Multi-Site Neuroimaging Trials

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Abstract

PURPOSE OF REVIEW: The intent of this article is to review trends in multi-center neuroimaging
trials and their value for research and implications for clinical treatment.

RECENT FINDINGS: The rise in availability of magnetic resonance imaging for detecting
disorders in the living brain has made it an attractive technology for assessing neural structure and
function in a number of prominent diseases. Geographic factors underlying diseased populations
coupled with complementary neuroimaging research programs have led to an increase in multi-center
neuroimaging trials and consortia. Neuroimaging has become a major focus for multi-institutional
research into a) progressive changes in brain architecture, b) proxy biomarkers of treatment response,
and c) the effects of disease on patterns of cognitive activation and connectivity. Notable consortia
and research trial studies have focused on Alzheimer's disease, pediatric brain cancer, and fetal
alcohol syndrome, in addition to multi-institutional collaborative programs for mapping the normal
brain. Such large-scale efforts necessitate close coordination of image data collection protocols,
ontology development, computational requirements, concerted data archiving and sharing.

SUMMARY: Multi-center neuroimaging trials, consortia, and collaboratives enable the acquisition
of large-scale, purpose-driven datasets that can then be used by the broader community to model and
predict clinical outcomes as well as guide clinicians in selecting treatment options for neurological
disease.

Keywords

Neuroimaging; Multi-Center; Clinical Trials; Consortia; Collaboration; Data Sharing

Introduction

With the advent of modern neuroimaging technologies in the early 1990's, the proliferation of
neuroimaging devices in neurological research centers around the world has made it possible
for many centers to conduct leading edge brain research into many clinical syndromes [1,2,
3]. However, it has also become recognized that investigators from across centers can pool
efforts, resources, and data toward large-scale research collaborative programs aimed at
refining understanding of frequently heterogeneous diseases of brain structure and function.
Studies that could not be conducted in any one site, due to lack of subject numbers or given
expertise, become possible in such collaborative efforts. Archives of raw and processed
datasets may be examined jointly by investigators at federated centers or by unaffiliated
researchers. With access to the large-scale research outcomes, clinicians can utilize this new
information to direct patient treatment plans.

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Multi-center collaborations, however, require careful coordination and division of labor, compliance with HIPAA regulations on data anonymization, etc. Additional considerations involve how differences in scanner make, model, manufacturer, field strength, field homogeneities, slew rates, and image reconstruction routines can influence the data and potentially lead to conflicting results. Computational resources are also important for how to maximize throughput toward results that can be put directly into clinical practice. In this article, we discuss several such multi-center efforts, note key clinical and research outcomes, and comment on the importance of careful coordination of such programs. Lastly, we discuss the potential that lay in large-scale archives of these data and how they may be potentially mined to identify unanticipated outcomes worthy of additional collaborative effort.

Rising Frequency of Multi-site Trials

While an increasing number of individual research centers now enjoy the latest in neuroimaging technology in the form of Positron Emission Tomography (PET) and high-field magnetic resonance imaging (MRI), researchers have been quick to recognize the importance of pooling effort and resources toward clinically-relevant goals that could not be achieved at one center alone. The numbers of established multi-site clinical trials, collaborations, and research consortia has dramatically increased since the first studies using modern imaging methods first appeared (Figure 1). These efforts seek to leverage complementary approaches toward mapping brain function and structure and relating these to genomic influences, psychopharmacological interventions, and treatment outcomes.

