I. Incidental Findings in Magnetic Resonance Imaging Research

Magnetic Resonance Imaging (MRI) is a widely available and versatile imaging modality that provides unprecedented spatial resolution and a variety of image contrast mechanisms within a single examination. Magnetic resonance images are derived from radiofrequency signals that readily penetrate dense tissue such as bone, making MRI by far the most sensitive method for imaging human brain structure in vivo. With 3-dimenstional imaging based on T1 contrast, isotropic image resolution of less than a millimeter through whole brain is readily achievable within a matter of minutes on most current commercial MRI scanners, and excellent contrast between gray matter, white matter, and CSF is provided. T1 contrast can also be used to image arteries with magnetic resonance angiography and to measure tissue perfusion with arterial spin labeling. T2 contrast adds sensitivity to inflammatory responses that occur in a broad range of neuropathology. A modification of T2-weighted MRI termed diffusion imaging enhances sensitivity to microscopic diffusion of water and can be used to detect changes in water diffusivity in conditions such as acute stroke or to image white matter tracts based on the anisotropic diffusivity of water in white matter. T2* contrast adds exquisite sensitivity to paramagnetic deoxyhemoglobin and methemoglobin that are deposited in hemorrhagic disorders, and this contrast mechanism is also exploited as a surrogate marker of changes in regional cerebral blood flow and metabolism that occur with regional brain activation in functional MRI (fMRI) with blood oxygenation level dependent (BOLD) contrast. A number of other contrast mechanisms such as magnetization transfer, T1rho, and quantification of metabolites using magnetic resonance spectroscopy are also available, but are used less commonly.

Brain imaging including all of the aforementioned contrasts can be routinely obtained within a single MRI scanning session of less than an hour. Because MRI uses no ionizing radiation and does not require exogenous contrast administration in routine use, it is considered entirely noninvasive. The only absolute contraindications to MRI are the presence of ferrous metal in the brain or orbit or the presence of certain electronic implants such as a pacemaker. In clinical applications, MRI is considered safe during pregnancy. In research applications, MRI is typically classified as an “insignificant risk device.” The main source of morbidity associated with non-contrast MRI is a risk of injury from metallic projectiles, which has resulted in at least one death in clinical practice (Colletti 2004). This risk is readily controlled using operational procedures to insure that no ferrous objects enter the magnet room.

The noninvasiveness and versatility of MRI has also made it an increasingly popular modality for brain research. The relative ease and low cost of imaging regional brain function with BOLD fMRI as compared to prior PET methods spurred an explosion in its use as a research tool in basic and clinical neuroscience for studying brain-behavior relationships. The development of advanced computational approaches for analyzing the complex brain morphometry of both gray matter and white matter in various populations has also rendered structural MRI an important neuroscience research tool. Because there are no known risks of cumulative exposure to MRI, it can be used for serial studies of brain structure and function during development, aging, pathological processes, and learning. A number of large database projects acquire cross-sectional or longitudinal MRI data from hundreds or thousands of individuals.

Although the MRI procedure itself carries little or no risk, MRI scanning is capable of revealing previously unsuspected neuropathology in subjects who are scanner for research. While detecting neuropathology is the expressed intent of clinical MRI examinations, it is typically not the objective of research MRI, particularly when applied to a healthy population. Even in clinical populations, MRI scanning may reveal neuropathology unrelated to the patient’s diagnosis.

Such findings are “incidental” to the purpose of the study. Although many incidental findings have little or no obvious clinical significance, certain incidental findings such as unsuspected tumors or vascular malformations may have immediate implications for the medical status of the person in whom they are found. While incidental findings have been commonly recognized in the setting of clinical testing and are therefore an accepted consequence of medical evaluation, the widespread use of sensitive medical testing such as MRI for research into normal brain function is unprecedented and has dramatically increased the likelihood of an incidental medical finding in otherwise healthy research subjects.

Although the exact incidence of incidental findings in an otherwise healthy population is unknown and depends on demographic variables such as age and the extent of diagnostically relevant imaging that is carried out, a number of studies now suggest that medically significant abnormalities may be found in 5-20% of diagnostic-quality MRI scans from normal subjects, and somewhat higher in elderly subjects (Yue, Longstreth et al. 1997; Katzman, Dagher et al. 1999; Weber and Knopf 2006; Vernooij, Ikram et al. 2007), though many such findings may have no immediate diagnostic or therapeutic implications. Incidental findings requiring urgent management are less frequent, and include brain tumors (~0.5-2%), aneurysms (~0.1%), and other vascular lesions (~0.2%).

