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Is ‘bench-to-bedside’ realistic for autism? An integrative neuroscience approach

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SUMMARY

Given the prevalence and societal impact of autism spectrum disorder (ASD), there is an urgent need to develop innovative treatments that will improve core social deficits, for which there is currently no reliable pharmacological treatment, prevention or cure. Development of novel biological interventions will depend upon the successful translation of basic neuroscience research into safe and effective medicines. This article outlines steps to bring neuroscience research from ‘the bench’ to treatment at ‘bedside’, from phenotyping the disorder to animal models to patient treatment. Although these steps appear simplistic, this is a daunting challenge because of the inherent complexity of the human brain, our lack of understanding of disease neurobiology underlying ASD, and the incredible heterogeneity of the disorder. For ASD, perhaps more than any other neurological or psychiatric disorder, progress will depend on integrative multidisciplinary approaches between basic scientists from varying neuroscience disciplines and clinicians to make ‘bench to bedside’ treatment a reality.

Basic science from the ‘bench’ is the engine that drives the advancement of applied science and treatment discovery in order to provide new tools for clinicians to bring to the patient’s ‘bedside’. This approach is often coined ‘translational research’ and has become a high priority for the NIH and private funding organizations. However, as diagnoses of autism spectrum disorder (ASD) rise at an alarming rate [1], physicians still have very little to offer their patients. If diagnosed early, intensive behavioral treatment of young children with ASD can offer some hope [2–4]. However, drug treatments are limited to targeting only peripheral symptoms such as aggression, anxiety and depression. There are no effective biological treatments for the social impairments present in every child with ASD [5,6]. Why has translating findings from basic science to practical treatment approaches been a major stumbling block for ASD research? ASD encompasses a variety of social and communication symptoms (mild to profound impairments), cognitive abilities (enhanced function to intellectual disability), brain growth (both micro- and macro-cephaly) and a multitude of associated medical problems (gastrointestinal dysfunction, seizures and immune abnormalities, among others) and is therefore unlikely to have a single biological etiology. Moreover, the field of social neuroscience is still relatively new, and we know

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surprisingly little about the neural basis of typical social development. Our lack of understanding of ASD disease biology, paired with limited knowledge of the basic neurobiology underlying social behavior, has hindered progress in developing treatments that target the social core deficits of ASD. In this article, we outline a list of potential steps to translate treatment for autism through animal models: phenotype the disorder; model the disorder; treat the model; and treat the disorder. Although these steps appear simplistic and the necessity for integrative neuroscience is obvious, they rarely occur in ASD research. Technology is rapidly progressing in fields such as neuroimaging, neuroimmunology, neuropathology and genetics; however, integrating these with the assessment, measurement and clinical definition of the disorder is still far behind (Figure 1). In fact, it appears that the different neurobiological disciplines are becoming more and more incompatible. There is a clear need for increased cross-disciplinary collaboration. We conclude with a discussion on the future directions of integrative neuroscience to evaluate the effect and success of treatment on the biology and behavioral impairments of the disorder.

Step I: phenotyping the neurobiology of ASD

Brain development & neuropathology

Researchers searching for neuropathology of brain development in ASD have typically taken one of two paths: brain imaging on 'live' individuals with ASD or post-mortem brain tissue studies on individuals who had ASD during life [7]. With MRI, large numbers of subjects can be imaged longitudinally over time to gain a macroscopic picture of brain development and begin to identify different phenotypes of ASD. Post-mortem brain tissue then provides the critical link to the neurobiological basis of ASD by addressing the underlying cellular and molecular pathologies of the disorder. Once identified, the neurobiological phenotype of ASD brain development and neuropathology can be used to create and evaluate an animal model.

