Research Malpractice and the Issue of Incidental Findings

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The ability to search for the truth implies also a duty; not to conceal any part of what one has found to be true.

- Albert Einstein

Magnetic resonance imaging (MRI) and functional MRI (fMRI) are important tools for neuroscience research because of their capability for investigating both the structure and function of the brain.¹ The fMRI image extends traditional anatomical imaging of the MRI to include maps of human brain function. The ability to observe brain function opens an array of opportunities to research brain organization, neurological status, and neurological risk.² Neurological research is, thus, burgeoning.³ For example, Columbia University currently has several ongoing protocols investigating fMRI’s future role in neurosurgical planning, pain management, and understanding the physiological basis for neurological disorders as well as cognitive and perceptual events.⁴ One can imagine research proposals, both important and trivial, on such topics as whether brain imaging can shed light on the nature of dreams, memory, speech development, love, anger, or addiction.

Consider this fact pattern from one of my case files.

A psychology professor at a well respected university designs a study to explore whether attention deficit hyperactivity disorder (ADHD) is associated with a physiologic defect in the brain. As principal investigator (PI), she recruits potential subjects in poor neighborhoods, offering $680 to any parent who signs the informed consent document allowing a child to participate. Each child as young as eight is given a single dose of methylphenidate or Ritalin, which the protocol says is equivalent to three cups of coffee. An MRI is then performed to see whether the brains of the healthy children show any physiologic difference from the brains of the children diagnosed with ADHD who had also just ingested the drug. The plan is to include 1000 volunteers, divided equally between those who had been diagnosed with ADHD and those who had not.

The PI and the IRB should know from the scientific literature, in designing and approving such a study, that brain MRI will reveal significant abnormal brain morphology in two to eight percent of the scans exam-
Indeed, recent studies reveal an extraordinary number of incidental findings in neurological research. One such study characterized the frequency and severity of incidental findings in brain MRI and fMRI of 151 adult volunteers. The results revealed incidental findings in 47 percent of the total number of scans examined, 6.6 percent of which required follow-up. Of the total findings, 9.8 percent required a routine referral and four percent required urgent referral. Although there were more findings in older subjects, all referrals of older subjects were routine, whereas 75 percent of the findings in younger subjects (although only four in number) were considered urgent. The study concluded that standards are needed to guide investigators in managing and communicating incidental findings, but did not propose standards other than addressing in the consent form the possibility of incidental findings.

Another study revealed even more disturbing data. Indeed, recent studies reveal an extraordinary number of incidental findings in neurological research. One such study characterized the frequency and severity of incidental findings in brain MRI and fMRI of 151 adult volunteers. The results revealed incidental findings in 47 percent of the total number of scans examined, 6.6 percent of which required follow-up.

Evaluating different procedures for managing incidental findings in brain research studies, one researcher found extraordinary variability in procedures to detect and disclose incidental findings to subjects. The variables included whether or not a neuroradiologist was involved and the competency and training level of the research staff. In this study, investigators detected incidental findings in 82 percent of the subject population. With respect to the qualifications of the staff primarily responsible for imaging, 41 percent of the staff were students and 21 percent were post-doctoral or professional personnel. Only 38 percent of the protocols required that radiologists conduct scans. Only 53 percent of the protocols involved procedures for managing and disclosing incidental findings to the subjects. All other protocols proceeded on an ad hoc basis.

IRBs required neuroradiologist involvement in only 22 percent of the research protocols. Of those that did not require a neuroradiologist, scans were consistently read 13 percent of the time, upon suspicious findings 69 percent of the time, and never read 18 percent of the time. The problem, of course, is money. As one commentator admitted, “Current procedures for handling incidental findings may be adequate...because more stringent procedures would be ‘difficult to implement in terms of both practicality and costs.’” The consequence of requiring researchers to budget for managing incidental findings, according to another commentator, is “in the present financial climate...that half as much research gets done, and that has, in my mind, a much greater impact on society and the health of society than the very, very low incidence of incidental findings which are actually correct and an even lower incidence where there is something you could have done.”