An important general concept concerning incidental findings is that their significance may be difficult or impossible to determine in isolation. As an example, the presence of a few subcortical white matter hyperintensities is typically insignificant in a subject with no history of neurological complaints, but may strongly support a diagnosis of Multiple Sclerosis in a patient with a clear history of transient neurological deficits. Accordingly, the significance of an incidental finding for any individual is optimally determined by their personal physician in the context of the their complete medical history. The risks associated with an incidental finding may also vary from individual to individual. One subject may accept the presence of a small aneurysm or tumor and decide to undergo periodic follow-up scanning to insure that it is stable, while another subject may want immediate surgery, despite a significant perioperative risk. The process of evaluating and managing an incidental finding may take months or years and is also optimally carried out under the direction of the individual’s personal physician.

II. Incidental Findings in MRI: Risk or Benefit?

While minor incidental findings have the potential to cause anxiety and stress, the more significant findings have the potential to alter life expectancy and insurability as well as mandate additional testing or interventions that carry associated morbidity. Accordingly, the possibility of an incidental finding must be considered as a potential “risk” of participating in research involving brain MRI. By the same token, if a life-threatening incidental abnormality is discovered and treated, it could also be considered as a “benefit” of participating in the research. Although most research MRI consent forms include specific verbiage indicating that the study is not intended for diagnostic purposes, existing data suggests that subjects participating in research MRI may nonetheless expect that clinically significant abnormalities will be found (Kirschen, Jaworska et al. 2006).

A basic tenet of human subjects research is a positive risk: benefit ratio (Emanuel, Wendler et al. 2000). Neglecting for the moment the risk of an incidental finding, MRI research in subjects without pacemakers or ferrous metal foreign bodies studied in an environment that carefully excludes ferrous projectiles carries no significant risk, hence as long as the research has some merit, a positive risk: benefit ratio is virtually guaranteed. In clinical populations, research studies may also provide some direct benefit to the patient if study results are also shared with

their physician. However, in most instances, the benefit of MRI research is not to the research subject, but rather to society or future patients based on the new knowledge that is anticipated to be derived from the study. The benefit to the individual research subject is usually limited to a small honorarium provided to offset the time and expense of participating in the study.

The risk: benefit ratio for participating in MRI research is clearly altered by the recognition that the discovery of an incidental finding represents a risk to the research subject of participating in the study. It has been argued that the requirement to minimize the risk: benefit ratio of human subjects research implies that MRI researchers must also maximize the potential benefit of discovering and disclosing a clinically-significant incidental finding, while at the same time minimize the risk of causing unnecessary anxiety by disclosing an insignificant finding (Wolf, Lawrenz et al. 2008). The problem with this argument is that many findings have uncertain clinical significance, or, as noted above, an assessment of the significance cannot be made based on the imaging data alone. In these instances, disclosure can actually increase the risk of unnecessary anxiety due to a false-positive finding (Kumra, Ashtari et al. 2006). Additionally, maximizing the risk: benefit ratio of an MRI study from the standpoint of determining the presence or absence of clinically significant abnormalities may require obtaining additional imaging data that are not needed for research purposes, and even then a conclusive determination may not be possible. While this type of screening could conceivably be explicitly built into the study design as an incentive for participating, as a general matter it does not seem necessary or even desirable to significantly alter the data acquired to try to derive clinical benefits that are unrelated to the intent of a research study.

III. Diagnostic review of research MRI studies.

Of course, MRI scanning per se does not lead to incidental findings. Rather, incidental findings are discovered through visual inspection or other forms of image analysis. The likelihood of discovering an incidental finding depends on the extent of diagnostic quality imaging that is carried out as well as the diagnostic skills of the individuals who are involved in the data acquisition and analysis. In neuroimaging research, there is considerable variability in both the extent and diagnostic quality of the imaging data that is obtained and in the diagnostic acumen of the research team. A cognitive fMRI study carried out by a psychologist may include only a single clinical-quality T1-weighted image series used for spatial normalization of the imaging data to a standard template and all of the data may be acquired and analyzed by a graduate student with no medical knowledge or training, in some cases in an institution with no medical personnel. In contrast, an fMRI study of motor activation in a patient recovering from stroke may include extensive structural imaging to define and characterize the ischemic lesion and may be reviewed by a neurologist skilled in clinical image interpretation. This variability in the quality of diagnostically useful MRI data and the clinical skills of the research team make it difficult to use a uniform approach for handling incidental findings in all MRI research studies.

