

 Open access • Journal Article • DOI:10.1038/NATURE15692

## Progress and challenges in probing the human brain — [Source link](#)

Russell A. Poldrack, Martha J. Farah

**Institutions:** Stanford University, University of Pennsylvania

**Published on:** 15 Oct 2015 - Nature (Nature Publishing Group)

**Topics:** Cognitive neuroscience

Related papers:

- [The WU-Minn Human Connectome Project: An Overview](#)
- [Large-scale automated synthesis of human functional neuroimaging data](#)
- [What we can do and what we cannot do with fMRI](#)
- [Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity](#)
- [Can cognitive processes be inferred from neuroimaging data](#)

Share this paper:    

View more about this paper here: <https://typeset.io/papers/progress-and-challenges-in-probing-the-human-brain-3lqcsqqpib>



10-2015


## Progress and Challenges in Probing the Human Brain

Russell A. Poldrack

Martha J. Farah

*University of Pennsylvania*, [mfarah@psych.upenn.edu](mailto:mfarah@psych.upenn.edu)

Follow this and additional works at: [https://repository.upenn.edu/neuroethics\\_pubs](https://repository.upenn.edu/neuroethics_pubs)

 Part of the [Bioethics and Medical Ethics Commons](#), [Neuroscience and Neurobiology Commons](#), and the [Neurosciences Commons](#)

---

### Recommended Citation

Poldrack, R. A., & Farah, M. J. (2015). Progress and Challenges in Probing the Human Brain. *Nature*, 526 (7573), 371-379. <http://dx.doi.org/10.1038/nature15692>

This paper is posted at ScholarlyCommons. [https://repository.upenn.edu/neuroethics\\_pubs/136](https://repository.upenn.edu/neuroethics_pubs/136)  
For more information, please contact [repository@pobox.upenn.edu](mailto:repository@pobox.upenn.edu).

---

## Progress and Challenges in Probing the Human Brain

### Abstract

Perhaps one of the greatest scientific challenges is to understand the human brain. Here we review current methods in human neuroscience, highlighting the ways that they have been used to study the neural bases of the human mind. We begin with a consideration of different levels of description relevant to human neuroscience, from molecules to large-scale networks, and then review the methods that probe these levels and the ability of these methods to test hypotheses about causal mechanisms. Functional MRI is considered in particular detail, as it has been responsible for much of the recent growth of human neuroscience research. We briefly review its inferential strengths and weaknesses and present examples of new analytic approaches that allow inferences beyond simple localization of psychological processes. Finally, we review the prospects for real-world applications and new scientific challenges for human neuroscience.

### Keywords

cognitive neuroscience, psychiatric disorders

### Disciplines

Bioethics and Medical Ethics | Neuroscience and Neurobiology | Neurosciences

# 1 Progress and challenges in probing 2 the human brain

3 Russell A. Poldrack<sup>1</sup> & Martha J. Farah<sup>2</sup>

4 Perhaps one of the greatest scientific challenges is to understand the human brain. Here we review current methods in  
5 human neuroscience, highlighting the ways that they have been used to study the neural bases of the human mind. We  
begin with a consideration of different levels of description relevant to human neuroscience, from molecules to  
large-scale networks, and then review the methods that probe these levels and the ability of these methods to test  
hypotheses about causal mechanisms. Functional MRI is considered in particular detail, as it has been responsible for  
much of the recent growth of human neuroscience research. We briefly review its inferential strengths and weaknesses  
and present examples of new analytic approaches that allow inferences beyond simple localization of psychological  
processes. Finally, we review the prospects for real-world applications and new scientific challenges for human  
neuroscience.

