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Three types of individual variation in brain networks revealed by single-subject functional connectivity analyses

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The human brain is organized into large-scale networks that can be noninvasively identified using functional connectivity (FC) functional magnetic resonance imaging. FC varies across individuals, and there is significant interest in associating individual variation in FC with external behavioral measures. However, only recently has FC variation been characterized by studying brain networks within individual humans. We review these recent efforts, and we argue that individual variation in FC networks comes in three distinct forms: 1) variability in connectional strength, in which brain regions in the same location have variable FC strength across subjects; 2) variability in spatial localization, in which regions exhibit the same connections across subjects, but are expanded/contracted or spatially displaced in specific subjects; and 3) topological variability, in which networks have variable sets of constituent nodes. Unfortunately, each of these three types of variation confounds attempts to measure the others, which significantly impacts research studying brain networks.

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Individual variation in human functional connectivity networks

The human brain is divided into a number of large-scale, spatially distributed networks consisting of multiple interacting cortical areas [1]. This network organization, which is held to be a fundamental organizing principle of the brain [2], has been the subject of intense interest for over fifteen years now, ever since the discovery that it was possible to noninvasively delineate these networks in the *in-vivo* human using a modification of standard functional magnetic resonance imaging (fMRI) techniques called functional connectivity (FC) [3]. In FC approaches, functionally related brain regions are observed to exhibit strong correlations between the temporal patterns of their fMRI signal that could not arise by chance. Simple extensions of this technique were shown to identify not just pairs or connected brain regions, but extensive, distributed networks of functionally connected regions that map closely to known brain systems dedicated to certain types of processing [4]. Since that time, a huge amount of effort has been devoted to identifying and mapping these networks in the human brain [5,6], and our ever-growing understanding of these brain networks has grown to serve as an indispensable framework for studies mapping the neural correlates of cognitive function [7].

The strength of FC between brain regions is well known to vary across individual humans. Indeed, recent work has emphasized that the magnitude of this cross-individual variation is very large compared to other types of FC strength variation, for example, within-subject variation across days or states [8], suggesting that FC variability functions as a trait-level measure that is well-suited to associate with variable trait-level measures of behavior across individuals. Indeed, a large body of research has argued that these variations are indeed related to individual differences in cognitive and motor function [9]. These findings make intuitive sense, as the most compelling interpretation of fMRI-derived FC is that it reflects a statistical lifetime history of co-activations between regions to perform processing needed during everyday life events [10]. This interpretation suggests that individual differences in FC between specific brain regions should reflect differences in the degree to which those regions are co-engaged during that processing, which would likely influence the efficacy of that processing.

However, many previous results identifying associations between FC and behavior have been relatively underpowered, and thus may have been reporting artificially inflated FC-behavior relationships [11]. More recent work has used very high-powered datasets to test the idea that

individual variation in FC might relate to individual differences in behavior. This work has found that while such relationships do exist, they are surprisingly weak [12•]. At first glance, this result seems to fly in the face of the widespread assumption that FC is strongly reflective of behaviorally relevant brain function. However, it is notable that highly powered *within*-subject designs do successfully describe robust associations between behavioral alterations and FC changes [13]. Thus, it seems that while FC is associated with behavior, individual variations in FC are not very strongly related to individual variations in behavior. Why?

One possibility is that we don't really understand the nature of individual variations in FC. The vast majority of works examining FC variation, and FC-behavior relationships, have treated FC as a continuously varying unidimensional measure, not different in principle from, for example, height, except that there are a large number of FC measures in the brain. Alternate approaches may employ summary measures of network features (obtained via e.g., graph theoretical approaches [14,15]), but the variation is still assumed to be at the level of the strength of FC. Implicitly assumed in these approaches is that two FC measures collected from a brain location in two different subjects are directly comparable.

Up until six years ago, we shared this assumption that FC strength was the only relevant measure, and our research focused on using group-averaged data to identify sets of brain regions that could be used as optimal regions of interest for FC analyses [16,17]. While we had superficially examined brain networks derived from individual subjects, these often appeared noisy and strange, and we did not trust them.

