Expectations of Participants, Ethical Responsibilities of Scientists & Incidental Findings in Neuroimaging Research

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Cincinnati Children’s Research Foundation

Empirical Bioethics: Emerging trends for the 21st century
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MRI Scans in normal healthy subjects

• Why do we need this data?
  – Reference data for studies of brain disease and disorders
  – Examples from ongoing neuroimaging studies at CCHMC

• Language & Reading
• Hearing & Deafness
• Speech Apraxia
• ADHD
• International Adoption
• TBI Rehabilitation
• Sleep Deprivation

• Neurosurgery planning
• Epilepsy mapping
• Psychiatric disorders
  – Mood disorders
  – Bipolar disorder
  – OCD
• Stroke & Rehab
Brain Activity Maps for Language Function

Stroke group
n=9

MRI Scans in normal healthy subjects

- Why do we want this data?
  - Mapping normal brain development
  - Example: fMRI study of Normal Language Development


Brain activity during a verb generation task in children age 5-18 years.
Left: Average activation map (n=285)
Center: Correlation of activity with age in this same group of children
Right: Changes in brain network for language as a function of age.
MRI Scans in normal healthy subjects

• Why do normal healthy individuals want to be want to participate in a MRI research study?

  – Curiosity
    • About the science
    • About themselves

  – Suspected pathology
    • Family history
    • Symptoms

  – Altruism
    • Desire to help others
    • Contribute to science

  – Profit
    • Want the study incentive $
    • School project/credit
MRI Scans in normal healthy subjects

– Why do normal healthy individuals want to participate in a MRI research study?
  • Surveyed 105 adult participants in neuroimaging studies
  • Most were college or graduate students

<table>
<thead>
<tr>
<th>Reason for volunteering</th>
<th>Total</th>
<th>Medical</th>
<th>Non-medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial compensation or course credit</td>
<td>64/104 (62%)</td>
<td>52/77 (68%)</td>
<td>12/27 (45%)</td>
</tr>
<tr>
<td>Contribute to scientific knowledge</td>
<td>22/104 (21%)</td>
<td>10/77 (13%)</td>
<td>12/27 (45%)</td>
</tr>
<tr>
<td>Favor to experimenter</td>
<td>17/104 (16%)</td>
<td>14/77 (18%)</td>
<td>3/27 (11%)</td>
</tr>
<tr>
<td>Worried about a health problem</td>
<td>1/104 (1%)</td>
<td>1/77 (1%)</td>
<td>0/27 (0%)</td>
</tr>
</tbody>
</table>

– Parents and children probably have different motivations than graduate students, for participation in brain imaging research
Subjects’ Expectations in Neuroimaging Research


– 84% of participants did not expect images to be reviewed

– But the majority reported that if a brain abnormality existed they would expect it to be detected
  • 51% 40/78 in the medical setting, and
  • 63% 17/27 in the nonmedical setting

– The majority wanted to know about findings

Table 2
Desired Disclosure of Incidental Finding Based on Severity of the Finding

<table>
<thead>
<tr>
<th>Significance of finding</th>
<th>Total</th>
<th>Medical</th>
<th>Non-medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>95/104 (91%)</td>
<td>70/77 (91%)</td>
<td>25/27 (93%)</td>
</tr>
<tr>
<td>Malignant, but curable</td>
<td>105/105 (100%)</td>
<td>78/78 (100%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>Malignant, not curable</td>
<td>102/105 (97%)</td>
<td>75/78 (96%)</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>Life-threatening emergency</td>
<td>105/105 (100%)</td>
<td>78/78 (100%)</td>
<td>27/27 (100%)</td>
</tr>
</tbody>
</table>
IRB Expectations in Neuroimaging Research

• IRB language for research scanner < 2008
  – Limited anatomical images for research only.
  – Not adequate to either diagnose brain pathology or to rule out pathology.
  – Not useful or ethical to provide a clinical review or report on the MRI brain scans performed as part of the proposed research protocol.

• High false-positive rate due to non-diagnostic scans
  – Unnecessary referrals
  – Unnecessary anxiety among participant families
  – Obviated review by radiologists
fMRI Map of Auditory Stimulation overlaid on T1-weighted images

11 m.o. male with normal hearing. Stimulation with stories read in female voice. Yellow-red = positive z-score, Blue-green = negative z-score, $p<0.01$, cluster = 3
Subjects’ Expectations in Neuroimaging Research

• Expectations and capabilities have changed with time
  – As technology has improved
  – As neuroimaging research has been disseminated

• History of MRI Technology
  – 1972 – First MR image
  ~ 1980 – First MRI scanners in hospitals
  ~ 1985 – 1.5 T clinical MRI scanners
  ~ 1990 – 3.0 T MRI scanners for research
  ~ 1994 – 3.0 T MRI research scanner at CCHMC
  ~ 2000 – 3.0 T clinical MRI scanners available
  ~ 2006 – 3.0 T clinical MRI scanners for research
  ~ 2010 – 7.0 T MRI scanners for research
Subjects’ Expectations in Neuroimaging Research

• Sagittal T1 MRI 1996 vs. 2011
  – Can you tell the difference?

