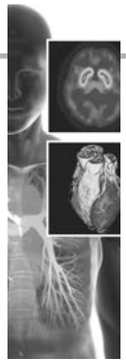

Is it possible to diagnose autism by brain imaging?

"*Unless and until a stable biological basis for the cause(s) of autism is discovered, diagnosis of autism by brain imaging will not be possible.*"

KEYWORDS: biomarker ■ neuro-essentialism ■ neuropathology ■ statistics

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The root biological causes of autism spectrum disorder – autism – remain to be a complex mystery despite 70 years of effort to solve the puzzle. A total of 6 years after Leo Kanner first identified 'early infantile autism' in 1943 through astute observation of 11 children [1], he retracted his initial biological theory. Since then, no alternative theory has yet been validated by genetics or molecular biology to take its place [2]. Today's autism research is awash with an abundance of statistically significant brain imaging results that provide little differentiation between individuals with the disorder and typically developing individuals [3], and this body of findings cannot yet be employed as useful diagnostic criteria in clinical practice.

As we know, and as the Oxford English Dictionary reminds us, any image is merely "an artificial imitation or representation of the external form", a "copy," "likeness," "similitude," "semblance," "appearance" and "shadow." Some researchers today have exclaimed, "science is imaging". Regardless of how 'real' the ever-improving spatiotemporal image resolution, brilliance of color and attraction of animation appear to be, this statement broadcasts a clear misconception. Much of science is measurement, and we continue to have difficulty measuring the same brain structure twice within a short time interval and getting the same number, even after accounting for the 'regression to the mean' effect. The reliability of autism imaging is a major present-day limitation of the technology. MR brain images are perhaps the most beautiful of all image types (so beautiful because so mutable?), and these beauties are sometimes subjected to 'circular analysis' in attempts to ground their impressions in solid statistics [4]. MR images, these quantized imitations of reality, are indeed measurements amenable to statistical regression and classification analysis, but they cannot yet constitute a sufficient test for the presence or absence of autism.

Why not? Why cannot one accept a present classification of individuals (known *a priori* either to have or not have autism) by a reliable MRI algorithm with very high sensitivity, specificity, positive and negative values as constituting a diagnostic test for the disorder? Simply because the MR images are not direct biological measurements, such as a blood test, cancer screen, bioassay and genetic or molecular biological marker. There is nothing substantial in them and hence they cannot yet reveal the underlying biological basis of autism neuropathology. That neuropathology remains hidden outside the image. Major medical breakthroughs always require a progressively clearer biological understanding of the illness that eventually leads to safe and effective treatments. The medical diagnosis and treatment of autism has yet to benefit from the critical advances shared by other better-understood disorders for which diagnostic imaging plays a key role.

In the absence of the critical biology, brain imaging seeks to find evidence of autism etiology and to further understand what goes askew during prenatal and very early childhood development that gives rise to the disorder. Unless and until a stable biological basis for the cause(s) of autism is discovered, diagnosis of autism by brain imaging will not be possible [5]. To believe otherwise at present is to rely too much on technology and its promises [6] and potentially to harm affected individuals, their parents, families and communities.

Part of the reason why autism remains so hard to pin down and treat is that we have yet to find any biological measurement, neither a gene nor gene set, to identify it without *a priori* knowledge of the presence of autism. Some genetic studies suggest that more than 400–600 genes

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may be involved as common variants (polymorphisms) and rare variants (mutations). The only candidate biomarker of autism to date is an elevated blood level of the neurotransmitter serotonin. Serotonin (5-hydroxytrypamine) is a brain chemical that plays an essential role in sleep, appetite, mood, anxiety, social affiliation, impulsivity, arousal, aggression and reaction to stress [7]. But 'hyperserotonemia' is hardly specific to autism. Tumors in the GI tract and recreational drug use (e.g., ecstasy and lysergic acid diethylamide) also increase blood serotonin. At present, the genetic causes of autism in the majority of our autism population are unknown, due in large part to its phenotypic and symptomatic heterogeneity.

Brain imaging has and will have lasting value in autism research. One need only consider the many articles in this journal, and many others, to appreciate its utility. Through *in vivo* imaging, we have learned that for individuals with autism, approximately 20% of children are born with larger brains, which level off to approximately normal size during the first 2 years of life [8,9]; that anterior circuitry in the corpus callosum may be diminished; autistic individuals often pay more visual attention to objects than human faces; that the roles of serotonin change throughout their lives, and everyone's life; and much more.

> "*The root biological causes of autism spectrum disorder – autism – remain to be a complex mystery despite 70 years of effort to solve the puzzle.*"

We still need to better understand the great breadth and depth of healthy typical and atypical neurobiology and the diversity of different types of brain features in the disorder. Brain scans, neuronal subtyping by brightfield and electron microscopy and genetics, are the signposts showing us where and how to look, see, ponder, hypothesize and test. Thus, we delve more deeply into the biological etiology and treatment of autism. We are making solid progress aided in large part by the rapid evolution of medical technology, including advanced imaging techniques and the key insights they help to provide.

Until the day arrives when imaging joins the present set of diagnostic criteria for autism, we will continue to employ subjective parental interviews and observations of individuals at risk for the disorder. The new diagnostic criteria for autism spectrum disorder in the Diagnostic and Statistical Manual of Mental Disorders redefine autism by joining five disorders into one by correcting accumulated logical inconsistencies of previous criteria, again without biological or imaging criteria. Its most widely used and reliably repeatable diagnostic techniques and the severity assessment instruments are the Autism Diagnostic Interview-Revised [10], an interview that takes 2–3 h to conduct with parents, and the Autism Diagnostic Observation Schedule that takes 30–60 min to conduct [11]. Subjective ascertainments and quantitative scores are derived, and cutoff values determine whether or not the individual has autism. The cutoffs for the Autism Diagnostic Interview-Revised are 10 in the social domain, 8 or 7 in the communication domain (verbal and nonverbal), and 3 in stereotyped or repetitive behavior; scores must be above the cutoffs in all three domains for a diagnosis of autism.

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What would it take to change this clinical picture to include imaging measures? The answer is obvious: the discovery of a valid and reliable biomarker of autism. Let us be clear, however, about what we mean by the term 'biomarker'. A biomarker is defined formally as "a characteristic that is measured objectively and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [12]. One may refer to a characteristic or phenotype as a biomarker "if it is minimally affected by the will, behavior and attitudes of subjects or the evaluator or by transient environmental influences" [13]. If such a characteristic or phenotype is a statistic derived from an image, it must also be shown to be on a causal pathway of a clinical end point to qualify as a biomarker. The potential to identify useful biomarkers of autism will be greatly expanded by the further understanding of its pathogenesis.

In brain imaging, we sometimes make a categorical error by implicitly equating subjectivity and personal identity to the brain, a concept termed 'neuro-essentialism' [6]. Neuro-essentialism falsely reduces individual differences to brain differences and, in the present context, differences in brain images. Just as the underlying neuropathology of autism is not contained in the image, so too are the individualities and subjectivities of the people that together weave the complex cognitive and behavioral mosaic of our autism population outside of the image. Let

us work to bring more 'bio' inside the biomedical image and thus improve the lives of people with autism more rapidly and more effectively.

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