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Ethical Considerations for Neuropsychologists as Functional Magnetic Imagers

Abstract
This discussion highlights ethical and practical issues potential neuropsychologist-imagers should consider in conducting functional magnetic resonance imaging (fMRI). While fMRI is not currently approved for clinical use, research is ongoing which has implications for clinical practice, from refining brain–behavior relationships, to assisting with diagnosis and treatment decisions. To protect the welfare of cognitively impaired populations requires special care with respect to MR risks and informed consent. Competent functional imaging requires an understanding of the strengths, limitations, and appropriate domain of applications of the measure.

Keywords
Functional MRI; Neuroimaging; Alzheimer's disease; Ethics; Law; Brain

Comments
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Ethical considerations for neuropsychologists as functional magnetic imagers

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1. Introduction

Functional MRI (fMRI) has great potential to enhance the characterization of brain integrity in people with cognitive dysfunction; hence, neuropsychologists have joined the rush to use this technology. This fact was strikingly evident at the 2002 International Neuropsychology Society meetings where 60 percent of the symposia revolved around brain imaging. Functional MRI is becoming more widely applied in part because it is noninvasive, can be performed in sites with clinical MRI's, and there are easily available, affordable, analysis tools. While fMRI is not yet approved for clinical use, techniques are being tested and validated which have the potential to become part of the tools of the neuropsychologist. Guidelines for use must thus follow both from the specific constraints of the MRI technology and the domains of appropriate application. While detailed descriptions of guidelines for the ethical and competent practice of clinical neuropsychology, psychological assessment, and test use have been described (American Academy of Neurology, 1996; American Psychological Association, 1992; Turner, DeMers, Fox, & Reed, 2001), these do not adequately cover the specific requirements and potential applications presented by fMRI. Below are suggested revisions of these standards.

The focus of this paper will be on aspirational goals for the manner in which fMRI data may be ethically applied to the practice of clinical neuropsychology; however, many of the recommendations are relevant to all fMRI users. The first section discusses informed consent for the procedure and risks. The second section outlines a series of core competences. For example, fMRI imagers must understand the kinds of questions that can be interrogated with the technique and they must cope with threats to validity, limitations on generalizability, and avoid analysis and interpretive errors. The final section briefly discusses examples of clinical applications and related ethical problems.

2. Informed consent, competence, and protection from harm

There are several protections for patients with cognitive impairments who participate in medical research. These issues are discussed in more detail elsewhere (Dunn & Chadwick, 1999) but will be briefly summarized below. The right of individuals to

choose what will happen to them would likely prevail in a situation, such as deciding not to perform functional imaging, where there is no clear benefit from undergoing the procedure (National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research, 1979). Even when there are approved clinical uses, the level of benefit to the patient and the existence of alternative procedures to address the clinical needs must be weighed against the risks of the procedure. Under no circumstances should anyone be allowed to participate in an fMRI study if there are significant safety concerns, even if they acknowledge and wish to participate in spite of the risks. During the process of obtaining informed consent, participants need to be provided with adequate information regarding planned procedures which they must comprehend and voluntarily agree to without undue coercion (for a clear discussion see Dunn et al., 1999; National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research, 1978; NBAC, 1998). Information typically important to include are the specific benefits to the individual or to patient care in general, risks, right to withdraw from participation, and to have questions answered. Procedures must be adapted to patients to compensate for cognitive deficits that interfere with comprehension, requests for information, or memory for information that would affect the patient's willingness to participate. A signature on a consent form is evidence that this process was completed successfully.

There are some special issues to consider with respect to informed consent and the MRI environment. In informing patients of potential risks, it is important for an imager to assess each patient carefully with respect to their risk in the MRI environment and to consult more expert colleagues, typically clinical radiologists, when there is any uncertainty. The most dangerous risks are from ferromagnetic objects which become projectiles in the strong magnetic field of the MR scanner, and from implanted electromechanical devices, such as pacemakers, that cannot function in the magnetic field. Sometimes a neuroradiologist will request an X-ray as part of a safety evaluation and patients must also provide informed consent for this procedure. When there is a question as to whether a patient is an accurate reporter of his medical history due to cognitive impairments, at a minimum, special precautions such as a medical record review or a careful interview with a spouse should be instituted. Shellock offers comprehensive reference materials on the subject both in published form (Shellock, 2001; Shellock, 2002) and on-line (www.mrisafety.com). Great caution should be exercised when studying people from certain occupations, particularly those involving grinding metal. If there is any concern that metal flakes entered the eyes, they should not be studied unless there is a compelling clinical need, and then only after a special workup (e.g., X-ray).