MRI studies have provided the greatest contribution to our understanding of how the brains in people with ASD deviate from early typical development by providing a framework for when (in postnatal development), where in the brain, and in whom there is deviation from typical brain development. Cross-sectional and longitudinal imaging studies that span toddler-hood through adulthood have revealed that there is brain enlargement during early childhood in the disorder, which is particularly noted in the frontal and temporal cortices and the amygdala, but normalization of volume in adolescence and adulthood [7,8]. Another important strength of MRI is its ability to acquire large enough samples of individuals to identify phenotype subgroups. For example, a recent MRI study identified subgroups of autistic children that had clear variations in amygdala growth rate relative to total brain volume; some children with ASD had a rapidly growing amygdala whereas others did not [9]. To further characterize and phenotype cases of ASD, different analytic MRI approaches can also be applied to the same dataset in order to relate structural and functional brain abnormalities. For example, abnormalities have been identified in cortical shape and cortical thickness [10–12]. As diffusion tensor imaging (DTI) methodologies and analytic approaches become more sophisticated, the organization of specific white matter tracts is becoming possible. Functional MRI and PET can also provide clues into functional abnormalities and, most importantly, a future avenue for biologically assessing the success of behavioral and pharmacological treatments on core behavioral impairments.

What, exactly, does the MRI finding of a certain structure being bigger, smaller, thicker or thinner mean? MRI is still so coarse that only gross, macroscopic abnormalities in brain development can be detected. It is clear from MRI studies that the brain undergoes an abnormal developmental time course that appears to include a period of early overgrowth followed by a deceleration in age-related growth in some individuals with ASD. There are

several possible explanations, from cell number and organization to long-range connections to immunological and genetic abnormalities (Figure 2). Unfortunately, few studies are able to focus on the early developmental time period due to the lack of brain tissue available. Interestingly, in contrast to increased brain sizes in childhood, post-mortem studies in adults often find evidence of decreased neuron numbers [13,14] and neuroimmune dysregulation [15–17]. For a comprehensive review of post-mortem brain tissue studies in ASD, see Schumann *et al.* [18]. With the integration of modern quantitative neuropathological techniques such as stereology of cell number and morphology [13], *in situ* hybridization for evaluating neurochemistry [19] and electron microscopy to detect axon connectivity abnormalities [20], these pathological markers can then be used to evaluate the accuracy and success of animal models for developing treatment.

Genetics of the brain

The expression of genes in the brain is different from that in the blood and varies between cortical regions [21,22]. Therefore, abnormalities in gene expression in the brain of a particular disorder such as ASD may not be detected in the blood. Gene-expression patterns in the brain are even attenuated to the degree that ASD can be differentiated from the typical control brain [22]. Seminal studies by Geschwind and colleagues implicate transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction [22]. By contrast, immune-glial module genes are not found to be enriched for ASD, thus suggesting a nongenetic/environmental etiology for this process. Given that MRI research over the last 10 years has thoroughly demonstrated that the age of the patient population studied plays a major role on study outcome, with brain enlargement typically found early in development and limited size difference in adulthood, it is critical for future genetic studies to focus on more specific periods of lifespan. Interestingly, a recent microarray study of prefrontal cortex found dysregulation in gene pathways governing cell number, cortical patterning, and differentiation in young children with ASD, but dysregulation of signaling and repair pathways in adults with ASD [23]. This suggests that age-dependent gene expression changes in ASD may reflect distinct pathological processes in the developing versus the mature autistic prefrontal cortex.

Another potential brain region for future focus of genetic studies would be the amygdala, since this structure, perhaps more than any other brain structure, has been implicated in the neuropathology of ASD [8,13,24–27]. Similar to cortical regions, the amygdala undergoes an abnormal growth trajectory that includes enlargement in young children and a decrease in neuron number in adulthood [28]. However, no study to date has carried out gene-expression analyses on amygdala brain tissue from patients who had ASD during life in any age group, likely due to the lack of adequate brain tissue. Future genetic studies will also begin to target specific cell populations rather than whole cortical regions. Therapies directed at neurons might be different than those directed at glial cells, or more specifically excitatory or inhibitory neuronal receptors. As mentioned above, neuropathological studies in adults show decreased neuron numbers [13,14] and increased microglial cell numbers [16,17], suggesting an abnormal immune response, potential neuron loss and a future mechanism for targeted treatments. Thus, knowing the genetic properties of specific cell types could be used as another pathological marker for developing animal models and targeted treatment.

