanism of action.

The third challenge to linking mutations with circuit dysfunction–causing behaviors is that mouse and human behaviors, as well as the circuits underlying these behaviors, are not always directly comparable. When attempting to align clinical and preclinical findings, investigators should bear two things in mind. First, DSM-5 and other symptom classifications are designed to provide a common framework for clinical purposes in the absence of mechanistic understanding and disease-relevant biomarkers. This clinical framework cannot be used to directly guide the common preclinical framework, which primarily concerns neurobiological measures and molecular signatures. Thus, a specific mouse behavior should not be regarded as an equivalent to a human symptom, but interpreted as a readout that can be used to study the underlying neurobiological defects. In addition, despite the fact that mice and humans have homologous brain regions and complex behavioral repertoires, there may be substantial divergence of neural circuitry, or even repurposing of existing circuits, caused by the unique evolutionary pressures on mice and humans. Specifically, unlike the similar evolutionary history and role of cortico-striatal-thalamo-cortical circuitry in repetitive behavior in humans, non-human primates and rodents[37–40,43,44], neural circuits that underlie rodent social behavior and primate social behavior may be vastly different, given their different evolutionary histories[45].

In contrast to these behavioral differences and the function of evolutionarily more recent neural circuits, which may diverge widely between rodents and primates, synaptic genes and their cellular functions are largely conserved throughout vertebrate and invertebrate evolution[46]. Thus, shifting emphasis from behavioral resemblance to studying evolutionarily conserved circuits and neurophysiological correlates of disease-specific mutations may substantially increase the translatability of preclinical studies.

Tackling polygenicity

The aforementioned monogenic models have markedly enhanced our understanding of underlying molecular, cellular and circuitry defects caused by these particular mutations. That being said, a major limitation with this approach is that we can only generate monogenic models for highly penetrant variants (for example, variants of SHANK3, MECP2). On the basis of current knowledge, such highly penetrant variants may account for only 5–15% of cases in ASD, whereas the majority of people with psychiatric disease may harbor many variants of small effect size that cumulatively confer genetic risk to disease[41,47–49]. In addition, the majority of variants may localize to non-coding regions, which are difficult to study owing to our limited understanding of the function of these regions and poor sequence conservation between species. For schizophrenia, the generation of animal models that reflect disease etiology is impeded by the lack of highly penetrant genetic variants that are replicated across more than just a few families[47]. In a few cases, such as deletions of *NRXN1* (encoding neurexin-1), a gene important for synapse development, mutations are highly penetrant and found in many people, but clinically they manifest as different disorders[50,51]. Thus, until further genetic and neurobiological studies reveal more information about these complex diseases, relatively simple genetic animal models are not within reach and alternative approaches are required to elucidate the fundamental biology underlying polygenic diseases.

iPSCs and polygenicity

Currently, a promising approach to enhancing our understanding of polygenicity is to use patient-derived induced pluripotent stem cells (iPSCs); the strength of this approach is that these cells have the same complex genetics as the affected individual, which is crucial for dissecting the pathophysiology of polygenic diseases. Although most initial human iPSC studies have focused on monogenetic disorders[52–55], a few new studies are starting to reveal interesting cellular phenotypes in iPSC-derived neurons from individuals with disorders with unknown genetic causes[56,57]. However, despite great promise, there are currently still several obstacles hampering major advances in modeling psychiatric diseases using these cells. Briefly, the main hurdles when using neurons differentiated from human iPSC are line-to-line variability owing to culture conditions and genetic backgrounds; the neurons differentiated from iPSCs are less mature than adult human neurons and form only a few spines, subcellular compartments that are strongly implicated in the pathophysiology of psychiatric disorders; there is a lack of robust ways to differentiate the vast variety of neuronal cell types; and the fact that neurons differentiated from iPSC do not form complex neural circuits, which substantially constrains the complexity of neurophysiological endophenotypes that can be studied.