Our mindset changed when we first began to examine individual-level datasets with large data quantities, in which FC measures were so reliable that we could not dismiss unusual features as noise-related (The MyConnectome dataset [18]; the Midnight Scan Club dataset [19•]). Critically, in each individual we examined, we found clear evidence of FC network features that varied from other individuals in unexpected ways. Soon we came to realize that, rather than there being a single type of variation in FC that differs across individuals on a single axis, there are at least three separate, independent types of individual variation in FC networks that, unfortunately, each confound attempts to estimate the other two types of variation.

Here we will review evidence for each of these three types of variability and how they confound our ability to estimate the other types. Notably, in our experience the best way to understand these variabilities is not to estimate population variation in FC across large datasets, but rather to examine brain networks at the level of individual subjects. As such, for each type of variation we propose, we will present specific examples of that variation within our own data that first convinced us of its presence.

Connectivity strength variation in functional connectivity networks

As detailed above, it is well known that the strength of FC—the magnitude of the correlation between distant brain regions—varies across individuals. Such variation is stable and of relatively large magnitude [8], such that they can be reliably used to uniquely identify individuals from each other [20]. Within our own data we do observe classic variation across subjects in FC strength between, for example, the lateral frontal and parietal aspects of the Fronto-parietal network.

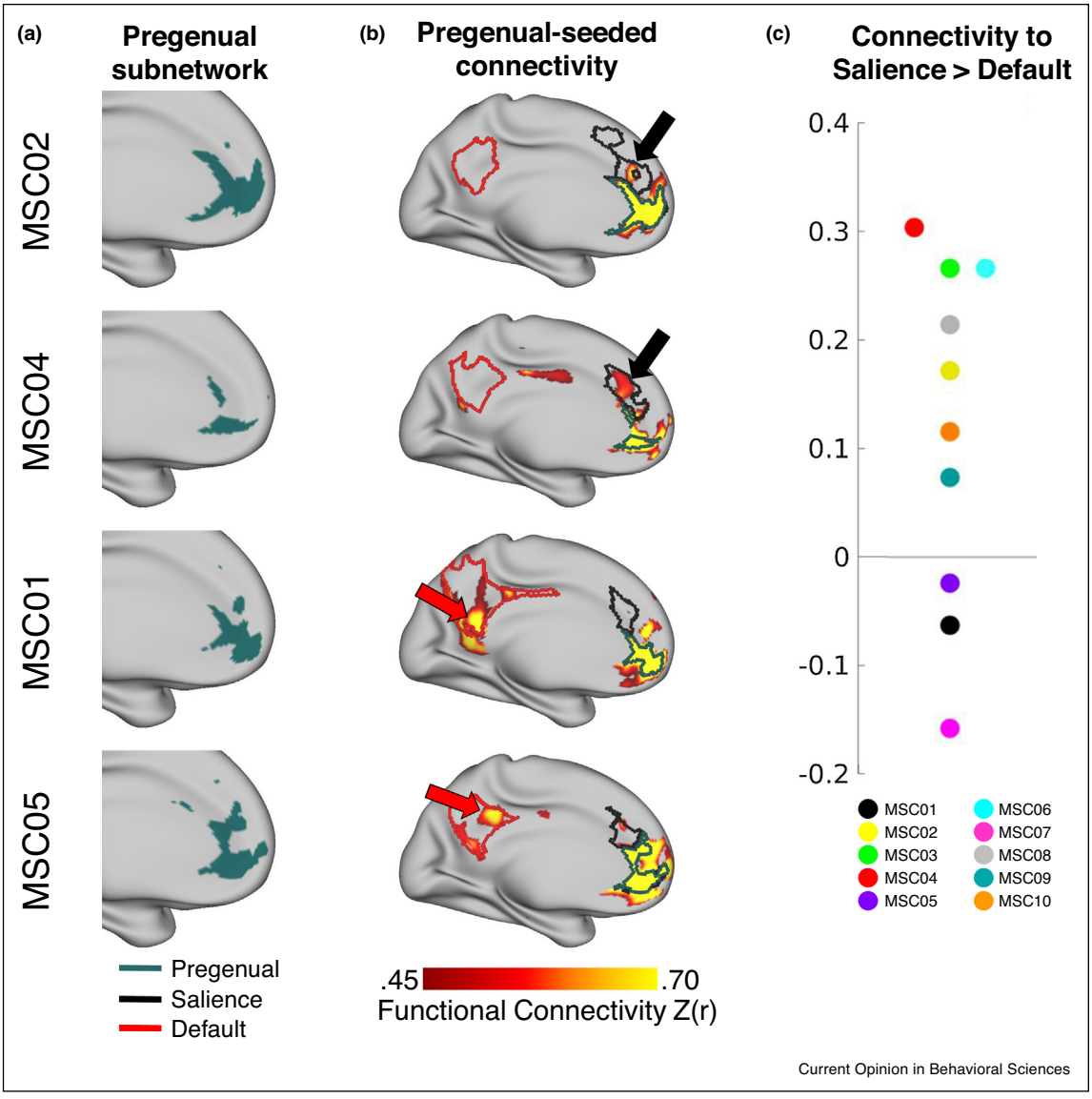
However, we also observe more dramatic and remarkable examples of individual variation in FC strength. For example, we have seen that every one of our individual subjects has a similarly shaped region that tracks the curve of the pregenual anterior cingulate cortex and extends forward into medial prefrontal cortex; this region is always strongly connected to ventral anterior insula and ventral caudate [21]. However, this region varies across individuals in which large-scale network it is connected to. In some subjects, we see this structure linked to anterior medial prefrontal and medial parietal regions within the Default network, while in others we see it linked to dorsomedial prefrontal regions of the Salience network (Figure 1). This observation—that brain regions can be spatially consistent and strongly linked to the same subcortical structures across subjects, but their large-scale network affiliations are variable—suggests that in some cases, individual variation in FC strength can be large enough to substantially reconfigure brain networks.

