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The early origins and the growing popularity of the individual-subject analytic approach in human neuroscience

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In the last three decades, functional magnetic resonance imaging (fMRI) has transformed the field of cognitive neuroscience. A standard analytic approach entails aligning a set of individual activation maps in a common brain space, performing a statistical test in each voxel, and interpreting significant activation clusters with respect to macroanatomic landmarks. In the last several years, however, this group-analytic approach is being increasingly replaced by analyses where neural responses are examined within each brain individually. In this opinion piece, I trace the origins of individual-subject analyses in human neuroscience and speculate on why group analyses had risen vastly in popularity during the 2000s. I then discuss a core problem with group analyses — their limited utility in informing the human cognitive architecture — and talk about how the individual-subject functional localization approach solves this problem. Finally, I discuss other reasons for why researchers have been turning to individual-subject analyses, and argue that such approaches are likely to be the future of human neuroscience.

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The origins of individual-subject human neuroscience: the early 1990s

An experiment carried out on May 9, 1991 transformed the field of cognitive neuroscience forever: flickering lights, compared to a no-visual-stimulation baseline, elicited a focal response in the human primary visual cortex [1]. This change was observed completely non-invasively, with no contrast agents, by simply leveraging the magnetic properties of blood in a magnetic resonance scanner. This experiment had a single participant.

It was no accident that the very first fMRI experiment used a visual stimulus. At the time when the BOLD signal was discovered, the primate visual system had already been richly characterized from decades of macaque neurophysiology (e.g. Refs. [2–4]). Consequently, much early fMRI work in humans (e.g. Refs. [5,6,8]) was aimed at identifying the visual areas that had been previously discovered and characterized in macaques. Given strong prior expectations about what to look for, these early visual fMRI experiments all relied on the analyses of individual brains because the same basic configuration of the visual cortex was (reasonably) expected to be clearly present and robustly detectable in every participant.

Things got more exciting when, building on this general analytic approach, Nancy Kanwisher went on to discover and characterize a region in the fusiform gyrus that responded selectively to faces compared to other objects. Although some had previously reported face-selective cells in macaques (e.g. Ref. [9]; see Ref. [10] for a review), Kanwisher found that such cells were apparently sufficiently clustered that a highly face-selective area could be found in every individual in approximately the same location [11]. Along with earlier evidence from psychophysics (e.g. Ref. [12]), intracranial recordings in humans (e.g. Ref. [13]), and investigations of individuals with prosopagnosia (e.g. Ref. [14]), this discovery paved the way for thousands of investigations aimed at understanding face perception mechanisms in humans and other animals (e.g. Refs. [15–18,101]).

The rise of group analyses: mid 1990s through late 2000s

However, vision researchers with backgrounds in — or intimately familiar with — monkey physiology work were not the only early users of fMRI in humans. Another community consisted of researchers who had previously conducted human brain-imaging work using positron emission tomography (PET). In PET, repeated measurements within individuals are extremely restricted due to the limit on the amount of radiation. Consequently, averaging data across individuals is the default (cf. [19,20]). In this group-averaging approach, individual activation maps are aligned in a common brain space and statistical inference is performed across participants

voxel-wise. For the simplest case, a *t*-test comparing the responses to two conditions is performed in each voxel. So, researchers, who had previously used PET brought to fMRI the analytic tradition they were familiar with.

Furthermore, in the mid-1990s, early versions of the Statistical Parametric Mapping (SPM) software (e.g. SPM94; [21]; see Ref. [22] for a discussion of SPM's history) were released for fMRI data preprocessing and analysis. SPM had a graphical user interface thus obviating coding expertise or a deep understanding of the steps happening 'under the hood', which made it appeal to a wide range of scientists and clinicians who could now easily analyze their data. The fact that a group analysis — averaging brains together in a common stereotactic coordinate space — was the default in SPM has almost certainly contributed to the widespread use of this approach.

