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Towards an Individualized Delineation of Functional Neuroanatomy

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Abstract

The functional neuroanatomy of the human brain is known to vary between individuals, yet current descriptions are based on group-averaged data. Laumann et al. (2015) present data from one highly sampled individual and show unique fine-grained differences representing subject-specific functional architecture.

Mapping the functional neuroanatomy of the human brain is one of the fundamental goals of neuroscience research. Lesion studies following stroke provided critical early information that specific functions such as motor function or language were consistently localized to certain parts of the cerebral cortex. Over the past three decades, research regarding functional neuroanatomy has markedly accelerated through the use of task-based functional magnetic resonance imaging (fMRI), which allowed the identification of localized brain responses during specific task conditions. However, such task-based approaches have increasingly been supplemented by studies examining task-free, intrinsic fluctuations that are present at rest (Power et al., 2014).

Use of resting-state fMRI is based on the critical observation that brain regions that activate together during a task display coherent signals at rest; correlation between such functional time series is called resting state functional connectivity (RSFC) (Biswal et al., 1995). Beyond scalability due to ease of acquisition, RSFC provides an advantage over task-based fMRI for studies of functional neuroanatomy, as it has the capacity to delineate the general functional organization of the brain apart from the demands of and responses to a specific task. Initially used to map small sections of the cortex (such as parietal cortex; Nelson et al., 2010), in the past 5 years, a series of high-impact studies using RFSC have increasingly mapped large-scale functional networks across the entire human cerebral cortex. Such networks correspond with known functional neuroanatomy from lesion studies and task-based fMRI, showing consistent patterns of connectivity that align with networks responsible for both primary (somatomotor, auditory, and visual) and higher-order (frontoparietal control, salience, and default mode) cognitive functions (Power et al., 2011; Yeo et al., 2011). The functional neuroanatomy delineated by these studies has proven to be

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highly replicable across samples. Increasingly, instead of mapping large-scale networks, studies seek to provide detailed functional parcellations the entire cortex (Honnorat et al., 2014; Gordon et al., 2014).

Such parcellation studies provide a general map of the functional landscape of the cortex. However, studies from animals, human lesions, and electrophysiological data emphasize that the functional neuroanatomy varies considerably across individuals. As all prior studies have used group-average data from many individuals, they can only describe trends present across the entire sample. The resolution of group-level data is further limited by two factors. First, group-level functional parcellation relies upon accurate anatomical registration of structural brain images. While such algorithms have improved vastly in accuracy, registration remains imperfect for anatomically variable regions such as prefrontal cortex. Thus, individual differences in brain structure may limit detailed functional parcellation. Second, even if image registration across individuals were perfect, individual differences in the cortical location of functional modules would inevitably lead to the mixing of signals that are averaged across individuals.

In this issue of *Neuron*, Laumann et al. (2015) present an approach that circumvents these problems: instead of using many subjects who were each scanned once, they delineate the fine-grained functional neuroanatomy of an individual who was scanned many times (Figure 1). In total, one of the authors of the study (Russell Poldrack) was scanned on 84 separate sessions, yielding approximately 14 hr of data. This huge amount of data from one individual was used to generate a detailed functional parcellation without group-level averaging. Such fine-grained mapping of one individual's functional neuroanatomy was contrasted with a previously calculated group-averaged parcellation obtained from a sample of 120 subjects (Gordon et al., 2014).

The parcellation techniques used are the result of a productive line of research from this group (Nelson et al., 2010; Power et al., 2011; Gordon et al., 2014) that has been improved and generalized over time. In brief, the entire connectivity pattern of each voxel is compared, and gradients in connectivity patterns are described. Sharp gradients are identified as parcel edges, which are subsequently refined. As expected, subject-specific parcellation fit the data of the highly sampled individual much better than either the group-level parcellation or a standard anatomic atlas. Furthermore, this parcellation was highly replicable, with split-half validation experiments producing very similar results.

One important validation of the decision to acquire a massive amount of data from one individual was that such replicability of results was highly dependent on the quantity of the data used. Improved agreement among patterns of connectivity within parcels was seen up to almost 100 min of data, after which returns diminished. Furthermore, the agreement between the parcellation obtained by using only 9 min of data—typical of many RSFC studies—and the parcellation obtained by the full dataset was poor. Interestingly, extended epochs of data acquisition were not required, and short periods of scanning (e.g., little over a minute) that were combined were as useful as a contiguous scanning period of the same duration.