To overcome these hurdles, more sophisticated approaches for using iPSC-derived neurons have been explored. One of them is the development of organoids for studying local circuits[58,59]. These organoids contain cortical layer–like structures and multiple neuronal cell

types[60], and they have been used to study neural developmental defects in ASD[61]. Another approach is to generate chimeric models by injecting fluorescently labeled human iPSCs into the developing brain of rodents or non-human primates. If the fluorescently labeled iPSCs become an integral part of the developing and migrating neuronal progenitor pool, iPSC-derived neurons may become incorporated into functional circuits[62,63]. In an experimental setting, fundamental biological processes can then be investigated in patient iPSCs and control iPSCs with different fluorescent labeling in the same animal, which intriguingly may also solve *in vitro* differentiation issues and the problem of neuronal maturation, including dendritic spine formation. The developing brain, being the natural environment for differentiating neurons, endogenously provides all the factors necessary for differentiation and the physiological formation of mature spines. Although the study of iPSC-derived neurons is still in the early stages, further developing these approaches could be critical for studying polygenic disorders.

Genome-wide association studies and polygenic diseases

In addition to iPSCs from human patients, we might also use genome-wide association study (GWAS) data to gain insights into the polygenicity of psychiatric disorders. GWAS studies reveal common genomic loci and alleles that convey increased risks for disease rather than identifying large effect rare mutations[20]. Risk alleles and other genetic or non-genetic (such as environmental) factors may converge and alter the function of the same disease-relevant pathway and circuit, and thus collectively push it toward a pathological state. Therefore, highly significant GWAS results allow us, with confidence, to identify genes that function in disease-relevant pathways and circuits. With the increasing numbers of risk-related alleles identified by GWAS and large numbers of rare variants discovered in whole-exome and whole-genome sequencing, it is conceivable that systematic analysis of risk-associated-gene functions with cell type specificity in simpler model systems may allow us to subgroup risk genes into converging pathways on the basis of their effects on cellular and circuit function. These pathway-specific gene groups can, in turn, inform bioinformatic analysis of large-scale genetic data to identify potential polygenic combinations and guide experimental validation.

Primate models for studying higher brain function and dysfunction

The ability to genetically modify the mouse genome has revolutionized biomedical research, including neuroscience. Mouse and rat models have been and will probably continue to be the main mammalian models for studying brain function and dysfunction. However, mice and humans are separated by 80 million years of evolution, which has led to substantial divergence in the structure and function of the brain, such as in the prefrontal cortex, which is one of the largest and most-developed portions of the human brain, whereas rodents have only a rudimentary prefrontal cortex and lack some of the counterparts of the primate prefrontal cortical regions (**Fig. 2**). Thus, on the basis of current knowledge, mice do not exhibit the same complexity in cognitive functions that are mediated by these regions in primates[64,65]. There are also many unique functional circuits and related behaviors that are frequently affected in human psychiatric disorders and almost impossible to study in rodents, such as face recognition, eye gazing and vocalization, all of which have important roles in social cognition and social communication[66–68]. These differences have led to the exploration of non-human primate models for research of higher brain function and psychiatric disorders[69].

Although the potential advantages of non-human primate models will be discussed below, as for any other animal model in biomedical research, it remains imperative to address any scientific questions in the phylogenetically lowest adequate species possible and to minimize adverse effects on the animal. With regard to the use of non-human primate models, there are additional ethical concerns, and these experiments should only be carried out if deemed absolutely necessary.

One issue relevant to the use of primate models more generally, even beyond neuroscience research, has been that until recently, precise genetic manipulations in mammals have been limited to rodents. The development of highly efficient clustered regularly interspersed short palindromic repeats (CRISPR) genome-editing technology has made it feasible to directly manipulate the genome in zygotes[70–72], thus expanding genetic manipulations to many species, including non-human primates[73]. A second issue is reproduction: although macaque monkeys are the most commonly used non-human primates in neuroscience research, they are less desirable as a routine genetic model owing to their long generation time and slow reproduction. Macaque monkeys live up to 30 and 40 years in captivity, reach sexual maturity at the age of 3–4 years and give birth once a year to a single offspring. Thus, establishing a sizable transgenic colony means years of waiting.

