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Editorial

Introduction to the NeuroImage Special Issue: "In vivo Brodmann mapping of the human brain"

To achieve the important goal of developing well-grounded mechanistic models of the function of neural circuits, localized changes in brain activity and the end-points of axonal pathways need to be associated with specific well-characterized neural substrates. The reawakening of scientific interest in myeloarchitecture, as implemented using high resolution structural MRI, affords deeper insights into principles of cortical organization which can be integrated with appropriate crossing-fiber dMRI tractography. Once the location of changes in brain activity in a given human brain has been identified, via the individual subject's own native myelin-based in-vivo cortical atlas, the corresponding cytoarchitecture could be looked up in a concordance atlas. The papers of this Special Issue offer analysis tools and examples of in-vivo native cortical atlases of individual human subjects, in which the boundaries of several cortical areas can be clearly identified. With a native cortical map for each subject, spatial smoothing can be viewed as no longer required. As described elsewhere by Turner (2013), mechanistic modeling of the relationship between structure, function and connectivity in anatomically distinct brain areas without spatial smoothing may gain greatly in plausibility.

Despite two centuries of neuroanatomy and the genius of such pioneers as Ramon y Cajal, we are still very unsure of the nature and function of the component parts of the human brain. The situation is worst when it comes to cortical gray matter. The 0.23 m^2 area of gray matter in human brain has been known for more than a century to show many compact subregions (e.g. Brodmann areas) defined by their distinctive cytoarchitecture and myeloarchitecture. Ideally, a mechanistic explanation that enables valid prediction requires clear definition of the given mechanism's components, their specific functional roles, and how these sub-functions are integrated into the operation of the mechanism as a whole. Some would argue that reasonably accurate predictions may only be achievable when we can specify components at nanometer scale across the entire brain. However, given the comparatively uniform structure of cortical areas and the anatomical discriminability of subcortical nuclei, it may be more pragmatic to start with these as the units of analysis and mechanistic modeling. This would limit the number of components to no more than 200, which together with more than 20 different neurotransmitters, neuropeptides and corticosteroids should already provide a requisite level of complexity.

Consensus remains to be built, however, regarding how many such cortical regions can and should be distinguished, and there is an urgent need for a useful concordance atlas between myeloarchitecture and cytoarchitecture in the same cadaver human brains. Research in the human myeloarchitecture has made little progress in a century. Details of myeloarchitecture, such as the heavily myelinated stria of Gennari in the primary visual cortex, are often far more easily visible than in cytoarchitecture. However, there has been little speculation or research regarding the functional role of specific myeloarchitecture in each cortical area. Even though different networks may be able to perform ostensibly the same task, it is obvious that brain areas with different microarchitecture have different information processing competences.

Human brains naturally show considerable variability, both in the pattern of sulcal folding and generally in the relative locations of cortical areas on the sulci and gyri. While some areas such as the primary visual and primary motor cortices are quite well defined by their sulcal location, their spatial extent can still vary dramatically across subjects, even after nonlinear coregistration into a template brain. Although the Big Brain dataset provides unprecedented access to details of human cytoarchitecture, in the absence of a concordance atlas between cyto- and myeloarchitecture it can give little insight into in vivo cortical parcellation. Myeloarchitectural boundaries, however, can show up plainly on high resolution in vivo MR images of the brain. Such boundaries are known to correspond frequently with cytoarchitectural boundaries, and can thus be used instead as an intrinsic method of cortical location.

The papers in this Special Issue show that relatively detailed in-vivo parcellation of the cortex can already be performed into regions comparable with those identified by Brodmann, which can then plausibly be taken as brain components with definable processing competences. A more suitable approach to fMRI analysis and richer modeling strategies can be based on such components, but this will require a scientific paradigm shift in the understanding of human brain function.

The value of improved in-vivo neuroanatomy has been emphasized repeatedly. Congruence of the cortical boundaries of Brodmann Area 17 established by retinotopy and by cortical structure has been successfully demonstrated. Tonotopic maps have a close relationship to the primary auditory cortex, identified by the structural feature of Heschl's gyrus. Recent work by the Editors of this Special Issue has shown that several Brodmann areas adjacent to the central sulcus can be easily parcellated using variations in T1 that can be firmly associated with the degree of cortical myelination. Thus the primary motor cortex can be discriminated from the primary somatosensory cortex, both by function and structure, and specializations within S1 cortex can also be distinguished.

The 13 papers included in this Special Issue cover several aspects of the problem of identifying distinct cortical areas in individual living brains. Most of them relate to the use of high resolution structural MR images to reveal evidence of differential myeloarchitecture between cortical areas.