A fundamental issue with group analyses

Over the years, fMRI has received substantial criticism given that a large number of studies fail to go beyond the 'where' question (e.g. Refs. [23,24]). Such studies set out to look for *where* in the brain some stimulus or task elicits a response, and the output of such studies is a set of coordinates in a template brain space. In describing the observed activation clusters, researchers would often resort to coarse macroanatomic areas (e.g. 'inferior frontal gyrus', 'superior temporal sulcus', or 'cerebellum') or to estimates of Brodmann area locations (e.g. BA44 or BA9). They would then attempt to interpret their findings using reverse-inference reasoning from anatomy to function (e.g. Refs. [25•,26]). For example, a study targeting some linguistic process may observe an activation cluster within the left inferior frontal gyrus (LIFG) and interpret this activation as reflecting working memory demands because an earlier study had observed activation in the LIFG for a working memory manipulation. This reasoning is flawed. In particular, outside of primary perceptual and motor areas and some subcortical structures, all macroanatomic cortical areaa (including Broadman area estimates[1]) are highly structurally and functionally heterogeneous, often containing adjacent regions with opposing functional responses (see Ref. [27••] for a discussion of this issue in the context of 'Broca's area'). As a result, the fact that a peak is observed within some macroanatomic area does not tell you more than, well, that you found a peak within that area (Figure 1). And it was unclear to cognitive scientists how anatomical locations of activation peaks could inform theories of human cognitive architecture.

A possible solution: functional localization

So can fMRI data ever inform theories of human cognition? I would argue the answer is yes (see Refs. [28•,29••] for discussions). One approach that makes it possible is 'functional localization'. In this approach, instead of asking *where* in the brain some stimulus or task elicits a response, a brain region or network that appears to support a mental process of interest (say, face perception, or language comprehension) is first identified with a functional contrast. Then, across dozens or even hundreds of studies, its functional responses are carefully and systematically probed in an effort to narrow down the hypothesis space about the possible representations it stores/builds and the computations it performs. Critically, anatomy alone is not sufficient to ensure that the 'same' brain region/network is examined across individuals, studies, and labs because anatomy is a poor predictor of function, especially in the association cortex (e.g. Refs. [30,31•,32•]). The solution is to use a combination of anatomical constraints and *function* (e.g. Refs. [33•,34•,35]). This approach, again, originates in animal physiology, where before performing the critical recordings, you would want to make sure that you are in the 'right' place: that is, that the cells show some expected functional signature. Importantly, although the regions of interest are defined within each brain individually, statistical inference is performed (on the signals extracted from these individually-defined regions) *across participants* to generalize the observed effects to the population.

This approach to fMRI, developed and popularized by Kanwisher in the late 1990s has been tremendously successful. Using this approach, Kanwisher and colleagues discovered the organization of the ventral visual stream and characterized several highly specialized areas (e.g. Refs. [11,36–38]). This approach was later extended to other domains, including social perception and cognition (e.g. Refs. [39–41]), language (e.g. Ref. [35]), executive functions (e.g. Refs. [42,43]), and intuitive physics (e.g. Ref. [44]).

Functional localization has sometimes been criticized for the use of particular contrasts to target the brain region/network of interest (e.g. Ref. [45]): how can we be sure that using a particular set of stimuli or a particular manipulation will result in a functionally meaningful unit/system? This concern would be reasonable if the activations depended on a specific contrast. However, functional localizers are usually extensively tested and validated before they become widely used, to ensure that variables

[1] Brodmann area estimates may seem better than macroanatomic areas as they should be closer to microarchitecture, which may, in turn, be closer to meaningful functional units. However, with standard scanning protocols, we cannot see microarchitecture *in vivo*, and the estimates in use in the field are based on Brodmann's or others' schematized drawings. Moreover, *ex-vivo* imaging has shown that inter-individual overlap among Brodmann areas in the common space is extremely low, especially in the association cortex. For example, not a single voxel overlaps among all 10 participants in the Juelich dataset of 10 post-mortem human brains for BA44 when using the MNI space ([65]; see Ref. [100] for better, but still poor, alignment in an inflated surface space). Thus, estimates of Brodmann areas in group-level maps are no more meaningful than macroanatomic areas, at least in the association cortex.

