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Scanning for Justice With Functional Magnetic Resonance Imaging

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If asked to predict the weight of a Major League baseball, you'd probably be able to do it rather easily; by weighing a representative sample, you could use the mean of your observations to predict the weight of the next ball to within 5 grams. By regulation, all balls must weigh between 142 and 149 grams—which is to say that if you guessed 145 grams, you would be right 100% of the time.

But what if we asked you to guess the weight of a human brain with the same margin of error? Though the average weight is known (~1350 grams), choosing that number for any one individual would almost certainly be off. This is not because there is a problem with the accuracy of the average weight; it is a function of the intrinsic variability that exists across individuals. Which is to say that while guessing the mean is clearly the best strategy, for any given brain you are likely to be wrong.

Imagine another guessing scenario: one in which the distribution of objects is not normal; perhaps it's even bimodal. For example, what if I gave you a set of baseballs and brains that were lumped together? If you measured the mean weight of objects in the group, the value would fall in the middle, to a number (~750 grams) that does not correspond to either a baseball or a brain. Whereas in our previous example it was unlikely that guessing the mean would be correct (albeit most prudent), in this case it would be impossible for your guess to be correct.

These examples illustrate a central tension intrinsic to the scientific process: group data do not necessarily allow for accurate prediction at the individual level. This issue has been termed the group to individual problem and, within modern neuroscience, is perhaps most evident in the use and interpretation of functional imaging data.

When it was first being developed, functional imaging was limited by a signal-to-noise problem: as revolutionary as it was to be able to visualize activity in the brain, the initial technology was insufficiently powered to allow for individual-level interpretation. Positron emission tomography imaging involved working with radioligands, with its attendant concern to limit individual exposure (and thereby signal). Early functional magnetic resonance imaging studies also struggled with a range of issues, including a relatively weak

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magnetic field (typically 1.5T), motion artifacts, a range of imaging parameters that were not yet optimized, and a high degree of individual variability. The only way to overcome these factors and obtain statistically significant findings was to average results across large numbers of subjects. Use of group level analysis—averaging data across many individuals—led to important breakthroughs in how we understand basic neural circuits and, in the process, became the established norm for the field.

The paper by Aghajani *et al.* (1) in this issue of *Biological Psychiatry* follows in this rich tradition. Their team pooled data from 50 juveniles with conduct disorder and compared that to data from 25 typical juveniles, finding substantial connectivity differences between the groups in several brain areas, including the anterior cingulate, medial prefrontal cortex, and basolateral amygdala. These data represent an important step in advancing our understanding of the neurobiology of conduct disorder.

Yet, in the wrong hands, findings like these run the risk of being misinterpreted or—given the provocative legal implications—being misused. The critical point is the same as where we began: how well can data that are obtained at a group level be applied to a specific individual? Can we expect data to follow a normal distribution—and, if so, how large is the standard deviation? Or is it possible that different people may have fundamentally different brain organizations? Recent research, including that of Randy Buckner, suggests that for functional imaging the latter possibility may be more common than previously thought: combining measurements from many people to create an “average brain” may inadvertently obscure meaningful individual variation. Their work suggests that patterns of activation and connectivity may both differ across individuals and also change overtime (2). By conducting serial scans on single individuals, Buckner's group has shown that elements such as mood and recent experiences (as transient as these states may be) are correlated with fluctuations in blood oxygen level-dependent signaling in the resting state (3)—which is to say that functional connectivity between regions is itself a dynamic process (4). Combined, these data indicate that the standard practice of assuming that individual scans are static measures that can be combined at the group level may lead us to overly simplified conclusions [as in the bimodal example above; see (2)].

Paralleling these findings, work from Edward Boyden's group [best known for his role in developing optogenetics (5)] is enriching our understanding of this same issue at a cellular level. Boyden *et al.* have recently developed an approach called expansion microscopy in which they use swellable polymers to physically expand and magnify tissues that are then amenable to super-resolution microscopy (6). Through this work, they have magnificently illustrated the vast complexity of different brain regions. For example, within the amygdala, a variety of different cell populations have been identified, each of which can be selectively targeted and activated, and each of which may each be involved in discrete processes. Thus, while it is common to refer to the function of the “amygdala” or one of its subregions—and while such findings may be broadly true at an aggregate level—this may not capture what happens in any individual brain, where differences in concentration and function of any particular cell type may be highly significant (7). This insight could potentially explain some of the mixed results in functional neuroimaging regarding whether a particular region of interest performs a specific function.

Taken together, this research highlights the need to direct future investigations toward better exploring individual-level data. Such approaches may be critical for answering a number of open questions in neuroscience and psychiatry. For example, how do transient states, such as love, hate, grief, or rage, influence our actions? Or, of greater clinical relevance, who is at highest risk for the onset or relapse of a psychiatric illness? Ideally, we might ultimately leverage neuroimaging findings so as to move psychiatry into the realm of personalized treatments, such as now exist in other fields of medicine.

While it is easy to imagine a bright future, psychiatrists and neuroscientists are already being asked to opine on these types of questions today. The most dramatic examples of this scenario occur in courtrooms, where experts may be called to testify in capital punishment cases, such as by predicting an individual's risk for future violence. Here, science and our legal system are at an impasse: most scientific data are collected and analyzed at the group level to understand broad phenomena; courts, by their very nature, must make decisions at the individual level (8). In other words, the situation is a quintessential group to individual problem.

So, what to do? Many individuals from both the legal and scientific communities have thrown their hands in the air citing the “intractability of the problem.” But not all have given up: a consortium of scholars led by David Faigman, supported by the MacArthur Foundation, was formed to study the problem further. This group developed a set of clear guidelines to help courts and scientists appropriately apply scientific findings to legal cases (8). Their work represents an important, practical step for navigating this issue. In the meantime, the key point is that neuroimaging findings of group level analyses should not be used in the legal context to say anything about an individual. Doing so could easily mislead a jury and, at its core, would be guesswork cloaked as science.

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References

1. Aghajani M, Klapwijk ET, van der Wee NJ, Veer IM, Rombouts SARB, Boon AE, et al. Disorganized amygdala networks in conduct-disordered juvenile offenders with callous-unemotional traits. *Biol Psychiatry*. 2017; 82:283–293. [PubMed: 27502216]
2. Wang D, Buckner RL, Fox MD, Holt DJ, Holmes AJ, Stoecklein S, et al. Parcellating cortical functional networks in individuals. *Nat Neurosci*. 2015; 18:1853–1860. [PubMed: 26551545]
3. Stevens WD, Buckner RL, Schacter DL. Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. *Cereb Cortex*. 2010; 20:1997–2006. [PubMed: 20026486]
4. Buckner RL, Krienen FM, Yeo BT. Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci*. 2013; 16:832–837. [PubMed: 23799476]
5. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nat Neurosci*. 2005; 8:1263–1268. [PubMed: 16116447]

6. Chen F, Tillberg PW, Boyden ES. Optical imaging. Expansion microscopy. *Science*. 2015; 347:543–548. [PubMed: 25592419]
7. Tye KM, Prakash R, Kim SY, Fenno LE, Grosenick L, Zarabi H, et al. Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature*. 2011; 471:358–362. [PubMed: 21389985]
8. Faigman DL, Monahan J, Slobogin C. Group to individual (G2i) inference in scientific expert testimony. *U Chi L Rev*. 2014; 81:417.