The way that we conceptualize brain function has always been constrained by the methods available to study it. Studies of patients with focal brain lesions in the nineteenth century led to the view of the brain as a collection of focal centres specialized for particular cognitive abilities, such as ‘Broca’s area’ for speech production. The development of neurophysiological recording techniques in the twentieth century led to Barlow’s ‘neuron doctrine’, according to which the functions of individual neurons can be extrapolated to explain the function of the brain as a whole. The cognitive neuroimaging studies of the 1980s focused on subtractive comparisons between cognitive tasks meant to isolate specific cognitive operations, and led to a relatively modular view of brain function as involving localized and separable regions that implement elementary mental operations.

The methods of contemporary human neuroscience have provided a much more complex and nuanced view of the human brain as a dynamic network with multiple levels of organization, in which function is characterized by a balance of regional specialization and network integration. Although current methods are limited in their utility for studying brain function at fine-grained levels of organization (such as single neurons or cortical columns), human neuroscience has nonetheless made remarkable progress in understanding basic aspects of functional organization, and with this have come a number of applications to address real-world problems. Our goal here is to review the current state of human neuroscience, focusing on what kinds of questions can and cannot be answered using current techniques and how those answers are relevant to real-world applications.

## How can we study the human brain?

Methods for studying human brain function can be organized according to the kinds of mechanistic insights that each technique provides. As shown in Table 1 the first characteristic is the level of mechanism captured by the method. Mechanisms range from the molecular level (neurotransmitters and receptors) to large-scale networks (the dynamic integration and coordination of different functional areas of the brain). Although this distinction is related to physical scale, it does not depend on the method’s spatial resolution per se. For example, positron emission tomography (PET) using neurotransmitter ligands measures molecular mechanisms, even though its spatial resolution is on the order

of one centimetre. The second characteristic is the ability of each method to elucidate the mechanistic role of an observed brain molecule, cell, region or network in a mental function of interest. By mechanism we mean the causal chain of events that result in the realization of a function. To fully understand human brain function is to know the causal chains of events at the molecular, cellular, population, and network levels that give rise to psychological function. For this reason, the power to identify causal relationships is a crucial dimension of difference among methods.

Some methods used in the study of human brain function provide relatively little insight into causal mechanisms. This includes methods that exploit naturally occurring variation by observing the strength of association between individual differences in brain function and behaviour. Analysis of relationships between behavioural traits, genes, brain structure, and brain function exemplify this approach (see Box 1 for a discussion of genomic approaches). For many important psychological phenomena, from effects of life history to personality traits, we are limited to observational methods. For example, individual differences in the personality trait of impulsiveness have been associated with differences in striatal dopamine release<sup>1</sup>, fMRI activation<sup>2</sup>, and cortical grey matter volume<sup>3</sup>. Observed associations between neural and psychological traits do not necessarily imply a causal relationship, as these associations could result from an unmeasured third variable that independently influences the two measures. Nevertheless, such associations provide a valuable starting point for theorizing about the neural mechanisms of human psychology, and their evidentiary value can be strengthened by measuring possible confounds to rule them in or out.

Although functional neuroimaging, electroencephalography/magnetoencephalography (EEG/MEG) and single-cell recordings are sometimes criticized as being purely correlative and therefore uninformative about mechanism, that criticism is only partly accurate. When psychological processes are experimentally manipulated by presenting a certain kind of stimulus and/or engaging the subject in a task, we can infer that any reliably elicited brain activity was caused by performing these psychological functions. We cannot, however, infer with confidence that the observed brain activity is causally responsible for the psychological process under study. Despite this limitation (which is shared by neuronal recordings in non-human animals), neuroimaging studies

<sup>1</sup>Department of Psychology, Stanford University, Stanford, California 94305, USA. <sup>2</sup>Center for Neuroscience & Society, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.