The functional parcels produced from the single individual shared general features with group-averaged data, but differed in many fine details. Specifically, within frontal and parietal cortex, parcel locations and boundaries were consistently different between the individual and group. Notably, repeated scanning and parcellation of a second individual (with 300 min of data) produced disparate parcellations in similar brain regions, suggesting that individual-specific differences in functional neuroanatomy were in fact being detected. Furthermore, several regions that were unassigned in the group parcellation were successfully parcellated in the single subject, suggesting that individual variance in these regions might prevent accurate assignment at the group level.

These same higher-order regions where fine details of parcellation varied between the individual and the group were also found to have high levels of between-subject variance in the group data, replicating results from an important recent study by Mueller et al. (2013). Such concordance between regions of high between-subject variance and observed fine-scale differences in individual parcellation suggests a link between the two: namely, that between-subject variability in higher order systems may be due to individual differences in functional neuroanatomy. However, as the authors appropriately note, such a concordance could also be produced by higher levels of individual variability in brain structure in such regions. Indeed, Mueller et al. (2013) established that sulcal depth shows a similar distribution of variability. Such anatomic variance could potentially result in increased registration error and contribute to increased variability in patterns of functional connectivity.

Interestingly, the same higher-order cognitive regions that have high between-subject variance conversely had low levels of within-subject variance in the highly sampled individual. Within-subject variance was higher in motor, visual, and dorsal attention regions, which have low levels between-subject variance. Such within-subject variance persisted even after accounting for differences between scans that were acquired on Tuesdays and Thursdays, which were systematically assigned to a fed/caffeinated or an unfed/uncaffinated state. The authors speculate that this within-subject, between-session variability may be to differences in levels of arousal, mood, or behavioral context that may vary by session. Such possibilities underline the importance of studies that seek to characterize sources of within-subject variability in both health and disease (e.g., mood states). The data from this highly sampled individual will be a rich resource for such research; future studies that incorporate studies of dynamic (non-stationary) patterns of connectivity that may describe “brain states,” in conjunction with electrophysiological measures (such as EEG), may be particularly important to understand the origins of such within-subject, between session variability (Tagliazucchi and Laufs, 2014).

While the results summarized above provide compelling data for individual differences in coherent patterns of resting state-connectivity, in isolation, such data are limited due to the unconstrained nature of resting-state fMRI. However, Laumann et al. (2015) provide an important validation of these functional parcels using a suite of task-based fMRI performed over 51 scanning sessions by the same highly sampled individual. Critically, in many of the tasks performed, alignment of foci of activation was considerably more likely to occur within a functional parcel, rather than on the boundary between functional parcels. This suggests that regions of cortex that are coherent at rest in an individual also activate as a unit

in response to task demands. This correspondence between resting-state connectivity and task activation was most striking for retinotopy (i.e., the V1 boundary) but was also quite significant for motion discrimination and an object localizer task. In contrast, results were weaker or non-significant for contrasts in working memory tasks. The authors plausibly suggest that this may be due to the complexity of the higher-order cognitive processes involved, which might be associated with variation in the cognitive strategy pursued. Technical limitations such as data resolution, partial volume effects, and registration error may further hinder the ability to directly map functional connectivity and activity in fine-grained parcels within higher-order cognitive systems. Moreover, such results emphasize that the higher-order brain regions that show the highest variability in functional neuroanatomy may also be the most difficult to validate, even with such a rich dataset.

Taken together, the data presented by Laumann et al. (2015) represent a critical in vivo example of individual variability in functional neuroanatomy, with potentially far-reaching implications for the study of brain networks. Studies of both individual and group differences in the brain's functional connectome have proliferated over the past decade, with many major developmental and neuropsychiatric illness now being conceptualized as "connectopathies" (Di Martino et al., 2014). However, nearly all such studies rely on group-level node assignment and thus assume a similar functional parcellation across individuals. The current data suggest that such procedures will mix signals from disparate functional regions across individuals. Thus, differences in the functional distribution of brain systems could manifest as diminished connectivity within a specific large-scale network. To the degree that functional parcels are likely to be even more variable in patient groups, this problem may be particularly acute in clinical populations and potentially change the interpretation of some of the most robust findings in neuropsychiatry (e.g., aberrant connectivity of executive networks in psychotic disorders) (Baker et al., 2014). Conversely, subject-specific nodal systems that account for individual differences may eventually allow for substantially more accurate measures of functional network connectivity.

