Incidental Findings in Neuroimaging Research: A Framework for Anticipating the Next Frontier

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ABSTRACT: while strategies for handling unusual and possibly clinically significant anatomical findings on brain scans of research volunteers have been developed and implemented across neuroimaging laboratories worldwide, few concrete steps have been taken to consider the next frontier: functional anomalies. Drawing on the genetics literature, early work in neuroimaging considered actionability to be a driving force for determining if and when findings should be disclosed to individuals in whom they are detected, as inherent uncertainty raises potential ethical dilemmas of misdiagnosing and mislabelling people as patients. Here we consider the possibility of incidental findings in brain function during the resting state. Our approach does not anchor the resting state as the *sine qua non* of functional incidental findings, but as a path to thinking about where they may emerge in the future and how our professional communities need to think about thinking about them. We suggest that considering the issues proactively today, within a framework that is maximally flexible and open to modification, is better than responding reactively after the fact and with no framework at all. We argue that there is a duty to consider possible incidental findings despite the ambiguities of data interpretation, while working hard to prevent unnecessary alarm.

KEY WORDS: functional magnetic resonance imaging, resting state, incidental findings, neuroimaging, neuroethics

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Several major themes have made a significant debut in human neuroscience over the past decade; epigenetics, optogenetics, and neuroethics are among them. For neuroethics, the focus of the paper here, questions about the discovery and management of incidental findings (IFs) in brain imaging research have been among the most significant.

The conversation started in earnest in 2001 when approximately 40 people from a wide range of disciplines spanning neuroscience, ethics, and law across the United States and Canada gathered at a roll-up-your-sleeves workshop in Bethesda, Maryland, to discuss the issue (http://www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm). The challenge was to define what constitutes IFs in research, what is clinically significant, who should look, and who should tell what to unsuspecting human subjects. The challenge was so immature at the time, however, that one significant source of contention was whether IFs posed an issue for human subjects research at all. On one hand, some neuroscientists argued that science is science: findings of health risk or not, research and clinical medicine should not be blurred lest the entire scientific enterprise grind to a screeching halt. Other scientists in the room, as well as ethicists and legal scholars, were troubled. Responding to actionable, potentially life-saving findings and drawing upon relevant work from the genetics community (National Bioethics Advisory Commission, 1999), they argued that trust and reciprocity, autonomy and transparency are fundamental principles of human subjects research and would be violated by this hard line.

The first deliverable from the meeting represented a compromise—a positive outcome that focused on upfront transparency about IFs in the protocol review and consent process (Illes et al., 2006a, b). Other issues about management could continue to be debated and resolved at a later time with further reflection and with the benefit of empirical studies to come. Downstream for discussion would also be IFs that might arise beyond primary research, in studies of banked data and functionality.

This paper considers the latter—IFs of functional anomalies, and specifically in the context of modern magnetic resonance imaging. In 2001, the NIH-led group predicted that anomalies of function, i.e., unusual patterns of blood flow and oxygenation in specific regions of the brain, would be task dependent. It did not consider the possibility, though, of function during the resting state. We explore that here, not as the *sine qua non* of functional incidental findings, but as a path to thinking about where IFs may emerge down the road and how we need to think about thinking about them. We suggest that considering the issues proactively today,

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within a framework that is maximally flexible and open to modification, is better than responding reactively after the fact and with no framework at all. We argue that there is a duty to consider possible IFs despite the ambiguities of data interpretation, while working hard to prevent unnecessary alarm.

A Case Study: Resting-State fMRI

The Case for the Resting State

Recent innovation in the field of functional imaging is captured by Thomas Kuhn's speculation that "[T]he scientist who embraces a new paradigm is like the man wearing inverting lenses" (Kuhn, 1962). To have suggested a decade ago that spontaneous signal fluctuations during the resting state—noise to be aggressively filtered from task-induced activity—could be a key to understanding brain function would have been to invite criticism and outright dismissal. Yet, analyses of energy allocation in the brain have since revealed that the brain is highly active during the resting state, devoting over 95% of its energy to spontaneous activity (reviewed in Raichle & Mintun, 2006). By searching for functional connectivity between different brain regions in the spontaneous fluctuations of blood-oxygen level-dependent (BOLD) signals recorded by rs-fMRI, neuroscientists have found distributed, large-scale resting-state networks (Biswal et al., 1995; Fox et al., 2005) that activate reliably across individuals and mirror those activated during tasks (Smith et al., 2009). To some researchers, this phenomenon suggests that resting-state signals are the long sought-after functional networks of the brain (Zhang & Raichle, 2010).