that are not expected to affect activations don't affect them. For example, before using our localizer for the high-level language network (e.g. Ref. [35]), we first demonstrated that it doesn't matter whether the stimuli are presented visually or auditorily, whether the stimuli are processed passively or with a task, whether the sentences are short and simple or longer and more complex, artificially constructed or taken from corpora, and so on. Moreover, recent work where large amounts of resting state data are collected within individuals has established that activations elicited by robust and validated localizers correspond nearly perfectly to the networks that emerge from patterns of intrinsic fluctuations (e.g. Refs. [46,47,48•,49•]; see Braga, this issue, for further discussion). And investigations of white matter architecture have shown that individually localized functional areas can be identified from patterns of connectivity as probed with diffusion-weighted imaging (e.g. Ref [90,102]).

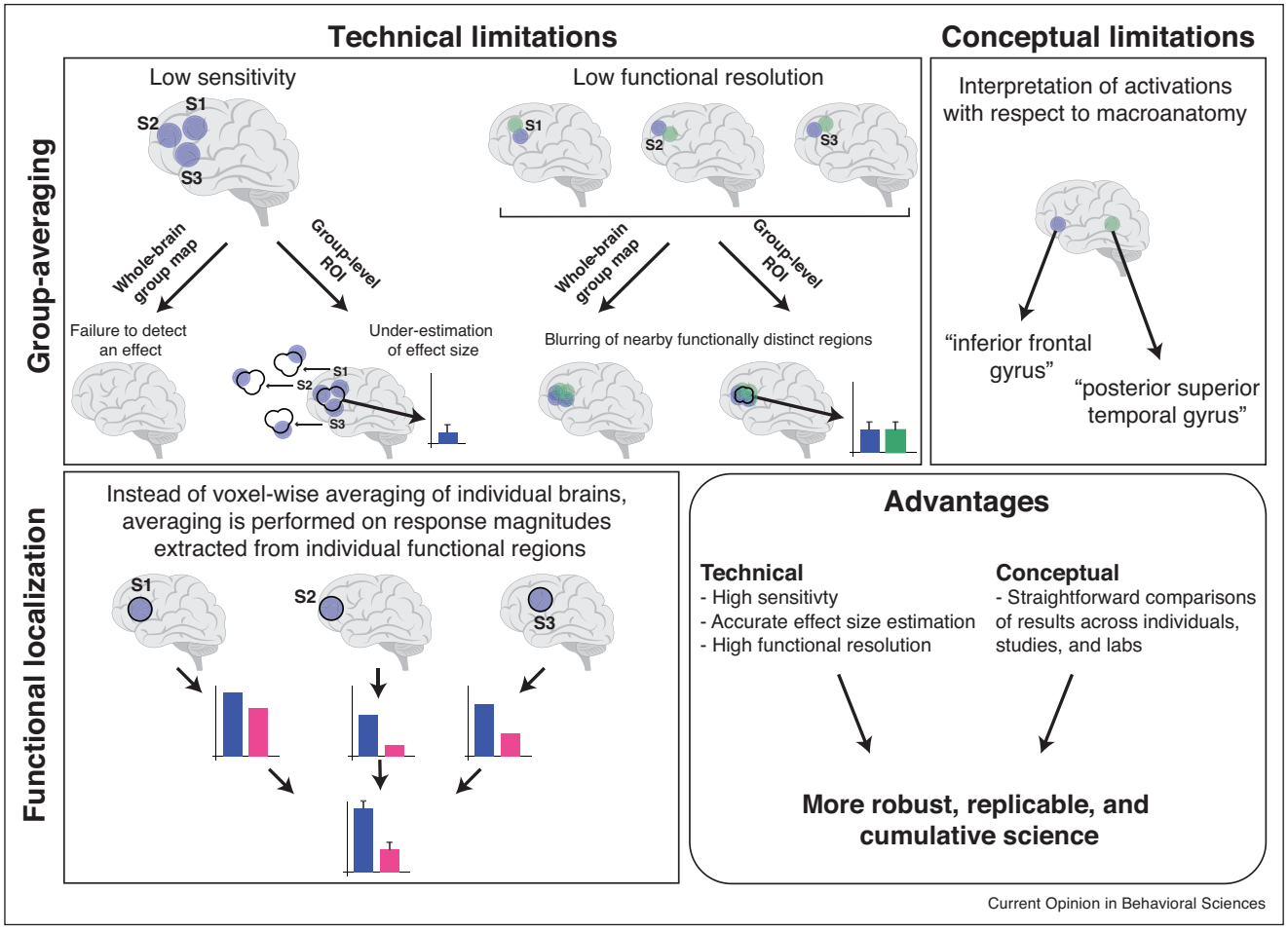
The versatility and growing popularity of individual-subject analyses