Neuroimmunology

While the brain was previously thought to be an immunologically ‘privileged’ body region, there is now substantial evidence that immune factors influence many aspects of the CNS. This paradigm shift regarding the interactions between the immune and nervous systems has led researchers to explore neural-immune-based mechanisms for complex brain disorders that have thus far eluded explanation [29]. ASD has been at the forefront of ongoing

neuroimmunology research efforts, due in part to the observation of neuroinflammation and microglial activation in post-mortem ASD tissue samples [15–17].

In addition to post-mortem brain studies, research on patients living with ASD have established evidence of broad immune dysfunction, peripheral immune abnormalities, and evidence suggesting that certain forms of ASD are specifically associated with a CNS autoimmune condition [30–32].

A subset of children with ASD harbor plasma autoantibodies that target brain proteins [33–37], which has been lower adaptive and cognitive function within the ASD population [38], as well as behavioral and emotional problems in children with and without an ASD diagnosis [39]. A separate population of children with ASD are born to mothers who have antifetal brain antibodies circulating during pregnancy [40–42]. During gestation, maternal IgG isotype antibodies cross the placenta and help to protect the immunologically naive fetus [43]. However, in addition to protective antibodies, autoantibodies that react to fetal ‘self’ proteins can also cross the placenta resulting in a number of neonatal conditions. While it is not known if these antibodies are causally associated with ASD, it is plausible that antibrain antibodies in the circulation of mothers during pregnancy cross the placenta and the immature fetal blood–brain barrier, bind antigens expressed in the fetal brain, disrupt neurodevelopment, and ultimately contribute to one form of ASD. In support of this, approximately 12% of women who have a child with ASD also have antibrain antibodies that are reactive to specific fetal brain proteins at 73 and 37 kDa [44,45], and this pattern of reactivity has not been observed in any mothers of typically developing children. The pathogenic significance of these antibodies is actively being investigated using multiple approaches (Figure 3), including brain and behavioral characterization of children prenatally exposed to the antibodies [44–46], maternal genetic variants associated with production of the antibodies [47] and, as discussed below, both mouse [48–50] and nonhuman primate models [51].

Step II: modeling ASD

Although animal models usually do not replicate all aspects of a human disorder, they do provide an experimental system to evaluate hypotheses that, for ethical and practical reasons, are impossible to test using human subjects. The strength of an animal model is determined by three criteria: construct validity – the extent to which the model reproduces the etiology and/or pathophysiology of the disorder; face – the degree to which the model resembles symptoms of the disorder; and predictive validity – the extent to which treatment of the animal model provides insight into therapeutic options for the human condition. Because ASD is a behaviorally defined disorder, the validity of animal models is based on behavioral outcome measures relevant to the complex behavioral deficits that comprise the core deficits of ASD, including social communication, social interaction and repetitive behaviors.

The majority of animal models utilize mice because they are highly social animals that can be used for a variety of inexpensive experimental approaches, including genetic manipulations that are not currently well-developed in other species [52,53]. While the genetics of ASD is exceedingly complex, valid mouse models provide important insights into the molecular biology of ASD. Numerous mouse models have been generated with experimentally induced deletions, truncations or overexpression of genes commonly implicated in ASD [54–57]. In convergence with human genetic studies, several genetic mouse models have yielded behavioral phenotypes that are potentially analogous to individual symptoms of ASD as well as evidence of brain pathology, including synaptic plasticity abnormalities in electrophysiology and synapse morphology assays [58–62].

