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SYSTEMS NEUROSCIENCE

A modern map of the human cerebral cortex

An authoritative map of the modules that make up the cerebral cortex of the human brain promises to act as a springboard for greater understanding of brain function and disease.

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The human brain's cerebral cortex is crucial for sensory and motor processing, as well as for mental functions such as interpreting language and logical reasoning, the complexity of which distinguishes us from other animals. In a paper online in *Nature*, Glasser *et al.*[1] describe an updated map of the human cerebral cortex. This long-awaited advance provides a reference atlas that will allow those researching brain structure, function and connectivity to work within a common, systems-neuroscience framework.

Regional differentiation within the cerebral cortex has long prompted attempts to identify the cortex's distinct compartments, from classical neuroanatomical studies at the beginning of the twentieth century[2] to modern non-invasive, *in vivo* methods based on magnetic resonance imaging (MRI). Such endeavours are complicated by the fact that every location in the brain can be described by an almost infinite set of features, including density of receptor proteins for various neurotransmitter molecules, long-range connections to other parts of the brain, and specialization for neural computations that support specific functions. Almost all previous studies have attempted to delineate cortical compartments using a single feature (Fig. 1). By contrast, Glasser and colleagues capitalize on the unprecedented quality and breadth of MRI data gathered by the Human Connectome Project, the aim of which is to elucidate the neural pathways that underlie brain function and behaviour using cutting-edge brain-imaging methods[3].

MRI provides unparalleled access to the living brain. A single MRI machine can take many different measurements (known as modalities) — from establishing the relative density of neuron-insulating myelin sheaths to determining the thickness of the cortex, both of which can vary sharply between cortical areas. Furthermore, functional MRI (fMRI) can measure the changes in blood flow that accompany mental tasks, as well as whole-brain activity in resting states, providing information about regional neural activity that accompanies different brain states. The authors' integration of information from several MRI modalities not only moves this work closer than previous attempts to the classical definition of a cortical area, but also has several key advantages over other investigations.

First, some modalities reveal borders not clearly reflected in others. For instance, the border between areas 3a and 3b of the somatosensory cortex (which processes information about touch and pain) is easily delineated by myelin mapping, but not by resting-state fMRI. As another example, Glasser *et al.* developed a resting-state fMRI technique that maps topographic neural connectivity within the visual cortex. The sharp transition between levels of topographic connectivity across area boundaries allows much clearer delineation of discrete areas involved in early stages of visual processing than do myelin maps or conventional resting-state fMRI approaches[4,5].

Second, convergence across different MRI modalities reduces the likelihood of misdefining borders as a result of feature-specific noise or bias. This is important, given the indirect nature of most modalities — for example, fMRI measures the blood-flow changes that accompany neuronal activity as a proxy for neuronal activity itself. Consequently, complex computational pre-processing is often necessary to differentiate signal from noise. Agreement across modalities increases confidence that borders reflect biological reality rather than measurement biases.

Finally, an integrative approach better equips researchers to describe the properties of each area, as exemplified by Glasser and colleagues' comprehensive supplementary material. The authors find, for instance, that a cortical area characterized in the 1950s by its low myelin content[6] seems to be involved in language processing as measured by task-based fMRI — a finding consistent with a recent meta-analysis of more than 10,000 imaging experiments across 83 behavioural tasks[7]. Therefore, Glasser and colleagues' map represents the convergence of decades of classical neuroanatomical studies with modern non-invasive studies.

In contrast to the burgeoning field of resting-state fMRI mapping, which has largely