**Table 1 | An overview of the levels of analysis and levels of causal inference afforded by different human neuroscience methods**

	Level of mechanism			
	Molecules	Cells	Populations	NETWORKS
Strength of causal evidence	Purely observational (associations do not necessarily imply causal relations between mind and brain)	Genetic associations with behaviour, brain function or brain structure Postmortem studies of gene expression Correlations of MRI spectroscopy or PET ligand imaging with psychological traits	Structural morphometry correlated with psychological traits	• Resting functional connectivity (fMRI, EEG/MEG) or structural connectivity (sMRI, DTI) correlated with psychological traits
	Manipulate psychological process and observe brain (neural measures may be epiphenomenal)	Task modulation studies using PET with neurotransmitter ligands or MRI spectroscopy	Intracerebral recording in surgical patients	• Task-based functional connectivity (fMRI, EEG/MEG)
	Manipulate brain and observe psychological results (demonstrates causal effect of neural system in behaviour)	Pharmacological manipulation (including hormones)	Direct brain stimulation in surgical patients	Focal cortical lesions Transcranial magnetic stimulation Transcranial electrical stimulation Cortical surface electrode stimulation in surgical patients

DTI, diffusion tensor imaging; EEG/MEG, electroencephalography/magnetoencephalography; fMRI, functional MRI; MRI, magnetic resonance imaging; PET, positron emission tomography; sMRI, structural MRI.

in which psychological processes are manipulated comprise the majority of current human neuroscience research, and have advanced our understanding of human brain function, as we will discuss in more detail below.

### BOX 1

## Challenges of merging neuroimaging and genomics

The substantial heritability of many psychological functions has driven great interest in finding genetic underpinnings of individual differences in neural function. Twin and family studies have demonstrated significant heritability for both task-related BOLD responses<sup>91</sup> and resting-state functional connectivity<sup>92</sup> in fMRI. In the past decade, a large number of studies have also reported associations between BOLD signals and common variants in candidate genes. Unfortunately, this approach has generally been unsuccessful in identifying genetic associations that are replicated in genome-wide association studies (GWAS). For example, a striking finding from the first well-powered GWAS of genetic variants associated with brain volume was that none of the associations previously identified through candidate gene studies were replicated at the genome-wide level<sup>88</sup>. Similarly, candidate gene associations with cognitive function (such as the association between polymorphisms in the *COMT* gene and working memory) and brain activation have generally not been confirmed in meta-analyses, and are subject to a substantial degree of publication bias<sup>93,94</sup>. Like for many other areas of genetics, this suggests that genome-wide approaches are the most likely to lead to reliable identification of common variants related to brain structure and function. However, GWAS approaches require large samples (in the tens of thousands) which are very difficult to amass for task-based fMRI studies; for that reason, GWAS-based approaches to probing the human brain will likely be limited to resting-state fMRI and structural MRI. Other strategies, such as targeted studies investigating rare variants of large effect identified using genome sequencing or studies using gene expression in peripheral tissues may have greater utility for genetic studies of task-based fMRI. Task-based fMRI may also be used to further investigate candidate variants identified on the basis of GWAS studies of psychiatric disorders or population variability.

More decisive evidence concerning causal necessity can be obtained by manipulating the brain itself to assess the resulting effect on the psychological process in question. Naturally occurring or surgical lesions, which provided the basis for most of what we knew about human brain function before the advent of neuroimaging, are still of great interest because they provide insight into the causal necessity of specific brain regions or connections. More recently developed methods of brain stimulation allow for reversible inhibition or excitation of a brain area, thereby expanding our ability to test the causal role of brain regions in the mechanisms of human thought and action. Deep brain stimulation (DBS) provides the most precise method for targeted stimulation by using surgically implanted electrodes, but is limited to situations where patients are undergoing implantation for medical reasons. Use of non-invasive brain stimulation for research purposes has grown rapidly in recent decades, starting with transcranial magnetic stimulation (TMS), in which pulsed magnetic fields induce currents in the brain. Various forms of transcranial electric stimulation (TES), in which current is delivered using external electrodes, have also been used, of which the most common variant is transcranial direct current stimulation (tDCS). Unlike DBS, non-invasive brain stimulation generally affects larger and more superficial areas of the brain, but researchers are seeking to improve spatial resolution with new magnetic coil shapes for TMS and new electrode configurations for tDCS. Focused ultrasound is also being explored as a means to stimulate more precisely delimited brain regions<sup>4</sup>. Pharmacological agonists and antagonists of particular neurotransmitter systems can be used to experimentally manipulate the human brain at the molecular level, although with imperfect specificity<sup>5</sup>. By combining each of these manipulations of brain function with functional brain imaging, one can leverage the causal information obtained through pharmacological challenges or brain stimulation. For example, the causal role of activity in specific brain regions, identified using fMRI, for a particular function has been tested by brain stimulation, using both direct cortical stimulation (for example, ref. 6) and TMS<sup>7</sup>.