Other typical safety issues include the necessity for all people, including any caregiver accompanying the patient in the MRI room, to wear MR compatible earplugs to dampen noise. There is also the potential for sensory stimulation, minor muscle twitches, particularly at higher field strengths than the standard clinical 1.5 Tesla MRI. There are no known residual health problems that result from these symptoms. Scanning claustrophobic people is problematic since the MRI environment is confining. Most people with claustrophobia will warn the investigator and probably choose to avoid the study, in which case of course they should neither be coerced nor even cajoled. Quite a

few individuals with claustrophobia, however, even among those who volunteer as healthy participants, are unaware of their condition or decide to try to overcome it by forcing themselves into anxiety provoking situations. A good practice is to warn every potential participant. An example of such a warning might be "We previously asked you if you were uncomfortable in confined places such as elevators. Most of us are a little nervous the first time we undergo an MRI; however, occasionally people are surprised by how anxious they become and would like to end the study. Please tell us immediately if this is the case by pressing this alarm button and we will stop everything and promptly pull you out of the MRI." Participants typically need a great deal of reassurance and support if this occurs. Commonly participants fear disappointing the investigator or that they have a newly discovered anxiety disorder. Stressing that nervousness is natural and that "toughing it out" despite extreme anxiety invalidates the study often facilitates admissions of reluctance to continue participation.

With respect to confidentiality, investigators in the behavioral sciences, where some disorders are still stigmatized, should be particularly vigilant with respect to whether their image files contain information that can identify patients. While there are no procedures available to identify uniquely someone on the basis of a picture of their brain, some image formats contain names if they were entered during data acquisition. It is possible to strip this information from the image files, however. This must be done if an investigator plans to provide data to larger databases such as the Neuroimaging Informatics Technology Initiative, or contribute to journals where there is the requirement to provide raw data (e.g., Journal of Cognitive Neuroscience). Several participants enter studies because they expect that their images will be reviewed by a physician. It is prudent to inform the participant whether or not this is the case during informed consent and to have in place a protocol for consulting with competent neuroradiologists in a situation where pathology is suspected. It is better yet to include a neuroradiologist who will routinely inspect the images and perform a "clinical reading" to the limited extent feasible from the structural component of the fMRI study. Regardless, it would be prudent to inform the participant that the fMRI procedure is not designed to screen for brain disorders and that if they suspect a problem they should consult a neurologist for referral to a clinical study. Of course, neuropsychologists are not competent to practice neuroradiology and need to inform participants about this limitation. If neuropsychologists detect an abnormality on an MRI scan, they should consult a neuroradiologist to decide whether a clinical referral should be made. Ethical issues associated with such incidental findings are discussed elsewhere (Illes, Desmond, Huang, Raffin, & Atlas, 2002; Kulynych, 2002).

Like other clinical investigators, functional imagers may confront situations where decisions must be carefully made as to whether a patient is competent to consent to undergo functional imaging. Obtaining informed consent from the cognitively intact participants themselves is the rule, but questions of competence to consent may arise with several populations such as children, retarded individuals, people with certain neuropsychiatric disorders or otherwise cognitively impaired patients. If there is a question as to whether the patient is capable of formal informed consent, it is possible to include a surrogate or proxy decision maker and to obtain the patient's assent. A person is capable of assent if they know the procedures they will undergo, unambiguously

communicate this willingness to participate, and understand their right to withdraw from participation at any time (National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research, 1978). Establishing that the patient can provide a reliable yes-no response is crucial (e.g., asking redundant questions with different responses "Do you want to stop? Do you want to continue?"). It is the recommendation of the National Bioethics Advisory Commission (NBAC, 2001) that assent alone is not sufficient to enroll a patient in a research protocol. The role of the proxy decision maker is to advise the investigator how the patient would have decided had he or she been cognitively capable. This topic is reviewed in depth elsewhere (Dunn et al., 1999; NBAC, 1998; NBAC, 2001).

The MRI environment imposes particular difficulties for investigators in monitoring patient's continued willingness to participate. Patients lie in the MRI so that many cues about their emotional status, such as their facial expressions, are not observable. It is thus crucial to assess carefully whether it is possible, and what kind of support patients need in order to remain motivated and oriented to the task at hand. For example, patients with severe memory disorders need to be repeatedly monitored since they are vulnerable to disorientation. Furthermore, it is important to be vigilant for cues that indicate the patient's willingness to continue has changed. For example, some patients are surprised to discover they have become claustrophobic in the MRI environment and might begin to try to escape from a head positioning device. It is advisable to agree ahead of time on a signal for distress, but it may be necessary to incorporate breaks and ask through the intercom or headphones whether the participant feels comfortable continuing the study.

3. General core competence in the use of fMRI measures

Most neuropsychological practice and potential applications of fMRI fall within the domain of assessment. Given the costs of using the MRI, fMRI is not likely to be used directly in therapy in the near future. Guidelines for test user qualifications for psychologists specify necessary general and domain specific knowledge and skills (Turner et al., 2001). This section focuses on general problems with which an fMRI user must cope. The next section will briefly outline examples of clinical translations and the manner in which ethical issues are relevant.

Current ethical guidelines dictate that psychologists not practice outside limits of their education, training, and experience. Because there are no FDA approved clinical uses for fMRI, credentials and training requirements have not been established. This situation will likely change as clinical applications are tested and validated (for excellent reviews on fMRI task design, see Aguirre & D'Esposito, 2000; Donaldson & Buckner, 2002; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). There are minimal and crucial skills to be acquired and knowledge that must be learned to assure valid fMRI results and these are not formally taught to psychologists as part of their training. Until there are significant technical advances, the burden is on the fMRI user to avoid confusing the scientific community with erroneous interpretations of artifacts. Below, there is a brief

description of some of the major threats to valid fMRI results. For more detail, Thulborn and Gisbert (2002) provide a readable description of what is involved in actually acquiring fMRI data in a clinical setting.

