Ethical and practical considerations in managing incidental findings in functional magnetic resonance imaging

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Abstract

Functional magnetic resonance imaging has emerged as a powerful tool for mapping the neurologic underpinnings of sensory, motor and cognitive function. Much of this evolution carries assumptions about the subject population under study and, in particular, the neurologic status of subjects entered into studies either as healthy controls or as belonging to a specific disease group. Recent reports of incidental MRI abnormalities in normal volunteers for fMRI studies have brought to attention a variety of practical challenges and ethical dilemmas for researchers, many of whom are not physicians and most of whom have no formal radiological training. We propose a minimum standard for consenting subjects in fMRI protocols, and consider strategies over the longer term that call for expert physician participation, archiving of incidental findings including false positives, and the adoption of guidelines for handling variation in neural activations or performance that appear outside expected norms.

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1. Introduction

Over the past decade, functional magnetic resonance imaging (fMRI) has emerged as a powerful tool for mapping sensory, motor and cognitive function, and has reaffirmed and expanded upon clinical neurologic and neuropsychological studies, and neuroimaging studies based on other modalities such as electroencephalography (EEG), positron emission tomography (PET), single photon emission tomography (SPECT), and magnetoencephalography (MEG). Several recent fMRI studies have even begun to elucidate the mechanisms of complex and abstract phenomena such as
decision-making and moral behavior. Using event-related fMRI, for example, Van Veen, Cohen, Botvinick, Stenger, and Carter (2001) have demonstrated a highly specific contribution of the anterior cingulate cortex to executive functions at response-related levels of processing; and, in a series of fMRI studies using moral dilemmas as stimuli, Greene, Sommerville, Nystrom, Darley, and Cohen (2001) have probed the influence of variations in emotional engagement on moral judgment. Thus, in this second decade of functional neuroimaging with MRI, it has become possible to detect an alignment of neural activation with some of the highest forms of human cognition; new perspectives and moral questions about rational thinking, intention, and individuality are certain to follow. Much of our thinking from neuroimaging studies, however, carries assumptions or presumptions about the subject population under study and, in particular, the neurologic status of subjects entered into studies as either healthy controls or belonging to a specific neurologic disease group. Despite reports of unexpected MRI findings in clinical and research brain imaging in both adult and pediatric cohorts (e.g., Illes, Kim, Kaplan, Reiss, & Atlas, 2002; Katzman, Dagher, & Patronas, 1999; Kim, Illes, Kaplan, Reiss, & Atlas, 2002) many, if not most, research fMRI studies involving volunteers are performed by non-physicians; unanticipated findings on these imaging studies may go unrecognized and thereby leave subjects without appropriate referral.

The detection, significance, and management of incidental findings are keys to the welfare of the research subject as well as to the integrity of the studies. We will focus on both of these issues here and consider short-term and long-term strategies involving informed consent, expert physician participation, archiving of incidental findings, and the adoption of guidelines for handling unusual variation in neural activations or performance as a first step in a call for debate and consensus in the fMRI community to address these issues.

2. Incidental findings in clinical studies and research

2.1. Clinical domain

Incidental neuroradiological findings are not uncommon in the clinical domain and have been reported variously in the literature. Imaging findings consistent with sinusitis have been reported, for example, in adult patients presenting with symptoms including chronic cough, seizures, head injuries, and various intracranial diseases in the adult population (Havas, Motbey, & Gullane, 1998; Iwabuch, Hanamure, Hirota, & Ohyama, 1997; Jensen & Black, 2000; Patel, Chavda, Violaris, & Pahor, 1996). Other studies have reported substantial variation of incidental findings involving white matter lesions (Autti, Raininko, Vanhanen, Kallio, & Santavuori, 1994; De Leeuw et al., 1999) and sinus disease (van der Veken et al., 1990), across the lifespan in symptomatic subjects.

2.2. Research domain

To our knowledge, a systematic analysis of incidental findings in research EEG, PET, SPECT, or MEG has not been conducted to date. Two studies, the first by Katzman et al. (1999) and a second by our own group (Illes et al., 2002), have been conducted for MRI. A third study of our own is ongoing. These studies are summarized here.

2.2.1. NIH incidental MRI findings (Katzman et al., 1999)

A systematic analysis of incidental neuroradiological findings in the research domain and in MRI, in particular, was described first in the literature by Katzman
et al. (1999). The Katzman group addressed the prevalence of incidental findings specifically in a healthy asymptomatic population in a retrospective study of approximately 1000 MRI research subjects with ages across the lifespan. Their cohort of subjects was 54.6% male and 45.4% female with an age range of 3–83 years (mean age 30.6 years). They reported an 18% incidence of findings, of which 15.1% required no referral, 1.8% required routine referral, 1.1% urgent referral, and .2% required immediate referral. In subjects categorized for urgent referral, at least two were primary tumors.