Spatial variation in functional connectivity networks

Cortical areas are likely the basic mesoscale structures that are linked together to form brain networks [1]. It is well established that cortical areas vary across individuals both in their physical size [22] and in their position along the cortical sheet [23]. It thus follows that features of brain networks would also spatially vary across individuals; and indeed, such spatial variation has been repeatedly demonstrated in cortex [24–28], basal ganglia and thalamus [29], and cerebellum [30,31]. This spatial variation (relative to anatomical features such as gyri and sulci) is of sufficient magnitude that many brain organizational features can be identified only in individual-specific data, not in group-average data [32•,33–38]. Such spatial variation comes in two primary forms: translation of brain network nodes along the cortical surface, and expansion/contraction of brain network nodes [24].

In our own data, we observed these variations most strikingly in two networks within the first highly sampled

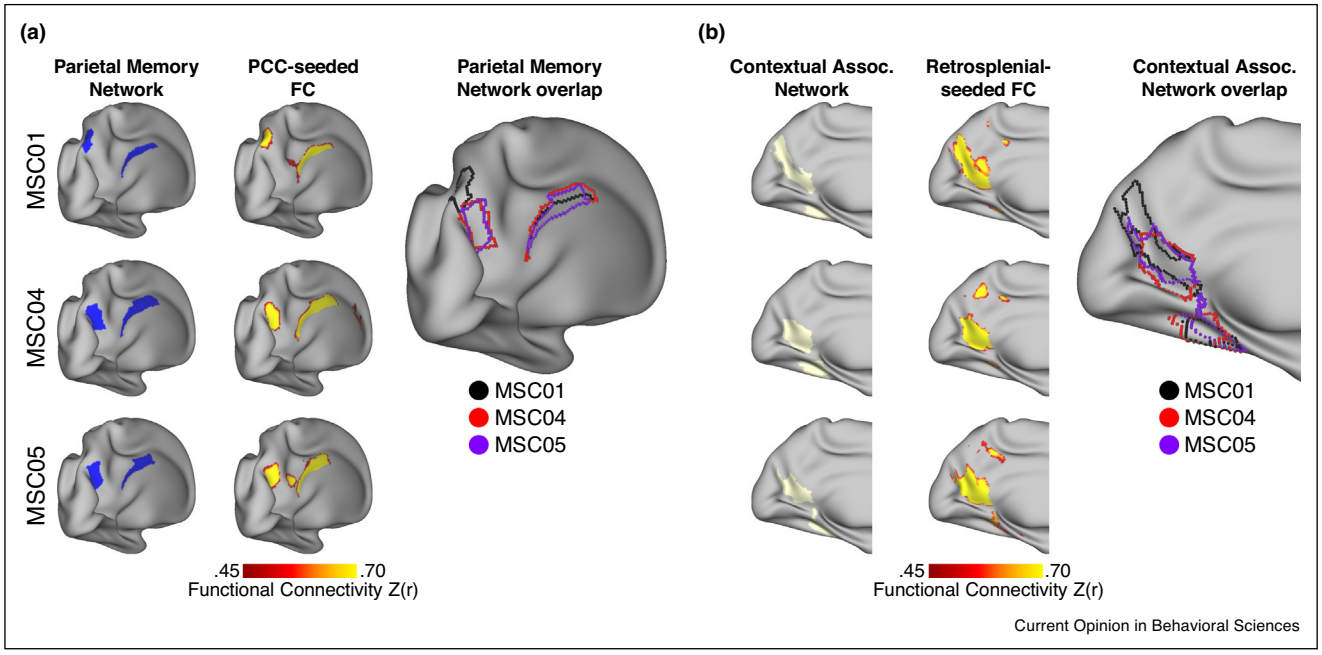
Figure 1



Variation in a region's functional network membership across subjects.
(a) A subnetwork was identified in every subject in pregenual medial frontal cortex (teal) that was connected to ventral anterior insula and ventral striatum (not pictured). **(b)** In some subjects (example subjects MSC02 and MSC04 shown here), this subnetwork was more strongly connected (black arrows) to the Salience network (black outlines). In others (MSC01 and MSC05), it was more strongly connected (red arrows) to the medial parietal node of the Default network (red outlines). **(c)** Difference between Pregenual connectivity to Salience and Default networks, across all subjects.