3.1. Selection and design of appropriate tests

A central area of competence for developers of fMRI paradigms is understanding what questions can be addressed with the method, and keeping pace with advances in task design. Brain imaging studies are uninterpretable unless carefully designed and applied. It is tempting to create imaginative experiments that try to address clinically relevant questions directly such as "which brain structures underlie driving competence?", and to have patients performing simulated driving evaluations in an fMRI study. These studies of complex tasks will essentially activate the entire brain. For example, visual cortex will be activated by looking at the road, and motor cortex will become active when one turns a steering wheel. Neither of these findings is likely to yield anything surprising or distinctive about driving. Ultimately, one would need to establish predictive or criterion validity, in this case, predicting driving accidents. Unless the external event occurs frequently, one would need to image many people to have a large enough sample to establish a correlation. In part, because of the expense of imaging, these studies are difficult to perform. For these reasons, it is hard, but not necessarily impossible, to apply functional imaging in a manner that would justify making specific recommendations about complex tasks such as a given functional capacity. As with other neuropsychological tests, a functional imaging evaluation would need to be interpreted in a larger context of a comprehensive cognitive evaluation.

In contrast, the underlying construct of a well-designed brain imaging paradigm is typically the definition of a single or network of brain structures subserving a specific cognitive process (e.g., Gur, Erwin, & Gur, 1992). Because fMRI analyses involve thousands of statistical comparisons (leading to a high likelihood of false positive results), an imager must have some a priori hypothesis about which specific brain structures are likely to be activated by the cognitive task. Hypotheses typically are developed from lesion studies in humans and animals, or from recordings from single neurons in which the human or animal is performing a behavior. While all tests must be interpreted within the context of a more comprehensive evaluation, fMRI is likely to be most valuable in situations where clinical decision making hinges on a limited number of brain functional systems.

In this context it is important to remember that many of the functional imaging studies performed hitherto included small samples and their effects may have limited applicability to individual cases. Without better knowledge of how many individual participants are expected to show an effect, it is hazardous to conclude about an individual that the pattern of activation is "abnormal." It will take the field a while to assemble the kind of "normative" data that would permit individual assessments. The ethical neuropsychologist will be careful to avoid inappropriate and premature use of the power of fMRI to show effects that to a layman may seem conclusive but that in reality may reflect dubious procedures or interpretations. Nonetheless, the power of the method

will eventually bring it to the clinical arena and those neuropsychologists who learn how to use fMRI competently and carefully will be poised to exploit its immense potential for assessment of disease and treatment effects.

An example of how an fMRI finding can lead to pressures for premature application is recent studies showing the ability of fMRI to detect deception (Langleben et al., 2002). Attorneys, judges, and law enforcement agencies rushed to try and use fMRI for lie detection, not realizing that the effects were demonstrated on group data and the road is long before the method can be justified for identifying individual deceivers, let alone specific items in which deception has occurred. It is an ethical obligation of a neuropsychologist to explain these limitations to potential clients who may want to use the study in litigation or law enforcement.

3.2. Sources of error variance

3.2.1. Artifacts from acquisition and individual differences in the MRI signal

A competent fMRI user is vigilant and aware of how to cope with acquisition artifacts, a major threat to the validity of imaging results. There are known artifacts at the level of image acquisition, such as signal loss (appearing as dark regions called susceptibility artifact). They are problematic in regions where tissue characteristics change abruptly, such as near air passages. Susceptibility artifacts abound near the orbitofrontal/anterior-medial temporal region of the brain. Other artifacts include movement artifacts, field inhomogeneity effects ("shading"), physiological artifacts related to heart rate and breathing, anatomic distortions and other causes of instability of the fMRI signal. There are techniques under development such as "on-line" movement correction, acquiring separate images within the susceptibility region, and compensating for image distortions. Until corrections or detection algorithms become routine, imagers must be able to recognize these problems and determine in each patient whether they can be ameliorated through post-processing or careful interpretation.

Aside from artifacts within an individual scan, fMRI researchers must be aware that there are differences across individuals and MRI sites, and scanner "drifts" within the same facility even within a single session, which introduce artifacts and error. Even if one follows the exact same imaging protocol, the MRI signal differs across individuals (Aguirre, Zarahn, & D'Esposito, 1998; Buckner, Snyder, Sanders, Raichle, & Morris, 2000; D'Esposito, Zarahn, Aguirre, & Rypma, 1999). Statistical comparisons across different patient groups must take into account these individual differences. MRI manufacturers, and upgrades of the same manufacturer, may change the image quality of the MRI so there must be user intervention to test and compensate for changes in parameters such as image contrast and field homogeneity. Methods of testing comparability of data across different sites are under development for structural (e.g., Styner, Charles, Park, & Gerig, 2002) and functional (G. Glover, personal communication) imaging protocols. The process typically involves scanning a phantom or relatively stable test subject (e.g., a person without a progressive dementia or a

developing brain) at several MRI sites and analyzing the inter- and intra-site stability of the measure of interest.