Among non-human primates, an attractive species for generating genetic models for the investigation of psychiatric disorders is the common marmoset [74]. The common marmoset is a small (300–400 g) New World monkey that is not evolutionarily as close to humans as Old World monkeys such as macaques. However, from the practical point of generating transgenic models, the marmoset has several advantages[75]. First and most importantly, marmosets reach sexual maturity around 12–15 months, and thus breeding is much faster than with macaques. Furthermore, marmosets give birth twice a year, usually with non-identical twins from each birth. This rapid reproduction cycle is advantageous for generating transgenic animals. Similarly, the relatively rapid maturation of marmosets compared to macaques is an advantage for longitudinal studies of postnatal development and for studying late onset brain disorders. With regard to behavioral characteristics, marmosets are highly social, with strong family structures and complex vocal communication, and thus could be a promising model for studying social cognition and communication, which are behaviors affected in ASD and schizophrenia. Like macaques but unlike rodents, marmosets have a well-developed prefrontal cortex, a region critical for the cognitive functions that are impaired in many psychiatric disorders[65].

However, non-human primate models do have their limitations. Although they are evolutionarily closer to humans than rodents, they are by no means perfect models for the human brain and human behavior. Most notably, non-human primates do not speak but communicate in vocal calls that are rudimentary compared with human language. Second, although non-human primates have a well-developed prefrontal cortex, transcriptomic analysis has revealed substantial differences in cortical gene transcript expression patterns and complexity between non-human and human primates[76]. Thus, the brains of non-human primates may be better models for human brains only in some aspects. At this early stage, neither failed nor successful translational attempts based on non-human primate models have been made, which would be necessary to assess the value of these models for human disease. Third, unlike for research in rodent models, extensive tools for detailed circuit interrogation and functional manipulation are not yet readily available. Fourth, studying genetic variants that may be related to more variable, subtle changes and thus require larger cohorts to warrant robust hypothesis testing is unpractical in primates. These scientific limitations, together with the ethical considerations and the high cost of maintaining non-human primate colonies, call for caution and clear reasoning regarding scientific necessity when considering these models.

