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## Unraveling the Complex Tapestry of Association Networks

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Prior group-level studies have described several large-scale distributed networks within association cortex. In this issue of *Neuron*, Braga and Buckner (2017) attend to the individual brain, revealing a challenging new portrait of its fine-grained organization.

Twentieth century human neuroanatomy was grounded on extensive mapping of a few individual brains. Amidst the numerous recent methodological innovations for investigating neuroanatomy, the open availability of large neuroimaging datasets has rendered the single brain, at least as a focus of study, obsolete. However, as Braga and Buckner (2017) illustrate in this issue of *Neuron*, some features of brain organization may still require the anatomic precision only accessible in the individual to be adequately captured.

Understanding the arrangement of large-scale distributed networks within the cerebral cortex remains a core research topic for the field of human brain mapping. While there is general consensus regarding a set of canonical networks, mapping these patterns to the individual brain raise both methodological challenges and opportunities for exploring how networks are arranged at ever finer spatial resolution. By acquiring extensive resting-state fMRI data from four individuals, Braga and Buckner (2017) demonstrate that three networks of association cortex can each be subdivided and that the arrangement of these networks reveals a consistent spatial

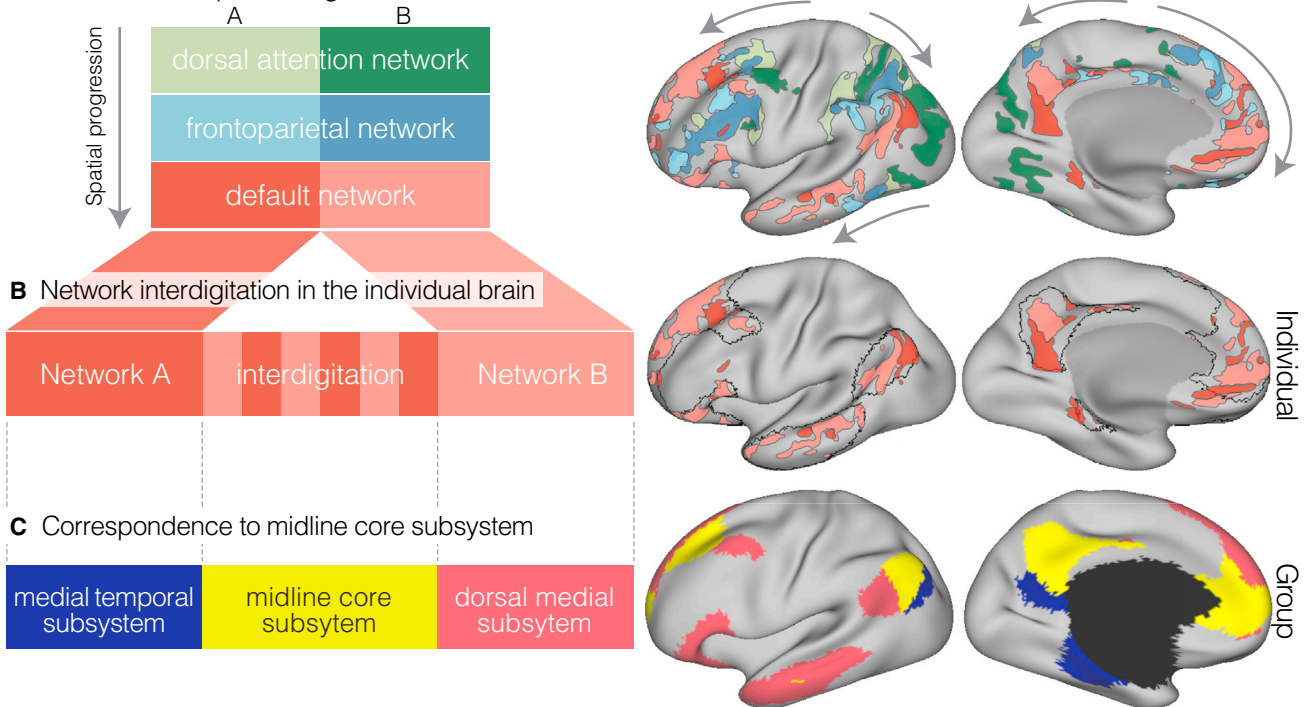
sequence throughout the cerebral cortex (Figure 1A). However, far from a sharp pattern of spatial adjacency, the fine-grained networks appear to interdigitate (Figure 1B) and to reveal aspects of cortical organization that may require reconsideration of well-established large-scale systems (e.g., Figure 1C).