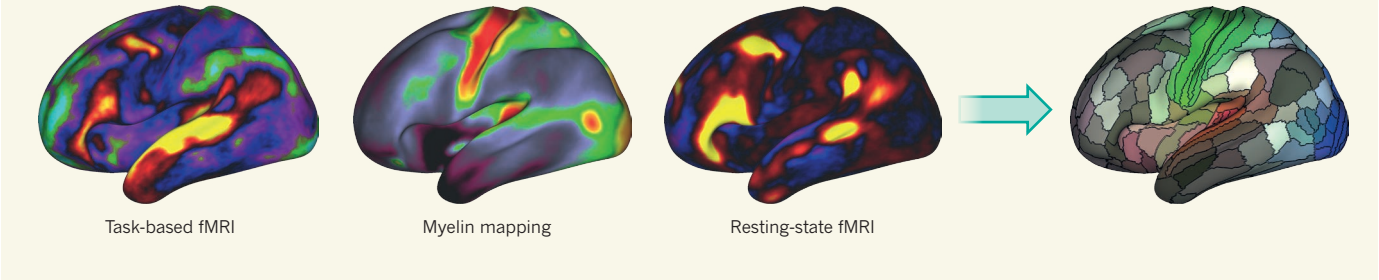

Figure 1 | Mapping function in the brain. Glasser *et al.*[1] defined distinct regions in the human cerebral cortex using a combination of brain-mapping techniques that have previously been used only separately, including: task-based functional magnetic resonance imaging (fMRI), which informs on the functions of different regions; relative density of the neuron-sheathing substance myelin, which provides information about cortical architecture; and resting-state fMRI, which details neural connectivity within and between different regions. In each of these three panels, colours provide a heat map of the measurements. The result is a map that delineates 360 distinct cortical areas. Different colours represent how connected each area is to sensory inputs (hearing, red; touch, green; vision, blue) and to systems involved in cognition (light and dark). Mixed colours show areas in which functional systems overlap. (Images taken from ref. 1.)

focused on fully automatic approaches to divide the brain into parcels that have homogeneous connectivity patterns[8], Glasser and colleagues used a semi-automatic approach that explicitly incorporates prior knowledge from neuroanatomical studies to define the borders in their map. This inclusion represents a crucial and long overdue advance over agnostic, exclusively computational approaches. However, using prior knowledge to choose which modalities to trust in cases of conflicting evidence entails the danger of introducing confirmatory biases. Moreover, it could result in differential mapping quality between areas in which there is relevant, well-known information — such as the somatosensory and visual cortices — and those for which less knowledge exists, such as the prefrontal and parietal cortices. The latter pair is of particular interest to many neuroscientists, because these areas compute most functions that are specific to humans. Indeed, given that the authors explicitly ignore certain modality information for their data set that is functionally meaningful but fractionates classical cortical areas, further investigation will be crucial to understand how borders that are strongly demarcated in only one modality can be differentiated from modality-specific noise.

On a related theme, although Glasser *et al.* have delineated 360 cortical areas, these regions could potentially be subdivided into smaller, more-uniform units that are less distinct from each other. For example, different portions of the somatosensory cortex that represent distinct body parts might be considered as distinct computational units. Furthermore, examples of new areas being defined with the advent of more-sensitive or complementary methods are commonplace[9]. As such, it remains unclear what the 'optimal' number of areas to be defined is — let alone the 'correct' number. We suspect that the optimal number might be application-dependent. The authors' work, although seminal, will therefore probably not be the final word on this topic.

A key innovation in the current study is an automatic algorithm that seeks to delineate cortical areas in individual human subjects, a much more complex task than producing a map of the average brain. Previous work has attempted to estimate, in individual subjects, 10–20 functional networks (for example, see ref. 10), but Glasser and colleagues' goal of delineating 360 areas is more ambitious. Capturing inter-individual biological variability and differentiating such variability from measurement noise is essential to understand the relationship between brain organization and individual differences in behaviour, as well as for clinical applications.

The authors' validation of this algorithm focused on only a small portion of the cortex, so further investigation will be crucial. Nevertheless, their work represents a major step towards individual-specific 'biomarkers' of brain dysfunction, because individual-specific quantities of each area, such as grey-matter volume or connectional strength to other areas, can now be computed, and could be strongly predictive of individual differences in behaviour or disease.

Glasser and co-workers' atlas is the first multimodal map targeted at defining cortical areas, and therefore represents a major advance in human brain mapping. It is now up to researchers to use the anatomical framework provided, compare it with alternative approaches to mapping the human brain, and populate the defined areas with functional and disease-related information. By doing so, we can begin to integrate multimodal data to understand how individual differences in brain organization can explain differences in function, behaviour and disorder. ■

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