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REVIEW ARTICLE

The vast potential and bright future of neuroimaging

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ABSTRACT

Significant advances in anatomical and functional neuroimaging techniques have allowed researchers and clinicians to visualize the brain in action. The field of neuroimaging currently includes newer and faster scanners, improved image quality, higher spatial and temporal resolution and diverse methods of acquisition and analysis. Beyond simply imaging brain structures, these developments enable quantitative assessment of the microstructural and functional architecture, perfusion and metabolism of the brain. The resultant highly granular data have the potential to greatly improve characterization of neurological, neurosurgical and psychiatric disorders without invasive neurosurgery. However, the surge in neuroimaging data that can be collected over a relatively short acquisition period has led to a “big data” problem, where novel methods are needed to appropriately extract and analyze information and integrate data with other types of big data, such as genomic and proteomic data. Another challenge is the translation of these new technologies from basic science into clinical practice, so that they can be leveraged to improve patient outcomes and alleviate human disease. Critical to this endeavor is research comparing the effectiveness and outcomes of these advancements to allow widespread acceptance in the modern, economically constrained healthcare system. This review aims to illustrate the different facets of cutting edge neuroimaging techniques, as well as the potential role of these methods as clinical tools for evaluating the breadth of diseases that affect the brain.

QUANTITATIVE NEUROIMAGING

Medical images traditionally relied on subjective visual interpretation by a radiologist. With the rapid growth of modern neuroimaging modalities, such as CT, MRI, positron emission tomography (PET) and single-photon emission CT, assessment of cerebral tissue and function can now be assessed quantitatively. Importantly, this unlocks the potential for unbiased and reproducible evaluation.

Through the work of disease-specific consortia, quantitative neuroimaging approaches have begun to permeate into clinical practice. For example, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) set out to develop biomarkers for the development of Alzheimer’s disease¹ by collecting and evaluating MRI, PET, genetic, cognitive, cerebrospinal fluid (CSF) and blood biomarker data. As a result of this endeavor, processing tools that provide quantitative volumetric measurements of hippocampi and cerebral hemispheres have become commercially available; the resulting data can then be compared with the normative ADNI database to provide output with respect to age-dependent controls. Thus,

neuroradiologists can use these tools to determine whether brain volume loss of a specific patient is suggestive of senescent changes in the context of normal aging or of dementia. These tools also facilitate the assessment of changes in brain volume over time to characterize the progression from mild cognitive impairment to Alzheimer’s disease.

Neuroimaging measures serve a variety of roles in clinical trials for treatment selection and/or monitoring. For instance, stroke therapy trials have exploited neuroimaging biomarkers for patient selection and randomization (e.g. the visualization/quantification of the ischemic penumbra or tissue at risk of imminent cell death)^{2–4} as well as for endpoint analysis (e.g. final infarct volume measured on follow-up imaging). Serial neuroimaging has also been leveraged in clinical trials as a secondary endpoint to monitor the effect of therapy on multiple sclerosis⁵ (e.g. changes in the number of white matter lesions) and brain tumors⁶ (e.g. changes in the size of enhancing and non-enhancing tumors). These research studies are laying the groundwork for future clinical practice.

Quantitative neuroimaging is well-suited for statistical modeling and systematic image analysis approaches that utilize canonical templates or brain atlases to measure changes in specific regions of interest.⁷ Quantitative methods are beginning to evaluate the brain as an integrated structural and functional network.⁸ These new approaches might be critical not only for deciphering brain circuitry but also for understanding the dysfunction of brain network connectivity that occurs during the progression of many neurological and psychiatric disorders.

UNDERSTANDING BRAIN CIRCUITRY

Brain pathologies are rarely confined to a single region in the brain. Instead, diseases often propagate to other areas by axons or fiber tracts. Only recently have neuroimaging techniques allowed scientists to comprehensively map the neural architecture. The field of imaging connectomics attempts to accurately evaluate properties of structural and functional brain connectivity. Structural connectivity can be observed either at the level of individual synapses (the microconnectome) or fiber tracts between brain regions (the macroconnectome). Structural connections of the macroconnectome can be evaluated using MRI approaches such as diffusion tensor imaging and diffusion spectrum imaging.⁹ The functional connectivity of the brain can be viewed using functional MRI (fMRI) methods; for example, blood oxygen level-dependent imaging relies on differences in cerebral blood flow between regions to delineate active connections.^{8,10,11} Electrical and magnetic activity associated with neuronal depolarization can also be used to depict functional connectivity, via electroencephalography and magnetoencephalography, respectively.^{12–16}