While individual variability might present difficulties for group-level network analyses, it also points to a potential opportunity: the size and distribution of functional parcels may itself be an informative brain phenotype. Data from both pathology and cognitive specialists provides potential support for this possibility. For example, in blind individuals, cross-modal plasticity allows visual cortex to be re-appropriated for somatosensory processing such as Braille reading (Cohen et al., 1997). Similarly, intensive musical training can induce functionally relevant structural changes (Hyde et al., 2009). Potentially, the distribution and relative surface area of critical brain systems may represent a more powerful marker of functional capacity than current imaging phenotypes in common use today. Furthermore, given recent evidence that the effect of neuromodulatory therapies such as TMS may depend on individual differences in patterns of functional connectivity (Fox et al., 2013), the accurate delineation of an individual's functional neuroanatomy could enhance the effectiveness of targeted interventions.

However, as noted by the authors, such "precision medicine" approaches remain impractical at present: acquiring sufficient data for an accurate parcellation of an individual precludes immediate clinical applications. However, given the rapid recent improvements in image

acquisition methods (e.g., multiband functional imaging methods), one cannot rule out future advances that will make such studies more feasible. Furthermore, the continual improvement of analytic techniques may allow fewer data to yield more accurate measurements of functional parcellation; in particular, the use of suitable regularization methods shows substantial promise (Honnorat et al., 2015). For now, the truly unique data presented by Laumann et al. (2015) provide compelling evidence for individualized differences in functional neuroanatomy, a topic which no doubt will only become more important with time.

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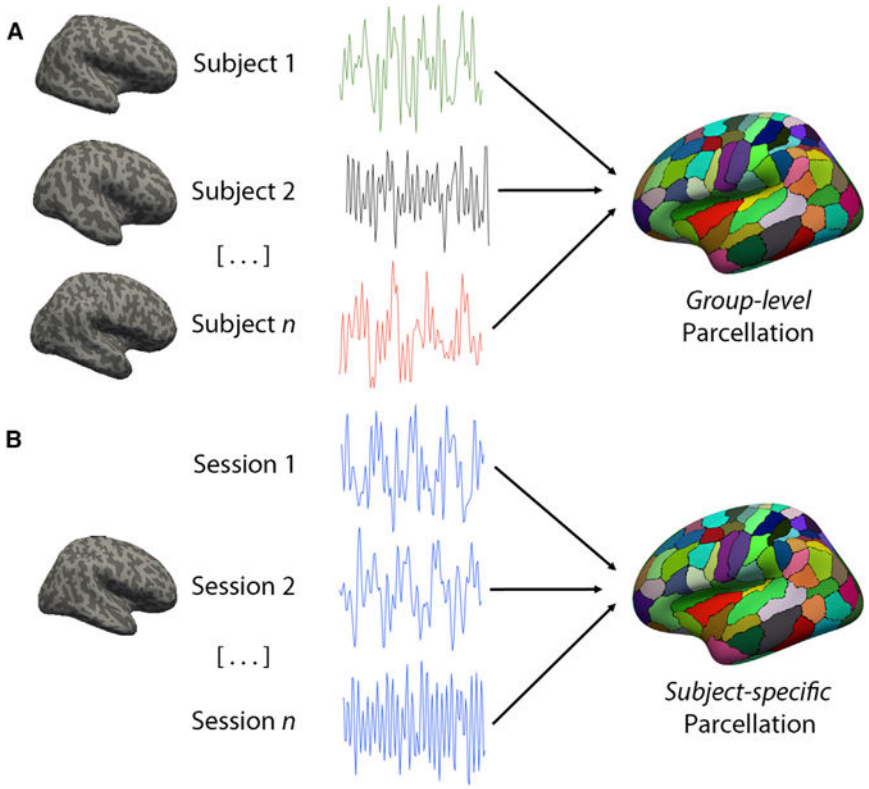

Figure 1. Schematic of the Single-Subject Approach

(A) Typical approach to parcellation using group-average data. In prior studies, data from a group of many individual participants is averaged to create a parcellation that delineates patterns of functional neuroanatomy. However, because group-average data across dozens of participants is used, this parcellation necessarily reflects common functional neuroanatomical features present across individuals.

(B) Single-participant approach used by Laumann et al. (2015). In this approach, one individual was scanned repeatedly, resulting in 14 hr of data. This data was then used to create a detailed functional parcellation that delineates the detailed functional neuroanatomy of that individual. Results show commonalities with the group-level parcellation but also reveal replicable, fine-grained differences that are present only in the individual.