• Image quality and sensitivity to pathology improves with technology

• Expectations have changed along with our capabilities
Research Community Expectations

  - January 6-7, 2005 – Panel conference in Bethesda, Maryland
  - Sponsored by the National Institutes of Health: NINDS, NIDA, NIBIB, NIMH, NIA and Stanford University
  - A set of recommendations were made stating that neuroimaging investigators should:
    1. Anticipate incidental findings (IFs)
    2. Arrange for qualified review of images
    3. Communicate findings to participants in a timely way
    4. IRB protocols and consents should layout a plan for handling IFs transparently

IRB Expectations Revised

• In 2008 the Imaging Research Center installed an identical pair of 3T MRI scanners for research and clinical scanning in children.

• Revised policy for review and reporting of findings now follows NIH guidelines
  – only the minimal necessary imaging required to answer a research question should be performed.
  – Images should be reviewed by a radiologist.
  – Incidental findings should be communicated to participants.
  – IRB protocols should contain language describing the quality and diagnostic value of images and the process for reviewing them
  – IRB consent should clearly explain the process for reviewing and reporting IFs.
How often do incidental findings occur?

“Incidental findings in magnetic resonance imaging of the brains of healthy young men”.

- 2536 healthy recruits for the German Air Force underwent MRI
  - Avg. age = 20.54 years.
  - Intracranial tumors (0.47%)
  - Vascular abnormalities (0.51%)
  - Arachnoid cysts (1.7%)
  - Total IFs ~ 2.5%
How often do incidental findings occur?

“Ethical consideration of incidental findings on adult brain MRI in research”

  - N=151 participants
  - Average age = 47.1 yrs
  - 6.6% rate of IFs requiring referral
How often do incidental findings occur in children?

“Incidental findings on pediatric MR images of the brain.”

- Kim B. S., Illes, J., Kaplan, R. T., Reiss, A., Atlas, S. W.
  - N = 225 (100 boys [44%] and 125 girls [56%])
  - Age range = 1 month to 18 years.
  - Neurologically healthy children

- 79% of the images were normal.
- 21% rate of Incidental abnormalities were detected in (47/225)
- 7.5% (17/225) IFs requiring referral
- 0.44% (1/225) required urgent referral
Incidental Findings in Pediatric Participants

N=211 research subjects @ CCHMC
Age 5 -18 years

Potentially abnormal findings
16/211 (7.6%)

- 4 – Chiari I (> 5mm, pointed, some crowding)
- 3 – Milder cerebellar tonsillar ectopia (still > 5mm)
- 3 – Non-specific WM signal (FLAIR)
- 3 – Significant sinus / mastoid opacification
- 1 – 4th ventricular mass
- 1 – non-specific pituitary lesion
- 1 - old infarct
Now that we review, what do we do?

• Procedure for review and reporting of incidental imaging findings in research participants
  1. Neuroradiologist reviews scans and detects abnormality.
  2. Neuroradiologist notifies PI and/or coordinators of findings in written report.
  3. PI or delegate contacts primary care provider (PCP) regarding findings:
     • Transmits radiology report to PCP
     • If no PCP, refer to CCHMC Primary Pediatric Clinic (PPC) for f/u.
  4. Neuroradiologist and neurologist available to PCP for consult.
  5. PCP contacts family regarding findings and any referrals needed
  6. PI to follow up with family and PCP in writing, 1-2 weeks later to insure that the above chain did not break at any point (standard format letter).
Images are classified using 3 quantitative ratings:

1. **Image classification**: 0,1,2,3,4 scale that classifies potential abnormalities

2. **Anatomical Distortion**: 0,1 binary scale indicating whether pathology detected in the image causes any significant distortion of brain ((0 – no, 1 – yes, e.g. displacement by a mass, or enlarged ventricles)

3. **Follow Up**: 0,1 binary scale indicating whether clinical follow-up is needed (0 – no, 1 – yes).
Quantitating Incidental Imaging Findings

• Quantitative rating scales for brain images:

  
  **Imaging classification:**
  
  0 - **Normal**: No abnormalities or anatomic variations detected
  1 - **Normal anatomic variants**: Anatomic variations with no clinical significance.
  2 - **Potentially significant abnormality**: Imaging findings out of the range of normal or normal anatomic variation, that require correlation with clinical findings to determine significance for the health of the subject (if any).
  3 - **Likely clinically significant abnormality**: Imaging findings out of the range of normal or normal anatomic variation that have a high likelihood of clinical significance requiring clinical and/or imaging follow-up.
  4 - **Imaging markedly degraded by artifact**: No interpretation possible.