At the level of fiber tracts between brain regions, the human connectome has been shown to differ in patients with brain

disorders compared to healthy controls. Stroke, multiple sclerosis, brain tumors, epilepsy, neurodegenerative disorders, such as Alzheimer's dementia¹⁷ and psychiatric diseases, such as depression and schizophrenia, have all been associated with abnormalities of the connectome. Thus, there is promise in leveraging connectomics to classify individual patients into diagnostic/prognostic groups and to predict outcomes related to therapeutic interventions. However, a number of hurdles must be overcome before diseases can be diagnosed and treated based upon the imaged connectome. For example, abnormalities of the functional or structural connectome might be very subtle in certain brain diseases or might vary in terms of which individual networks are affected across patients. The current methods to distinguish between group differences in the connectome might not be adequate to diagnose disease or indicate the best treatment option for an individual patient.¹⁸ As such, analysis tools to identify abnormalities of the connectome with high sensitivity and specificity for individual subject classification must be developed before meaningful clinical translation can be realized. In this regard, the field of connectomics is currently building large databases of structural and functional data, including those of the Human Connectome¹⁹ and the 1000 Functional Connectomes^{20,21} projects. These databases will be crucial for large-scale studies aimed at better defining the range of normal and abnormal with respect to the human connectome.

UNDERSTANDING BRAIN FUNCTION AND DYSFUNCTION

Another breakthrough with the potential for robust application for understanding brain function/dysfunction is new hybrid imaging technology that incorporates PET functional imaging with MRI morphological imaging (Figure 1).²² In addition to taking advantage of the relative strengths of each individual

Figure 1. PET-MRI scan obtained in a 73-year-old male patient, APOE-E4 homozygous, 90–110 min after administration of 5.4 mCi Florbetaben (Neuraceq). While this patient was cognitively normal, the positive beta amyloid scan (lack of differential uptake between cortical gray matter and white matter) together with his APO-E4 status, puts him at increased risk to develop Alzheimer's disease. PET, positron emission tomography.

technology, simultaneous acquisition of PET and MRI minimizes patient inconvenience and reduces radiation exposure compared to PET-CT. MRI represents the first-line diagnostic imaging modality for numerous indications, and several specific PET tracers are currently available to assess functional and molecular processes in the brain (e.g. neuroinflammation and microglial activation, hypoxia, necrosis and apoptosis).²³ The synergy of these methods may improve *in vivo* assessment of multiple neuropsychological processes, such as changes in cerebral hemodynamics, including cerebral blood flow, cerebral volume and oxygenation, and the relationship between metabolism and oxygen consumption (neurovascular coupling).

Prior to being integrated with MRI, PET was largely limited to studying physiology that was difficult to characterize with MRI. For example, PET has been used to identify changes in metabolism associated with seizures or to distinguish recurrent brain tumors from radiation necrosis.²⁴ The combination with MRI opens up a large array of possible applications. For example, MRI along with ultra-small superparamagnetic iron oxide nanoparticles can be used to create high-resolution CBV maps, which can be applied to refine the calculation of oxygen extraction fraction measurements performed concurrently with oxygen-15 PET. Similarly, MRI can be used in epilepsy to identify a region of focal cortical dysplasia, which can then be immediately confirmed on accompanying and inherently co-registered fluorodeoxyglucose PET images.

The combination of anatomical, functional and metabolic measurements during identical examination conditions could also be quite powerful for use in mental disorders such as depression, dementia, schizophrenia and obsessive-compulsive disorders.²⁵ In these conditions, a patient's mental state may change on a timescale of minutes to even seconds. PET-MRI enables simultaneous acquisition of the PET and MRI information, which might not be possible using sequentially acquired data. Similarly, physiological and metabolic changes can occur on the order of minutes in some disease conditions (e.g. migraine) and rapid changes in baseline physiology can occur with therapeutic interventions.²⁵

BIG DATA

Because of the plethora of new neuroimaging techniques allowing for assessment of brain structures and functions and of the widespread use of genome-wide analysis, the new field of imaging genomics has been born. This field aims at identifying genes associated with specific imaging features and correlated with cognition, behavior and/or risk for disease (Figure 2).²⁶

As well-discussed by Siebner et al²⁶ genes have different roles and influence brain activity in different ways. Furthermore, the human phenome, composed of clinical phenotypes, shows high variability and can be defined at different levels: the proteome, the cellular pathways, the neural systems and the cognitive and behavioral outcomes. Therefore, neuroimaging-based phenotypes, rather than syndromal phenotypes, may offer a better insight into how genetic variants affect neural systems and how this leads to specific brain disorders because they are closer to genomic profiles.²⁶

Neuroinformatics tools that can probe highly multidimensional datasets acquired at multiple biological scales and can capture the large genomic and phenomic complexity will be needed, including supercomputers (Figure 3).