### New capabilities of fMRI

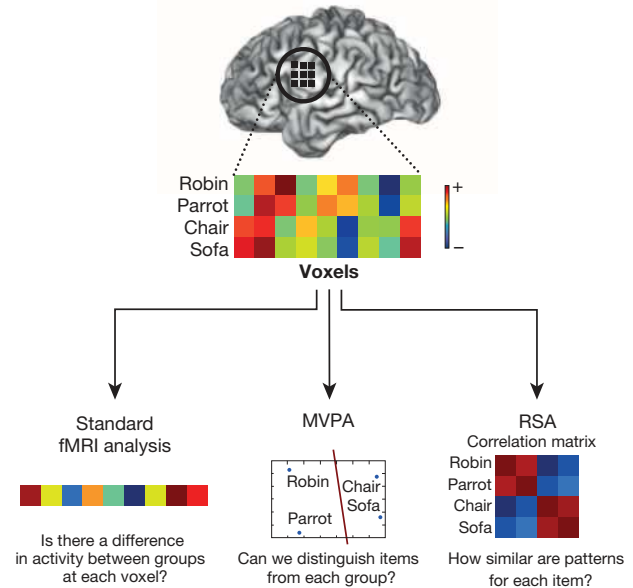
Because fMRI has become the main method for the study of human brain function, our review focuses on this method and new ways of using it. In the last two decades, fMRI has developed from a newly developed technique for revealing neuronal activity to being the workhorse method of cognitive neuroscience (see the recent special issue of *Neuroimage* on

the first twenty years of fMRI<sup>8</sup>). Much has been learned about the biological mechanisms underlying blood oxygen level dependent (BOLD) signals<sup>9,10</sup>, but still much remains to be understood, such as the roles of specific glial and neuronal cell types in the coupling of neuronal activity to blood flow (for example, refs 11, 12). This limited physiological understanding poses problems for the interpretation of fMRI data. In particular, although fMRI signals often correlate strongly with both action potentials ('spikes') and local field potentials, they are largely reflective of post-synaptic processes, and in some cases they can be dissociated from spiking altogether<sup>13</sup>. The relative sensitivity of fMRI to post-synaptic processes as opposed to spiking has been seen as a drawback by some who view spikes as the essence of brain function, but it is worth noting that this discovery has actually rekindled interest in the analysis of local field potentials in electrophysiology (where these signals have long been discarded) (for example, ref. 14), and suggests that fMRI may sometimes be sensitive to subthreshold signals that would be missed by analysis of spikes only. Uncertainties in relating fMRI to psychological, as well as physiological, processes have also been debated, and progress has been made on this front too. From experimental approaches such as adaptation paradigms for probing representations to analyses of functional connectivity, fMRI is routinely used to answer questions about mind-brain relationships that go far beyond localization<sup>15</sup>. Here we discuss three examples of new approaches to understanding human brain function with fMRI that address questions of representation, computational processes and network interactions across the brain.