Advantages of Multi-site Trials and Collaborations

Despite the fact that many neuroimaging centers may be well equipped to carry out focused studies individually, the greatest benefit in multi-center efforts is the ability to, in principle, obtain more neuroimaging data per unit time across a wider variety of the patient population in question. This provides a great number of clinical exemplars while also attempting to at once control issues of selectivity of patients while being able to more precisely examine patients having varying etiology. In the sense of greater data acquisition, an analogy exists with parallel computing where with multiple-CPUs it is possible to increase throughput manifold in the same amount of time. Other major advantages of multi-site neuroimaging trials include: 1) as a tool for cognitive neuroscience research into patterns of normal and altered brain function; 2) for prediction of which normal or slightly impaired individuals will develop alterations in brain anatomy and over what time period; 3) for early identification of neurological disease in at risk individuals (*e.g.* test sensitivity) and separation of certain forms of disease from others (*e.g.* disease specificity); 4) for monitoring the progression of disease across a geographically, culturally, and environmentally diverse population; and 5) for monitoring response to interventions and therapies. Functional imaging methods (fMRI, PET, and SPECT) have tended to be best suited toward tracking symptomatic therapy response, whereas anatomic imaging (structural MRI and diffusion tensor imaging) and amyloid PET [4] tend to be best suited toward disease modulation studies [5 **]. The additional potential for human neuroimaging with respect to pharmacological intervention or candidate gene studies is enormous [6 *]. By taking advantage of a wider variety of patient types, etiologies, and range of symptoms, multi-site studies can be better representative of the larger patient population with greater generality for population-level atlases of brain structure/function and, by their association with clinical variables, suggest treatment options with the widest possible efficacy. For the clinician, this translates into the greater ability to consider treatment options for patients against a number of demographic, case history, and etiological backgrounds.

Challenges in Multi-site Trial Coordination

While being geographically distributed is, from a patient demographics point of view, a principal strength of multi-center efforts, a number of challenges exist in coordinating such programs. These include issues concerning variation in scanner technologies across centers in which even the same make and model MRI system may demonstrate differing field inhomogeneity effects that can influence how data might be interpreted [7]. Even subtle distortions in scanner magnetic field homogeneity across sites can form an unwanted source of variance that must be controlled through the use of standardized phantom studies and strict quality assurance of imaging protocols [8 *]. Trial considerations also involve patient confidentiality and how investigators can have access to patient data and private health information stored at other institutes while also being compliant with Health Insurance Portability and Protection Act (HIPAA) privacy regulations [9]. At the same time, methods for ensuring seamless computational access for researchers to digital archives of neuroimaging and clinical data for use in comparative analysis and modeling necessitate careful examination. Factors include: 1) site-to-site networking requirements [10]; 2) user authentication protocols [11]; 3) means for rapid design and deployment of analysis workflows [12], data ontological definition, description, and data management [13], and large-scale data storage capabilities [14 *]. Regularly scheduled "all-hands" meetings supplemented with conference calls and web-meetings are necessary for measuring progress toward the stated aims of the trial. Multi-center trials, especially involving neuroimaging, are expensive, involving multiple investigators, imaging center hourly rates for scanning, travel, and other associated costs. Despite these challenges, the recent increase in the numbers of such multi-site trials and collaborations is indicative that policy makers and funding organizations recognize their benefits and understand them to be a worthy scientific, clinical, and financial investment.

Successful Examples in Multi-site Neuroimaging

Table 1 [15,16,17,18,19,20,21,22,23,24,25 **,26,27,28,29,30 *,31,32] describes a brief list of several ongoing or newly developed multi-site trials or collaborations working toward applying neuroimaging methods for mapping the normal brain and examining the brain in various neurological diseases. Here we summarize several major neuroimaging consortia:

Alzheimer's Disease Neuroimaging Initiative (ADNI)

The pathophysiologic process leading to neurodegeneration in Alzheimer's disease (AD) is thought to begin long before clinical symptoms develop. Existing therapeutics for AD improve symptoms, but increasing efforts are being directed toward the development of therapies to impede the pathologic progression of the disease. Although these medications must ultimately demonstrate efficacy in slowing clinical decline, there is an essential need for biomarker trials that will indicate whether a candidate disease-modifying therapeutic agent is actually altering the underlying degenerative process. A number of in vivo neuroimaging techniques, which can reliably and noninvasively assess aspects of neuroanatomy, chemistry, physiology, and pathology, hold promise as biomarkers. These neuroimaging measures appear to relate closely to neuropathological and clinical data, such as rate of cognitive decline and risk of future decline. As this work has matured, it has become clear that neuroimaging measures may serve a variety of potential roles in clinical trials of candidate neurotherapeutic agents for AD, depending in part on the question of interest and phase of drug development.