Functional MRI investigators must also be familiar with artifacts that constrain processes that can be studied. For example, tasks that require overt verbal responses are not often studied with fMRI because of the associated head movement and susceptibility artifact from changes in the vocal cavity. In addition, it is difficult for the participant to hear auditory stimuli, or for the investigator to hear responses over the noise of the MRI, without special equipment. Some cognitive tasks that are part of a standard cognitive evaluation, such as confrontation naming, verbal fluency, and memory recall are thus problematic to study with fMRI. There are specialized image processing techniques to compensate for talking-related artifact in the MRI (e.g., Birn, Bandettini, Cox, & Shaker, 1999), however, the burden is on the imager to demonstrate that activation is not artifactual.

3.2.2. Inappropriate controls

Functional MRI depends on differences between conditions and hence the choice of comparison tasks affects the sensitivity of the measure. Activation and control conditions are carefully matched for motor and sensory stimulation, as well as other hypothesized confounding cognitive processes. Often, a resting baseline (control) or a less carefully matched condition is included. The choice of baseline condition has been a subject of controversy (e.g., Stark & Squire, 2001) since, for example, if participants continue to rehearse mentally the experimental task, the difference in activation between task-on and task-off will be reduced. Ultimately, a competent imager must be familiar with the opinions in the field and able to defend how well the choice of comparison tasks controls for activations that are unrelated to the domain of interest.

3.2.3. Standardized administration procedures

While the standardized neuropsychological assessment rigidly adheres to carefully worded scripts and particular stimulus materials, and hence neuropsychologists are well trained in rigorous testing procedures, fMRI has additional requirements. Several of the problems of selecting appropriate control conditions are similar to those involved in standardization since one goal involves minimizing task-irrelevant brain activation. Imagers are responsible for monitoring the literature on processes invoked during imaging (e.g., sensory, motor, and rest) to increase the chance that appropriate standardization procedures will be instituted. For example, failure to standardize image contrast and visual angle generally has only subtle effects on neuropsychological tests. Variability in these and other perceptual and movement parameters has a large impact on brain activity because of differences such as amount of stimulation to visual cortex, eye movements, and spread of attention to the periphery. There are attempts to standardize the stimulus display and behavioral measurements in fMRI (e.g., Integrated Functional Imaging System, MRI Devices, Waukesha, WI); however, the costs are high and development is complex since MRI manufacturers build different sized MRI's and stimulation paradigms vary considerably in their requirements.

3.2.4. Characteristics of the test takers and generalizability

Functional MRI users must be vigilant for motivational, cognitive, and functional disabilities which interfere with valid test performance. Not only is it unethical to perform fMRI on an unwilling patient, in most situations it is nearly impossible to obtain valid results. In some analyses, a head movement of greater than 2 mm over the course of a minute or an hour will render data useless. Investigators should aim to obtain on-line performance data and at least intermittently monitor the accuracy of behavioral responses during MRI scanning (typically there is a signal in the control room to the investigator, indicating the participant's response). Such monitoring is needed to confirm that patients have not lost the instructional set or are responding intermittently. Paradigms that do not collect any measure of accuracy are problematic since one cannot be certain that patients are performing the desired cognitive operations.

Certain aspects of the MRI environment make a task more cognitively complex than an evaluation outside the MRI. These nonspecific environmental effects may interact with certain forms of cognitive dysfunction. In addition to the constraints of the small space and complicated interaction between participant and investigator, there is a loud, distracting, radiofrequency pulse. Patients must often be able to remember and shift between different cognitive tasks based on cues or instructions given before the imaging task begins. Patients with severe memory or executive dysfunction may have difficulty remaining oriented or controlling the impulse to move. Patients may even fall asleep. All of these cognitive and motivational issues must be considered in interpreting data collected on patients in the MRI environment.

Clinical assessments require compensation for disabilities that affect the validity of the measure; however, once the patient enters the MRI environment, changes to the paradigm in individual patients are ill advised unless the change in concomitant brain activity is part of the study. Furthermore, all items placed in the MRI environment have the potential for either producing artifact or being safety risks. For example hearing aids cannot be used. Acuity correction is not simple since most eye glasses contain metal and specially designed glasses need to be used. Sometimes investigators have every participant wear glasses, some with no correction, so that the periphery of the visual field is occluded equally in all participants.

These practical and ethical problems, and difficulties with scanning unwilling or cognitively impaired patients, limit the population of patients that can undergo fMRI and hence the generalizability of findings. Essentially, fMRI will likely be restricted to mildly impaired patients until there are significant changes to the testing environment. This must be considered when one attempts to extrapolate findings to more cognitively and functionally impaired groups.