Similar results have been obtained in environmental manipulation mouse models, including attempts to determine how prenatal environment, and in particular the maternal immune environment, may be playing a role in some forms of ASD. In this line of research, mouse models are being used to directly evaluate how maternal infection may alter brain and behavioral development of the offspring and to examine the underlying biological mechanisms [63–65].

Mouse models, however, are faced with the challenges of relating the rodent brain to the human brain and rodent behavior to human behavior. Portions of the human ‘social brain’, such as the prefrontal cortex and fusiform gyrus, that have been implicated in ASD are not well developed or may not exist at all in the rodent brain. Nonhuman primates share many features of human physiology, anatomy and behavior, thus making the nonhuman primate an ideal species to study a variety of human disorders [66]. Although not all human behaviors (i.e., theory of mind) can be modeled in a nonhuman primate, these animals are a closer approximation to humans in both neural and behavioral complexity and provide a valuable tool for bridging the gap between mouse models and ASD patient populations.

Our research group has recently reported a convergence of findings between a nonhuman primate model of maternal antibody exposure described above [Bauman *et al.*, submitted], and children that were exposed to these same antibodies *in utero* [46]. Both human children and macaque monkeys prenatally exposed to the 37/73-kDa antibodies have significantly larger brains than controls [67]. There are currently no known post-mortem tissue cases of individuals prenatally exposed to these maternal antibodies, thus the nonhuman primate model will allow, for the first time, a histological evaluation of the neural changes associated with precocious brain growth associated with human ASD (Figure 2). Identification of the cellular and molecular mechanisms underlying the abnormal brain growth in the animal model will allow us to potentially identify the neural circuits disrupted in at least one form of ASD. This vital information could provide targets for pharmacological interventions that may limit, reverse or prevent the course of behavioral pathology associated with this and perhaps other forms of the disorder. We have highlighted ongoing research effort related to the maternal antibody hypothesis of ASD as it represents an integrated approach among basic science, animal models and clinical research efforts to understand a risk factor associated with ASD (Figure 3).

Step III: treating the ASD model

Novel pharmaceutical compounds targeting the social impairments of ASD will likely become available in the near future [68] and will ultimately require sophisticated animal models to evaluate drug efficacy. As evidenced from recent mouse models, high-throughput behavioral assays provide a powerful tool to evaluate the therapeutic potential of novel classes of pharmacological agents [69–72]. While there are clear advantages to initiating the drug-discovery efforts in rodent models (i.e., genetic manipulations, lower cost, potential for extensive pilot research and shorter duration of experiments), it is possible that pharmacological interventions targeting the symptoms of ASD may ultimately require the use of an animal model more closely related to humans. This may be particularly germane to attempts at developing novel pharmacological interventions that target complex social behaviors. Efforts are underway to develop maximally parallel behavioral assays between mice and nonhuman primates, thus establishing a pipeline for preclinical treatment development studies where the most promising compounds can be rapidly advanced from mouse to monkey to clinical trials.

Step IV: translate treatment to patients with ASD

While there are currently no effective biological treatments for the core symptoms present in every child with ASD (i.e., impairment in social behavior), one of the most promising avenues of ASD treatment research stems from basic science research on the oxytocin (OT) system. OT is a neuropeptide that enhances social attachment and motivation in animal models and may improve social functioning in individuals with ASD. Recent evidence suggests that adults with ASD who were treated with regular doses of OT showed improvements in recognizing others' emotions [73]. While there are plans to carry out similar trials in children with ASD, it is important to acknowledge that we know very little about the mechanisms underlying prosocial behaviors associated with OT treatment in humans [74]. Indeed, much of our understanding of OT comes from pioneering studies carried out in voles and knockout mouse models, which have established a clear role for OT in facilitating species-typical social behaviors [75,76]. We do not know, however, if these prosocial properties are conserved in nonhuman primates. For example, it is not known if the effects of intranasal OT in humans are mediated by activity of central OT receptor or OT receptors in peripheral tissue. This is due, in part, to our incomplete understanding of the primate OT system. Because the radioligands used to map OT receptor distribution in rodents are not selective for primate or human receptors, we know very little about the distribution of these receptors in the primate. Recent studies using nonhuman primates indicate that inhaled OT in rhesus monkeys penetrates the CNS and increases prosocial behaviors in a reward allocation test [77]. These data suggest a conserved role of OT in humans and macaque monkeys, and establishes a nonhuman primate model to further explore the mechanism underlying OT-based treatment. While it is clear that animal models will continue to play an important role in basic science discoveries that lead to ASD treatments, the OT story indicates that the relationship between basic research and clinical trials does not always follow a linear path. Development of ASD treatment will ultimately require basic and clinical approaches to inform one another, collaborate and occasionally 'back track' to fill in gaps in our knowledge.