2.2.2. Stanford pediatric incidental findings study (Illes et al., 2002; Kim et al., 2002)

In a study of incidental findings in research MRI scans by our own group (Illes et al., 2002; Kim et al., 2002), we conducted a retrospective review of 225 research MR scans obtained for functional brain imaging from a cohort of children presumed to be neurologically healthy. The age range of the cohort was newborn to 17 years; 100 boys (44%) and 125 girls (56%). MR scan parameters varied, but T1-weighted images were available for more than 90% of the subjects, T2-weighted images were available for 64%, proton density images for 52%, and SPGR images for 46%. All scans were read and then classified using the method described by Bryan, Manolio, and Schertz (1994) by a board-certified neuroradiologist.

We found incidental abnormalities in the brain images of 47 (21%) subjects, with the other 79% of the scans found to be normal. Of the 47 abnormalities detected, 17 (36%) were determined to have required routine referral for further evaluation; in a single case (2% of the total abnormalities; .5% of the cases studied) a cerebellar lesion was detected and categorized as an urgent referral.

The occurrence of the neuroradiologic abnormalities in the male cohort was twofold that of the females ($\chi^2 = 5.12$, $p < .05$). The percentage requiring either routine or urgent referral showed no significant gender difference (39% and 37%, respectively).

These findings in children broadly replicate those of the Katzman study in adults and other findings, for example, consistent with ventricular asymmetries in neonates (Shen & Huang, 1989) and a predominance of arachnoid cysts in males (Oberbauer, Haase, & Pucher, 1992; Wester, 1999). While it is unlikely that the findings in our study compromised the interpretability or validity of the research brain mapping studies in any way, even the limited presence of anomalies in a cohort of young participants is a matter of medical concern.

Notwithstanding the rather low frequency of clinically important abnormalities, we believe that the presence of any such findings, particularly in a pediatric age group, is significant and highlights the possible need for routine involvement by trained radiologists in these studies, for both detection and as well as appropriate follow-up.

2.2.3. Stanford adult incidental findings (Illes et al., work in progress)

In an ongoing study of adult fMRI research subjects in our institution, we have retrospectively reviewed an initial 129 cases to date. Scans were obtained from research fMRI studies of language, spatial processing and higher cognitive function, with subjects ranging in age from 18 to 81 years. Sixty-three subjects were male (49%, age 23–70); 66 subjects were female (51%, age 18–81). T1-weighted images, T2-weighted images, and thin-section, T1-weighted, three-dimensional volume (SPGR) images were available for almost all subjects.

We found incidental abnormalities in 48 (37.2%) cases. Of the 48 abnormalities detected, three (6.3% of the 48; 2.3% of the total) were classified as requiring routine referral; two were categorized as requiring routine referral for midbrain infarcts, and one was categorized for routine referral for non-specific white matter lesions without
volume loss or signs of aging (Table 1). Table 1 also shows incidental findings not classified as requiring referral. Of this latter group, four findings (44.4%) were due to volume loss with accompanying white matter changes and were detected in subjects 68–81 years of age with a mean age of 74.3 years. No findings categorized as requiring either urgent or immediate referral were detected.

In this relatively small sample, the overall percentage of findings was 39.6% in the male cohort (25/63) and 34.8% in the female cohort (23/66). Of the total number of abnormalities, one finding in the male cohort and two findings in the female cohort was classified as requiring referral.

Figs. 1 and 2 illustrate the case of a 42-year-old male subject, outside the adult cohort reported above, in whom a lesion was detected by one of the authors during MRI pre-scan. In the absence of guidelines for handling such an unexpected finding—either frank, as in this case, or more subtle—the image was sent within 24 h to a board-certified neuroradiologist known to the investigator but not part of the research team. The subject was diagnosed with a vascular malformation and referred for immediate clinical follow-up. Notwithstanding the appropriate medical management of the subject by the research team, this case highlighted dual concerns for us: (1) a primary need for well-established procedures for handling incidental findings and for communicating findings to subjects and (2) a secondary need for

| Table 1 |
| Classification of MRI abnormalities in a cohort of presumed healthy adult subjects participating in fMRI studies of language, spatial processing, and higher cognitive function |
| No referral | Prominent basilar artery | 1 |
| | Left frontal venous angioma | 1 |
| | Mild ethmoid sinus disease | 1 |
| | Asymmetric ventricles | 1 |
| | Volume loss | 5 |
| Routine referral | White matter changes without signs of volume loss | 1 |
| | Midbrain infarct | 2 |

Fig. 1. Sagittal MRI of a 42-year-old male with a vascular malformation initially entered as a healthy control into an fMRI protocol of picture naming. The lesion was detected and subject referred for immediate clinical follow-up. Fast spin echo 2D scan with TR = 2000 ms, TE = 90 ms, flip angle = 90°, 5 mm slice thickness, and 24 cm field of view.
re-examining subject confidentiality, as this lesion was detected in the presence of the subject’s companion who was an observer during the scan.

2.3. Discussion and recommendations

In research studies by other investigators and in our own work, incidental neuroradiologic findings have been detected in 20–40% of cases, with a small percentage requiring referral. Although the majority of the cases are in fact normal, we believe that the presence of any significant clinical findings in an otherwise non-clinical research setting is still a matter of bioethical and medical concern. We propose a minimum standard for consenting research subjects for incidental findings in fMRI and call for, over a longer term, the adoption of universal guidelines for research neuroimaging that would serve the research community and our subjects.