subject we collected in the MSC dataset (subject MSC01, who is author SMN). The Parietal Memory Network (PMN) is a relatively small network with four primary nodes in the left and right posterior cingulate cortex and posterior dorsomedial precuneus. While often mistaken for the DMN due to the adjacent large DMN representation in medial parietal cortex, this network is strikingly distinct from the DMN, as it has no representation in medial prefrontal cortex, angular gyrus, or temporal cortex [39–42]. Among association networks, the PMN is one of the more spatially consistent networks in the brain. Thus, we were surprised when we examined the PMN of various subjects and found substantial spatial variation in the location of their precuneus node. This variation is most remarkable in subject MSC01, in whom this node is not actually located in the precuneus. Instead, the node is substantially displaced approximately 30 mm along the cortical surface such that it is not even on the medial surface of the brain (Figure 2a). Such huge displacements are not explained by, for example, areal distortions due to

Figure 2



Spatial variation in functional connectivity networks across subjects.
(a) Identified Parietal Memory Network (PMN) (left column) and PCC-seeded FC (middle column) across three example subjects (overlap shown in right column). In subject MSC01, the posterior medial precuneus node of this network is wrapped around to the lateral side of the brain. **(b)** Identified Contextual Association Network (CAN) (left column) and retrosplenial-seeded FC (middle column) across three example subjects (overlap shown in right column). In subject MSC01, the CAN is expanded all the way up the parieto-occipital sulcus, filling the gap left by the displaced PMN.

the surface-based registration procedure [24], which are in the range of ±1 mm in most subjects including MSC01. Thus, this is a dramatic example of spatial variability via displacement: a strong, clearly identifiable node of a very simple four-node network that is *located on the wrong side of the brain*.