ARTIFICIAL INTELLIGENCE AND NEUROIMAGING

Our understanding of the neurobiology of psychiatric and neurological disorders has significantly progressed. Much of these advances are due to mass-univariate analytical techniques (e.g. statistical parametric mapping) that enable scientists to image the brains of psychiatric and neurological patients. Using these tools, studies have compared patients with a diagnosis of interest against disease-free individuals and reported neuroanatomical or neurofunctional differences at a group level. Despite the simplicity and interpretability of this approach, there has been little translational impact of neuroimaging findings from these studies. Mass-univariate analytical techniques suffer from at least two significant limitations. First, statistical inferences are drawn from multiple independent comparisons (*i.e.* one for each voxel) based on the assumption that brain regions act independently

Figure 2. Imaging genomics for brain tumors consists of combining imaging phenotype with genotype in order to improve the characterization of these tumors as well as outcome prediction in patients affected by these tumors.

Figure 3. Big data approach to neuroimaging data allowing to extract quantitative neuroimaging features. dw, diffusion-weighted; MEG, magnetoencephalogram; BOLD, blood oxygen level-dependent.

from one another. This assumption, however, is inconsistent with our current understanding of brain function in health and disease.^{21,27} For example, several psychiatric and neurological symptoms are best explained by network-level changes in structure and function rather than focal alterations.^{28,29} Second, mass-univariate techniques can be used to detect differences between groups but do not allow statistical inferences at the level of the individual. In contrast, a clinician has to make diagnostic and treatment decisions about the person in front of them.

One possible solution to these limitations is the combination of neuroimaging with machine learning.³⁰ Machine learning is an area of artificial intelligence that aims to develop algorithms that recognize trends and patterns in existing data and use this information to make predictions on new data.³⁰ Machine learning methods utilize computational statistics and mathematical optimization.³¹ Because they are multivariate, they take into account the inter correlation between voxels and therefore overcome the first limitation of mass-univariate analytical techniques. In addition, machine learning methods allow statistical inferences at a single-subject level. Thus, these methods could be used to inform diagnostic and prognostic decisions of individual patients, overcoming the second limitation of mass-univariate analytical techniques.³²

Researchers have had varying degrees of success applying several machine learning methods to neuroimaging data from psychiatric and neurological patients.³² The most commonly used methods are Support Vector Machines (SVMs), which are supervised techniques that analyze data for classification analysis. SVMs separate two classes using an optimal hyperplane; in cases where classes are not linearly separable, it uses external

functions (kernels) that map the original data into a new feature space where the data become linearly separable.³³ Despite its popularity, SVM performs poorly on raw data and requires the expert use of design techniques to extract less redundant and more informative features (known as “feature selection”).³⁴ These features, rather than the original data, are then used for classification.

An alternative type of machine learning method known as deep learning³⁵ has garnered considerable attention in the scientific community at large.³² Deep learning methods automatically extract features without requiring prior data processing. This removes a level of subjectivity from the previous approaches such as SVMs. Indeed, distinct to deep learning, rather than being manually engineered, the features are learned from the data, resulting in a more objective and less bias-prone process. With its ability to achieve higher orders of abstraction and complexity relative to other machine learning methods, deep learning is ideally suited for detecting complex, scattered and subtle patterns in the data.³⁶ Therefore, deep learning is particularly attractive for the investigation of psychiatric and neurological disorders, which are often associated with subtle and diffuse neuroanatomical and neurofunctional abnormalities.³⁰ Deep architectures could prove useful in identifying diagnostic and prognostic biomarkers for these disorders compared to conventional machine learning methods, as high-level features can be more robust against noise in the input data.³⁰ In addition, the multifaceted nature of psychiatric and neurological disorders, including cross-modality relationships (e.g. neuroimaging and genetics), likely occur at a deeper conceptual level, making them well-suited for use with deep learning methods.³⁶ Not surprisingly, an increasing number of neuroimaging studies are

beginning to use deep learning to probe the neural correlates of these disorders.³⁷

STANDARDIZATION, DATA SHARING AND RESEARCH NETWORKS

There has been a significant global push to advance anatomical and functional neuroimaging of central nervous system diseases. We now have an opportunity to exert a profound and positive impact on brain research by making the resulting large body of data more accessible to researchers. Sharing this body of knowledge would accelerate our fundamental understanding of the brain, advance the diagnosis and treatment of psychiatric and neurological diseases, reduce research costs, increase the return on current research investments and foster new research in neuroimaging, which could ultimately improve clinical practice.