### Representational analyses

Early work in neuroimaging focused largely on 'brain mapping'—identifying regions based on the mental processes that cause them to be activated. This approach has provided a large body of reliable associations between function and structure, but has not been particularly successful in providing new insights into how psychological functions are implemented<sup>16</sup>. However, two relatively recent approaches, known as multi-voxel pattern analysis (MVPA)<sup>17</sup> and representational similarity analysis (RSA)<sup>18</sup>, can more directly relate psychological contents to brain function (Fig. 1). MVPA involves the use of methods from the field of machine learning to decode or predict psychological states from patterns of brain activation across voxels (hence the term 'brain-reading'). Since its introduction more than a decade ago, MVPA has been used in a number of domains to demonstrate the predictive ability of fMRI activation patterns. Perhaps the most impressive are demonstrations of the ability to successfully reconstruct visual scenes<sup>19</sup> and faces<sup>20</sup> from BOLD activity patterns; similar advances have been made for higher cognitive functions such as word meaning<sup>21</sup>. These studies go beyond simply differentiating between experimental conditions, as they show how the underlying representational spaces relate to brain activity; for example, Huth and colleagues<sup>22</sup> developed a model that estimated the response at each location on the cortical surface to a large number of visual and semantic features present in natural movies (Fig. 2). MVPA approaches have also provided new insights into the neural organization of cognitive functions. For example, MVPA has informed our understanding of the mechanisms of visual attention, by showing that attention changes both the representation of stimuli across regions of visual cortex as well as the mutual information between regions<sup>23</sup>. In the domain of memory, MVPA has been used to show that competition between memory representations in working memory leads to poorer subsequent memory for those items, demonstrating a nonmonotonic relationship between competition and subsequent memory<sup>24</sup>.

Whereas MVPA is generally used to decode individual psychological states, RSA instead asks how the patterns of brain activity evoked by different stimuli are related to one another, and thus provides the means to directly address questions of how mental representations are implemented in the brain. RSA has enabled the demonstration of direct isomorphisms between psychological representations