As a first step, Braga and Buckner (2017) targeted the default network using an exploratory approach to interactively map connectivity patterns from a seed region of interest. Recent work demonstrated the robust mapping of cortical connectivity that can be achieved through extensive data acquisition from a single individual (Laumann et al., 2015). The connectivity analyses were thus conducted on almost 3 hr of resting-state fMRI data acquired from each of four individuals during 24 scans. By dividing these scans into discovery and replication samples, the patterns could be explored and then validated within the same cortical anatomy.

In each individual's discovery sample, seed regions consisting of single cortical surface vertices were interactively selected within the lateral prefrontal cortex to maximize the separation of two

subnetworks, “A” and “B.” Both networks included regions across all cortical zones of the default network, with the exception of parahippocampal cortex, which, unexpectedly, was only included within Network A (Figure 1B). For all other zones, the regions belonging to each network were adjacent, but spatially distinct. This dissociation was confirmed across all four subjects using a two-way ANOVA of connectivity between the seed region and other network nodes, as well as data-driven segregation of the two subnetworks using k-means clustering. While seed-based functional connectivity from lateral prefrontal cortex was able to dissociate two default subnetworks, these additional analyses help to assuage concerns that the current findings are sensitive to thresholding or the selection of specific seed regions.

The clear dissociation of two networks across all four individuals suggests similar patterns should be discernible on the group level. However, transposing seed vertices that were optimized for one brain to others nullified the distinction between Networks A and B. Braga and Buckner (2017) attribute these negative results to the subtle anatomical

**A** Parallel and sequential organization of fractionated networks**Figure 1. Large-Scale Spatial Motifs and Fine-Grained Interleaved Structure Of Networks within Association Cortex**

(A) Three canonical networks can be fractionated into parallel distributed subnetworks that are organized sequentially, as indicated by the arrows. Brain images are modified from [Braga and Buckner \(2017\)](#) with the permission of the authors.

(B) Two default networks are interdigitated within several cortical zones, notably, medial prefrontal and lateral temporal cortex. Black outline delineates the default network from the group-level 7-network parcellation of [Yeo et al. \(2011\)](#). Brain images are modified from [Braga and Buckner \(2017\)](#) with the permission of the authors.

(C) The interdigitated zones may correspond to the midline core subsystem of the default network ([Andrews-Hanna et al., 2010](#), here depicted using the 17-network parcellation of [Yeo et al., 2011](#)), which could emerge on the group level through averaging interleaved Networks A and B across individuals.

variation across individuals within these subnetworks. This example indicates the need for caution in assuming anatomical correspondence across individuals, especially within complex association regions.

[Braga and Buckner \(2017\)](#) observe an additional novel and provocative feature of connectivity organization: the presence of fine-scale, interdigitated patterns of network pairs (Figure 1B). For example, within medial prefrontal cortex, default networks A and B appear to be interleaved. As this pattern may result from spatial artifacts introduced when sampling the volumetric fMRI data onto the two-dimensional cortical surface, [Braga and Buckner \(2017\)](#) confirm the interdigitated default subnetworks in native volumetric space.