There is an emerging trend towards sharing neuroimaging data, as illustrated by a number of global research initiatives. Groups such as the Biomedical Informatics Research Network, the Stroke Imaging Research Consortium, the Cancer Genome Atlas, the ADNI³⁸ and the Autism Brain Imaging Data Exchange³⁹ have produced the infrastructure necessary to enable their respective groups to share data. Furthermore, the National Institutes of Health has encouraged and supported the development of common data elements in order to facilitate the ability to merge multiple databases.^{40,41}

In spite of this progress, several barriers continue to impede momentum. Many researchers and institutions remain uncertain about how to share data or they lack the tools and expertise necessary to participate in data sharing. Often, data are not generally accessible, and are limited by issues like cost, privacy and limited manpower. The size and complexity of neuroimaging datasets have attracted radiologists, multidisciplinary communities of applied mathematicians, statisticians, image processors, data miners and bioinformaticians, who all wish to apply their disciplines' techniques to neuroimaging data.⁴² Although the work of these researchers may seem tangential to neuroscientists, cross-disciplinary research can lead to major breakthroughs and precipitate domain paradigm shifts. Neuroimaging stands to benefit significantly from these multidisciplinary interactions. Tools to ease and eventually automate the practice of data sharing will allow researchers to easily share raw, processed and derived neuroimaging data with greater ease.^{42,43} The data should contain the appropriate metadata and provenance records so that researchers can observe a significant overall improvement in the reproducibility of neuroimaging studies.⁴³

The future of neuroimaging research depends on the integration of several types of data (e.g. multimodal imaging, imaging genomics). If researchers and institutions can have assurances of robust anonymization and privacy, the global scientific community can acquire and aggregate existing datasets and the results from several sites can be combined to create extremely rich databases from which we can test novel hypotheses. Neuroimaging may then enter an age where research can lean towards knowledge management rather than data management. This shift in research focus can accelerate the construction of predictive models, which may be useful in predicting and/or diagnosing brain diseases.⁴⁴ Given that the overarching goal of the scientific endeavor is to develop predictive models for the system under study, we can hope to see improvements in existing models as researchers continue to generate new data.

OUTCOME RESEARCH AND COMPARATIVE EFFECTIVENESS

Outcome research is applied clinical- and population-based research that involves the study and optimization of healthcare to benefit the patient and society. Outcome research can (1) help legislative bodies make informed decisions on healthcare; and (2) help financial bodies like governments, insurers and employers minimize cost and waste, while ensuring an acceptable level of care. Patients have a significant stake in outcome research because it informs their decision-making ability with respect to choosing an optimal medical intervention and choosing a procedure for which the patient must be financially responsible. Outcome research identifies shortfalls in practice and develops strategies to improve care. Similar to clinical trials, outcome research can provide evidence about which interventions work best for specific types of patients and under a given set of circumstances. Whereas traditional clinical trials focus primarily on therapeutic efficacy and safety, outcome research may consider additional parameters such as cost, timeliness, convenience, geographical accessibility and patient preferences.

CONCLUSION

Since the development of CT and MRI, the field of neuroimaging has exploded. Advanced imaging techniques are now firmly integrated into clinical practice, allowing to visualize the brain not only as an organ but also at the level of axons and fiber tracts. These significant achievements offer great hope for progress in understanding the human brain, its miraculous structure and function, and the diseases that plague it. The large array of ongoing advancements and the combination of different techniques will hopefully become the mainstream of clinical neuroimaging and pave the way for new therapies and cures for the neurological, neurosurgical and psychiatric disorders.