3.2.5. Reliability and sensitivity

A competent fMRI user is familiar with the particular statistical problems fMRI data raise; however, fMRI research is only beginning to address the quantification of

reliability and measurement error. Imaging patients introduces another layer to this complex problem. New acquisition, experimental designs, and statistical analyses will likely be developed and optimized to address such concerns. Approaches to setting statistical thresholds are still heatedly debated in fMRI. Part of the reason is that task design markedly affects the sensitivity to activation. For example, an fMRI study that attempts to measure individual events (event-related fMRI) may demonstrate less robust results than one in which several events are averaged in a blocked design. On the other hand, event related fMRI could be particularly useful when comparing patients and controls since one can select only accurate trials across the groups (provided that the design has enough power for such an evaluation) and thus be more certain that the cognitive processes underlying the functional effects are similar. One could increase the number of trials to compensate for having a weaker ability to detect activation but then validity can be compromised by the ability of participants to tolerate the environment for a long period of time. Nonetheless, it is encouraging that studies examining reliability of fMRI results across different sites and within individuals have yielded promising results (Aguirre et al., 1998; Casey et al., 1998; Cohen & DuBois, 1999; Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000; Ojemann et al., 1998; Rombouts, Barkhof, Hoogenraad, Sprenger, & Scheltens, 1998). The number of tasks in which reliability has been described, however, is quite small at present.

3.3. Interpretation of results

Conclusions about the role of a particular brain region in a cognitive process should be based on a convergence of information, not a given fMRI experiment. Functional MRI results are merely a statistical representation of a relationship between temporal changes in a cognitive task and recruitment of blood flow to a brain region. This co-occurrence does not definitively demonstrate that a brain region is involved in a task, only that the region may be active during the task. Even then, blood flow is only an indirect measure of neuronal activity. Because functional activation is defined based on statistical significance, failure to activate is a statistical null effect and should also be interpreted with great caution mindful of Type II error. Inappropriate control conditions and any of the above-described artifacts can reduce the chance of detecting an fMRI result or yield spurious findings. Neuropsychologists can provide crucial complimentary information to fMRI data as they are likely to be familiar with research demonstrating relationships between lesions and cognitive deficits that may suggest that the damaged area is necessary or provides connections to regions crucial for performance of a task. Performing fMRI on patients with brain dysfunction provides clues to the process of functional reorganization when effectiveness of recovery is associated with particular patterns of activation (e.g., Horwitz, Rumsey, & Donohue, 1998; Maguire, Vargha-Khadem, & Mishkin, 2001).

3.4. Consultation with colleagues and institutional support

Because techniques are evolving quickly, it is recommended that anyone using fMRI in a program of research have significant institutional and expert collegial support. For example, sites should include a staff MR physicist who assures that the scanner performs

to specifications and that data acquisition is maximally sensitive to functional activation. A physicist is also likely to understand and be familiar with artifacts that can disrupt image quality. Just as current, validated and sensitive tests should be used in the neuropsychological evaluation, there must be institutional support and adequate resources to pay for the MRI infrastructure, including software and hardware upgrades to MRI scanners. Special MR compatible equipment is needed for displaying stimuli and collecting behavioral data in the MRI and this poses difficult challenges. Sites should have access to engineers and machinists to develop and maintain such devices. Even experienced MR technicians need to be trained to avoid various artifacts that may distort the fMRI signal. For example, fMRI data are particularly vulnerable to artifacts from certain dental work or medications that affect blood flow and these are less of a problem for standard pulse sequences used in structural imaging for clinical purposes. Many sites have "image processors," people dedicated exclusively to image analysis and software development. Most investigators performing functional neuroimaging also obtain advice from software developers through on-line list servers. An imager must be competent to understand and evaluate the accuracy of this advice. This usually involves learning new approaches to statistical modeling and image processing and vigilant monitoring of new analysis techniques. Developers of research-dedicated image analysis products (e.g., AFNI, Statistical Parametric Mapping) recommend against clinical application because the source code is written by multiple users in the community and thus it is nearly impossible to guarantee it as error free. In its current implementation this software is far from "fool proof" and indeed not very "user friendly." Translating a paradigm from an experimental to a clinical application to be administered in multiple sites, as is done with neuropsychological tests, therefore requires much careful pre-testing and possibly debugging of computer code.

4. Approaches to clinical translation

There are several approaches the neuropsychologist might take to using data from fMRI. Potential clinical applications of fMRI are reviewed in more depth elsewhere (Detre & Floyd, 2001; Hammeke, 2002; Stern & Silbersweig, 2001; Thulborn et al., 2002). Ethical problems and dilemmas are omnipresent when translating research to clinical applications. In general, the more autonomy and flexibility fMRI users have, the greater the potential for error. Developing fMRI paradigms for potential clinical use in individual patients requires the highest level of skill and competence. Some day, there will likely be clinical protocols where both acquisition parameters and analyses have been well worked-out and established as valid and reliable across sites. Until such technical advances are achieved, fMRI users will still need to assess data quality and upgrade equipment and software. However, there will be less of a demand to innovate, as has been the case with the traditional clinical neuropsychological examination. Another approach to clinical application is using fMRI to validate other measures or techniques. For example, rather than applying fMRI to individual patients, one could study a subgroup of controls and validate new neuropsychological tests as indicators of the integrity of a particular brain system. Alternatively, one might use fMRI as a marker of drug treatment response in a patient group. In this form of clinical research, the burden on the researcher is to describe limitations to interpretation and generalizability. For example, careful

description of the patients tested and methods by which areas of activation are defined is crucial for describing the manner in which a paradigm is applied. For instance, some investigators limit the number of statistical comparisons by a priori definition of a small brain region on the basis of structural landmarks. Some investigators interrogate a small, functionally defined, region of interest (e.g., using retinotopic mapping) before beginning a study. Most investigators perform analyses on the entire brain. Each of these approaches affects statistical power tremendously.