The highly successful NIA-funded Alzheimer's Disease Neuroimaging Initiative (ADNI) program was established to increase knowledge of the mechanisms of AD through the use of neuroimaging - thereby informing the development of treatment strategies aimed at slowing down or preventing neuronal death. ADNI has been instrumental in helping to identify clinical, neuroimaging, and biomarker outcome measures and longitudinal changes and the prediction

of disease transitions. In particular, this has included neurodegeneration: the clinically and pathologically heterogeneous disease entity associated with slowly progressive neuronal loss in different anatomical and functional systems of the brain. Owing to increasing knowledge about the mechanisms leading to neurodegeneration as a result of ADNI, the development of treatments able to modify the neurodegenerative process will be easier. While more research is clearly needed to determine the continued value of newer neuroimaging modalities, i.e. diffusion, perfusion and functional MRI and MR spectroscopy, for clinical trials with neuroprotective drugs, the ADNI project can be considered to have been a highly successful first step in large-scale neuroimaging and the sharing of that information with a larger community studying the efficacy of leading-edge treatment.

Additionally, researchers at NIA-funded Alzheimer's Disease Research Centers (ADRC) have worked to translate research advances into improved diagnosis and care for Alzheimer's disease (AD) patients while, at the same time, focusing on the program's long-term goal--finding a way to cure and possibly prevent AD. Although each center has its own unique area of emphasis, a common goal of the ADCs is to enhance research on AD by providing a network for sharing new ideas as well as research results. Collaborative studies draw upon the expertise of scientists from many different disciplines. Some ADCs have satellite facilities, which offer diagnostic and treatment services and research opportunities in underserved, rural, and minority communities. The National Alzheimer's Coordinating Center at the University of Washington in Seattle, WA coordinates data collection and fosters collaborative research among the ADCs. Additionally, the National Cell Repository for Alzheimer's Disease maintains a database of family histories and medical records and provides genetic researchers with cell lines and/or DNA samples. Several of the ADRC's also conduct neuroimaging investigations but these data may not necessarily be widely available to researchers outside of each individual center.

Brain Function and Morphometry

The FIRST [29] and Morphometry [33] testbeds of the Biomedical Informatics Research Network (BIRN; www.nbirn.net) are multi-site projects funded by the NCRR and NIH to develop the methods for data collection, combination, and sharing from imaging protocols, for the following goals: 1) standardized calibration of equipment and imaging activation paradigms using geometric and human phantoms; 2) collection of MRI and/or fMRI data using a standardized protocol on clinical populations at different sites, while including the added value of each site's own methods; 3) combining MRI, fMRI, clinical and behavioral data into a federated database, leading to a deeper understanding of the functional neuroanatomy of the underlying disease than would be possible with any individual site's data. The eleven sites involved in the projects have people dedicated to the purposes of collecting calibration imaging data, developing analysis methods, determining experimental paradigms where needed, developing robust and expandable data storage and retrieval methods, populating a virtual data grid, and designing a searchable federated database of MRI and clinical data from multiple sites. Results from their examinations suggest that even previously obtained (legacy) structural data from across the multiple sites can be pooled to investigate questions of scientific interest [33]. In particular, statistical analyses suggested that a mixed-effects model employing site as a random effect best fits the data, accounting for site-specific effects while taking advantage of expected comparability of age-related effects. In combining samples from three research sites, significant age-related decline of hippocampal volume and right-dominant hippocampal asymmetry were detected in healthy elderly controls. These findings support the feasibility of combining legacy as well as new data from across multiple sites toward investigating novel scientific questions.

Fetal Alcohol Spectrum Disorder (FASD)

A recent neuroimaging thrust has been added to the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). One of the driving goals of the entire CIFASD has been to determine if innovative techniques can be used to identify brain alterations, neurobehavioral deficits and facial characteristics and relationships between these variables to help define prenatal alcohol spectrum disorders (FASD). To help address this, brain mapping using high-resolution structural and functional MRI collected cross-sectionally and longitudinally from 80 FASD children evaluated across three distributed, multi-cultural data collection sites (San Diego, Los Angeles, and Cape Town). Their proposed longitudinal project seeks to highlight how an integrated approach relating neurobehavioral, functional and structural brain imaging data, and measures of facial (dis)morphology might yield important new insights on the complex nature of brain-behavior interactions and how they are altered by prenatal exposure to alcohol. Ultimately, this project, armed with neuroimaging outcomes, will enhance the capability for definitive FASD diagnoses that, in turn, will help clinicians manage and treat neurobehavioral deficits and associated secondary disabilities in FASD children.

