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Form Determines Function: New Methods for Identifying the Neuroanatomical Loci of Circuit-Based Disturbances in Childhood Disorders

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Since the time of Aristotle, western science has known that form determines function.¹ In systems neuroscience, form is the geography of the brain, the locations of nodal centers within distributed neural systems for information processing. Specific nodes within specific neural systems process specific kinds of information in specific ways. The computational functions that those systems perform determine the behaviors that an organism exhibits. The cytoarchitectural characteristics of those nodes, including their cellular morphology, cellular density, their extent of dendritic and axonal arborization, the density and neurochemical specification of synapses, and the connections of cells within and between nodes, determine the macroscopic appearance of those nodes.² If the geography of those nodes and their connections differ, the behaviors that the circuits support will differ as well. Form determines function.

Two articles in this issue of the *Journal* represent related and complementary approaches to mapping brain features to behavior in persons with Autism Spectrum Disorders (ASDs). The first, by Groen et al.,³ maps a diagnosis of autism to the overall volumes of the amygdala and hippocampus. This represents a standard approach to brain imaging in both child and adult disorders. It compares volumes of a brain region across groups of participants, one with a disorder and one without, in a case control study design. Various demographic and clinical variables, such as age and symptom scores, are then correlated with the overall volume of that brain region within the patient group. Another approach, exemplified by the article by Qui et al.,⁴ employs essentially the same study design – comparing a brain measure across two groups in a case control design and then correlating the brain measure with demographic and clinical variables within the patient group – but it examines a different set of brain regions, the basal ganglia nuclei, using a spatially finer-grained measure of brain anatomy to identify the locations within the basal ganglia that are most likely involved in the pathophysiology of ASDs. Thus both approaches provide important information about the geography of the brain in persons with an ASD and correlate the geographic disturbances with symptoms of the disorder, but they do so at varying degrees of spatial resolution and therefore with differing abilities to identify the specific neural circuits involved in the pathogenesis of ASDs. Because finer-grained anatomical analyses are revolutionizing studies of brain-behavior associations and the

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neurobiological bases of childhood disorders, the methods used to produce those finer-grained analyses and the ways in which they differ from the measures of conventional volumes warrant a few words of editorial comment.

Anatomical imaging studies have long strived for increasingly finer degrees of spatial resolution in the analysis of anatomical data. Every brain region, such as the hippocampus studied by Groen et al.³ and the basal ganglia studied by Qui et al.⁴, has anatomically distinct subregions. Those subregions have anatomical boundaries that can be discerned histologically but not when using most in vivo human imaging techniques. Each of those subregions has neurocomputational functions that are distinct from those in other subregions within the same overall nucleus. One overall function of the hippocampus, for example, involves memory formation. Nevertheless, the hippocampus has many complex subregions, including its head, body, and tail, each of which has differing functions that support differing components of memory formation. The head of the hippocampus, for example, is involved in the encoding of spatial and temporal relationships between sensory stimuli, and the tail consolidates those relationships for storage in long-term memory.^{5,6} Furthermore, within those general regions are located the CA1, CA2, CA3, and CA4 subfields and the dentate gyrus, each of which has its own neurocomputational functions that contribute uniquely to memory processing. The likelihood is low that all of these subregions are involved in the pathophysiology of ASDs, and the normal volumes in those subregions that are not involved will dilute the effects of volume reduction in the subregions that are involved, if the volumes from all subregions are summed together and lumped into an overall volume of the hippocampus. Including the volumetric contributions from all anatomical subregions in a conventional measure of overall hippocampus volume is therefore likely to undermine the utility of volumetric analyses in discriminating diagnostic groups, or in correlating with the severity of clinical symptoms within a patient group (Fig.1). If the involved subregion is reduced in size by, say, 10% (a relatively large effect in anatomical studies), and if the involved subregion accounts for only 20% of the overall hippocampus volume, then the overall volume of the hippocampus would be reduced by only 2% (Fig.2). Detecting a volume abnormality of only 2% is exceedingly difficult, and most studies will be underpowered for that effort. This anatomical heterogeneity of brain regions is likely responsible in large part for the difficulty reproducing anatomical imaging findings across relatively small studies. If a study is fortunate enough to detect an abnormality in overall volume of a brain region, as it was in the Groen et al.³ study of the hippocampus, then a subsequent finer-grained analysis of local morphological features can help to identify the subregions where local volume abnormalities are driving the abnormalities in overall volume of that brain region. This was the general strategy invoked in the Qui et al.⁴ study of the basal ganglia and in prior anatomical studies of other disorders using similar fine-grained analytic techniques.⁷⁻¹⁰