Yet controversy surrounds the meaning of resting-state data, and appropriately so. Questions remain about the validity of the measures and even what constitutes rest. There are no standard protocols for acquisition, no consensus on whether subjects should have their eyes open or closed, and no agreement on whether people should think of "nothing" (if this is even possible) or engage in remedial tasks such as making shopping lists. Partly neutralizing these debates, however, is the recent finding of Biswal et al. (2010) that individuals display similar functional connectivities regardless of differences in image acquisition and definitions of resting. Moreover, although functional imaging has traditionally relied on signal averaging to increase the signal-to-noise ratio, van Dijk et al. (2010) demonstrated that a single 5–6 minute scan is sufficient to stabilize estimates of correlations between brain regions, with reliability on par with estimations across multiple scans. Indeed, both Cohen et al. (2008) and Dosenbach et al. (2010) were able to detect changes in functional connectivity within individuals that were corroborated by group data. Tensions aside about the nature of the resting state, the consistent observation of resting-state networks across populations of individuals and under varying conditions strongly suggests their role in biological function.

Recently, investigators showed that intrinsic connections are sculpted and trained by learning (Lewis et al., 2009), substantiating the claim for biologic relevance and further lending support to their role in function. But perhaps the greatest potential for understanding brain function lies in the perturbations of these connections. Analyses of functional connectivity in these circuits have revealed changes in synchrony and connection strength correlated with neurological diseases such as Alzheimer's and stroke, as well as psychiatric diseases such as depression and schizophrenia, attention deficit hyperactivity disorder, and autism. Accordingly, there is potential for these characterized changes in functional connectivity to be used as clinical biomarkers. To this end, Dosenbach et al. (2010) suggest that acquiring resting-state data during the standard clinical workup would be invaluable for diagnosing and prognosticating disease states.

A Functional Frontier for Incidental Findings?

The ease of data collection, the ability to detect changes in connectivity within individuals from a single scan, and the implications of these changes for prediction and diagnosis of brain disease taken together support the exploration of functional IFs in resting-state fMRI. Can we learn from the literature on structural incidental findings to guide future directions for functional anomalies of any type? Can the policies regarding structural findings be adopted wholesale to these new considerations? In response to the first question, we say: yes, a great deal; to the second question, we argue: probably not.

Marked differences in the nature of potential risk and harm set the ethical considerations of functional IFs apart from those in the structural domain (Illes et al., 2006a, b; FDAnews, 2010; Illes et al., 2008; Marmourian, 2004; Wolf et al., 2008). Chief among these are the potential for a detected aberration to signal (a) a functional, clinical issue that may manifest in the future as opposed to a structural issue that is unequivocally present albeit with varying significance, and (b) one that may be classified as both psychiatric and neurologic. Given the significantly greater lifetime prevalence of psychiatric disorders (Kessler et al., 2007) in contrast to neurological disorders (MacDonald et al., 2000), the economic implications of such prediction in terms of the cost to health care involving follow-up or

intervention in relation to IFs will not be trivial (Sadatsafavi et al., 2010). Further complicating the observation of a functional IF is the (in)ability of the healthcare community to intervene, as current treatments for the psychiatric disorders for which aberrant connectivities may be relevant pale in comparison to those available for many neurological diseases. Indeed, early work by Katzman et al. (1999) in neuroimaging and even earlier work in genetics by the National Bioethics Advisory Commission presented in its 1999 report both considered the availability of an effective intervention to be a driving force for determining if and when findings should be disclosed to individuals in whom they are detected. Moreover, given that biomarkers are predictive and probabilistic in nature, when intervention should occur, if at all, is a key question. Inherent uncertainty raises potential ethical dilemmas of misdiagnosing and mislabelling people as patients.

Apropos of intervention is the timing of detection. Unlike structural incidental findings which are likely to be detected in real-time during the course of imaging, functional incidental anomalies will only be detected during the offline processing of fMRI data and potentially well after an individual has left the imaging suite. The future development of real-time fMRI raises the possibility that incidental functional findings (in resting state as well as task-related) could potentially be identified online during the actual scan. Until then, anonymization of the data will be limited if a window for subject recontact is needed. This problem will also test the feasibility of entering anonymized primary imaging data into repositories for secondary uses as has been recently proposed (Biswal et al., 2010).