4.1. Applications and ethical dilemmas

Functional imaging may provide information about brain localization in individual patients that is unavailable with other technologies. For example, there is hope that fMRI can reveal islands of functional sparing within, and subtle functional decrements outside of lesions that are only grossly apparent on MRI scans. Interpreting lesion-function relations is confounded by the fact that there is functional reorganization after brain damage. Defining regions of brain activation with fMRI in individuals rather than on the basis of group studies further refines localization information. The fMRI study can describe the neural substrates of component processes of which behavioral neuropsychological tests detect only the result. For example, event related fMRI has not only separated the functional activation related to encoding from retrieval, but has also demonstrated differences in the same person in brain functioning during encoding of items that were remembered versus those that were forgotten (Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner et al., 1998). There are several important potential clinical fMRI applications that follow from these advantages.

In neurosurgical interventions, accurate localization is critical and treatment risks are high. In the case of tumor removal or medial temporal lobe resection for seizure control, outcome can be improved (i.e., halting tissue destruction from invasive pathology or seizure control) as larger tissue volumes are removed; however, this must be balanced against the risk of damaging adjacent functionally active tissue. Localization errors can lead to significant disability and thus this application presents one of the highest levels of risk. Functional MRI can be applied to help the neurosurgeon walk this tightrope by identifying regions where there may be a greater risk of deficit following removal. Such paradigms can provide convergent data complementing information obtained by temporary inactivation techniques (e.g., Wada, TMS, or cortical stimulation during neurosurgery). Given the current state of technology, using fMRI alone without inactivation techniques is problematic.

Just as structural imaging is central to the diagnosis of tumors and strokes, functional imaging is being tested as a potential method to improve the quality of diagnosis where a specific distribution of brain functional pathology is expected but difficult to detect with existing technologies. For example, various types of lesions within the medial temporal lobe (MTL) may disrupt memory; however, differences in functional activity across different MTL subregions may differentiate older adults who have Alzheimer's disease (AD) pathology from other disorders (e.g., Small, Perera, DeLaPaz, Mayeux, & Stern,

1999). The risk of misdiagnosis to the patient is significant, but more harmful if the result is delay or denial of effective treatment.

Functional imaging may assist in demonstrating the brain regions being affected by drug treatment (e.g., Rombouts, Barkhof, van Meel, & Scheltens, 2002; Sperling et al., 2002), functional compensation (e.g., Horwitz et al., 1998; Maguire et al., 2001), and disease progression. It is possible that different patterns of brain activation could be associated with similar behavior in the present, but different responses to psychological and pharmacological treatments. Functional MRI is thus under development as a marker of treatment response. Errors could result in denial of effective treatment while appropriate use may lead to a more cost effective distribution of limited resources. Some fMRI approaches could be applied to define subgroups at-risk for the development of brain disease. Clinical trials performed on at-risk subgroups typically require fewer participants (due to less intersubject variability of response); however, this limits the generalizability to these populations and thus may result in treatment guidelines that restrict access of other groups. Ultimately fMRI is an expensive technology and appropriate use must take into account the manner in which results complement and augment information already available about the function of healthy and impaired brains.

5. General conclusions

Functional imaging, if applied responsibly, has great potential to enhance neuropsychological assessment and to be a useful component of a comprehensive evaluation in certain conditions. Because the technique reveals new information about the brain, it is essential to consider its limitations. Perhaps most importantly, current implementations of fMRI only have the power to answer a few questions at a time. Therefore, fMRI should only be used in a given patient in the context of a broader cognitive and clinical evaluation. Competent use of fMRI requires an understanding of when imaging applications are appropriate. Furthermore, acquisition, analysis, and interpretation of imaging results must be informed by an acute awareness of the technical characteristics and limitations of the measure (e.g., Jezzard, Matthews, & Smith, 2002; Moonen & Bandettini, 1999; Toga & Mazziotta, 2000). There are multiple practical hurdles to performing fMRI research. Obtaining informed consent in a cognitively impaired population is more complex than in the standard neuropsychological context. In addition, the risks to participants are higher than in traditional neuropsychological procedures. With careful screening and safety procedures, the long term effects of exposure to the magnetic field are believed to be negligible; however, emotional and physical responses to the stress of prolonged immobility and confined environment must be considered when testing cognitively and emotionally disabled individuals. For now, performing competent brain imaging requires intensive time commitment and institutional support. In addition, much work is needed before current brain imaging tools have the psychometric rigor to be applied to the clinical evaluation of individual patients. It is an ethical responsibility for a neuropsychologist involved with fMRI to recognize the current state of knowledge and the extent to which it justifies procedures and conclusions applied to individuals. The ethical neuropsychologist will resist pressures to make premature interpretations, particularly when the audience is not qualified to evaluate their

factual basis. While these techniques are relatively young, they are rapidly maturing and will likely revolutionize the field of clinical neuropsychology by illuminating aspects of brain–behavior relationships that were previously inaccessible. The neuropsychologist who will enter the field now will be in a position to work at the forefront of an exciting new field, which at some point will be recognized as a legitimate subspecialty of neuropsychology.