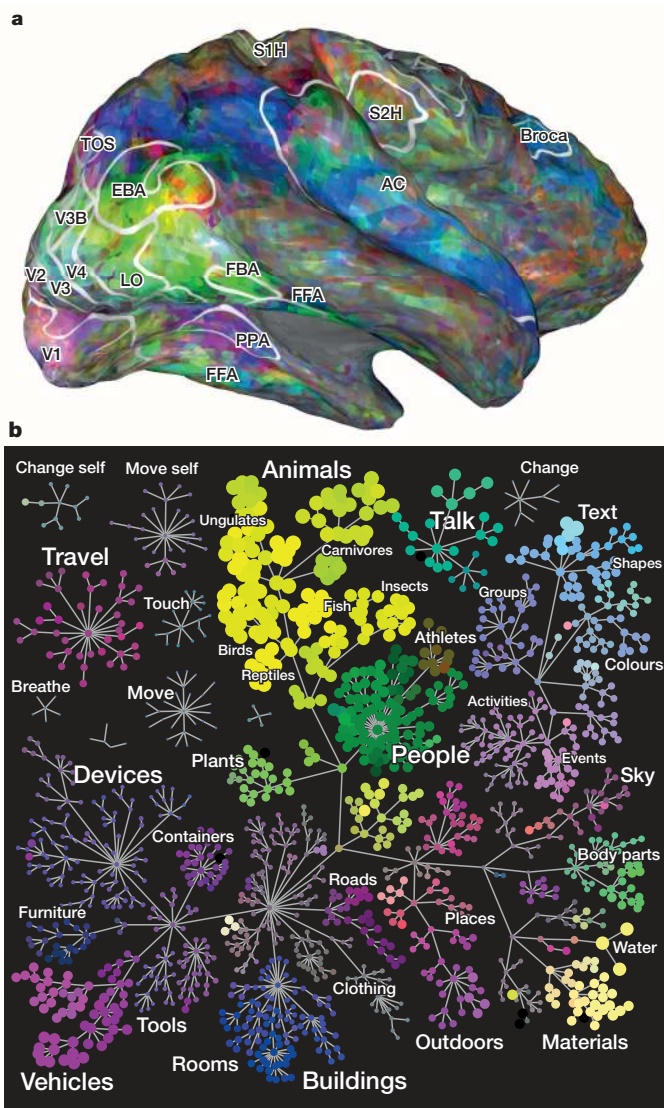


**Figure 1 | Different approaches to the analysis of fMRI data.** This example depicts data from a study in which four different stimuli were presented (two birds and two items of furniture) and response measured for each item across nine voxels; intensity of activity is depicted from blue (negative) to red (positive). The standard univariate fMRI analysis approach would examine the difference at each voxel between the averages of the two categories. Multi-voxel pattern analysis (MVPA) examines the multidimensional relationship between patterns of activity, in this case projecting the nine-dimensional space of voxel patterns (the voxel vector) into a two-dimensional space and identifying a boundary that separates items from the two classes. Representational similarity analysis (RSA) examines the correlations between activity patterns for each item, in this case showing that items within category show a high correlation (red), whereas the correlation of items between categories is low (blue).

of stimuli (such as the similarity or typicality of objects) and the neural patterns associated with those stimuli<sup>25,26</sup>. Because psychological theories often make predictions regarding the similarity of different stimuli, RSA has also enabled the direct testing of theories, such as theories about how categories are represented<sup>27</sup> and theories of how repeated experiences lead to enhanced learning<sup>28</sup>. RSA can be applied to any kind of multidimensional data, and this has enabled the demonstration of systematic mappings of visual object representations between humans (using fMRI) and non-human primates (using electrophysiological recordings)<sup>29</sup>—an example that highlights how human neuroscience can also help to establish more direct parallels with findings in non-human models, allowing insights to filter in both directions.

Although much MVPA and RSA work (as depicted in Fig. 1) has focused on the representations found in localized brain regions, these methods are equally useful for assessing representations that are spread across the brain. For example, recent work has shown that mental states such as physical pain can be decoded by analysis of patterns of activation across brain regions<sup>30</sup>.

The legitimate enthusiasm about these methods is tempered by lingering questions regarding the interpretation of multivariate analyses<sup>31,32</sup>. In addition, recent work combining electrophysiology and fMRI in non-human primates has demonstrated that the sensitivity of MVPA is limited by the spatial characteristics of the neuronal representations that code for particular features, such that some kinds of neuronal patterns may be more difficult to decode using MVPA than others<sup>33</sup>. Finally, it is important to stress that, like standard neuroimaging approaches, MVPA and RSA approaches do not inform about causal mechanisms.



**Figure 2 | A mapping of high-dimensional semantic space onto the cortical surface.** Here, voxel patterns for 1,705 different action and object categories, based on brain activity obtained during viewing of natural movies<sup>22</sup> are mapped onto the cortical surface image generated using online browser at (<http://gallantlab.org/semanticmovies/>). **a**, Mapping of semantic categories to each point on the surface; the colours on the surface map to the semantic map in panel **b**. **b**, A depiction of the semantic space for a specific surface point in the extrastriate body area (EBA). Data from ref. 22.

### Integrating fMRI and computational modelling

Computational models play a central role in our understanding of both cognitive and brain functions and, increasingly, of the relationship between the two. By making assumptions explicit, computational models enable more direct testing of theories, as well as providing the means to link computations at the neuronal level with higher-order functions. An example of an area in which substantial progress has been made using this approach is reinforcement learning, in which an animal selects actions and learns from the rewards gained from those actions. Computational models of reinforcement learning (RL) have long played a central role in artificial intelligence and psychology, and the discovery by Schultz and colleagues<sup>34</sup> that dopamine neurons appear to signal one of the important quantities in these models (reward prediction error) has brought these models to the forefront of the neuroscience of decision making. For example, a set of publications in 2003 applied RL models to neuroimaging data and thereby identified correlates of reward prediction error signals in dopaminergic target regions such as the ventral striatum<sup>35,36</sup>. Subsequent neuroimaging work has established that there

