Measuring the Individual: Understanding sources of variability in task and resting fMRI

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1205
Symposium
Functional neuroimaging stands at a crossroads; new imaging sequences, advanced analytical approaches, as well as publicly available large sample, multimodal, or repeated sampling datasets provide opportunities to drive new and innovative areas of research. To fully realize these opportunities in basic and clinical neuroscience, a growing consensus suggests it is critical to expand research beyond standard group aggregate analyses and begin to explore the full range of variability across individuals. High-quality neuroimaging data that include larger samples and repeatedly tested individuals allow for a deeper understanding of variability and the numerous factors driving differences across individuals. This symposium will examine different sources of variability in both healthy and psychiatric populations, how variability can impact resting-state and task-based functional measures, and the range of variability both within and between individuals. We will consider the impact of individual variability from a diverse range of perspectives, providing a broad overview of how variability can impact neuroimaging results and how better understanding this variability can drive new discoveries. Specifically, we will examine variability in the context of resting-state functional connectivity, task-based connectivity and activity, and both healthy and clinical samples. The audience should gain a fuller understanding of sources of variability in fMRI data, how we can leverage that variability for discovery, and ways that undesired variability can be minimized.

Objective

1. Gain perspective on the types of individualized fMRI approaches that are being developed.
2. Learn how to characterize sources of variability in fMRI data, how they can impact our data, and how they can be leveraged for discovery.
3. Appreciate the range of variability that can be observed across individuals within task and resting fMRI data, and how this variability can skew our understanding of cognitive functions or within psychiatric populations.

Target Audience

The current symposium would be appropriate for researchers who are interested in applying individualized fMRI approaches to their research questions, researchers interested in learning about the sources of variability influencing their data, as well as for clinician-scientists who are considering new translational techniques. The talks will be appropriate for a broad audience at various levels of expertise.

Presentations

Factors influencing the test-retest reliability of functional connectivity

Once considered mere noise, functional connectivity has become a major neuroscience tool in part due to early studies demonstrating its reliability. These fundamental studies revealed only the tip of the iceberg; over the past decade, many test-retest studies have continued to add nuance to our understanding of this complex topic. Diverse and contradictory perspectives now exist, with almost as many recommendations for study design and analysis. Here, we address open questions using 1) an empirical study and 2) a comprehensive meta-analytic review of the literature. The empirical study uses a small dataset of extensively sampled individuals (Yale Test-Retest) and a large dataset of twice-sampled individuals (Human Connectome Project). Overall, both empirical and meta-analytic results suggest that the historical 5-min scan produces poor reliability at the level of individual connections. However, reliability is dependent on many factors. Within-network cortical connectivity, particularly within frontoparietal and default mode networks, is typically most reliable, whereas subcortical connectivity is typically least reliable. Notably, there is disagreement about the effect of certain analytical strategies (e.g., global signal regression) on reliability, complicated by the fact that some strategies that improve reliability may reduce validity. We will discuss the prevailing consensus and/or disagreement regarding the data needed for reliability, multivariate reliability, acquisition strategies, preprocessing strategies, and recommendations based on these findings.

Presenter

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Differentiating anatomical and functional sources of variability to improve neuropsychiatry research.

In research using neuroimaging to discover clinical biomarkers and inform treatment response, we aim to use realignment methods and parcellations to boost reduce some sources of variability (i.e. variability in the locations of brain areas) in order to make meaningful comparisons between people. Surface-based (vs. volume-based) approaches for between-subject realignment have been proposed as a method for reducing unwanted variability caused by cortical folding. In addition, multi-modal realignment or “individualized” parcellations, based on connectivity patterns, can push analyses into a common “functional” brain space. However, the true impact of these analytic choices on results is not well understood. It is important for users to realize that volume-based and surface-based representations of the same cortical atlases differ within the same participant. We demonstrate this using the Human Connectome Projects minimally preprocessed anatomical data (n = 1113) where we measured anatomical variability in the cortical vertices of parcels from the Schaefer parcellations (Schaefer et al., 2018) extracted three ways: volume-based, anatomically aligned surface-based (MSMSulc) and multimodal-aligned surface-based (MSMAll). These differences between volume, MSMSulc and MSMAll parcel locations are not ubiquitous across the cortex, meaning that results from some cortical networks (especially frontal-parietal and visual attention) are more impacted by realignment-approach than others. It is more important to consider is the impact of these choices on the results of clinical statistics - for example, comparisons of resting-state fMRI from people with Schizophrenia Spectrum Disorders (SSD) and healthy controls (HC). Using resting state and anatomical MRI data from n=494 participants (n = 202 SSD, n = 292 healthy controls (HC), age M(SD) = 28.8(8.9), 294 Males) we show that improving between subject functional alignment can boost signal and yield more interpretable results. Pooling four datasets ((1) Centre for Addiction and Mental Health 2) Zucker Hillside

Hospital 3) The Center for Biomedical Research Excellence (Christensen et al 2014), and 4) UCLA Consortium for Neuropsychiatric Phenomics LA5c Study (Poldrack et al 2016) functional timeseries were extracted from subcortical subregions as well as from 80 cortical regions of interest using 1) a volume-based approach 2) a surface-based group atlas approach, and 3) Personalized Intrinsic Network Topography (PINT), a personalized surface-based approach (Dickie et al., 2018). In SSD vs HC comparisons, controlling for age, sex, scanner and in-scanner motion, we observed robust patterns of dysconnectivity that were strengthened using a surface-based approach and PINT (Number of differing pairwise-correlations: volume: 357, surface: 562, PINT: 630, FDR corrected). These patterns were found from four different cortical networks - frontal-parietal, sensory-motor, visual, and default mode -- to subcortical regions. This work suggests that our choice of neuroimaging analysis tools really do matter. Spatial patterns of brain functional connectivity can vary substantially at the individual level. Improving unwanted sources of variability via anatomical and functional alignment provides our models to more meaningfully patterns of variation in brain activity across people. However, surface-based techniques are still more challenging to apply - as greater tooling and support is available to volume-based techniques and atlases. More education and simpler tooling will be needed for these techniques to be applied at a wider scale.