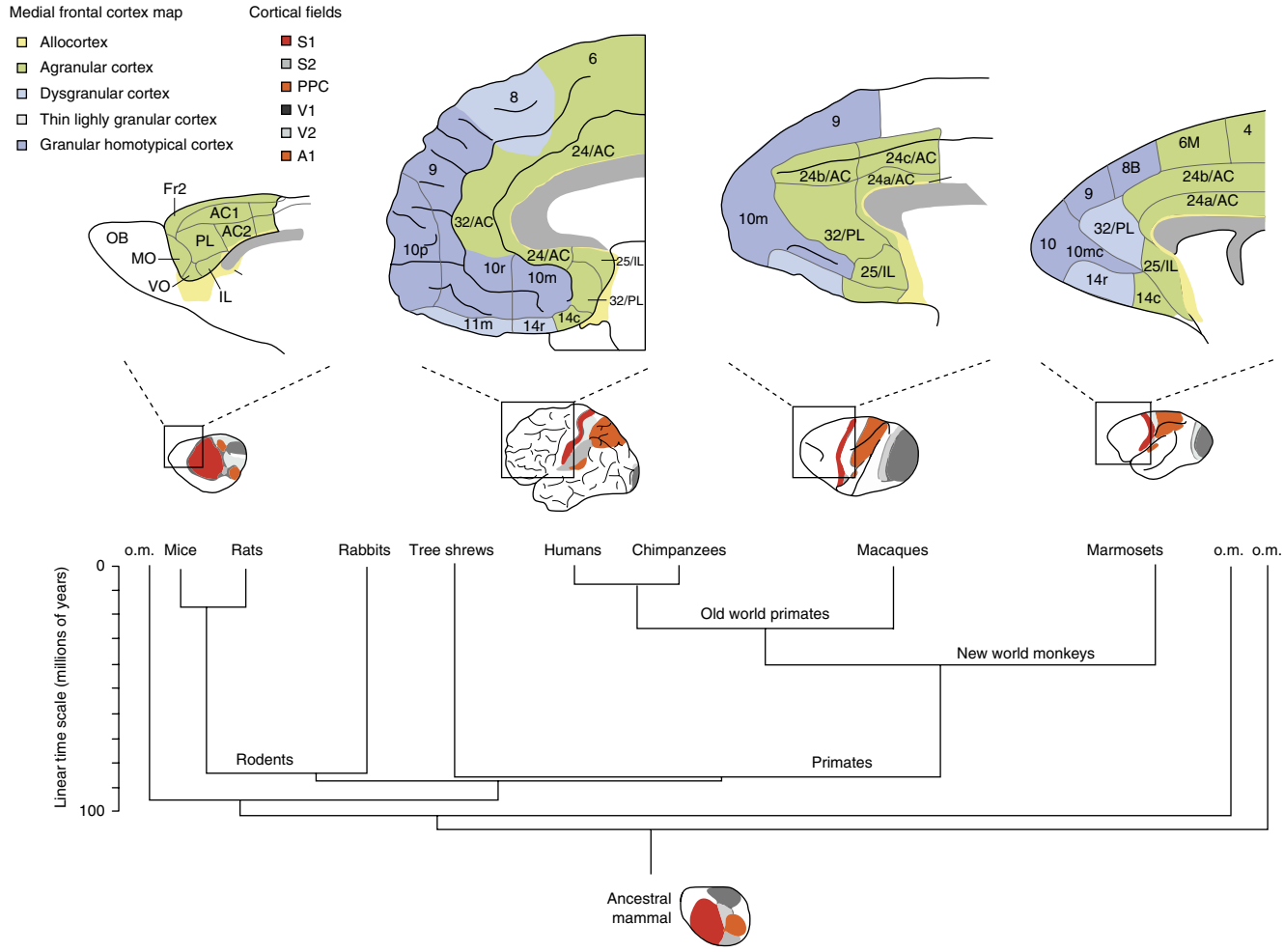

Figure 2 The change in cortical fields and medial frontal cortex architecture since the last common ancestor of rodents and humans. Bottom, the common ancestor of mice, monkeys and humans is likely to have displayed extended somatosensory areas, but small parietal fields. On a gross scale, similar organization can be found in the rodent brain, whereas humans and monkeys, most probably driven by their visual specialization, have profoundly expanded parietal fields and reduced somatosensory areas. In brain architecture revealed by histological staining, the absence of a well-developed granular homotypical cortex in rodents is striking. Although rodents may possess functionally analogous regions, distinct cell type composition and computations in these regions, which are implicated in psychiatric disease in patients, may be unique to primates. Illustrations are schematic and not drawn to scale. A1, primary auditory cortex; AC1 and AC2, anterior cingulate cortex area 1 and 2; Fr2, frontal area 2; IL, infralimbic cortex; MO, medial orbital cortex; OB, olfactory bulb; o.m., other mammals; PL, prelimbic cortex; PPC, posterior parietal cortex; S1 and 2, primary and secondary somatosensory cortex; V1 and V2, primary and secondary visual cortex; VO, ventro-orbital cortex. Numbers correspond to Brodmann areas. Adapted and modified with permission from refs. 93–95.

In pursuit of translation: aligning preclinical to clinical research

The shortcomings associated with the assessment of animal models on the basis of face, construct and predictive validity in the past, as outlined above, and with the low translatability of findings from animal models to human patients indicate that the validity evaluation and study of animal models should fundamentally change[64]. Specifically, NIMH recently launched the Research Domain Criteria (RDoC) initiative, which is spearheading the initiative to extend clinical research beyond the mere assessment of subjective symptoms and observable signs to an assessment that is also based on objective genetic and neurobiological measures[65]. We suggest that preclinical animal research should follow this example by de-emphasizing face and predictive validity and focusing on neurobiological validity, encompassing neuropathology, molecular pathways, and cellular and circuit mechanisms[66]. Admittedly, assessing neurobiological validity in an animal model is still difficult due to the lack of knowledge regarding the precise nature of neurophysiological abnormalities in humans. However, it is worth noting that with advanced neuroimaging, electroencephalography (EEG) and magnetencephalography (MEG) recording, and transcranial magnetic stimulation (TMS) approaches, ongoing clinical research has great potential to build a framework of disease correlates in the near future. Furthermore, we already know several neurophysiological abnormalities that occur in humans, which can guide mechanistic studies in animal models and be considered for validity assessment of an animal model.