REFERENCES

- Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack C, Jagust W, et al. The Alzheimer's disease neuroimaging initiative. *Neuroimaging Clin N Am* 2005; 15: 869–77xi-xii. doi: <https://doi.org/10.1016/j.nic.2005.09.008>
- Lansberg MG, Lee J, Christensen S, Straka M, Silva DA, Mlynash M, et al. Rapid automated patient selection for reperfusion therapy. *Stroke* 2011; 42: 1608–14.
- Jovin TG, Nogueira RG, DAWN Investigators. Thrombectomy 6 to 24 hours

- after stroke. *N Engl J Med* 2018; **378**: 1161–2. doi: <https://doi.org/10.1056/NEJMc1801530>
4. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; **378**: 708–18. doi: <https://doi.org/10.1056/NEJMoA1713973>
 5. Mahajan KR, Ontaneda D. The role of advanced magnetic resonance imaging techniques in multiple sclerosis clinical trials. *Neurotherapeutics* 2017; **14**: 905–23. doi: <https://doi.org/10.1007/s13311-017-0561-8>
 6. Brindle KM, Izquierdo-García JL, Lewis DY, Mair RJ, Wright AJ. Brain tumor imaging. *J Clin Oncol* 2017; **35**: 2432–8. doi: <https://doi.org/10.1200/JCO.2017.72.7636>
 7. Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain. *Neuroimage* 1995; **2**: 89–101.
 8. Lv H, Wang Z, Tong E, Williams LM, Zaharchuk G, Zeineh M, et al. Resting-state functional MRI: Everything that nonexperts have always wanted to know. *American Journal of Neuroradiology* 2018; **60**. doi: <https://doi.org/10.3174/ajnr.A5527>
 9. Toga AW, Clark KA, Thompson PM, Shattuck DW, Van Horn JD. Mapping the human connectome. *Neurosurgery* 2012; **71**: 1–5. doi: <https://doi.org/10.1227/NEU.0b013e318258e9ff>
 10. Biswal BB. Resting state fmri. *Neuroimage* 2012; **62**: 938–44.
 11. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995; **34**: 537–41. doi: <https://doi.org/10.1002/mrm.1910340409>
 12. Maldjian JA, Davenport EM, Whitlow CT. Graph theoretical analysis of resting-state meg data. *Neuroimage* 2014; **96**: 88–94.
 13. Brookes MJ, Hale JR, Zumer JM, Stevenson CM, Francis ST, Barnes GR, et al. Measuring functional connectivity using meg. *Neuroimage* 2011; **56**: 1082–104.
 14. Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC, et al. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. *Proc Natl Acad Sci U S A* 2011; **108**: 16783–8. doi: <https://doi.org/10.1073/pnas.1112685108>
 15. de Pasquale F, Della Penna S, Snyder AZ, Lewis C, Mantini D, Marzetti L, et al. Temporal dynamics of spontaneous MEG activity in brain networks. *Proc Natl Acad Sci U S A* 2010; **107**: 6040–5. doi: <https://doi.org/10.1073/pnas.0913863107>
 16. Luckhoo H, Hale JR, Stokes MG, Nobre AC, Morris PG, Brookes MJ, et al. Inferring task-related networks using independent component analysis in magnetoencephalography. *Neuroimage* 2012; **62**: 530–41. doi: <https://doi.org/10.1016/j.neuroimage.2012.04.046>
 17. Toga AW, Thompson PM. Connectomics sheds new light on Alzheimer's disease. *Biol Psychiatry* 2013; **73**: 390–2. doi: <https://doi.org/10.1016/j.biopsych.2013.01.004>
 18. Wintermark M, Coombs L, Druzgal TJ, Field AS, Filippi CG, Hicks R, et al. Traumatic brain injury imaging research roadmap. *AJNR Am J Neuroradiol* 2015; **36**: E12–E23. doi: <https://doi.org/10.3174/ajnr.A4254>
 19. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K. The wu-minn human connectome project. *Neuroimage* 2013; **80**: 62–79. doi: <https://doi.org/10.1016/j.neuroimage.2013.05.041>
 20. Dolgin E. This is your brain online. *Nat Med* 2010; **16**: 351.
 21. Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A* 2010; **107**: 4734–9. doi: <https://doi.org/10.1073/pnas.0911855107>
 22. Jadvar H, Colletti PM. Competitive advantage of PET/MRI. *Eur J Radiol* 2014; **83**: 84–94. doi: <https://doi.org/10.1016/j.ejrad.2013.05.028>
 23. Catana C, Drzezga A, Heiss WD, Rosen BR. PET/MRI for neurologic applications. *J Nucl Med* 2012; **53**: 1916–25. doi: <https://doi.org/10.2967/jnumed.112.105346>