Two articles by Van Essen (2014) and Glasser (2014) discuss some of the insights that can be gleaned from the possibility of mapping cortical myelin in vivo. Van Essen shows that myelin maps can reveal cortical organization both in individuals and group averages, and that they can aid in compensating for individual variability. They also enable fruitful comparisons between humans, great apes, and monkeys. Glasser further considers why myeloarchitecture might vary across brain areas, noting that primary areas have much higher myelination, which may

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be associated with metabolism that includes cortical aerobic glycolysis. He also develops Turner's intriguing suggestion that cortical myelin may inhibit synaptic plasticity, and thus act as a marker for brain areas that have particularly stereotypical functions. This hypothesis is supported by earlier work by Lozano and coworkers.

Lutti et al. (2014) review methods for obtaining good myelin-related MRI contrast, and use maps of R1 (=1/T1) to delineate several visual and auditory cortical areas. Cohen-Adad et al. (2014) provide very useful technical details for the creation of quantitative maps of T2* to delineate specific cortical regions, which typically have increased iron content. They also point out the difficulties arising from the use of such images, which include the anisotropy of T2* with respect to the relative orientation of cortical myelinated fibers and the static magnetic field.

With an isotropic spatial resolution of no better than 0.7 mm, the highest that can be obtained with a living human subject at 3 T in a reasonable scan time, details of cortical myeloarchitectural layer structure remain mostly invisible due to partial volume effects. However, to discriminate many more cortical areas by their myeloarchitecture requires a more sophisticated assessment of layer structure. The current capability at 7 T is about 350 μm isotropic resolution, using a FLASH T2*-weighted sequence, which shows cortical layering in several brain areas, such as the primary visual cortex V1 and in visual area V3A. To make a full quantitative assessment of such structural MRI scans with high resolution requires more powerful software that is already widely available. Bazin et al. (2014) here describe an efficient and well-validated computational framework that copes well with whole-brain MRI data even with such a high resolution.

Comparing layer structure across cortical areas is made much more difficult due to the folded nature of human cerebral cortex. This causes the depth of a given layer to depend on the local cortical curvature, which can easily confound parcellation based on layer structure. In this Special Issue, Waehnert et al. (2014) describe a method for image analysis that takes account of cortical curvature, compensating for cortical folding using a principle due to the Dutch neuroanatomist Bok in 1929 that ensures that cortical segments retain a constant volume independently of curvature.

Dealing with specific areas, Sánchez-Panchuelo et al. (2014) use T2*-weighted images to compare structurally-delineated regions of the primary somatosensory cortex with their functionally-determined counterparts. Bridge et al. (2014) provide a survey of studies that seek to identify the visual motion area known as V5 or MT, based on its higher myelin content than surrounding cortex. They use T1- weighted or T2*-weighted images for this purpose. Wasserthal et al. (2014) use T1-weighted and so-called T2-weighted scans to outline primary auditory cortex.

Other papers in this Special Issue deal with cadaver human brain, expanding the existing cytoarchitectonic parcellation to the human frontal pole (Bludau et al., 2014) and the medial temporal lobe (Augustinack et al., 2014). These data will be very useful in future work that seeks to parcellate these regions in-vivo using myeloarchitecture.

Cortical parcellation in-vivo is developing rapidly using a very different strategy via the observation of highly significant spatial coherence in the spontaneous fluctuations in brain activity that can be observed at low temporal frequencies in the BOLD signal. This suggests that a form of cortical parcellation can be developed based on functional connectivity. The article by Wig et al. (2014) explores this possibility, reviewing progress to date and discussing potential improvements in visualization and validation. It is already becoming clear that the parcellation from functional connectivity may not everywhere be congruent in the brain with that from cortical microstructure. It will be highly worthwhile to explore such mismatches in some depth, with the potential of teasing apart mechanisms that (for instance) distinguish peripheral from foveal regions of the primary visual cortex. This topic is discussed in some detail in the commentary by Buckner (2014) .

A more powerful strategy is clearly desirable for neuroimaging studies of human cognition. One important concept might be the idea of 'cortical competence', that is, the description of the relationship between input and output streams of action potentials for any given clearly identifiable area of the cortex — and for completeness, the linked concept of 'nuclear competence', with regard to the deep brain nuclei such as the thalamic nuclei and the basal ganglia. Careful study of cyto- and myeloarchitecture may afford important clues regarding such competences. The fact that some details of myeloarchitecture can be observed in vivo, and correlated with task-related activation, invites attempts at interpretation of why it varies across cortical areas.

Fundamental research on the neuroscience of cognition should progress far more rapidly when cortical areas supporting specific psychological tasks can be more unambiguously identified. This topic is discussed more fully in a book chapter by Turner (2013). Currently, standard functional image analysis methodology is unable even to assign brain activity to a particular bank of a sulcus, once smoothing and averaging have been performed across human brains. The great power of spatial mapping of brain activity for understanding when differently labeled tasks are in fact the same, and when apparently similar tasks are actually dissociated, can only be used to its fullest when the neuronal substrate of brain functional activity has been properly identified. Meta-analysis, already showing great promise, should really take off when such correlations have even been partly established.

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