This is exemplified by schizophrenia research, in which reported neurophysiological alterations in humans include abnormalities in local gamma and sleep spindle activity[67–70], long-range functional connectivity[71,72], impaired long-range structural connectivity (see ref. 73 and references therein), and morphological changes such as decreased dendritic spine density and cortical thinning[74–76].

How are these neurophysiological phenomena studied in humans? Functionally, local oscillatory cortical activity arises from synchronous activation of large neuronal ensembles. This is

measured with extra-cranial EEG, electrocorticography (ECoG) or MEG as steady-state evoked potentials (SSEPs) or as strength of gamma-oscillation in testing paradigms engaging the auditory or visual sensory systems[69,70,77,78]. Similarly, one can use covariance analysis of the functional magnetic resonance imaging, blood oxygen level–dependent (fMRI BOLD) response from two regions to study long-range functional connectivity of neuronal ensembles in distant brain regions[71,72]. The morphological framework for such oscillations is laid by the hard-wiring and structural connectivity of brain regions. Here, diffusion tensor imaging (DTI) allows the visualization and quantitative assessment of long-range projections on the macroscopic scale. Lastly, both dendritic spine counting upon Golgi impregnation in postmortem tissues and structural MRI in patients can be carried out to study structural alterations such as atrophy or hypertrophy of certain regions.

Can preclinical research move toward using the same or equivalent approaches in animal models to study neurobiological correlates? Although studies such as those outlined above are still scarce in animal models, various examples are listed in **Table 2**, together with a non-exhaustive summary of both widely and rarely adopted useful methodologies for the elucidation of functional and morphological neurophysiological disease correlates. Using and developing more such methods to better align preclinical research with clinical work requires basic scientists to closely collaborate with clinical scientists to learn disease relevant knowledge.

Regarding the investigation of functional properties, two studies are of particular interest. By using paired recording of spikes and field potentials with multiple recording electrodes in a model for deletion of a schizophrenia-associated 22q11.2 region, one study revealed impaired fronto-temporal synchrony as a neurophysiological abnormality[79], while the other study used ECoG measurements in mice lacking the schizophrenia-associated 15q13.3 homolog to reveal impairments of SSEPs and a reduction of evoked gamma power[80]. In terms of structural changes that correlate with disease, a study investigating gross anatomy of the brain found an increased caudate volume in a mouse model of ASD[29], which is consistent with findings in humans[81]. Macroscopic structural mapping of fiber tracts using DTI is not yet routinely performed in common laboratory animals. With improved resolution down to 50 μm^3 for *ex vivo* and 200 μm^3 for *in vivo* interrogations, this technique can be used in animal models such as the common marmoset[82]. In addition, recently developed tissue-clearing techniques such as CLARITY (clear lipid–exchanged acrylamide-hybridized rigid imaging/immunostaining/*in situ* hybridization-compatible tissue-hydrogel), for mesoscale optical investigation, which renders the brain transparent in its native three-dimensional state, can be used to reveal morphological abnormalities in animal models[83]. Together with classical electrophysiological and molecular interrogation of disease-relevant brain circuits in model organisms chosen on the basis of the evolutionary conservation of such circuits, such as basal ganglia and amygdala for studying compulsions and innate fear in rodents, respectively[7,84–86], these approaches help elucidate neurophysiological disease correlates that are likely to be comparable between humans and animal models.