In the last decade, reliance on individual-subject analyses has been on the rise (e.g. Refs. [50,51,52•,53–56,57•,58,48•,59•,60], among others). In addition to enabling the probing of the cognitive architecture via the functional localization approach discussed above, individual-subject analyses confer other advantages and have other uses. I highlight three below.

1 "All the better to see with, my child".
Looking at high-quality data in an individual participant versus looking at a group-level map is akin to using a high-precision microscope versus looking with a naked myopic eye, when all you see is a blur. As noted above, the precise locations of functional areas vary substantially across individuals, especially in the association cortex (e.g. Refs. [30,31•,32•]). As a result, analyses that average activation maps across participants and perform statistics in a voxel-wise manner suffer from two fundamental limitations (e.g. Ref. [61••]). First, they can miss an effect because of insufficient voxel-level overlap across individuals (low sensitivity; Figure 1). And if they do detect activation, they are certain to underestimate the effect size, which is critical for interpretation (e.g. Ref. [62]). And second, they can blur distinctions between nearby functionally distinct areas (low functional resolution; Figure 1) (see Ref. [61••], for evidence of these two issues based on simulations; see Refs. [34•,35,63,64], for evidence from real data).
Although poor alignment of activations across individuals is a technical/statistical issue, it can have profound theoretical implications. Indeed, individual-subject analyses have already uncovered numerous critical features of the human neural and cognitive architecture that were lost in the blur of group averaging and had led to misguided theorizing. For example, [65]; also [66,67]; see Ref. [27••] for a review) have shown that the left inferior frontal gyrus contains subsets of (at least) two functionally distinct networks: the language-selective network (e.g. Ref. [68]) and the domain-general Multiple Demand network (e.g. Ref. [69,70]). Similarly, the cortex at the junction of the temporal and parietal lobes has been shown to contain nearby but functionally distinct areas: one highly specialized for Theory of Mind [71], and another supporting exogenous attention [72]. And the famous Default (Mode) Network (e.g. Ref. [73]) has been found to consist of two interdigitated functionally distinct networks: one supporting social cognition, and the other — episodic projection [49•,56,60].
In some cases, fine-grained spatial distinctions — only observable within individuals — have been reported, but their functional significance remains to be discovered. Such distinctions have been found in the cortex (e.g. Refs. [51,74–76,47,55,57•,58,59•]), the cerebellum (e.g. Ref. [77]), and some subcortical areas (e.g. Refs. [78,79]).
Finally, laminar imaging (e.g. Ref. [80]), which requires the highest possible spatial resolution — achievable with strong-field magnets and special sequences — only makes sense at the individual-subject level. Such studies aim to illuminate the contributions of top-town versus bottom-up processes to human perception and cognition and have already yielded numerous exciting discoveries (e.g. Refs. [81–84]).

2 To investigate inter-individual differences in neural architecture in the service of understanding the relationship among cognition, brain, and genes.
Cognitive neuroscience strives for generality: we want to discover properties common to all brains, not idiosyncratic properties of any single brain. Functional localization, discussed above, aims to circumvent the inter-individual variability in the precise locations of functional areas to be able to refer to the 'same' brain region or network across individuals. However, stable inter-individual variability can also be leveraged to infer general principles of the human cognitive, neural, and genetic architecture by examining the correlational structure of diverse features across individuals (e.g. Refs. [85•,86]).
Aside from the stable inter-individual variability in the topography — locations, sizes, and shapes — of the different regions/networks, some features of neural responses appear to be stable within individuals and variable across them. For example, for the language network, such features include the strength of response during language processing, the hemispheric bias in response strength, and the stability of the fine-grained activation landscape [87•,103,104]. For the domain-general Multiple Demand network, the degree to which neural responses increase with increases in cognitive effort appears to be stable within individuals

Figure 1



A schematic illustration of the technical and conceptual issues inherent in the traditional fMRI group-averaging analytic approach (top), and of the basic principle and the advantages of the functional localization approach (bottom).