Nevertheless, further research is needed to understand the anatomical substrates underlying the interdigitated

connectivity patterns observed on the individual level. Is it the result of interwoven long-distance cortico-cortical projections? Support can be found in the gold-standard technique for mapping connectivity in the primate brain: tract-tracing studies conducted in the macaque monkey. Using anterograde tract-tracing injections to investigate projections to the principal sulcus, association projections from the intraparietal sulcus and callosal projections from the contralateral principal sulcus interdigitate ([Goldman-Rakic and Schwartz, 1982](#)). In addition, cortico-striatal projections may also play a role in discriminating finely interleaved functional systems (see Figure 14 in [Selemon and Goldman-Rakic, 1985](#)), as well as the thalamo-cortical projections discussed by [Braga and Buckner \(2017\)](#). A third possibility is that the interdigitation reflects the discontinuous patterns of intrinsic con-

nections within association cortex itself ([Levitt et al., 1993](#)).

Armed with the fractionation of the default network into two distinct and parallel subdivisions, [Braga and Buckner \(2017\)](#) then extended their approach to two other large-scale systems within association cortex: the frontoparietal and dorsal attention networks. They repeated the same procedure for each network, selecting two seed vertices that optimized a distinction between respective spatially distributed and parallel subnetworks for each individual. Division of these additional networks was clearest in two of the four individuals.

Taken together, the spatial arrangement of the six fractionated networks revealed several macroscale organizational features. Similar to the findings within default networks A and B, the subnetworks were all represented within each zone of association cortex. This general motif of parallel,

spatially adjacent network organization was previously observed in the cortico-cortical connectivity between association regions of the macaque monkey (Goldman-Rakic, 1988). Braga and Buckner (2017) further observe that the networks are arranged in a roughly consistent order (Figure 1A), which aligns with the recent description of a principal gradient in macroscale cortical connectivity between unimodal sensory/motor areas and the paradigmatically transmodal default network (Margulies et al., 2016).

The novel contribution of Braga and Buckner (2017) suggests a metaphorical shift for distributed cortical networks from mosaic to tapestry. Higher spatial resolution may reveal further examples of interleaved connectivity as a foundation of functional organization. While Braga and Buckner (2017) interpret their results with appropriate caution, the implications of gerrymandered canonical networks are worth considering.

One prior example is the prior group-level fractionation of the default network into three subsystems: medial temporal lobe, midline core, and dorsal medial prefrontal cortex (Andrews-Hanna et al., 2010) (Figure 1C). But how to reconcile the three network fractionation with the two subnetworks identified by Braga and Buckner (2017)? Network A appears to correspond to the medial temporal subsystem, and Network B to the dorsal medial prefrontal subsystem. Based on spatial correspondence with the interdigitated zones of Networks A and B, the midline core may emerge as a distinct subsystem on the group level due to

anatomical variance across individuals. However, there may also be functional consequences. The interwoven arrangement may facilitate communication between the medial temporal and dorsal medial prefrontal subsystems, establishing regions of convergence as an integrative hub. Interdigitation as an anatomical scaffolding for inter-network communication may also facilitate dynamic control more efficiently than spatial adjacency.

Perhaps it is no coincidence that precisely in the far end of this connectivity spectrum the interdigitation is most articulated. The functional organization of the default network, consisting of markedly expanded regions within in the human cerebral cortex (Buckner and Krienen, 2013), may reveal “stretch marks” as networks become integrated to varying degrees. The two systems being integrated—memory-related and higher-order transmodal association cortex—may together form the functional constituents of the default network.

The current findings offer a further innovative perspective regarding the underlying anatomy of interindividual differences in connectivity. As Braga and Buckner (2017) demonstrate, group-level analysis obfuscates the network fractionation observed on the individual level due to misalignment. Although connectivity differences across individuals have emphasized variance in the strength of functional connectivity as the critical feature, what if the source of differences is instead the variation in underlying anatomy or degree of local integration within interdigitated regions?

We want our networks to provide a simplified abstraction of brain organization. While data-driven approaches to cortical parcellation have unquestionably advanced the field, as Braga and Buckner (2017) demonstrate provocatively, some insights may first need to be gleaned by unravelling the tapestry thread by thread.

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