are multiple RL signals in the brain, some reflecting the simple association between actions and values (known as ‘model-free’ RL) and others reflecting more complex contextual and hierarchical learning processes (known as ‘model-based’ RL)<sup>37,38</sup>. Similarly, in the study of memory, progress has been made in the mapping of medial temporal lobe subregions to specific computational operations such as pattern completion and pattern separation (for example, ref. 39). In each of these domains, the computational interpretation of neuroimaging signals has been greatly enhanced by parallel studies in non-human animals, allowing imaging signals to be linked more directly to direct measures of neuronal activity.

### Functional connectivity analysis and resting-state fMRI

Perhaps the most revolutionary development to arise from human neuroimaging research is the realization that the resting brain is far from quiescent, and that important insights into brain function can be gained from studying the correlated fluctuations of signals across the brain at rest. Much of the research into the resting state has focused on a set of regions (including anterior and posterior midline regions, lateral temporoparietal cortex, and the medial temporal lobe, known as the ‘default mode’ network<sup>40</sup>) that are consistently less active during performance of difficult tasks<sup>41</sup>, and are functionally connected in the resting state<sup>42</sup>. Similar patterns of resting connectivity have been observed in non-human primates<sup>43</sup> and awake rodents<sup>44</sup>, suggesting that they reflect fundamental principles of mammalian brain organization. There is also growing evidence that these networks may be important in brain disorders. For example, the posterior portion of the default mode network appears to play a critical role in the memory deficits observed in Alzheimer’s disease, showing a convergence of amyloid deposition, structural atrophy, and decreased metabolic activity<sup>45</sup>.

Data collected in the resting state can provide insights into the broader functional organization of the brain as well. In particular, the organization of resting state signals bears a close relation to the organization of brain activity evoked by mental tasks. For example, Smith *et al.*<sup>46</sup> used independent component analysis to identify spatially independent sets of voxels from resting-state fMRI data and from task-based data (obtained from the Brainmap meta-analytic database), and demonstrated that the components extracted from resting-state fMRI showed a high degree of concordance with those extracted from task-based data. The overlap between resting-state and task-based functional organization can also be seen within individuals; for example, the longitudinal examination of a single individual revealed reliable spatial parcellation of activity in the cerebral cortex (using resting fMRI data) that mapped systematically to the activation patterns observed across a large number of task measurements<sup>47</sup>.

Despite the substantial excitement around resting-state fMRI findings, numerous concerns have been raised about their interpretation. In particular, there are lingering questions regarding the ways in which artefacts related to head motion and physiological fluctuations may influence estimates of resting state connectivity, and whether common data analytic methods may induce systematic artefacts<sup>48,49</sup>. In addition, potential confounds such as light sleep<sup>50</sup> may drive differences in resting state signals. The unconstrained nature of resting-state fMRI is a double-edged sword; it is potentially very useful for the study of clinical groups for whom task performance may be difficult, but at the same time, it is not possible to determine whether group differences reflect fundamental differences in functional connectivity or relative differences in the ongoing mental content of different groups during rest (see ref. 51).

### Applications of human neuroscience

With the development of new methods have come attempts to apply them to real-world problems, in both medical and non-medical contexts. (See Box 2 for a discussion of the ethical, legal, and societal issues raised by these applications.)

## BOX 2

## Ethical, legal and societal impact of human neuroscience

As the methods of human neuroscience find broader application, they affect human life in new ways. The field of 'neuroethics' is concerned with ethical, legal and societal issues raised by these new applications<sup>95</sup>.