Leaving aside the question of whether the study from my case files above is ethical — and in my view it clearly is not — the unforeseeability of such incidental findings raises several questions for the IRB and for the design and budgeting of the research protocol. These include the following:

1. Must a board-certified or board-eligible radiologist review the MRI scans to look for any abnormality?
2. Must the MRI scanning be conducted in accordance with standard medical practice for reviewing the clinical status of the whole brain even if
the PI is concerned with only one portion of the
brain captured in one MRI sequence?
3. Must the informed consent document disclose the
potential that incidental findings of abnormalities
might be revealed, and what consequences might
follow if they are?
4. If any abnormalities are incidentally revealed,
must the subjects be promptly informed by a phy-
sician capable of explaining the significance of the
findings and the alternatives available?

Perhaps not surprisingly, I would answer each of
these questions with an emphatic “yes” because of the
researcher’s duty to protect human subjects. More-

over, I would submit that if the failure to take any of
the above actions results in the exacerbation of disease
or injury that was or should have been revealed by the
MRI, then the PI and the members of the research
enterprise should face substantial liability. The basis
for such liability lies in the special relationship between
researcher and human subject.

Once the research subject or the guardian for a
minor subject signs the informed consent document,
a fiduciary relationship is formed between the PI and
the research subject. The very nature of scientific
research on human subjects creates special relation-
ships out of which fiduciary duties arise, similar to the
physician/patient relationship. The fiduciary rela-
tionship is formed not only by the informed consent
agreement between the parties, but also by the trust
the subject necessarily places in the researcher. In the
context of human subjects research, a special relation-
ship is created between the human subject and those
responsible for the design, approval, and implementa-
tion of the experiment because the latter have a duty
to protect human subjects both under the Common
Rule and common law.

In Grimes v. Kennedy Krieger Institute, the high-
est court of Maryland held, in the context of a human
subject experiment, that (1) informed consent docu-
ments create “special relationships” giving rise to
duties; (2) such “special relationships” are normally
created between researchers and their human sub-
jects; and (3) government regulations can also create
duties on the part of researchers toward human sub-
jects out of which “special relationships” can arise.
The court held that “[a] ‘special relationship’ exists
in circumstances where such experiments are con-
ducted,” based upon the consent form, the relation-
ship between researcher and research subject, federal
regulations governing human subjects research, and
the Nuremberg Code.

With respect to the informed consent document, the
court found that the representations in the document
create a bilateral contract between the parties, hold-

In one example, a former neuroanatomy teacher, soon-to-be father and
professed “neuro-nerd,” volunteered for an MRI of his brain which revealed
a golf-ball sized tumor. The diagnosis came just before he applied for additional
insurance for his family, which was subsequently denied as a result of the
incidental finding. He now says that he “should have thought about the
consequences of volunteering more thoroughly.”
Incidental findings in human subject research

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then could the research enterprise ever justify having unqualified personnel review the MRI scans? Unqualified personnel will predictably miss important incidental findings. Virtually every hospital requires that, if an MRI is performed, it be read by a qualified radiologist who is certified in radiology or diagnostic radiology by the American Board of Radiology. This is the standard of care in medical malpractice actions as well. If the MRI images reveal an abnormality that a reasonably careful radiologist would detect, then it would be a hollow defense to claim that the researchers or their assistants had neither the training nor the expertise to properly interpret the data.

The National Institutes of Health approaches the issue by giving full clinical brain scans to every subject participating in its intramural neuroimaging studies. Many research institutions currently require, consistent with the standard of care proposed here, that a radiologist read every research scan. Many institutions, however, still use what is referred to as the “Good Samaritan approach,” in which they tell the subject in the informed consent process that their scans are not of clinical quality and are not being interpreted by medically qualified personnel; if by chance, however, the researchers stumble upon a finding, they will inform the subject. Such an approach invites litigation and ignores the duties owed to the subject in human research. After all, it is the participant in a nontherapeutic research study who is the Good Samaritan, and that status entitles the subject to the highest standard of care the researcher can offer.