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References

Aguirre and D'Esposito, 2000. G.K. Aguirre and M. D'Esposito , Experimental design for brain fMRI. In: C.T.W. Moonen and P.A. Bandettini, Editors, *Functional MRI*, Springer-Verlag, Berlin (2000).

Aguirre et al., 1998. G.K. Aguirre, E. Zarahn and M. D'Esposito , The variability of human, BOLD hemodynamic responses. *Neuroimage* **8** (1998), pp. 360–369.

American Academy of Neurology, 1996. American Academy of Neurology (1996). Assessment: Neuropsychological testing of adults. Considerations for neurologists. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* **47,** 592–599.

American Psychological Association, 1992. American Psychological Association (1992). *Ethical principles of psychologists and code of conduct*.

Birn et al., 1999. R.M. Birn, P.A. Bandettini, R.W. Cox and R. Shaker , Event-related fMRI of tasks involving brief motion. *Human Brain Mapping* **7** (1999), pp. 106–114.

Brewer et al., 1998. J.B. Brewer, Z. Zhao, J.E. Desmond, G.H. Glover and J.D. Gabrieli , Making memories: Brain activity that predicts how well visual experience will be remembered. *Science* **281** (1998), pp. 1185–1187.

Buckner et al., 2000. R.L. Buckner, A.Z. Snyder, A.L. Sanders, M.E. Raichle and J.C. Morris , Functional brain imaging of young, nondemented, and demented older adults. *Journal of Cognitive Neuroscience* **12** (2000), pp. 24–34.

Casey et al., 1998. B.J. Casey, J.D. Cohen, K. O'Craven, R.J. Davidson, W. Irwin, C.A. Nelson *et al.*, Reproducibility of fMRI results across four institutions using a spatial working memory task (In Process Citation). *Neuroimage* **8** (1998), pp. 249–261.

Cohen and DuBois, 1999. M.S. Cohen and R.M. DuBois , Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging. *Journal of Magnetic Resonance Imaging* **10** (1999), pp. 33–40.

D'Esposito et al., 1999. M. D'Esposito, E. Zarahn, G.K. Aguirre and B. Rypma , The effect of normal aging on the coupling of neural activity to the bold hemodynamic response. *Neuroimage* **10** (1999), pp. 6–14.

Detre and Floyd, 2001. J.A. Detre and T.F. Floyd , Functional MRI and its applications to the clinical neurosciences. *Neuroscientist* **7** (2001), pp. 64–79.

Donaldson and Buckner, 2002. D.I. Donaldson and R.L. Buckner , Effective paradigm design. In: P. Jezzard, P.M. Matthews and S.M. Smith, Editors, *Functional MRI: An introduction to methods*, Oxford University Press, Oxford (2002), pp. 178–195.

Dunn and Chadwick, 1999. C.M. Dunn and G. Chadwick , Protecting study volunteers in research: A manual for investigative sites. , CenterWatch Inc., Boston, MA (1999).

Gur et al., 1992. R.C. Gur, R.J. Erwin and R.E. Gur , Neurobehavioral probes for physiologic neuroimaging studies. *Archives of General Psychiatry* **49** (1992), pp. 409–414.

Hammeke, 2002. T.A. Hammeke , Functional MRI in neurology. In: C.T.W. Moonen and P.A. Bandettini, Editors, *Functional MRI*, Springer-Verlag, New York (2002), pp. 475–512.

Horwitz et al., 1998. B. Horwitz, J.M. Rumsey and B.C. Donohue , Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proc. Natl. Acad. Sci. USA* **95** (1998), pp. 8939–8944.

Illes et al., 2002. J. Illes, J.E. Desmond, L.F. Huang, T.A. Raffin and S.W. Atlas , Ethical and practical considerations in managing incidental findings in functional magnetic resonance imaging. *Brain and Cognition* **50** (2002), pp. 358–365.

Jezzard et al., 2002. P. Jezzard, P.M. Matthews and S.M. Smith , Functional MRI: An introduction to methods. , Oxford University Press, Oxford (2002).

Kulynych, 2002. J. Kulynych , Legal and ethical issues in neuroimaging research: Human subjects protection, medical privacy, and the public communication of research results. *Brain and Cognition* **50** (2002), pp. 345–357.