With these approaches, it is conceivable that investigators will be able to make more valid inferences about human pathophysiology and better predictions of treatment responses in human patients, but what other opportunities can be explored to improve our understanding of pathophysiology? Upon reviewing the recently developed animal models, arguably one of the most striking disconnects is the fact that

Table 2 Preclinical and clinical research converges through the use of comparable approaches in conserved domains

Neurobiological domain	Technology	Examples of findings in human	Examples of application in animal models	Highlights
Functional connectivity: local synchrony	Wireless Electroencephalography (EEG), Electrocorticography (ECoG), Magnetencephalography (MEG)	Reduced gamma power and abnormal sleep spindles in schizophrenia[67–70]	Auditory processing deficits in mice heterozygous for a 15q13.3 deletion[80] and abnormal spike discharges after seizure onset in *Cntnap2*-mutant mice[31]	Longitudinal study over months Possible in freely behaving animals
Functional connectivity: long-range synchrony	Functional magnetic resonance imaging (fMRI), Positron emission tomography (PET), paired electrophysiology in two regions	Abnormal functional connectivity in schizophrenia[71,72]	Impaired fronto-parietal synchrony in 22q11.2-deletion schizophrenia model[79]	fMRI: Repeated non-invasive imaging/longitudinal studies for drug effects, unbiased whole-brain measurements, equivalent readout in humans and primates
Structural connectivity	Diffusion tensor imaging (DTI), CLARITY, electron microscopy	Abnormal connectivity in schizophrenia[73]	No defects in *Nlgn3*-knock-in mice with DTI studies[105]	DTI: longitudinal study possible CLARITY: allows probing molecular signatures in native three-dimensional brain
Anatomy	Three-dimensional MRI Golgi impregnation	Increased caudate volume in ASD patients[81] Reduced spine density in schizophrenia[76]	Increased caudate volume and reduced spine number in *Shank3*-deficient mice[29]	MRI: longitudinal study possible Equivalent readout in humans and animal models
Gene and protein expression, transcriptional dynamics, single-cell transcriptome	*In situ* hybridization, Immunohistochemistry, mass spectrometry, bilsulfite sequencing, chromatin immunoprecipitation, isoform-specific RNA-seq	Reduced parvalbumin expression in prefrontal cortex in schizophrenia post-mortem tissue[106,], Mid-fetal transcriptional networks in ASD[87]	Abnormal synaptic protein expression in *Shank2*- and *Shank3*-deficient mce[29,96] Reduced parvalbumin-positive interneurons numbers in *Cntnap2*-mutant mice[31]	High sensitivity Potential to identify molecular signatures of developmental periods Identification of converging candidate pathways
Neuronal transmission and synaptic plasticity	*Ex vivo* and *in vivo* electrophysiology (sharp electrode, stereotrodes, tetrodes, large electrode arrays)	Impaired LTP and LTD in schizophrenia[107,108]	Abnormal synaptic transmission in *Shank2*- and *Shank2*-deficient mice[28,29]	Unprecedented temporal resolution, robustness and molecular insight (when used with pharmacology in *ex vivo* preparation)

This non-exhaustive summary lists various useful techniques that help reveal neurobiological abnormalities, which are largely conserved and therefore likely to be comparable between human patients and animal models. Note that invasive preclinical approaches have the potential to identify molecular signatures and pathways that may serve as treatment targets, whereas classical clinically used approaches allow for the longitudinal study of treatment effects while also ensuring better translatability.

interrogation of neurobiological mechanisms is largely conducted in adult animals, whereas a substantial portion of psychiatric disease is developmental. Thus, instead of revealing developmental neurobiological abnormalities that are potentially causal to the abnormal neurobiology observed in the adult and still malleable to interventions, current studies focus on studying potentially less malleable consequences of such developmental abnormalities at the adult stage. Specifically, it is conceivable that molecular signatures during development characterize fundamental neurobiological wiring and circuit maturation steps with different potentials regarding reversibility, such that some circuit abnormalities are reversible in adulthood, while others may only be sensitive to treatment in early development[32]. Regarding future preclinical research, one critical advantage of the technologies outlined above is that they permit longitudinal studies on functional and morphological abnormalities along development, with the potential to help identify critical plasticity periods or neurophysiological and molecular signatures of prodromal stages[87]. In an experimental setting, animal models offer the unique opportunity to invasively probe early interventions targeted at linked candidate pathways or circuits by using drug treatments or deep brain stimulation and TMS, respectively[88], while also facilitating the study of these effects on defined neurobiological abnormalities at various stages of development.