Pediatric Brain Tumor

The Pediatric Brain Tumor Consortium (PBTC) was formed by the National Cancer Institute (NCI) in 1999 to improve the treatment of primary brain tumors in children. The PBTC's primary objective has been to rapidly conduct novel phase I and II clinical evaluations of new therapeutic drugs, new biological therapies, treatment delivery technologies and radiation treatment strategies in children from infancy to 21 years of age with primary central nervous system (CNS) tumors. They develop and coordinate innovative neuroimaging techniques and their use in early diagnosis of pediatric brain cancer [31], with resulting neuroimaging research being used to evaluate new treatment response criteria and the use of neuroimaging methods to understand regional brain effects [32,34].

While this is not an exhaustive list of ongoing multi-site efforts, it represents several examples of where neuroimaging has become a necessary and valuable part of collaborative research programs in the US. It might not be surprising that the successes of these and other programs have been replicated in countries around the world [35,36 *] with interest rising in international collaborative efforts toward mapping the brain and its disorders [37 *,38].

Future Needs

Throughout the coming decade of human brain imaging research, given the trends toward collaborative effort across multiple institutions, we can expect to see still more multi-site trials focused on particular neurological diseases and disorders. One such disease domain that is particularly poised for a multicenter collaboration is that of HIV and AIDS. In August 2008, the Center for Disease Control (CDC) published the first national HIV incidence of new HIV infection estimates using new technology and methodology that more directly measure the number of new HIV infections in the United States [39]. Their new analyses showed that in 2006, an estimated 56,300 new HIV infections occurred - a number that is considerably higher than the previous estimate of 40,000 annual new infections. However, though considerable progress has been made toward understanding the clinical response to various drugs designed to treat HIV/AIDS [40], the examination of the long term effects of the virus in the brain and its resistance to drugs via brain mapping technologies has only recently begun [41,42]. Whereas multi-center efforts have focused on magnetic resonance spectroscopic (MRS) neuroimaging in HIV/AIDS [43], a more broadly-based effort employing fMRI of cognitive functional changes, structural imaging of altered cortical thickness and other parameters, MRS, arterial spin labeling (ASL), as well as white matter imaging is sorely needed for assessing the effects

of HIV on brain morphometry and function as well as the efficacy of extant and emerging HIV therapies.

While the potential for clinical and treatment understanding is enhanced in multi-site neuroimaging, considerable attention must be afforded to how such data might be efficiently organized, processed, and, firstly, made available to researchers at participating centers and then openly as a resource from which the entire neurological community might draw. The Laboratory of Neuro Imaging (LONI) has, for many years [44], been at the forefront of 1) providing the computational resources specifically tailored to support multi-center efforts [26,45], 2) providing a large-scale Image Data Archive (IDA) for use in the secure databasing of clinical research neuroimaging data [46], with 3) long term storage capabilities for petabyte levels of imaging study data. Still with advances in neuroimaging data acquisition methods that obtain more data per unit time, thereby making data computation considerations more serious, careful attention must be given to large-scale distributed Grid computing approaches [47] and their use in processing ever larger quantities of data. The importance of neuroimaging informatics cannot be overstated in the context of multi-center collaborations and will be an active area of work that will help to maximize the success of any neurological research domain using neuroimaging data.

Evaluation of Multi-Site Outcomes

For many clinicians, interpreting the outcomes from multi-site collaboratives can be challenging given the variety of neuroimaging terms being used, statistical methods being reported, and the sometimes lofty claims reported to justify the importance of the collaboration itself. Several factors are important to look for in evaluating the strengths of multi-site trials and the outcomes from research collaboratives: 1) Identifying whether the study has published or is using openly available human imaging protocols; 2) site-to-site quality assurance using standardized brain imaging phantoms; 3) whether the sites involved are using the same or differing scanner platforms; 4) performing a critical examination of whether the data were specifically obtained for the purposes of the study in question or if it is apparent that they were selected from a database for a secondary analysis; and 5) clear and understandable experimental goals and their relation to the multi-site effort should be articulated in the article. Each of these considerations will put the work into the overall context of the multi-site effort and guide the clinician in evaluating its quality, impact, and relevance to the patient-level (Table 2). Though multi-center efforts can frequently provide highly useful recommendations for the individual clinician, careful examinations of study quality and relevance remain important considerations before embarking on any new treatment programs based on their results.