 24. Marner L, Henriksen OM, Lundemann M, Larsen VA, Law I. Clinical PET/MRI in neurooncology: opportunities and challenges from a single-institution perspective. *Clin Transl Imaging* 2017; **5**: 135–49. doi: <https://doi.org/10.1007/s40336-016-0213-8>
 25. Yang ZL, Zhang LJ. PET/MRI of central nervous system: current status and future perspective. *Eur Radiol* 2016; **26**: 3534–41. doi: <https://doi.org/10.1007/s00330-015-4202-5>
 26. Siebner HR, Callicott JH, Sommer T, Mattay VS. From the genome to the phenome and back: linking genes with human brain function and structure using genetically informed neuroimaging. *Neuroscience* 2009; **164**: 1–6. doi: <https://doi.org/10.1016/j.neuroscience.2009.09.009>
 27. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 2005; **102**: 9673–8. doi: <https://doi.org/10.1073/pnas.0504136102>
 28. Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: a review. *Neurosci Biobehav Rev* 2015; **56**: 330–44. doi: <https://doi.org/10.1016/j.neubiorev.2015.07.014>
 29. Kennedy DP, Courchesne E. The intrinsic functional organization of the brain is altered in autism. *Neuroimage* 2008; **39**: 1877–85. doi: <https://doi.org/10.1016/j.neuroimage.2007.10.052>
 30. Zaharchuk G, Gong E, Wintermark M, Rubin D, Langlotz CP. Deep learning in neuroradiology. *AJNR Am J Neuroradiol* 2018;. doi: <https://doi.org/10.3174/ajnr.A5543>
 31. Friedman J, Hastie T, Tibshirani R. The elements of statistical learning. In: Bickel P, Diggle P, Fienberg S. E, Gather U, Zeger S, eds. *Springer series in statistics*. New York: Springer; 2001.
 32. Arbabshirani MR, Plis S, Sui J, Calhoun VD. Single subject prediction of brain disorders in neuroimaging: promises and pitfalls. *Neuroimage* 2017; **145**: 137–65. doi: <https://doi.org/10.1016/j.neuroimage.2016.02.079>
 33. Pereira F, Mitchell T, Botvinick M. Machine learning classifiers and fMRI: a tutorial overview. *Neuroimage* 2009; **45**(1 Suppl): S199–S209. doi: <https://doi.org/10.1016/j.neuroimage.2008.11.007>
 34. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**: 436–44. doi: <https://doi.org/10.1038/nature14539>
 35. Bengio Y. Learning deep architectures for AI. *Foundations and Trends® in Machine Learning* 2009; **2**: 1–127. doi: <https://doi.org/10.1561/22000000006>
 36. Plis SM, Hjelm DR, Salakhutdinov R, Allen EA, Bockholt HJ, Long JD, et al. Deep learning for neuroimaging. *Front Neurosci* 2014; **8**: 229.
 37. Payan A, Montana G. Predicting alzheimer's disease: A neuroimaging study with 3d convolutional neural networks. *arXiv*. arXiv:1502.02506.
 38. Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W. Ways toward an early diagnosis in alzheimer's disease. *Alzheimers Dement* 2005; **1**: 55–66.
 39. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry* 2014; **19**: 659–67. doi: <https://doi.org/10.1038/mp.2013.78>
 40. Duhaime AC, Gean AD, Haacke EM, Hicks R, Wintermark M, Mukherjee P, et al. Common data elements in radiologic imaging of traumatic brain injury. *Arch Phys Med Rehabil* 2010; **91**: 1661–6. doi: <https://doi.org/10.1016/j.apmr.2010.07.238>

41. Haacke EM, Duhaime AC, Gean AD, Riedy G, Wintermark M, Mukherjee P, et al. Common data elements in radiologic imaging of traumatic brain injury. *J Magn Reson Imaging* 2010; **32**: 516–43. doi: <https://doi.org/10.1002/jmri.22259>
42. Nichols BN, Pohl KM. Neuroinformatics software applications supporting electronic data capture, management, and sharing for the neuroimaging community. *Neuropsychol Rev* 2015; **25**: 356–68. doi: <https://doi.org/10.1007/s11065-015-9293-x>
43. Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, et al. Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci* 2017; **20**: 299–303. doi: <https://doi.org/10.1038/nn.4500>
44. Woo CW, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. *Nat Neurosci* 2017; **20**: 365–77. doi: <https://doi.org/10.1038/nn.4478>