[88]. And the strength of inter-regional functional correlations has also been shown to be stable within individuals over time for many key large-scale networks [57•,59•], with the variation having functional relevance [89•]. Inter-individual variability in the structure of both grey and white matter have also been commonly examined, although in most studies. this has been done based on macroanatomy alone (e.g. examining the cortical thickness of a gyrus or the depth of a sulcus). Performing these analyses on functionally meaningful units (e.g. the thickness of the language-responsive area in the inferior frontal gyrus) may lead to more robust, replicable, and interpretable findings (e.g. see Ref. [90] for this kind of approach to investigations of white-matter connectivity).

Which functional and/or structural features of the brain end up being most important in linking our genetic composition to cognitive abilities and behavior remains to be discovered. Critical to this enterprise will be the quality of the data collected from each individual. Investigations of individual differences require large numbers of participants (hundreds, or even thousands/tens of thousands for studies of genetic-neural relationships; e.g. Ref. [91•]), but these large numbers should not come at the cost of poor data quality: without collecting sufficient data from each individual, the resulting measures extracted from those data will be meaningless (e.g. Ref. [92]).

3 To address novel research questions.

Certain research questions and analytic approaches require vast amounts of fMRI data to be collected from the same individual (dozens/hundreds of hours worth, and sometimes over the timespan of months or years), making it prohibitive to collect a typical-size fMRI sample of 15–30 individuals. Such questions/approaches include a) data-driven structure discovery that requires large numbers of conditions or many hours of naturalistic stimuli (e.g. Refs. [93–95]); b) any

approach where responses to individual stimuli (rather than conditions (groups of stimuli)) need to be estimated: for example, when decoding the stimulus from brain activity (e.g. Refs. [96,97,105]) or when relating neural data to representations extracted from artificial neural network models (e.g. Ref. [98]); or c) longitudinal investigations of experience-dependent plasticity, like when acquiring expertise in a particular domain or recovering from brain damage. Such studies are commonly criticized for their inability to generalize beyond a particular individual or a small set of individuals (cf. Naselaris *et al.*, this issue, for discussion), but they can be indispensable for illuminating human cognitive, computational, and neural architecture.

Summary: the individual-subject analyses as the future of human neuroscience

The scientific enterprise of fMRI research began with an experiment on a single individual. In the years to follow, a relatively small subset of the field has continued to rely on analyses where a target region/network is identified functionally within each individual brain and then the responses of this region/network to some new critical condition(s) are examined across individuals. However, a large fraction of fMRI researchers have adopted an alternative approach, where activation maps are averaged across individuals voxel-wise. The former studies average *neural responses* and tell us something new about the mental process (e.g. face perception or language comprehension) targeted by the localizer. The latter average *brain maps* and tell us where in the brain activation clusters emerge (Figure 1). As discussed above, interpreting cluster locations based on their approximate anatomical locations is precarious given that macroanatomical divisions do not correspond to functional ones. In the last decade, many researchers have begun adopting functional localizers or turning to individual-subject-level analyses for other reasons. At this point, it is unclear under what circumstances traditional group analyses would have advantages over individual-level analyses. Even in cases where we may want to test whether some novel manipulation elicits spatially consistent responses, we now have analytic approaches that allow for variability in the precise locations of functional areas (e.g. Refs. [35,99,106]). Thus, individual-level analyses — with their superior sensitivity, functional resolution, interpretability (Figure 1), and general versatility for addressing diverse research questions — appear to be the way to go if we want to make cognitive neuroscience more robust, replicable, and meaningful.

Conflict of interest statement

Nothing declared.

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