Discussion

On a domestic or international scale, multi-site neuroimaging efforts offer the promise for gaining insights into major brain disease and the characterization of normal structure and function. Multi-site trials are an important element in the study of a disease or the process of evaluating an intervention. Linking together multiple sites facilitates the recruitment of large samples that yield high statistical power for both main analyses as well as secondary analyses of subgroups. Generalizability of results to the level of the population also is maximized. Because data come from multiple sites, investigators can explore how a treatment's effects vary across geographical diverse sites and how such variation relates to site characteristics, cultural and socio-economic factors. Such information can directly inform clinical decision making at the level of the patient and guide the selection of treatment options. Multi-site trials are costly, however, so the decisions that must be made, such as the population which to study and the expense of gathering neuroimaging data, have particular importance for policy makers and site PIs.

Many authors have noted how neuroimaging technologies has emerged over the past twenty years and changed forever how we view the brain in health and disease across temporal and spatial dimensions [48,49 *,50]. But, clearly, neuroimaging as a research site-specific tool cannot begin to fully probe the subtleties of diseases that may vary culturally and geographically, whose effects may vary by age or gender, or that may result from a highly variable exposure to environmental or pharmacological mechanisms. Leveraging expertise and technologies from across distributed institutions, with inherent variation in technological infrastructural, theoretical, and clinical emphasis is valuable toward building data resources of unprecedented size and scope. These may be mined and modeled to produce high-resolution maps of disease states in the brain and their responses to clinical intervention or treatment.

Coincident with developments in brain imaging technology and analysis approaches, the advantages for multi-site neuroimaging endeavors have resulted in a steadily increasing number of multi-site efforts in neurology and the brain sciences. Moving forward, we expect multi-site efforts to form a mainstay of major scientific exploration of the normal and diseased brain.

Conclusion

Multi-site efforts toward mapping the human brain in health and disease will continue to grow over the next decade. These important efforts will link the intellectual talent and resources of leading research centers toward better understanding of primary brain diseases, cancer, as well as the normal brain in development and aging. With more data being obtained with a view toward greater spatiotemporal precision, the informatics of neuroimaging will be an important consideration. Finally, these efforts are imperative for guiding treatment recommendations for neurological disorders domestically and internationally as well as at the level of the individual patient. Multi-center collaborations can be expected to strengthen understanding of brain diseases that affect all walks of life, all ages, and all cultures. This helps to translate neuroimaging trial outcomes directly into clinical applications.