Alongside questions of anonymization are those of confidentiality and implications for third parties. As phenotype is the outward expression of genotype, functional imaging may come to confirm suspicions that arise at the level of the gene. The reverse may also hold true, as people may seek confirmation of their imaging results through genetic testing. Indeed, recent studies have demonstrated a possible heritability of resting-state networks (Glahn et al., 2010), suggesting that the discovery of the underlying genetic networks is within our grasp. When coupled with the predictability of a growing number of anomalies, the possibility of heritability is unavoidable and, alongside it, questions of disclosure.

Finally, functional imaging raises questions and concerns that are largely unaddressed by structural imaging, touching upon potentially sensitive issues such as thought on the one hand, and gender and race on the other. The research community, policy-makers, and society may have to contend with evolving boundaries for understanding cognitive capacity, emotional learning, and geographic variability and their attendant ramifications for health and disease.

A Framework for Thinking about the Range of New IF Possibilities

In early 2001, not everyone agreed that the research community was tackling a real problem with IFs, but with the endurance of a few and the work of many, understanding and delivering best practices for structural anomalies were ultimately recognized as necessary first tasks. The response to structural findings was reactive, when the lack and variability of management strategies across and even within imaging laboratories came to the fore. It had the effect of creating positive changes, including action plans, transparency, and disclosure of management strategies in research protocols and consent. Today, these strategies for handling IFs have been adopted in many areas of biologic and nonbiologic research, with guidelines articulated by national funders in the United States and in revised Canada's Tri-Council guidelines for the use of human subjects in research. However, our response to emerging challenges, such as those presented by resting-state fMRI, can be proactive, more efficient, and less contentious if we build on lessons learned in the past to develop an anticipatory framework that can flexibly inform future practice and policy (Racine and Illes, 2007).

Envisioning a Research Agenda

The question of functional IFs raises a host of fundamental issues that can only be resolved through additional research. To test the plausibility of detecting functional IFs from resting-state data, it is critical that the neuroimaging community reach consensus on a reliable definition of resting state to allow comparisons between data sets. Similarly, attention should be paid to the standardization of data acquisition, especially with regard to the subsequent analysis of scans collected independently and cached within international databases. The issue of single scan acquisition is not trivial; indeed, if it is no longer necessary to acquire time-consuming multiple scans for offline statistical processing to visualize functional connectivities, acquiring a rapid one-shot scan may become an important part of the investigator's toolbox. For this method to become viable in the detection of functional connectivities, however, it would be desirable to combine single scan image acquisition with real-time image processing and analysis. Identifying further ethical challenges in the field of functional neuroimaging should be an international

endeavor, especially regarding worldwide image repositories (Gardner et al., 2003; Van Horn & Toga, 2009).

Educating and Implementing

It is likely that the essential role of education for identifying and handling functional IFs will be very similar to that for structural incidental findings. As recommended by Racine and Illes (2007), bridging the gap between neuroethics researchers and neuroimaging trainees is an integral first step. Trainees who conduct resting-state fMRI must be instructed in the detection of functional IFs, associated ethical issues, and best practices for addressing such findings. Education of other stakeholders, including research participants, should be coordinated across imaging centers and advanced by the neuroethics community.

Conclusion

The seemingly static, insignificant problem of incidental findings was anything but that once the discussion got going. Today, no fewer than two thousand papers have been published on IFs and imaging, and their contexts are diverse: research and clinical medicine, incidence and type, research ethics and law. Many topics are still being explored, such as special issues for children, subjects with mental illness, and community ownership of results—incidental or not—in research with indigenous peoples. We are already discussing IFs and return of results in the context of massive genetics biorepositories (Scott et al., 2012). While the direct healthcare costs of genetic IFs may be greater than neuroimaging IFs given the ubiquitousness of tissue sampling, the problems are no less suitable for proactive consideration. The case of functional IFs may be futuristic, but it provokes significant questions about when is the time to start thinking about IFs of emerging neurotechnologies. Using a framework that draws upon past contributions, embraces case-specific nuances, and aims for the protection of human subjects as its final product, we think that time is now.

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