Langleben et al., 2002. D.D. Langleben, L. Schroeder, J.A. Maldjian, R.C. Gur, S. McDonald, J.D. Ragland, C.P. O'Brien and A.R. Childress , Brain activity during simulated deception: an event-related functional magnetic resonance study. *Neuroimage* **15** (2002), pp. 727–732.

Machielsen et al., 2000. W.C. Machielsen, S.A. Rombouts, F. Barkhof, P. Scheltens and M.P. Witter , FMRI of visual encoding: Reproducibility of activation. *Human Brain Mapping* **9** (2000), pp. 156–164.

Maguire et al., 2001. E.A. Maguire, F. Vargha-Khadem and M. Mishkin , The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. *Brain* **124** (2001), pp. 1156–1170.

Miezin et al., 2000. F.M. Miezin, L. Maccotta, J.M. Ollinger, S.E. Petersen and R.L. Buckner , Characterizing the hemodynamic response: Effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage* **11** 6 (2000), pp. 735–759.

Moonen and Bandettini, 1999. C.T.W. Moonen and P.A. Bandettini , Functional MRI. , Springer-Verlag, Berlin (1999).

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978). *Report and recommendations: Research involving those institutionalized as mentally infirm and appendix* (Report No. DHEW (OS) 78-0006, 78-0007). Washington, DC: US Government Printing Office.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979). *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research* (Report No. DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014). Washington, DC: US Government Printing Office.

NBAC, 1998. NBAC (1998). *Research involving persons with mental disorders that may affect decision making capacity. Vol. I. Report and recommendations of the National Bioethics Advisory Commission*. Washington, DC: NBAC.

NBAC, 2001. NBAC (2001). *Ethical and policy issues in research involving human participants*. Washington, DC: National Bioethics Advisory Commission.

Ojemann et al., 1998. J.G. Ojemann, R.L. Buckner, E. Akbudak, A.Z. Snyder, J.M. Ollinger, R.C. McKinstry *et al.*, Functional MRI studies of word-stem completion: Reliability across laboratories and comparison to blood flow imaging with PET. *Human Brain Mapping* **6** (1998), pp. 203–215.

Rombouts et al., 1998. S.A. Rombouts, F. Barkhof, F.G. Hoogenraad, M. Sprenger and P. Scheltens , Within-subject reproducibility of visual activation patterns with functional magnetic resonance imaging using multislice echo planar imaging. *Magnetic Resonance Imaging* **16** (1998), pp. 105–113.

Rombouts et al., 2002. S.A. Rombouts, F. Barkhof, C.S. van Meel and P. Scheltens , Alterations in brain activation during cholinergic enhancement with Rivastigmine in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* **73** (2002), pp. 665–671.

Shellock, 2001. F.G. Shellock , Magnetic resonance procedures: Health effects and safety. , CRC Press, LLC, Boca Raton, FL (2001).

Shellock, 2002. F.G. Shellock , Reference manual for magnetic resonance safety. , Amirsys Inc., Salt Lake City, Utah (2002).

Small et al., 1999. S.A. Small, G.M. Perera, R. DeLaPaz, R. Mayeux and Y. Stern , Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Annals of Neurology* **45** (1999), pp. 466–472.

Sperling et al., 2002. R. Sperling, D. Greve, A. Dale, R. Killiany, J. Holmes, H.D. Rosas *et al.*, Functional MRI detection of pharmacologically induced memory impairment. *Proceedings of the National Academy of Sciences of the United States of America* **99** (2002), pp. 455–460.

Stark and Squire, 2001. C.E. Stark and L.R. Squire , When zero is not zero: The problem of ambiguous baseline conditions in fMRI. *Proceedings of the National Academy of Sciences of the United States of America* **98** (2001), pp. 12760–12766.

Stern and Silbersweig, 2001. E. Stern and D.A. Silbersweig , Advances in functional neuroimaging methodology for the study of brain systems underlying human neuropsychological function and dysfunction. *Journal of Clinical and Experimental Neuropsychology* **23** (2001), pp. 3–18.

Styner et al., 2002. M.A. Styner, H.C. Charles, J. Park and G. Gerig , Multi-site validation of image analysis methods—Assessing intra and inter-site variability. *Society for Perception in Engineering* (2002).

Thulborn and Gisbert, 2002. K.R. Thulborn and A. Gisbert , Clinical applications of mapping neurocognitive processes in the human brain with functional MRI. In: P. Jezzard, P.M. Matthews and S.M. Smith, Editors, *Functional MRI: An introduction to methods*, Oxford University Press, Oxford (2002), pp. 329–349.

Toga and Mazziotta, 2000. A.W. Toga and J.C. Mazziotta , Brain mapping: The methods. , Academic Press, New York (2000).

Turner et al., 2001. S.M. Turner, S.T. DeMers, H.R. Fox and G.M. Reed , APA's guidelines for test user qualifications. *American Psychologist* **56** (2001), pp. 1099–1113.

Wagner et al., 1998. A.D. Wagner, D.L. Schacter, M. Rotte, W. Koutstaal, A. Maril, A.M. Dale *et al.*, Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science* **281** (1998), pp. 1188–1191.