

The Researcher



- AW is a Ph.D. psychologist.
- She has conducted numerous studies using neuroimaging to assess brain function.

The Researcher's Limitations



- AW is not qualified to assess the clinical implications of brain scans.
- For instance, she is not qualified to assess brain scans for structural pathology, such as brain tumors.

The Study



AW designs a study to assess changes in brain function in response to cognitive tasks in 15 normal volunteers.

The Procedures



- AW will assess brain function using functional MRI (fMRI) scans.
- Subjects perform a simple task in the scanner for baseline measures, and then increasingly difficult tasks to assess associated changes in brain function.

The Screening



- As part of the screening, a fellow will take a thorough history and physical.
- In addition, AW will administer a series of psychological tests to assess whether each subject is within the normal range for attention.

Scans for Research



- AW will analyze the data to assess changes in brain function.
- For the purposes of answering the research question, there is no need for a clinical MRI of subjects' brains.

The Ethical Question



- AW learns that other researchers in the Clinical Center have a practice of submitting MRI scans to clinical radiology to be read for clinical purposes.
- AW wonders whether she should follow this practice.

The IRB Meeting



- AW explains the issue to the IRB.
- She emphasizes that, for research purposes, there is no need to assess the subjects for structural elements.

The Research Scans



- She points out that she could send the data she receives from the research scans to clinical radiology.
- These data would provide limited information on possible structural pathology.

Possible Clinical Scans



- AW also could ask each subject to undergo a standard clinical MRI specifically to look for structural pathology.
- This process would likely increase each subjects' time in the scanner from 30 minutes to approximately 40 minutes.

Pursue the Research Scan



- One IRB member points out that, although very unlikely, AW's research scans *may* provide clinically suggestive information.
- He argues that AW should send the research scans to clinical radiology.

Get a Clinical Scan



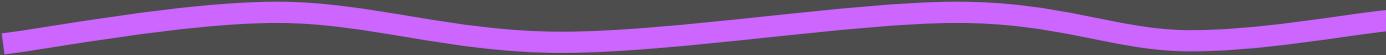
- A second member points out that adding a clinical scan would require very little time or effort, and may yield important clinical information.
- This member argues AW has an ethical obligation to add a clinical scan, and have it read by clinical radiology.

Don't Send the Clinical Scan



- A third member responds that research scans that do not meet clinical standards should not be sent to clinical radiology.
- She concludes the information obtained from AW's research scans should not be sent to clinical radiology.

Don't Get a Clinical Scan



- Other members respond that we do not obtain clinical MRIs outside the research setting for individuals without symptoms.
- This suggests that scanning healthy volunteers is not a cost effective practice, and should not be pursued.

The IRB Asks for Help



- After prolonged discussion, the IRB is undecided about what to recommend.
- The board asks for input from a clinical radiologist, a wise IRB chair with experience on this issue, and a renowned expert in research ethics.

ORIGINAL CONTRIBUTION

Incidental Findings on Brain Magnetic Resonance Imaging From 1000 Asymptomatic Volunteers

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UNEXPECTED ABNORMALITIES are occasionally discovered during brain magnetic resonance imaging (MRI), usually in the setting of an investigation for some other reason. The radiologist and referring physician are then placed in a position of determining relevance of the abnormal finding and considering its impact on the patient. To this end, decisions must be made concerning the seriousness of the finding, including whether it is merely within the realm of normal variation.

Studies have been described that attempt to report on the prevalence of such incidental findings. This includes articles pertaining to discussions of sinusitis,¹⁻³ white matter lesions,^{4,5} and even pineal cysts.^{6,7} In each case, data are offered addressing prevalence within certain populations, establishing a foundation on which other MRI studies can be compared. All of these prior reports establish statistical occurrence on MRI examinations that had been performed for other reasons, yet not on healthy subjects.

Several investigational protocols throughout the various institutes that make up the National Institutes of Health (NIH) use brain MRI analysis, and many of these also require a healthy brain MRI database for comparison purposes. Each protocol independently ad-

Context Previous reports have discussed incidental disease found on brain magnetic resonance imaging (MRI) scans that had been requested for an unrelated clinical concern or symptom, resulting in a selection bias for disease. However, the prevalence of unexpected abnormalities has not been studied in a healthy population.

Objective To evaluate the prevalence of incidental findings on brain MRI scans obtained for a healthy, asymptomatic population without selection bias.

Design, Setting, and Participants Retrospective analysis of brain MRI scans obtained between May 17, 1996, and July 25, 1997, from 1000 volunteers who participated as control subjects for various research protocols at the National Institutes of Health. All participants (age range, 3-83 years; 54.6% male) were determined to be healthy and asymptomatic by physician examination and participant history.

Main Outcome Measure Prevalence of abnormalities on brain MRI by category of finding (no referral necessary, routine referral, urgent referral [within 1 week of study], and immediate referral [within 1 to several days of study]).