Conclusion & future perspective

So is 'bench to bedside' realistic for ASD treatment discovery? Optimistically, we would answer yes, although clearly there are substantial hurdles to overcome. First and foremost is the incredible heterogeneity of the disorder, which undoubtedly slows scientific progress. Second, it is becoming increasingly apparent that understanding the cause(s) and developing novel preventative and treatment strategies for ASD will require expertise in diverse fields of child psychology, neuroscience, genetics, immunology, epidemiology and animal models. Our conclusion that true progress in ASD will require an interdisciplinary approach is by no means a novel concept [78]. We are, however, hard pressed to find successful examples that illustrate truly interdisciplinary efforts and often it seems that the different disciplines are becoming increasingly incompatible. Any single approach used to study ASD, whether it is neuroimaging, animal models, genetics or other approaches, is unlikely to result in novel treatments without collaboration from other disciplines. In spite of these challenges, autism research efforts and funding have increased dramatically in the last decade, drawing basic neuroscientists into ASD-focused research efforts. We have also observed more focus on interdisciplinary training programs, providing the next generation of scientists and physicians a framework for carrying out multidisciplinary research. Translational research for ASD may be a reality within the next decade with increased support from national funding agencies and changes in university policies that promote 'team science' efforts and cross-disciplinary collaborations [79–81].

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Practice points

- Progress toward a biological treatment for the core symptoms of autism spectrum disorder (ASD) will depend on integrative multidisciplinary approaches and successful translation of basic research to clinical application.
- Although animal models do not directly replicate ASD, they provide a viable translational course.
- Because ASD is a uniquely human disorder, the success of an animal model will depend on how well the disorder is characterized both behaviorally and biologically.

Neuroscience research efforts (MRI, post-mortem brain tissue and neuroimmunology) can be used to provide a phenotypic neurobiological definition of ASD, and identify potential avenues for treatment development.

- Mouse models are currently being used to evaluate novel pharmacological treatments for ASD.
- Efforts are underway to establish nonhuman primate models of treatment discovery, thus establishing a pipeline for preclinical efforts.
- Promising clinical trials in patients with ASD have emerged from basic science research and highlight the need to better understand the neural basis of social behavior.

Figure 1. Steps to translate basic science to biological treatment via animal models

When combined with genetic, neuroanatomical and neurochemical information, animal models provide powerful experimental approaches to test a specific etiological theory, evaluate efficacy of a novel treatment or contribute to our basic understanding of neurobiological mechanisms.

ASD: Autism spectrum disorder.

Figure 2. Model of brain growth in autism by age from MRI studies, which has shown an increase in brain size early in development in children with autism followed by a generally undetectable difference in adulthood

Several possible cellular mechanisms can account for the abnormal growth trajectory and remain largely unexplored.

ASD: Autism spectrum disorder.

Figure 3. Maternal antibrain antibodies and autism spectrum disorders

An example of cross-discipline science integrating epidemiology and immunology studies [41,42] with ASD behavioral measures [44,45], MRI [46], genetics [47] and animal models [48–51] to determine if maternal antibrain antibodies are causally associated with ASD [67]. ASD: Autism spectrum disorder.