Presenter

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Precision measurements reveal trait-like variations in human functional brain networks

Over the last decade, large advances have been made in our ability to measure human functional brain networks and use them to address cognitive and clinical neuroscience questions. Most of this work has focused on group measurements, based on data averaged across large samples of individuals. However, the application of this work to clinical or individual differences questions may be limited, given large heterogeneity in both neurobiological and behavioral characteristics among individuals. Recent findings have suggested that the use of repeated “precision” fMRI approaches can address these questions by sensitively measuring brain networks in individuals, while addressing issues of reliability in more limited time datasets. When coupled with behavioral or phenotypic information, this approach opens the door to address questions of how individual differences in brain organization affect individual differences in cognition. In expansions on this work, we have demonstrated that prominent and reliable network differences occur between individuals that are much larger in magnitude than daily or cognitive variation. Motivated by these findings, we recently investigated the characteristics of individual differences in more detail using a combination of precision data from the Midnight Scan Club as well as the large sampling dataset from the Human Connectome Project. We find that individual differences in functional networks occur in punctate locations, which we call “network variants”. Network variants are common and associated both with shifts between networks as well as isolated ectopic intrusions far from typical. Moreover, the distribution of network variants shows a number of trait-like characteristics, including stability over time, systematic localization (being most associated with association brain systems), and ability to cluster individuals. Interestingly, network variants are also associated with characteristic shifts in activations during tasks, suggesting that they represent brain regions with shifted functional profiles. Finally, clusters of individuals with different network variants also show some differences in behavior. This work suggests that network variants may be trait-like characteristics of brain organization and opens an exciting new window into the study of functional brain networks and their variation, relevant for understanding network contributions to variability cognition and clinical deficits.

Presenter

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Clustering Task-fMRI Activity in Large Samples of Schizophrenia or Healthy Populations Reveals Patterns of Individually-Variable Activity

Functional neuroimaging has resulted in a dramatic increase in the understanding of human cognitive processing in the brain. Group statistical analysis remains the main-stay of neuroimaging research in healthy populations and patients groups. This approach considers group-mean patterns of brain activity, and fundamentally assumes within-group homogeneity and consistent between group heterogeneity (i.e. groups being compared differ systematically in specific ways which are common across group members). However, substantial variability exists between individuals leading to violation of these assumptions, which may exceed the differences observed between clinical populations. Previously in Hawco et al., (2019), 179 individuals (mixed schizophrenia spectrum and controls) performed a social cognitive functional magnetic resonance imaging (fMRI) facial Imitate/Observe task. Hierarchical clustering based on patterns of brain activity revealed three distinct sub-groups which did not differ by diagnostic category: 1) typical activators, showing the expected pattern of activity; 2) hyper-activators with widespread activity; 3) deactivators who minimally activated the appropriate cognitive network while suppressing activity in other social processing regions. This pattern of deactivation was considered an 'efficient' pattern of activity, and was associated with better out-of-scanner cognitive scores. Building on these findings to better capture and understand variable spatial patterns of fMRI task-activity between participants, a clustering based approach was explored in a population of healthy adults to identify data-driven patterns of fMRI task activation and compare their overlap to group mean patterns. Data were examined from 822 healthy young adult participants from the Human Connectome Project. Hierarchical clustering was applied separately to brain activity from six cognitive fMRI tasks across a range of cluster numbers from 2-10. Similar to our previous study, clustering identified sub-groups of participants with distinctive patterns of activity, which tended to fall along a 'positive-to-negative' axis of brain activation regardless of the designated number of clusters. Interestingly, cluster membership was not strongly related between tasks (e.g. participants did not tend to fall into the same clusters across the six tasks), though clustering was significantly related to out-of-scanner cognitive test scores for most tasks. To better understand clustering, a bootstrapping approach was used. Across 1000 bootstraps, 75% of the sample was clustered, repeated for the six cognitive fMRI tasks. A cluster probability matrix was then constructed as the percentage of times a given pair of participants clustered together when both present in a given bootstrap. Results from bootstrapping demonstrated that rather than distinct clusters, participants best fit along a spectrum with no clear group boundaries. Next, a principal component analysis (PCA) was performed on the cluster probability matrix and participants were plotted according to the top three components. Plots of PCA clusters identified two characteristic shapes; a "S" shaped pattern, or a folded circle pattern, each observed in three HCP tasks. These plots represent a lower-dimensional similarity manifold capturing the range of task activity across participants. Simulation data confirmed the "S" pattern was present in tasks where participants fell along a spectrum of activity magnitude (e.g. negative to positive), while the folded circle shape was present when clustering was driven by two independent systems/networks. These results demonstrate that although standard approaches collapsing participants into a single group may work well to extract a 'common-core' of regions involved in a given task, important variation across individuals is missed. This variation may be driven by a functional network or structural variability, or related to different task performance strategies. Better understanding the full range of this variability may be critical to a more complete understanding of human cognitive brain function.

Presenter

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