The next question became: if the posterior PMN node is displaced away from its original position, what is filling its original position? We found that in MSC01, the retrosplenial/ventral precuneus node of the Contextual Association Network (CAN), a known subnetwork within the DMN [21] related to processing contextual information [43], was expanded very far up the parieto-occipital sulcus relative to other subjects, taking over the real estate vacated by the PMN (Figure 2b). Tasks probing the functional engagement of the CAN verified the unusual expansion of the posterior node in this subject [19•].

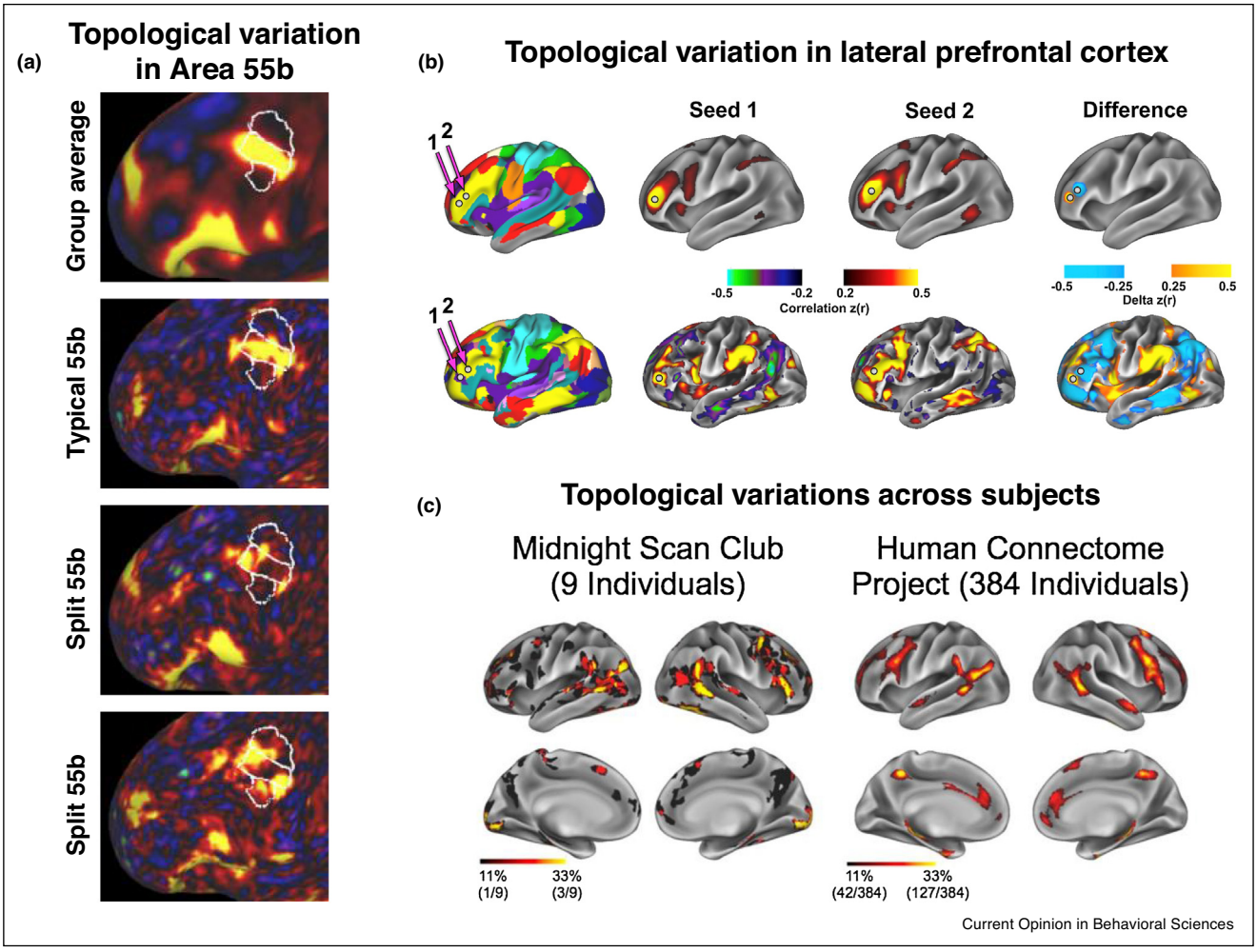
The relative magnitude of this particular spatial variation in CAN was large, as the node nearly doubled in surface area. However, once we started looking, we found variations in the size of network nodes all over the cortex, even in primary cortex where we expected individual variation to be relatively low. For example, while the hand-somatomotor and mouth-somatomotor networks are usually constrained within the banks of the pre and postcentral gyri, there can be substantial variation in the dorsal-ventral position of the border between these two networks [24].