One possible approach to dealing with the heterogeneity in research MRI is to require a basic set of diagnostically useful imaging data for each research study and to mandate the review of these data by a skilled interpreter, typically a neuroradiologist. This approach is operationally appealing in that each study can be managed in the same way from the standpoint of detecting incidental findings. It is also much easier and faster for a skilled interpreter to review a standard set of data than to try to make clinical interpretations from a variable set of data acquired for other purposes. However, this approach is also likely to yield the highest number of incidental findings, many of which may have uncertain clinical significance. In a retrospective review of structural MRI data sets acquired during fMRI studies in normal volunteers, skilled neuroradiologists were able to identify reportable abnormalities approximately half of the cases,

with 4% requiring urgent referral (Illes, Rosen et al. 2004). This approach would make the most sense under the scenario that maximizing the ability to identify incidental findings is a benefit of participating in the MRI study from the research subject's standpoint, or to minimize the medical and medical-legal consequences from missing a clinical disorder that presents later. This approach is also best suited to facilities where the effort of skilled interpreters is available at a reasonable cost.

An alternative approach links the extent of data acquisition and scrutiny for incidental findings to the intent of the research MRI study, and more naturally applies to research MRI carried out in non-clinical settings or for non-clinical purposes. In this approach, studies carried out in healthy volunteers with no clinical hypothesis or intent do not require any formal review for incidental findings, whereas studies involving clinical hypotheses and clinical populations must be reviewed more systematically. In neither case are additional imaging data required for clinical interpretation, but studies in clinical populations may already include imaging sequences to further characterize the pathological condition being examined as part of the research design. For example, an fMRI study of cognition in Alzheimer's patients may include T2-weighted MRI to exclude clinically unsuspected cerebrovascular disease. Such data are typically already acquired and reviewed with a clinical intent in mind, and hence it is a natural extension of this process to develop a more formal clinical interpretation of the imaging data. Indeed, a "doctor-patient" relationship is essentially implied in the study design, even if the investigator is not the research subject's personal physician.

This dichotomized approach is also consistent with research subjects' reasonable expectations. As long as healthy volunteers for a non-clinical study truly understand that a research MRI study is not intended for diagnostic purposes and will not be reviewed as such, there should be no expectation of any medical value to the study, particularly if it is being carried out in a non-clinical environment such as a department of psychology. In contrast, clinical populations studied in a clinical setting and recruited because of their known neuropathology might reasonably expect their diagnosis to be at least confirmed, and any medically significant deviations to be detected. Control populations scanned under a clinical research protocol should be managed as if they were patients, particularly if they are matched to the patient population in other ways.

Even if no special scrutiny is given to MRI data from healthy volunteers acquired for non-clinical purposes, there remains the possibility that study personnel will notice an incidental abnormality, and this finding will need to be reviewed by someone with appropriate clinical skills. Accordingly, all research MRI facilities must include some mechanism for timely access to this expertise. However, this expertise will likely only be required sporadically for non-clinical studies.

IV. Disclosing incidental findings

Research subjects are entitled to be informed of incidental findings that carry a significant risk to their health (Emanuel, Wendler et al. 2000), and the possibility of such notification should be described as part of the consent procedure for all research MRI studies. The principal investigator is ultimately responsible for insuring that this disclosure is made in a timely fashion, though this responsibility may be deferred to another study investigator with greater clinical expertise. It is less clear what actions should be taken in response to incidental findings with questionable or unlikely clinical significance, since the stress and anxiety generated by disclosure may outweigh any potential heath benefits.