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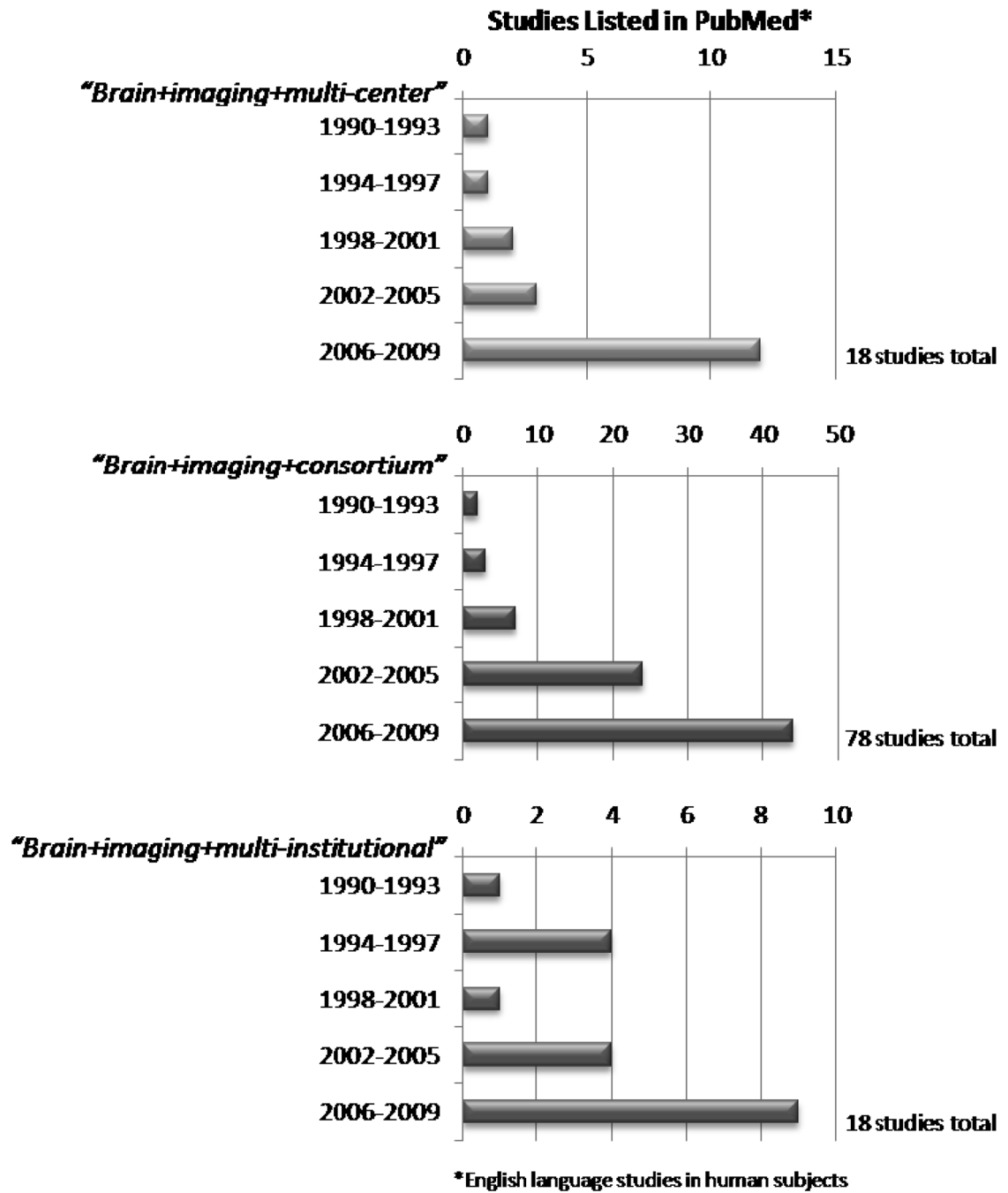
Figure 1.
Multi-center clinical trials and research collaborations have resulted in increasing methods, primary research, and clinical outcome studies appearing the peer-reviewed literature. Exploration of PubMed citations, grouped into three year periods, reveals consistent increases in the numbers of publications from such efforts since the early 1990's. Examples of several leading multi-center programs are listed in Table 1.

Table 1

Neuroimaging Trials or Collaborative Efforts Involving Multiple Research Sites

Multi-Site Trial	Participating Institutions	Subject Population	Imaging Modalities	URL	Citations
Alzheimer's Disease Neuroimaging Initiative (ADNI)	UCSF, NCIRE, VA – U. California, San Diego; Arizona State U.; Banner Good Samaritan Med Ctr; U. California, Davis; Mayo Clinic, Rochester, Minnesota; U. California, Berkeley	Mild cognitive impairment; Alzheimer's disease; normal control subjects	sMRI, PET	www.adni-info.org www.loni.ucla.edu/ADNI/index.shtml	[15,16,17,18,19,20,21,22,23]
Collaborative Initiative on Fetal Alcohol Spectrum Disorder (CIFASD)	San Diego State U.; Indiana U. Sch. Med.; U. California, San Diego; U. California, Los Angeles; U. New Mexico; Texas A&M; Indiana U.-Purdue U. Sch. Sci.; Ukrainian-American Birth Defects Program; U. North Carolina at Chapel Hill; Harvard; U of California, Davis; Folkhälsan Research Center-Helsinki; U. Cape Town, South Africa; Emory U.; Moscow Inst. Obs. and Gyn.	Fetal alcohol syndrome children (with and without facial dysmorphia), normal control subjects	sMRI, fMRI, DTI	www.cifasd.org	[24]
International Consortium for Brain Mapping (ICBM)	U. California, Los Angeles; Montreal Neurological Inst.; U. Texas, San Antonio; Vogt Inst., Jülich, Germany	Normal subjects; Methamphetamine patients; HIV; children; and Williams Syndrome	sMRI; MRS; MRA; DTI/DWI; PET	www.loni.ucla.edu/ICBM/	[25 **,26,27]
Functional Imaging Research in Schizophrenia Testbed (FIRSTBIRN)	U. California, Irvine; U. California, San Diego; U. California, Los Angeles; Stanford U.; U. New Mexico; U. Minnesota; Massachusetts General Hosp.; Brigham and Women's Hosp.; Duke U.; U. North Carolina; U. Iowa	Schizophrenia spectrum disorders, normal control subjects	sMRI; fMRI; DTI	www.nbirn.net/research/function	[28,29,30 *]
Pediatric Brain	Children's Memorial	Children with	sMRI; PET	www.pbtc.org	[31,32]