Topological variation in functional connectivity networks

The assumption with both of the above two types of variation in FC is that every individual has the same set of networked brain areas. These areas may vary in their size or spatial position, and even in some cases in their network membership, but ultimately they do represent the same cortical object in approximately the same area of cortex, and thus are directly comparable across people. Individual connectomes composed of such matched areas can be said to have the same cortical topology.

However, the assumption of matched network topologies appears to be only mostly valid. Broadly, individuals always seem to have the same networks composed of the same distributed sets of regions [19•,33]. However, on a local level, specific areas that appear unitary in most subjects have been demonstrated to split into multiple discontinuous regions in a minority of subjects. Glasser *et al.* [44•] explored this in detail with putative area 55b, where they demonstrated that a network node that is

Figure 3



Topological variations in functional connectivity networks.
(a) Local topological variations can cause areas to be split, such as Area 55b, which is unitary in group average data (top image) and in typical subjects (second image), but is anterior-posterior split in some subjects (bottom images). Figure reproduced from Ref. [44•]. **(b)** Network-level topological variations cause intrusions of network nodes into unusual areas. Top: in group average data, two regions in lateral prefrontal cortex are both within the Fronto-parietal network (yellow), and have very similar functional connectivity patterns. Bottom: in the MyConnectome dataset, one of these regions (Seed 1) is instead connected to the Cingulo-opercular network (purple), causing the two regions to have dramatically different functional connectivity patterns. Figure reproduced from Ref. [18]. **(c)** Localization of such topological variations identified their presence in every subject studied, and suggested similar spatial distributions across subjects in the MSC dataset (left) and in the Human Connectome Project dataset (right). Figure reproduced from Ref. [45•].

singular in one individual may exist as multiple dissociated regions in another (Figure 3a).

We have identified additional individual variations in network topology in densely sampled individual data. Indeed, one of the first major features of interest we observed in Dr Russ Poldrack's MyConnectome data [18] was a region in anterior lateral prefrontal cortex—an area always assigned to the Fronto Parietal network in group studies—which was uncorrelated with Dr Poldrack's Fronto-Parietal network, but strongly linked to his Cingulo-Opercular network (Figure 3b, Seed 1). This region was so punctate, so spatially distant from the rest of the Cingulo-Opercular network, and so divergent in its connectivity pattern from the surrounding Fronto-Parietal tissue (e.g., Seed 2), that it is hard to interpret it as anything other than an entirely idiosyncratic node, not topologically comparable to areas we have seen in most individuals. Since then, we have identified putative topological 'variants' in every individual we have studied [45•] (Figure 3c).

The interpretation of this topological variation is still unclear. It is possible that such variants simply represent extreme examples of the spatial or connectional variability described above. A Cingulo-Opercular node in the middle of lateral prefrontal cortex, as in Figure 3b, could

be a normally Cingulo-Opercular-linked area that has been substantially displaced. Or, it could be a normally Fronto-Parietal-linked area that exhibits wildly different connectivity patterns from its standard functionality. Alternately, it could be a node that simply doesn't exist in the networks of most individuals, in the same way that area 55b doesn't split in most individuals.

