Twin and family studies have shown that autism spectrum disorders (ASDs) are highly heritable neurodevelopmental disorders (~90%) that can be functionally very disabling, presenting more commonly in boys with a male to female ratio of approximately 3–4:1; recent prevalence estimates are as high as one affected child in every 110 children in the USA [1]. Although phenotypic presentations are quite heterogeneous, affected individuals have symptoms in three core domains: qualitative impairments in social interactions, qualitative impairments in communication and restricted repetitive and stereotyped patterns of behavior [2]. In addition to symptoms in these core domains, children with ASDs can have a variety of associated symptoms that further contribute to a poor quality of life and care burden on families and caregivers, including agitation, irritability, aggression, temper tantrums, sleep disturbance and seizures. Intellectual disability (ID) is also a common comorbidity, which can influence presentations of deficits of sociability, but are a separate domain of psychopathology. Specifically, individuals with near-normal or normal IQ can have deficits of sociability that are as severe as those seen in persons with ASDs and ID. To date, there are no approved medications that target the core symptom domains; seminal trials led to approval of risperidone and aripiprazole by the US FDA with labeling indications for the important associated symptom of irritability [3–6]. Ideally, experiments would be performed in complementary, overlapping mouse models. To date, there are many genetically-engineered transgenic and knockout mouse strains and inbred strains that show reliably measured and replicated quantitative impairments of sociability in standard paradigms [10]. These models may also reveal instances when core symptom domains are dissociated from each other (e.g., the genetically-inbred Balb/c mouse model shows greater impaired sociability and less intense stereotypic behaviors during free interaction with a social stimulus mouse than the outbred Swiss Webster comparator mouse strain). Unfortunately, measuring sociability in mice is a time-intensive, inefficient process of rating, counting and timing operationally-defined target behaviors in real-time and/or after they are video recorded [10–12]. In most cases, the behavior of only a single test mouse can be studied in a sociability apparatus at one time; the behavior of the test mouse is rated with respect to such things as approaching and exploring an enclosed and freely-behaving salient social stimulus mouse. In our laboratory, we observe the live session for 15 min and spend another 15 min observing a randomly selected coded video recording of a single test mouse [11–15]. Clearly, in order to be useful for medication development programs, these preclinical models must be shown to have ‘predictive validity’ for targeting impaired sociability.
in persons with ASDs [9,10]. Very importantly, computer-automated approaches to the analysis of mouse movements and social behavior must be developed in order to permit high-throughput screening of candidate compounds for medication development; these automated methods should compress the analysis of a 15-min movie into seconds. Further, medication development will necessitate translational clinical trials methodologies that facilitate testing these promising compounds in man. In addition to getting critically important data on safety, tolerability, routes of administration and dosing, these clinical trials methodologies should also be able to provide preliminary evidence of an efficacy signal. However, legitimate questions arise about the fidelity of mouse models for these distinctively human disorders.

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At best, the models may be imperfect, but nonetheless informative. There are certainly similarities in corticogenesis between mice and primates [7,16]. Cortical neurons are not generated in the cortex itself, but arrive in the cortex after their differentiation from pseudostratified neuroepithelium in the ventricular zone that lines the primitive cerebral vesicle and tangential migration in a ‘gliophilic’ manner along radial processes of ‘radial glial cells’, whose distal end-feet project to the pial surface of the cerebrum. At some point, asynchronously dividing precursor cells venture out of the ventricular zone where they germinate into the subventricular zone to become bipolar migrating neurons, which travel across other ‘transient embryonic zones’ (e.g., the subplate zone immediately below the cortical plate) along the radial processes to their final destination in the cortical plate. The cortical plate ultimately becomes the laminated six-layered cerebral cortex with the disappearance of the transient embryonic zones. The arrangement of neurons within the cortical plate assumes an inside–outside gradient with respect to their time of appearance in neurogenesis (i.e., the more recently differentiated neurons travel past the neurons that were formed earlier toward the cortical surface). Modulatory efferent projections from aminergic nuclei in the developing midbrain and cholinergic nuclei in the developing basal forebrain wait patiently in the subplate zone for the arrival of neurons with which they make connections; thalamic projections to the subplate zone arrive later than these aminergic and cholinergic projections [7].