Numerous techniques for processing anatomical images have been developed recently that provide those finer-grained analyses of volumes within anatomical subregions. Strictly speaking, these techniques rarely if ever measure local volumes per se, but instead measure something akin to it, such as the local indentation or protrusion of the surface of the region, or an index of how much the brain locally has been stretched or compressed to fit into the corresponding subregion of a canonical template brain. What all of these techniques have in common, and what is absolutely central to their ability to provide finer-grained measures or indices of local volume, is identification of corresponding subregions across differing brains. This ability is nontrivial, as many of the subregions do not have identifiable borders that can be defined manually on MR images. Therefore, each approach incorporates a clever method for lining up, for example, the CA3 subfield in one person's hippocampus with the CA3 subfield in another person's hippocampus, and likewise for all other portions of the hippocampus and all other regions within the brain. That method for lining up and identifying corresponding brain subregions is termed "coregistration".

Coregistration of two brains involves stretching or compressing, or “warping”, a brain to fit the template brain. Some warpings deform each portion of the brain in an identical way, treating the brain as a rigid body. Others deform each portion of the brain differently and in differing directions, treating the brain as either an elastic or even liquid entity, in what is termed a “nonlinear” deformation. Most coregistration algorithms align all brains in the dataset as rigid bodies, overlaying all points in each brain in a rough approximation to the corresponding points in the template brain. Once in that rough approximation, these algorithms usually then employ a nonlinear deformation to bring corresponding points into the closest possible proximity that the warping will allow, which for some algorithms produces a brain that is identical in appearance to the template brain (Fig.3). When in this so-called “template space”, each corresponding point in each brain is given a unique label. The warped brain is then unwarped by reversing precisely the second (nonlinear) deformation, bringing it back to its original shape but now closely overlying the template brain in rough approximation after the first rigid warping, but with corresponding points newly labeled.

From this position of rough approximation, various brain measures can be assessed at each corresponding labeled point, either comparing measures across diagnostic groups or correlating measures with demographic and clinical features within a diagnostic group. Those measures could include such diverse features of the brain as cortical thickness, indices of the degree of stretching or compression each brain undergoes during the nonlinear warping (indexing the local volume difference from the template brain), or distance from the surface of the template brain (as an index of local indentation or protrusion of the surface relative to the template surface, which is presumed to reflect a difference underlying volume of tissue at that point on the surface) (Fig.3). Because these measures are compared at each corresponding point either throughout the entire volume or across the surface of the brain region being investigated, and because those points typically number in the tens or even hundreds of thousands, the likelihood of detecting significant statistical effects simply on the basis of chance alone is high when conducting so many statistical tests. Therefore, each algorithm must also include a method for protecting against an excessive number of false positive findings associated with multiple statistical comparisons.^{11,12} Finally, because these coregistration and statistical algorithms are so complex and sophisticated and therefore offer so many opportunities for error, each algorithm ideally should undergo thorough validation procedures that assess their ability to detect known deformations introduced into computer-generated datasets with acceptable sensitivity and specificity and to reproduce findings that are known to exist in real-world datasets collected in healthy control and patient samples.¹³ The validity of the fine-grained analytic techniques used in the Qui et al⁴. study have received preliminary support from findings detected previously in one real-world dataset from a cortical region¹⁴ but not from prior studies of the basal ganglia or computer-generated datasets. In addition, its findings from fine-grained morphological analyses of the basal ganglia in persons with ASDs compared with a healthy comparison group did not survive correction for multiple statistical comparisons, indicating that the group differences could be spurious.

A deep understanding of the disturbances in the distributed neural circuits that produce ASDs and all other childhood disorders requires knowledge not only of the brain regions that are anatomically and functionally abnormal, but also those that are normal, and similarly for all brain subregions. Disturbances in brain subregions must map to neural circuits much more correctly than do the larger regions of which they are a part, and presumably their involvement in one set of neural circuits rather than another is why one particular set of symptoms rather than another set is exhibited by an individual or group of individuals. Involvement in one set of circuits rather than another therefore is likely the basis of phenotypic heterogeneity. Involvement of one set of circuits, as represented in anatomical and functional disturbances in specific subregions, will also likely map more readily than will conventional volumes to variations in specific genes or to environmental or epigenetic exposures. Involvement in that

set of circuits rather than another is therefore likely the basis of etiological heterogeneity. The fine-grained localization of anatomical disturbances using these advanced techniques for image processing thus offer the hope of mapping more precisely and specifically the causal pathways that lead from genes and environmental exposure to the formation of brain circuits and, ultimately, behavior.

