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Neuroimaging Research in Autism: The Next Decade

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The 1990s were hailed by the National Institutes of Health in the USA as the decade of the brain. This was indeed a remarkable decade, which not only yielded new insights into how the brain works, but also produced several important tools; chief among these tools was functional magnetic resonance (fMRI). Functional imaging allows for examinations of the neural systems that may be involved in the pathobiology of the autism spectrum disorders (ASD), even when gross anatomy appears normal. Although the decade of the brain was an important one for neuroscience in general, it produced very few findings and sustainable models of the patho-biology of ASD. The current decade, by contrast, has seen a rapidly accelerating number of ASD imaging studies. The field is now slowly finding its way, with several areas beginning to yield robust, replicable findings, and the construction of the first solid heuristic models of the pathobiology of ASD. For example, it now seems clear that brain size is larger in children with autism; some evidence suggests the enlargement is greatest in the white matter compartment, which in turn raises questions about axonal connectivity. In addition, certain key nodes in the social brain exhibit abnormal activity levels during tasks that persons with an ASD find difficult, e.g., those that involve social perception, reward motivation, and various aspects of social cognitive processing.

Although we can be greatly encouraged by the amount of progress since the turn of the century, we have several challenges ahead as we work toward a more fully explicated neurodevelopmental model of ASD. Although our near term goal is to thoroughly characterize the pathobiology of ASD, it is important to remind ourselves of the real goal—to improve the lives of those with an ASD. In several forums over the last few years, the Director of the National Institute of Mental Health (NIMH) in the US, Tom Insel, has challenged those doing neuroimaging research in autism to make their work more “clinically relevant.” This indeed is important advice, as sometimes it is easy to lose sight of the goals of our work. Dr. Insel has cited the need to use neuroimaging in combination with studies directed at symptom change, and to characterize clinically relevant characteristics of ASD that vary significantly among individuals on the spectrum, i.e., individual differences. Although NIMH and other organizations that fund our work are supportive of basic science and explicitly recognize that it is hard to predict what areas of discovery might have the largest health benefits, it nevertheless seems wise to aim for clinical relevance whenever possible.

Looking forward, there are several areas where we might expect the greatest progress from the field of neuroimaging. It is a safe bet that imaging technology and analytic methods will continue to improve. Of particular relevance to the study of ASD is the advent of diffusion tensor imaging (DTI). DTI has come into the fore over the last several years as an exciting new tool to precisely measure and test hypotheses about brain connectivity in autism. The human brain has approximately 100 billion neurons connected through complex networks;

DTI promises to help define those connections and identify how they differ in ASD, and how these differences relate to specific sets of cognitive processes and behaviors.

We should also expect great strides in data analytic methods. Techniques such as fMRI produce many more observations than we typically know how to sensibly use and interpret. Nearly all studies continue to independently examine activity in small chunks of tissue (e.g. 3 mm “voxels”); until recently we have lacked the statistical tools to look at distributed patterns of activity. Although fMRI can depict what individual parts of the brain are involved in any given activity, traditional data analytic methods cannot account for functional relationships between regions. Newer functional connectivity methods and multivariate pattern analytic tools now allow autism researchers to define distributed networks that are involved in aberrant psychological processes. These system-level techniques are much more realistic portrayals of the coordinated nature of brain activity, and these techniques will undoubtedly help clarify to the nature of brain functioning in ASD.

There has also been the unfortunate tendency to use imaging techniques in isolation—very little is known about the relationship *between* neuroimaging signals, based on PET, magnetoencephalography, fMRI, etc. The breadth of imaging modalities available to researchers provides a unique opportunity to examine whether multiple measures in combination provide a more sensitive and specific assessment of brain mechanisms underlying ASD. High dimensional multivariate pattern classification techniques are emerging in technical sub-fields, which when employed in ASD studies, will capture signal information arising synergistically from multiple measurement approaches. This will greatly improve our sensitivity for characterizing the distributed nature of the pathobiology in ASD.