The same logic demands that the MRI research procedure be performed in accordance with at least the standards according to which MRIs are routinely conducted clinically. Again, the American College of Radiology has established protocols for the sequencing of MRI images, as does virtually every hospital in its Policy and Procedure Manual governing such diagnostic tests. Performing an MRI in a manner contrary to these protocols would be contrary to the required standard of care, even when the MRI was not indicated by any medical condition. Thus, even in those research studies in which the PI is looking only at a specific area of the brain such as the hypothalamus and believes one sequence of MRI images is adequate for the limited purpose of the research, the full sequence of MRI images is required. No radiologist would take a limited sequence of images because the referring neurologist advised he or she was only concerned about one area of the brain. Such conduct would surely be contrary to the hospital’s protocol requiring a full sequence of images and, thus, below the requisite standard of care. No less a standard would be required of the radiologist in the research enterprise.

If brain research using MRI is to be performed, and if the results of such procedure may have some consequence to the subject, the PI must disclose and discuss this information with the subject or his or her guardian during the informed consent process, because it may be material to the decision of whether or not to participate in the research. Some subjects, wisely or unwisely, may choose not to participate in such circumstances. That is their right. Others may be concerned about the potential effects of learning such information, such as whether it might impact their ability to obtain insurance or participate in certain activities. Incidental findings may impose a substantial psycho-
logical and financial burden on the human subject. In one example, a former neuroanatomy teacher, soon-to-be father and professed “neuro-nerd,” volunteered for an MRI of his brain which revealed a golf-ball sized tumor. The diagnosis came just before he applied for additional insurance for his family, which was subsequently denied as a result of the incidental finding.

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Finally, if abnormalities are found, the subject must be promptly informed of those critical findings so as to decide whether to seek whatever treatment is required. This means that the researchers must have a way to contact the subject and a physician who understands the import of the findings and the available treatment alternatives. In a study such as the one from my case files, in which the poor and uninsured are the likely recruits, more difficult issues may arise. Suppose the MRI reveals in the brain of an eight-year-old a tumor easily removable, but certain to kill if it is not removed. The child’s single mother tells the physician that she has no insurance, no regular doctor, and no idea of what she can do to help her child. Though current research ethics do not require the investigator to treat the anomaly, it is worth asking whether researchers should have some obligation to notify the mother of the incidental finding and then help her address it therapeutically. We are forced to face the broader question: what does medicine owe to the person who volunteers his or her body for medicine’s progress?

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References

3. Id.
6. Id.
7. Id.
8. Id.
9. Id.
10. Id.
11. See Alphs et al., supra note 1, at 1-7.
12. Id.
13. Id.
14. Id.
15. See Illes et al., supra note 4.
16. Id.
17. Id.
18. Id., at 745.
19. Id.
20. Id.
21. Id.
22. Id., at 746.
23. K. Ross, “When Volunteers Are Not Healthy,” EMBO Reports 6, no. 12 (2005): 1116-1119, available at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1369211> (last visited February 20, 2008) (quoting Alan Evans, neuroimaging researcher from McGill University, Montreal, Canada); see also Illes et al., supra note 5, at 890 (“[W]e must balance the benefit of involving medical personnel trained to read scans and interact with participants against the legal risk and financial burden of clinician assessment of all participant MRIs and the workload challenges associated with sheer volume.”).
24. The study exposed children to greater than minimal risk with no benefit and induced participation for money not altruism.
27. Id., at 113.
28. Id., at 89, 91-100, 103.
29. Id., at 101.
32. Id. (citing Faya v. Almaraz, 820 A.2d 327, 333 [Md. 1993]).
33. See Illes et al., supra note 5.
34. Id.
35. Id.
38. Id. (citing Illes et al., supra note 4).
39. Id.

41. 45 C.F.R. § 46.116 (2007).
42. Id.
43. See Ross, supra note 23.