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Figure 1. The Anatomical Heterogeneity of the Brain and Its Subregions

Left: On the top is a surface rendering of the cerebral cortex, viewed from above (frontal cortex is at the top of the image). Beneath is a subdivision of the cortex by gyri, each of which has function that differs from the functions of other gyri. The overall volume of the brain only rarely differs between groups of patients and healthy comparison subjects, even though several gyri may differ in volume substantially between groups. Therefore the overall volume of the brain obviously is unlikely either to discriminate groups or to reveal the neural circuits involved in pathogenesis of the disorder under study.

Middle and Right: Similar difficulties plague the use of overall volumes of brain subregions. Even relatively small subregions, such as the amygdala and hippocampus (middle) have numerous subregions, each of which has a specific and unique function that differs from the functions of other subregions (the drawing of the right amygdala in the bottom middle images is coronal section, viewed from the front; the drawing of the left hippocampus adjacent to it is shown from above). Even regions such as the thalamus, which have a quite uniform appearance on anatomical images (green in top-right most image), is anatomically and functionally highly heterogeneous (green outlines in bottom-right most image). Therefore, the overall volumes of these regions are also unlikely to discriminate groups or reveal the neural circuits involved in the disorder.

Figure 2. Finer-Grained Analyses of the Morphological Features of the Hippocampus

Left: Shown is a whisker plot for the overall volumes of the right hippocampus in 81 persons with schizophrenia and in 30 healthy comparison participants.¹⁵ Although average overall volumes are smaller in the schizophrenia group than in the healthy controls, the distributions of volumes overlap substantially, making overall volume a poor diagnostic discriminator across groups.

Right: Morphological features are compared across these same groups of participants at each point along the surface of the right hippocampus. The reduction in overall volume of this region can be seen to derive from highly significant local reductions in volume (represented in purple, $p < 0.001$) over the head and tail of the hippocampus. These local reductions in volume are somewhat offset, however, by significant increases in local volume (red, $p < 0.001$) over the anterior body of the hippocampus. Local volumes in the midbody of the hippocampus do not differ significantly across groups (green) (B. Peterson and B. Wexler, in preparation). These differing morphological effects in differing subregions of the hippocampus likely represents differing involvement of these subregions, and the neural circuits of which they are a part, in the pathophysiology of schizophrenia.

Figure 3. Brain Deformations Used in Fine-Grained Comparisons of Morphology Across Diagnostic Groups

This figure depicts one of several common strategies used to compare morphological features across diagnostic groups at each point on the surface of the brain. Similar procedures are used for analyses of brain subregions, such as the amygdala, hippocampus, thalamus, and basal ganglia.

Left: The brain of each participant in the study is first brought into rough approximation with the template brain using a linear rigid body transformation (not shown). Then a nonlinear transformation warps each point of the participant's brain (lower left) to corresponding points of the template brain (upper middle). The warping affects each portion of the brain differently and is visualized here by showing the effects on a rectangular grid overlaid on an outline of the unwarped participant's brain (upper left). When warped using this nonlinear transformation, the participant's brain is identical in appearance to the template brain (lower middle), permitting each point in the template brain (shown in the numbers placed at the surface of the brain) to be mapped to the corresponding point in the participant's brain. The nonlinear warping that was applied to the participant's brain is now precisely reversed (represented by the undistorted rectangular grid in the upper right of this panel) to bring the participant's brain back to its original shape, but bringing along during the reverse warping all of the template labels assigned to each point in the participant's brain (lower right).

Right: The corresponding labeled points are shown at the contours representing the surfaces of the participant's (white) and template (red) brains in their original shapes after reversal of the nonlinear warping that was used to coregister the two brains. At some points, the surface

of the participant's brain will protrude out from the surface of the template brain, yielding a positive numerical distance, and at other it will be indented relative to the surface of the template brain, yielding a negative numerical distance from the template. When these same procedures are applied to the brains of all the participants in a study, each point at the surface will have associated with it a population of positive and negative numbers, one for each participant in the study. Conventional statistical analyses are then used to compare those values across diagnostic groups to indicate whether the surfaces of the brains from one diagnostic group on average protrudes significantly relative to the surfaces of the brains from the other diagnostic group (significantly more positive values of distances from the template brain at that point) or whether the surfaces of the first group are significantly indented relative to the surfaces of the other group (significantly more negative values of distances from the template brain). Additionally, the numerical values for these distances from the template surface can be correlated with clinical or demographic measures within a diagnostic group to determine how local morphological features vary systematically with that clinical or demographic variable.