Cross-confounding effects of different types of variation

The difficulty with multiple simultaneous types of network variation is that effects of each one can confound estimates of the others. For example, in an approach using a priori parcels, which ignores inter-subject spatial variability, FC estimates for an individual with a highly displaced parcel (as in Figure 2a) will appear wildly abnormal. While this is most evident for large displacements, even small displacements will produce signal mixing within a priori parcels, and will result in reduced FC estimates—which would then be interpreted as 'lower' FC. Indeed, initial attempts to understand the relative contributions of spatial and connectional variability have suggested that spatial variability contributes relatively more to observed individual differences than connectional variability [32•]. Importantly, as the scale of spatial variation is probably relatively consistent across the brain, this issue will always affect smaller network nodes (which overlap worse with a priori regions) to a greater extent than large network nodes [37].

At the same time, FC differences may confound attempts to understand spatial variation in networks. A network node may be relatively spatially consistent across individuals, but if it had strongly varying FC patterns, then it can be interpreted as spatial variation in large-scale networks that are dramatically expanding or contracting to encompass or exclude the network node (as in Figure 1). These cross-confounding effects are likely exacerbated when varying estimates of FC strength may also be driven by variation in data quality. For example, it can be very hard to interpret variability of FC strength in striatal and thalamic regions as meaningful, because that FC strength is often critically driven SNR within those regions, which varies with the distance from the MR coil and thus can be influenced by variation in head size.

How to get around these issues? One promising approach may be to employ machine learning classification approaches for network node matching [26,44•], especially ones specifically designed to simultaneously model both spatial and connectional variability [32•,37]. However, such approaches often critically rely on having good priors, and it is not clear whether we know enough about the range of inter-individual variation in FC networks to generate such priors. Another approach might be to estimate networks at a hierarchically lower level—network substructures—where connections are more likely to be direct and connectional variation may be reduced [21], and subnetworks matched across individuals based on similarity of spatial distributions. However, just because connectional variation might be reduced at this hierarchical level doesn't mean it would be eliminated altogether.

Importantly, it is not clear that any of these approaches can deal with the existence of putative topological variations. Whether the observed topological variants represent idiosyncratic, *de novo* brain regions or not, they represent areas that are so spatially/connectionally divergent from other subjects and from a group-derived prior that they may not be classifiable by any extant approach.

Implications for brain network research

Ultimately, these confounding effects mean that it is very difficult to accurately compare FC across individuals. A subject may exhibit abnormally low or high FC, but that deviation from the mean is not easily interpretable, since it is not clear what aspect of the deviation might be driven by spatial or topological rather than connectional variation. This may be somewhat disheartening. At the same time, it may also explain some of the replication failures and low effect sizes that have been revealed in the field recently using the standard approach of measuring FC using a priori seeds [12•]. This standard approach will inevitably collapse these multiple types of variability, introducing uninterpretable noise into the FC measure and reducing the ability to observe FC-behavior associations. Importantly, this conceptualization not only helps explain why the field has had trouble linking individual differences in FC to cognition, but also points towards a path forward. We believe that solving the problem of matching network nodes across individuals, while challenging in the face of the multiple simultaneous types of variability we have outlined, is a critical step towards being able to effectively compare brain function across people.

We want to emphasize the critical role that we believe individual-focused analyses must have in the development of these techniques (see also Ref. [46]). Without the ability to look at the brain networks of individuals and see real, concrete examples of how people vary, these types of variability remain abstract and nebulous. We hope that by presenting the dramatic examples of individual variation in FC that first struck us in our own data, we can help the field move towards understanding and ultimately accounting for this variability more broadly. Finally, we believe that the development of future classification priors must be built on individual-level data, not group averages, as group average data almost by definition cannot represent the types of spatial, connectional, and topological variation we see in individual brains.

Conflict of interest statement

Nothing declared.

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