  **Anatomic distortion:**
  
  0 - **No**: No significant distortion of normal anatomy on the T1 weighted images.
  1 - **Yes**: Possibly significant anatomic distortion on the T1 weighted images.
Quantitating Incidental Imaging Findings

- A classification system for incidental imaging research findings in normal health children:

<table>
<thead>
<tr>
<th>Imaging Classification</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Normal anatomic variant</td>
<td>1</td>
</tr>
<tr>
<td>Potentially clinically significant abnormality</td>
<td>2</td>
</tr>
<tr>
<td>Likely clinically significant abnormality</td>
<td>3</td>
</tr>
<tr>
<td>No interpretation possible due to poor image quality</td>
<td>4</td>
</tr>
<tr>
<td>Anatomic distortion</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Follow up Required</td>
<td></td>
</tr>
<tr>
<td>No, findings do not need medical follow up</td>
<td>0</td>
</tr>
<tr>
<td>Yes, clinical correlation with symptoms and/or potential imaging follow-up is appropriate</td>
<td>1</td>
</tr>
</tbody>
</table>

- Each scale and value is defined explicitly and documented by panel of experts.
- Pediatric Radiologist assigns values at time of scan review
- Numeric values flow into research database for meta analysis
Exam Date:

Subject ID#:

Imaging Classification:
___ 0 - Normal
___ 1 - Normal anatomic variant
___ 2 - Potentially clinically significant abnormality
___ 3 - Likely clinically significant abnormality
___ 4 – No Interpretation possible due to quality

Findings:

Notes:

Anatomic distortion: ___ Y (1) ___ N (0)

Notes:

Follow-up: ___ Y(1) ___ N (0)

Evaluation recommendation:

Reported to: Holland, Scott;

Date/Time Reported:

Signature:

Selected Images:
Incidental Findings in Pediatric Participants

Incidental findings for CMIND study as of Sept. 25, 2012
N=85, Age range: Birth to 18 years

<table>
<thead>
<tr>
<th>Imaging classification</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – Normal</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>1 – Normal variant</td>
<td>7</td>
<td>7.8</td>
</tr>
<tr>
<td>2 – Possible abnormality</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>3 – Likely abnormality</td>
<td>2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Total: 12.2% rate of incidental findings requiring notification

Anatomic distortion:

Yes: 5
No: 85
Abnormalities:
- Cerebellar tonsillar ectopia (>5mm, CSF space effacement): 2
- Increased white matter signal on FLAIR T2: 5*
- Callosal hypogenesis: 2^*
- Remote infarct: 1
- Sinus disease / antral choanal polyp: 1

*One subject with callosal hypogenesis also had increased FLAIR signal
^ One subject with callosal hypogenesis also had an associated lipoma

Normal variants:
- Pineal cyst: 1
- Prominent cisterna magna: 2
- Mild (<5mm) tonsillar ectopia: 1
- Cavum vergae: 1
- Tiny isolated WM signal foci: 1
- Slight asymmetry of the mammillary bodies: 1
Examples of Incidental Findings

Exam Type: Collosal Hypogenesis - Excluded

Subject ID#: IRC04H_08M010_P_1

Potentially clinically significant findings requiring further evaluation (see note)

1. Posterior callosal hypogenesis, fairly marked
2. Minimal scattered foci of increased FLAIR signal within the white matter, presumed gliosis.

Evaluation recommendation: Clinical correlation with potentially related symptoms. Callosal hypogenesis may interfere with grouped data analysis for normal if this area would be important for the study research goals. Clinical MRI only if potential related symptoms.
Examples of Incidental Findings

Subject ID#: IRC04H_08M010_P_1 - Excluded
Exam Type: Sinus disease – Not excluded

Subject ID#: IRC04H_14F001_P_1

Clinically significant findings requiring further evaluation (see note)

Brain normal. Extensive pan sinus opacification. Large rounded polypoid lesion in right nasal cavity with obstruction. This appears to extend from the right maxillary sinus. Likely represents an antral choanal polyp. There is marked obstruction of the posterior nasal cavity

Evaluation recommendation:
ENT consultation. Sinus CT would be next step as far as imaging.
Examples of Incidental Findings

Subject ID#: IRC04H_14F001_P_1 – Not Excluded
Incidental findings impact on research?

• Which subjects should be excluded?
  – Image classification threshold?
  – Anatomic distortion?
• If excluded, do we complete neuropsych test battery?
• Should neuropsych scores be reported?
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