The significantly enlarged surface area of the human cerebral cortex, relative to other primates and mice, has much less to do with the width of its cortical mantle than the amount of time precursor cells spend in synchronous proliferative activity within the ventricular zone, which creates more ‘columnar units or cortical columns’ [7]. The ‘radial unit hypothesis’ proposed by Pasko Rakic is a generative working hypothesis that suggests each radial unit or cortical column is derived from a discrete region of clonally related precursor cells that originated in the same area of the ventricular zone [7]. The longer the length of time precursor cells spend in synchronous proliferative activity within the ventricular zone before venturing out on their migratory path as differentiated neural cells results in both the ontogenetic and phylogenetic enlargement of the cortical surface area, due to the lengthening of the ventricular zone’s horizontal axis; this prolonged proliferative activity in the developing human brain leads to an important difference between mouse and man (i.e., the existence of a much greater number of cortical columns and cortical surface area in the human brain). Clearly, the difference between mouse and man, as recognized and discussed by Rakic and colleagues, is not simply quantitative, because in man there is columnar and regional specialization and greater lateralization of function (e.g., language is left-sided), in addition to greater width and number of cells in the cortical plate, and dramatically greater dendritic elaboration; this dendritic elaboration reflects the enormous synaptic complexity that is man, whose brain has the highest density of synapses, compared to other species. In humans, dendritic elaboration of layer IIIC pyramidal neurons is remarkable (reflecting cortico–cortical associations, among other kinds of complex circuitry), and occurs most dramatically during the second half of the second postnatal year; also, in humans, the density, differentiation and variety of γ-aminobutyric acid (GABA) inhibitory interneurons are not matched in other species [7,16]. Furthermore, humans and closely-related hominoids have a distinctive class of ‘spindle cells’, termed ‘von Economo neurons’, which are largest and most dense in humans, as compared with other hominoid species, and located in layer V of the anterior cingulate and frontoinsular cortex, whose roles are not truly known but thought to relate to rapid transmission and integration of ‘emotion- and reward-relevant information’ that applies particularly to large-brained social hominoids [17]. Clearly, relative to mice, human social
behaviors are flexible and varied, and influenced greatly by learning and motivation, whereas mouse social behavior is far more limited and hard-wired. An evolutionarily late appearance that clearly phylogenetically distinguishes the human social brain from most, if not all, other species is the distinctively human ability known as ‘mentalizing’ or ‘theory of mind’, which is the ability to adopt the perspective of another person and infer his or her feelings, thoughts and beliefs [8]. This special ‘human’ ability to appreciate the thoughts, feelings, intentions and beliefs of others may be dependent on elaborations of the medial prefrontal cortex and medial parietal cortex, areas that are implicated in neuroimaging studies of people making inferences about others.

The human brain is also regionally specialized for language; we have the capacity for imaginative thought and our social communications are not stimulus-bound and confined to the present tense. Perhaps, however, because mice lack as much regional specialization and lateralization of function as humans, they may serve as good models of at least some types of ASD presentations. Some individuals with ASDs may have lost their regionally asymmetric patterns of cortical expression of mRNA; specifically, autopsy data suggest that individuals with autism show attenuation of typically observed regional differences in gene expression between the frontal and the temporal lobe [18]. Moreover, in the postmortem brain of individuals with autism, there may be underexpression of networks of genes related to modules for interneurons and synaptic function. Importantly, A2BP1, a neural- and muscle-specific alternative splicing regulator gene, was an important underexpressed gene that was a hub in the network of underexpressed genes in the postmortem autism brain related to interneurons and synaptic function [18,19]. Thus, abnormalities of the post-transcriptional processing of genes involved in brain development or the structure of the synapse may be an etiological mechanism.

Complicating research further, the genetics of ASD are complex; only a small percentage of all cases are due to the effects of single major genes that are inherited in Mendelian fashion [1]. Interestingly, ASD is not an invariant comorbidity of genetic disorders due to the effects of a single major gene, such as fragile X syndrome and tuberous sclerosis. Recent thinking suggests that complex genetics may contribute to risk; for example, an unfortunate combination of multiple genes, some of which may be rare or even common polymorphisms, each of which contributes a small effect by itself, interact epistatically with each other to increase risk of an ASD. Other considerations include epigenetic dysregulation, which may relate to altered structure and remodeling of chromatin due to the acetylation status of histone proteins, methylation of cytosine residues in enriched CpG islands, and/or insufficient expression of a DNA binding protein that affects efficiency of transcription, such as the MeCP2 protein that is insufficiently expressed in X-linked Rett syndrome (there are data suggesting that the MeCP2 deficiency in Rett syndrome affects the coiling of the 15q11-13 region and leads to diminished expression of the α7 nicotinic acetylcholine receptor coded in the 15q13.3 region) [20]. Finally, risk may be due to hotspots along the genome that are prone to microdeletions and microduplications, so-called ‘copy number variants’, which can lead to haploinsufficiency or overexpression of some genes, or altered coiling of DNA and inefficient transcription [21]. In any event, powerful bioinformatics techniques are revealing ‘relatedness’ between risk or susceptibility genes for ASDs that superficially appear to have little or nothing in common with each other. Thus, these genes may be part of networks that affect the efficiency of synaptic transmission within circuits that subserve normal social behaviors.

“Different mouse models may converge in terms of their ‘biochemical/genetic/anatomic lesion(s)’ affecting efficient information processing within specialized circuits for social cognition.”

Importantly, several mouse models of ASD have emerged, which will hopefully lead to better understanding of underlying etiology and pathophysiology of at least some subgroups of persons with ASDs and facilitate development of pharmacotherapeutic strategies that target core symptoms, especially impaired sociability [10]. Thus, rather than competing with each other, different mouse models may converge in terms of their ‘biochemical/genetic/anatomic lesion(s)’ affecting efficient information processing within specialized circuits for social cognition. Thus, behavioral readouts in complementary mouse models of promising novel compounds that target sociability may have predictive validity with respect to their effects on the impaired sociability of individuals with ASDs. Human clinical trials would benefit from behavioral outcome measures and complementary neuroimaging measures of activation of specific nodes within social cognition circuits. Mouse models have limitations, but also show much promise.
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