Results Eighty-two percent of the MRI results were normal. Of the 18% demonstrating incidental abnormal findings, 15.1% required no referral; 1.8%, routine referral; 1.1%, urgent referral; and 0%, immediate referral. In subjects grouped for urgent referral, 2 confirmed primary brain tumors (and a possible but unconfirmed third) were found, demonstrating a prevalence of at least 0.2%.

Conclusion Asymptomatic subjects present with a variety of abnormalities, providing valuable information on disease prevalence in a presumed healthy population. A small percentage of these findings require urgent medical attention and/or additional studies.

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mits both patients and healthy volunteers, and a participant history taking and a physical examination are performed by a physician for both populations. Healthy volunteers are actively recruited and are paid for their participation. Subjects with signs or symptoms are excluded. Such MRI studies are widely used, and the topics of investigation vary from measuring specific anatomic structures to complex-functional MRI scans to whole-brain spectroscopy, all of which share a common denominator in generating

an initial diagnostic brain evaluation for a clinical review.

We recognized the wealth of information this situation affords in the evaluation of true incidental findings in a population actively selected for healthiness by both the history taking and physical examination. Thus, we retrospectively analyzed brain MRI re-

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1000 normal volunteers



- 82% normal
- 15% no referral
e.g. sinusitis
- 2% routine referral
e.g. old infarct
- 1% urgent referral
e.g. tumor
- 0% immediate referral
e.g. hematoma

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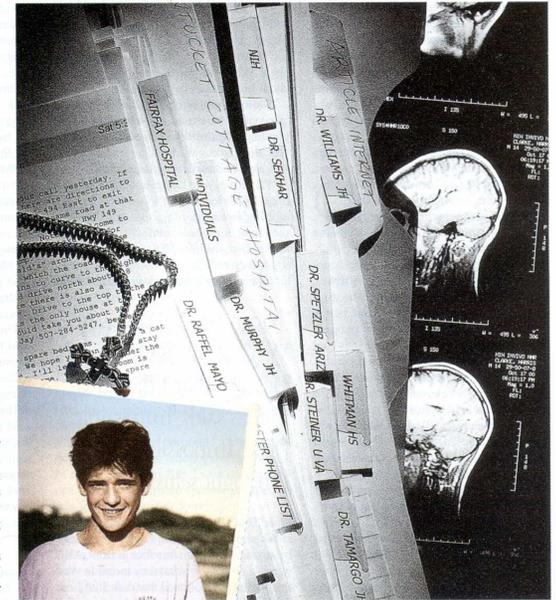
My Son Was Very Sick. Suddenly I Was Dealing With Brain Surgeons, an Ex-Husband, the White House Physician—and the Biggest Challenge of My Life. By **ANN COCHRAN**

I'VE NEVER BEEN ONE TO worry that too much happiness tempts the fates, and I'm well aware that rain falls on the just and the unjust. Still, I took notice of the stretch of contentment I'd been experiencing over the previous two years. I was happily married to Chuck, and our blended family of six had hit its stride. In addition to love and three additional grandparents, Chuck had given my two sons and me the gift of financial stability. Our house in Bethesda was surrounded by a picket fence that could be white if we ever hired someone to paint it.

On Sunday, October 22, 2000, I woke up in my cousin Silvia's co-op in New York City, where I was visiting her and my 26-year-old son, Clayton. I called my voice mail at home, expecting messages from friends, clients, and my husband, who'd be checking in from a business trip.

"This is Dr. Castellanos from NIH," a voice said. "I was assigned to review your son Harris's MRI from the attention-deficit-disorder study. I'm sorry to tell you this, but it shows something of concern that needs to be addressed. It's not a tumor. You can page me through the NIH operator."

I called back and listened to the doctor explain my 13-year-old's condition. Harris's participation in the ADD



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trial wasn't altruistic. He was a "normal volunteer" mercenary, saving up for a PlayStation 2 video-game system.

While Dr. Castellanos talked, I strained to think up questions. Good parents ask good questions at times like this, but I was frozen.

I took notes while Dr. Castellanos explained that Harris's

Clinical neuro MRI at NIH



- 80% “upstairs” in DRD
 - ~6000 cases/year
- 20% “downstairs”
 - ~1800 cases/year
 - LDRR
 - NMR center
 - 3T magnets

What is the appropriate screen?



- Entry criteria for study – “normal volunteer”
- Prior probability
- Initial Examination
 - Research MRI
 - Clinical MRI
- Follow up examinations
 - Yearly interval
 - Limited or not

Questions for the IRB



- Is there a scientific rationale for a clinical scan?
- What is the likelihood of an abnormal finding?
- What are the expectations of subjects?
- Is there relevant policy on this issue?



“What we didn’t have but obviously needed was an alarmist.”

Cases that raise related questions



- HIV testing in the Clinical Center
- Blood tests drawn only for research purposes (e.g., thyroid function tests)
- Clinical syndromes that emerge during the conduct of a protocol.
- Protocols that include mood ratings obtained for research purposes.
- Epidemiological studies.