In addition to harnessing the power of multiple modes of brain measurement, we should work toward and expect great progress from studies that integrate imaging with other areas of science, particularly genetics. The next decade should see progress in linking genes to brain, and brain to behavior (including behavioral change as a result of intervention). The challenge is magnified as we now recognize more clearly that we are studying the autisms, not autism—ASD is clearly a heterogeneous category at both phenotypic and genomic levels. Not only there are a variety of different genes that confer risk for ASD, but it has become clear that there are also a variety of genetic mechanisms at the root of autism (and many other neuropsychiatric disorders). Genetic studies of ASD indicate that both common forms of genetic sequence variation and rare forms (i.e., those affecting only a very small number of individuals) confer ASD risk. In addition to sequence variation, there is a newfound appreciation that structural variation—deletions and duplications of genetic material—also play a prominent role in the pathophysiology of ASD. The emerging lesson from genetics is that ASD is likely to be individually specified by combinations of rare and common variations across multiple genes. This means that each person with ASD could be relatively unique in their exact genetic profile of risk factors, and that the exact nature of each person’s genetic risk profile likely determines the degree of disability, thereby creating the autism spectrum within the population.

Despite the diversity of genetic mechanisms, there is emerging evidence and strong speculation that the different genetic risk factors converge on a relatively small set of

biologically relevant processes. For example, many of the rare variants identified in recent ASD samples involve genes that affect growth and development of the synapse (i.e., the neuroligands, neurexin, contactin-associated proteins). This is remarkable because neuroimaging studies over the last few years suggest that structural and functional brain connectivity is aberrant in ASD. Thus, genetic and neurobiological evidence points to the first solid causal model of ASD, namely genetically mediated abnormalities of synaptic maturation and connectivity (at both micro and macro levels). There is a tremendous opportunity for science—across the next decade we will combine neuroimaging with genetics, and to begin to describe how specific sets of genetic risk factors give rise to different profiles of risk factors at the level of both brain structure and brain function. In this regard, neuroimaging is uniquely positioned as the link in the chain that binds genetic determinants to behavioral outcomes. It is both daunting and exciting to imagine the number of ways this expanding knowledge will unfold to yield more precise models of the pathobiology of ASD. As we make progress in integrating our understanding of genetics, brain and behavior, we will undoubtedly also begin to see more clearly the boundaries, or lack thereof, between ASD and other neuropsychiatric disorders, and our often naïve categorizations of disorders will give rise to an even greater appreciation of the uniqueness of each individual (as well as the need for personalized medicine).

There seem to be no shortage of opportunities over the next decade for neuroimaging to contribute to our understanding of the pathophysiology of ASD; the scientific menu seems reasonably clear, and very exciting. However, it seems less clear how we establish the clinical relevance of current and new knowledge. Tom Insel's challenge resonates even more strongly during these difficult economic times when funding budgets will undoubtedly be restricted. One approach is to use neuroimaging as a marker of change in treatment studies. It seems clear that we have missed opportunities to use imaging to measure growth and development, and there is no doubt that children with an ASD do grow and develop, often in response to interventions.

A further challenge to be faced in the next decade will be integrating not only across areas of science but also across time, as biological development unfolds. ASD is a developmental disorder, and genetic variations interact with experiential and environmental factors in an ongoing, dynamic fashion. Here, again variation appears to be the rule, rather than the exception, as studies show that onset patterns for ASD are heterogeneous. Neuroimaging is uniquely positioned to provide valuable biomarkers for developmental processes that yield ASD outcomes, and to describe developmental processes that produce the wide range of individual differences we see in the spectrum. The hope is that biomarkers will be observable before the onset of behavioral symptoms, allowing for predictions of ASD vulnerability and preemptive or prophylactic interventions. One can imagine that patterns of functional activity or changes in anatomy during development in the first year of life will enable accurate predictions of later disorder onset, in a manner similar to other fields of medicine (e.g., cardiac imaging during a stress test to diagnose vulnerability to a heart attack, or the identification of polyps as a risk factor for colon cancer).

Another approach to the issue of clinical relevance is to make sure that we have well-characterized samples, so that we can use neuroimaging data to describe different clinically

relevant profiles—to help explain the phenotypic heterogeneity. This approach demands large samples. All current ASD research is affected by the heterogeneity of the disorder, which increases variance in our observations, and reduces our statistical power. The only solution at this point is to use larger sample sizes. Although the 1990s was the decade of the brain (and the current one has been dubbed the “decade of discovery” by NIMH), the next decade might end up being the decade of collaboration. As we discover ways to parse the spectrum at genetic and phenotypic levels, it will become increasingly difficult for individual laboratories to generate appropriate subpopulations for further study. Change is coming, and communication and collaborative skills will be more critical than ever for successful science in the next decade. Although I have emphasized neuroimaging as a vital subfield within autism research, the implications are clearly broader.

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