Some existing recommendations regarding disclosure conceptually stratify incidental findings into categories (Illes, Kirschen et al. 2008; Wolf, Lawrenz et al. 2008). One category includes the minority of findings with obvious and urgent health consequences such as tumors and aneurysms, where the need for disclosure is clear-cut. Another category includes findings with possible health significance that may or may not require further evaluation or management, where the benefits of disclosure is less clear-cut, and disclosure is optional. An example of this is the finding of an occult venous malformation deep in the brain that carries a small risk of hemorrhage but for which no therapy is available. A third category includes findings of no health consequence for which disclosure is not required, though if a subject was interested in the findings there is no good reason why such inconsequential information should not be disclosed. An example of this would be a cavum septum pellucidum, a congenital variation in the ventricular system. A shortcoming of this stratification scheme is that, as noted previously, the health consequences of an incidental finding cannot be completely assessed in the absence of additional knowledge about the subject's medical history and risk tolerance. An additional complication for determining whether to disclose an incidental finding of uncertain significance is the limited imaging data that may be available in research MRI, which may preclude an accurate characterization lesion based on that study alone.

A less well recognized issue is how the transition is made from research data to clinical care in those subjects in whom the decision is made to disclose an incidental finding. Although several publications on the management of incidental findings recommend making the research study images demonstrating the abnormality available to the subject and their physician, the standard "currency" of diagnostic studies in the clinical realm is not raw images but rather a written radiological report describing the abnormality and its differential diagnosis. Uninterpreted brain images are of little use to primary care physicians, and even for neurologists and neurosurgeons it may be difficult to interpret data acquired using non-clinical protocols. Furthermore, if an incidental finding is to be the basis for additional medical evaluation or therapy under the subject's health insurance, it is necessary for this finding to be formally incorporated into their medical record. For these reasons, it may be preferable to again consider two options for incidental findings based on the intent of the study and the diagnostic quality of the imaging obtained in the research protocol. For studies in healthy volunteers with more limited diagnostic data, if a potentially significant incidental finding is detected, a recommendation to obtain a clinical quality study to confirm the findings would allow a formal and radiological interpretation to be generated that is not qualified by limited imaging. On the other hand, studies in clinical populations with more extensive diagnostic imaging may provide sufficient information for a formal clinical report to be generated without an additional clinical study. To respect the privacy of research subjects, any such recommendation or report should be given directly to the subject or their guardian. It should be up to the subject and their guardian to determine whether to pursue it further through their health care provider, though the investigator should endeavor to assist in this process to whatever extent possible.

Several recent articles on the management of incidental findings suggest that research subjects should be offered the opportunity to "opt out" of being notified of incidental findings (Illes, Kirschen et al. 2008; Wolf, Lawrenz et al. 2008). In the event of a potentially life-threatening finding, the recommendation is then for the investigator to recontact the subject to confirm that they really do not wish to be informed of even a potentially serious finding. This approach adds unnecessary complexity to the management of incidental findings and places the investigator in a difficult position of judging what severity of findings would prompt the confirmatory contact and how hard to push the subject to reconsider their opt-out position. It is not clear that it is necessary or desirable to allow subjects to opt-out of notification. In the absence of evidence that subject recruitment for MRI research would be dramatically reduced unless subjects are

offered this alternative, a more straightforward solution to this issue would to have such subjects opt-out of being research subjects for the study.

Conclusions

The potential for an incidental finding of definite or possible clinical significance is a predictable risk of participating in MRI research. Procedures for detecting and verifying incidental findings and disclosing them to research subjects must be included in the research protocol and consent process. Incidental findings can adversely impact subjects by causing anxiety or requiring additional evaluation and treatment with additional risk. Although there is some potential for health benefit if a life-threatening finding is observed and successfully treated, the clinical significance of most incidental findings is uncertain, so it is unclear that comprehensive screening for incidental findings is truly a benefit to participating in MRI research for the subject. Although the acquisition of extra clinically oriented images may facilitate screening for incidental findings, the acquisition of such data is ideally motivated by the research design rather than for the convenience of image interpretation or to protect against future litigation. For non-clinical studies in non-clinical populations it is reasonable to perform no specific screening for incidental findings as long as research subjects are clearly aware that the study has no diagnostic intent. However, even in this situation there is still a risk of an incidental finding and some mechanism for timely access to the clinical expertise to evaluate it must be in place. The most useful format for translating an incidental finding into clinical care is a written radiological report. If image quality is insufficient for formal interpretation, a recommendation to proceed to a clinical study to verify a questionable finding may be preferable to attempting to make clinical recommendations on incomplete data.

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