Despite the notion that focusing on neurophysiological defects is critical for better translatability of studies using animal models, studying behavior will not become irrelevant, because behavior is an important organism-level readout of circuit dysfunction and correction. Rather, bearing in mind the limitation that a change in animal behavior upon experimental treatment is by itself insufficient as readout for successful treatment response, future preclinical work may use it as one of many readouts for the correction of the mechanistically understood neurobiological abnormalities.

The path forward: convergent science

Attempts to develop effective treatments for psychiatric diseases with the help of animal models were largely unsuccessful in the past decades. In brief, the main reasons for this disconnect are that heterogeneous

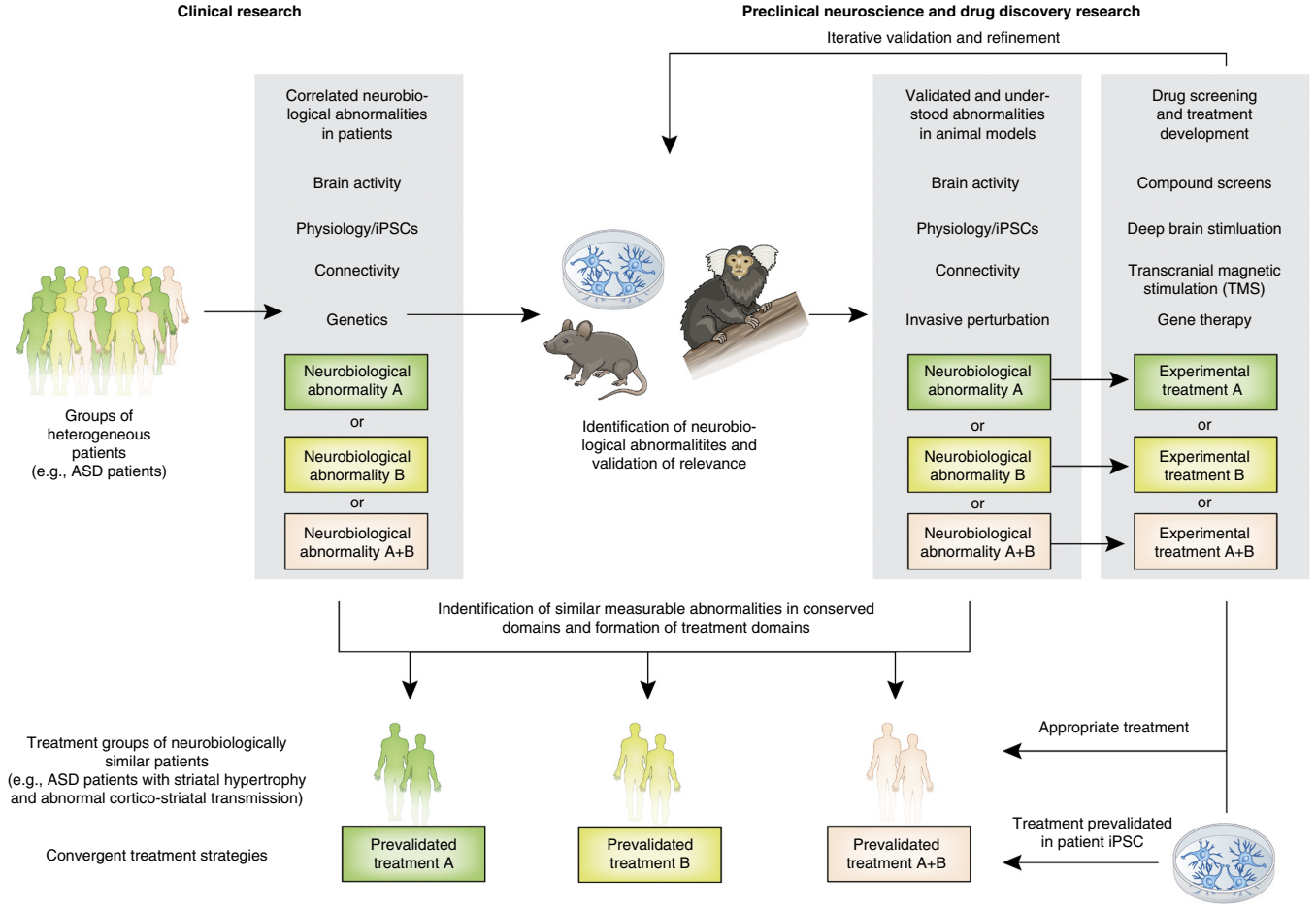

Figure 3 The path forward: convergence of clinical and preclinical research. In this hypothetical example of the way forward in treatment development, a heterogeneous group of ASD patients is sub-grouped on the basis of genetics and comprehensive NIMH Research Domain Criteria (RDoC). The genetic information obtained in this process also informs preclinical neuroscience and enables the generation of animal models that are biologically similar to the patient. Mirroring the patient RDoC, the same neurophysiological abnormalities are identified, understood and tested in terms of their relevance to disease. Shown schematically here, testing causation through invasive perturbation in animal models represents the next step after correlative genetic observation in human patients. Once robust neurobiological abnormalities have been identified in these valid models, investigators can use them for invasive and iterative treatment development. Finally, homogeneous treatment domains are formed on the basis of comparable abnormalities in conserved domains, and patients within these clusters receive the appropriate treatment for their specific abnormality—for example, the patient with neurophysiological abnormality A receives the treatment that has been developed for the corresponding abnormality in animal models. In another conceivable scenario, a group of patients displays neurobiological abnormalities A and B and thus receives a combination of treatments A and B.

patient populations were treated as homogeneous units, the fundamental underlying biological mechanisms were and mostly remain unknown, and the readouts used for treatment response in preclinical research were poor predictors of treatment response in the clinical setting.