Multi-Site Trial	Participating Institutions	Subject Population	Imaging Modalities	URL	Citations
Tumor Consortium (PBTC)	Hosp., Chicago; Duke U. Med. Ctr.; Texas Children's Cancer Ctr.; St. Jude Children's Research Hosp.; The Children's Hosp. of Philadelphia; Children's Hosp. of Pittsburgh; U. California, San Francisco U. California, San Francisco; Children's National Medical Ctr Children's National Medical Ctr.; NCI.	primary brain tumors			

Table 2

Multi-Site Neuroimaging Evaluation Criteria

Consideration	Factors	Rationale	Example
Study Description	Has clear relationship to focus of multi-site effort.	Some studies simply use the data but may only have peripheral importance to the main goals of the consortium effort.	An a priori hypothesis involving a comparison between patients and controls during an fMRI task of complex cognition versus a methods paper describing a new analytic processing approach using existing data obtained during another study.
Technological Aspects	Scanner make, model, field strength, and other factors that could vary across sites.	Even the same make and model scanner can have considerable variability between related scans. This is compounded across scanner manufacturers.	Data from one center in the study comes from a 1.5 Tesla scanner while data from another was obtained using a 3T Philips system.
Protocol Description	Uses published or openly available image acquisition protocols.	Imaging protocols are best when they have been subjected to peer-review by experts in pulse-sequence design and are openly available for use by the community.	The authors report using a proprietary scan acquisition sequence, thus making it hard to validate results against the appropriateness of pulse-sequence parameters.
Imaging Quality Assurance	Data quality across centers is maintained through the regular scanning of standard MR phantoms.	Scanner distortions accumulate with time and the use of phantoms helps to ensure these are held to a minimum and differences in quality can be compared/equated across centers.	One center reports using the BIRN agar-filled phantom to calibrate its data while another uses the ACR standard phantom.
Statistical Aspects	Data are reported using well known and validated statistical packages/algorithms.	While novel analytic approaches are worthwhile, statistical analyses using well understood and cited approaches will lend confidence to their interpretation and meaning.	The authors report using Statistical Parametric Mapping v. 5 (SPM5) to analyze their fMRI data versus reporting results coming from software they wrote themselves.
Graphical Depiction of Results	Figures from the studies show the results of neuroimaging comparisons clearly and concisely.	Multi-site studies often include investigators expert in data visualization. However, many brain renderings are highly stylized with heavy doses of photo editing software used to embellish them. Care is required to keep "pretty pictures of the brain" in perspective.	An overlay of significant BOLD activity on a T1 anatomical image versus interpolated false-color activation maps painted onto flattened surface representations of the cortex. Data from an individual patient may not appear the same.
Caveats and Alternatives	The authors are forthcoming concerning limitations of their study or alternative explanations of results	The experimental design may have confounds and the data may be open to multiple interpretations. This will have implications for extrapolation to the patient-level.	The authors report anatomical changes in patients relative to controls but the selection of controls may have been biased across centers, thereby resulting in the reported effect.
Implications for the Patient	In reviews of the multi-center effort, the PIs provide a perspective on what their results, findings, and outcomes mean for the treatment considerations of individual patients.	Without eventually bring results into the context of the individual patient, multi-site efforts can fail to provide the information needed to guide treatment, suggest new clinical trials, or even justify the importance of the multi-center effort.	The multi-center effort is, in and of itself, held up as a justification for the multi-center effort.