2.4. Informed consent

As a first measure toward articulating the clinical limitations of the research scans performed, the following text is being incorporated widely in fMRI consent forms used in our institution. The language was generated internally and IRB-approved:

“Incidental Findings: The investigators for this project are not trained to perform radiological diagnosis, and the scans performed in this study are not optimized to find abnormalities. The investigators and Stanford are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice a finding on a MRI scan that seems abnormal. When this occurs, a neuroradiologist will be consulted as to whether the finding merits further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting neuroradiologist, and Stanford are not responsible for any examination or treatment that you undertake based upon these findings. Because the images collected in this study do not comprise a proper clinical MRI series, these images will not be made available for diagnostic purposes.”

The text represents a clear minimum standard for dissociating the research scan from a clinical scan. There are, however, several caveats to consider. Among them:

(1) While it is assumed that informing prospective subjects about the risks and benefits of research protects their rights as autonomous decision-makers, the
literature suggests that subjects and patients defer substantially to the subject–investigator relationship to guide them through research participation decisions (e.g., Capron, Faden, & Beauchamp, 1987; Kass, Sugarman, Faden, & Schoch-Spana, 1996; Sugarman et al., 1998).

(2) The text “The decision as to whether to proceed with further examination on treatment lies solely with you and your physician…” presumes that the subject has a primary care physician (PCP). However, an undue burden may be placed on individuals who are drawn from university or other subject pools whose access to medical care may not specify a PCP per se.

(3) When the subject is screened and entered into a protocol as a healthy control, “healthy” is a dominant attribute. However, even with extensive and methodical screening for medical and psychiatric history, there remains no verification of this in fMRI protocols in which a clinical reading of the image is not done. Limitations of informed consent, evidence for incidence of neuroradiologic abnormalities in subject pools, and the nature of fMRI as advanced medical technology typically situated in a medical setting, triangulate to make a compelling case for further deliberation of fMRI protocols with respect to clinical review of the image data.

2.5. Working toward a universal set of principles and consensus for fMRI research

In light of the data presented here, we urge major professional societies representing the interests of fMRI researchers to actively support a platform for discussion and debate of the following questions:

1. Should all fMRI studies be conducted by a research team that includes a physician qualified to review images for clinical findings and provide follow-up referral to a healthcare provider selected by or available to the subject?

2. What formal, standardized procedures are needed for facilitating the transfer of information, although not necessarily the transfer of the research-grade images, to either the PCP or a physician within a medical clinic?

3. If neuroradiologic readings of all fMRI studies are introduced, what are the new risks posed if subjects enroll in fMRI research studies motivated by possible clinical benefit? What revisions to the informed consent process will be needed to ensure protection of both the research team and the subject?

4. What are the implications for medical insurability if a benign lesion is detected in an asymptomatic subject not seeking medical attention who enrolled in a research study?

5. Even in the absence of any disagreement about the need for radiologic review of all fMRI scans, what are the practical considerations given the sheer volume of studies conducted?

6. How do we best harness the information about incidental findings across our laboratories? We can consider creating a national database for incidental findings, including false positives, for which the following data are recorded:

   (i) the circumstances in which a finding was detected (e.g., age of subject, gender, type of study);
   (ii) how the finding was handled;
   (iii) to whom the finding was reported;
   (iv) the manner in which the finding was reported in writing (as a clinical report, email, memo), verbally;
   (v) how the finding was followed up;
   (vi) the outcome for the individual.

7. By extension to the incidental anatomical findings, what are the appropriate guidelines for handling and communicating variation in neural activations or
performance variations that appear outside expected norms? This may be especially vital in the case of studies of sexual attitudes or behaviors in which the information may be potentially anxiety-provoking to subjects (The Ethics & Humanities Subcommittee of the American Academy of Neurology, 1998).

8. Is there an imperative for handling research neuroimaging studies with the same confidentiality as clinical studies?

There is no doubt that standardized introduction of expert physician readers would impact the high cost and overall experimental burden of research MRI already inherent to these studies. However, with approximately 3500 brain and behavior fMRI studies published between 1991 and 2001 alone (NLM PubMed search: key word “FMRI”; at least 30,000 research participants assuming an average of 10 subjects per study), the number of studies and people we may impact with improved protocols is substantial. We can address added personnel costs with academic currency to some extent, by attracting more radiologists as active contributors to the intellectual challenges of fMRI research, for example, and through joint authorships on peer-reviewed publications and presentations. Alternatively, we can consider formally instituting center-wide expert physician consultation supported by operating budget, shared extramural funding, or both. Regardless of the strategy, any increase in costs will need to be recognized and supported by our sponsors in both the federal and non-federal arenas, and built into our research budgets.

3. Conclusion

We have brought to the foreground ethical and practical dilemmas raised by findings of unexpected abnormalities in research fMRI. The issues are significant and complex. With both subject welfare and fundamental knowledge about the relationships between brain and behavior at stake, however, dialogue, debate, and consensus have become imperative.

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References