Psychiatric diseases stand in contrast to other diseases, such as cancer, in which preclinical research substantially advanced our understanding of underlying disease mechanisms and revealed many robust biomarkers. For some types of cancer, mechanistic understanding and the availability of robust biomarkers facilitated the evolution of therapy from unspecific cytotoxic drugs to the highly effective compounds that target cancer subtype–specific pathways and thus provide more-personalized medicine[89,90].

To introduce a similar process to psychiatric disease research, we envision a path forward that leads to the convergence of clinical research, preclinical neuroscience and drug discovery (**Fig. 3**). This path comprises of four key steps. First, driven by the new NIMH RDoC program, groups of highly heterogeneous patients diagnosed with a given disorder are deconstructed parsed and categorized into more homogeneous clusters on the basis of genetics, observable signs and neurobiological abnormalities revealed by imaging and neurophysiology[65,91]. Second, mirroring the principles of RDoC, preclinical neuroscience uses genetics-based animal models and patient iPSC models to identify, understand and validate the relevance and underlying mechanisms of neurobiological abnormalities found in patients. Third, preclinical researchers develop treatment strategies targeting distinct, relevant neurobiological abnormalities with specific compounds and other interventions, such as deep brain stimulation or TMS, while using animal and cellular models to iteratively validate and refine these treatment strategies. In this step, it is critical to identify comparable abnormalities in conserved domains between humans and animal models. Finally, treatment domains and more homogeneous clusters of patients are formed on the basis of shared measureable abnormalities and biomarkers that are conserved and comparable between animal or cellular models and human patients. In clinical trials, these treatment groups receive the appropriate treatment developed on the basis of shared mechanisms, some of which could potentially have been pre-validated in patient iPSC-derived neurons, thus markedly increasing the chances of treatment success.

As in cancer research, this convergent approach will help close the gap between clinical and preclinical research, establish a fundamental understanding of pathophysiology, and bring more precise and effective treatments to patients. Although this is unlikely to result in a singular treatment strategy for all patients with the same DSM diagnosis, several specific mechanism-based treatments can be used in combination, potentially even cutting across similar disorders, to match an individual's specific needs.

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