Two kinds of problems have emerged from the increasing ability of brain imaging to reveal aspects of individual psychology: problems that arise from the current and imminent capabilities of these methods, and problems that arise from their lack of claimed capabilities. To the extent that imaging can predict important personal characteristics such as health status, academic achievement, and criminal behaviour, its use must be managed with care to protect privacy and avoid discrimination<sup>96</sup>. To the extent that imaging cannot provide help with high-stake problems, the public should be protected from claims that it can. For example, a seemingly 'scientific' method for detecting lies or diagnosing psychiatric disorders<sup>66,97</sup> has a strong appeal to the general public who cannot be expected to appreciate the gap between what is claimed and what is established fact.

New ways of changing brain function pharmacologically, and with electromagnetic stimulation, also raise new ethical issues. Of course, humanity has long manipulated brain function to modify mental states using substances such as alcohol and caffeine. However, psychopharmacology has broadly penetrated our everyday lives and the scope of psychiatric diagnoses and treatment has expanded—a societal shift that some find troubling<sup>98</sup>. Furthermore, many now use psychoactive drugs purely for enhancement of healthy brain function rather than to treat a medical condition<sup>99</sup>. Aside from issues of safety and efficacy, brain enhancement raises issues of fairness (is it akin to doping in sports?), justice (will the ability to access enhancements widen the already existing gaps between haves and have-nots?) and social standards (will unenhanced job performance become sub-standard?).

Non-invasive brain stimulation is the newest method for brain enhancement. Simple transcranial electrical stimulation (tES) devices are available to consumers at relatively low cost and regulation is minimal<sup>100</sup>. Given the public interest in this method and the rudimentary state of knowledge about its effects, it is crucial that the safety and efficacy of these methods are established. The efficacy of cognitive enhancement with tDCS is hotly debated<sup>101</sup> and whether long-term use of tDCS is safe has yet to be studied. In addition, neuroethical issues of fairness, justice and social standards mentioned above also apply to enhancement of brain function by brain stimulation.

## Brain disorders

The methods of human neuroscience hold particular promise for understanding and treating psychiatric disorders, because these disorders do not have clear analogues in non-human animals, and animal models currently used for preclinical screening of potential therapies are increasingly regarded as being inadequate<sup>52</sup>. In the absence of valid animal models, it becomes all the more crucial to apply new methods for understanding human brain function and dysfunction. The goal of improving the treatment of neuropsychiatric disorders is made even more challenging because of our current diagnostic system. Although depression, schizophrenia, autism and other serious psychiatric disorders have long been considered disorders of the brain, they are still diagnosed exclusively by behavioural signs and symptoms. These diagnostic criteria do not seem to have clear relations to the biological processes that would be targeted by new medical treatments.

In response to this problem, an alternative way of systematizing psychiatric disorders has been developed—the NIMH Research Domain

Criteria (RDoC)<sup>53</sup>—that describes disorders according to impairments in specific functional systems of the brain (such as fear or reward learning) and at different levels of mechanism of the kind represented in Table 1 (for example, molecules or circuits). RDoC characterizations cut across traditional diagnostic categories and are intended to capture the underlying pathophysiology more accurately. Given the multiple levels of mechanism captured by the RDoC, the system encourages research with a broad array of methods to identify potentially targetable dysfunctions.

The application of several human neuroscience methods has led to the development of targeted treatments, for example, in the field of depression. Functional imaging studies have highlighted the role of the subgenual anterior cingulate cortex in a network of regions involved in mood, leading Mayberg and colleagues to use deep brain stimulation in this area to regulate mood in depressed patients<sup>54</sup>. Lateral prefrontal regions, implicated through imaging studies in depression, have been targeted with non-invasive brain stimulation, including the FDA-approved use of TMS for treatment-resistant depression. Functional neuroimaging can itself be used as a treatment, by providing patients with a real-time measure of regional brain activity to use as a biofeedback signal. This approach is being tested for the treatment of chronic pain, depression and addiction<sup>55</sup>. In contrast, neuroimaging has not so far been very successful in aiding differential diagnosis of disorders in terms of current diagnostic categories. A recent large meta-analysis identified a set of regions in which structural abnormalities were consistently associated with psychiatric disorders, but found very little specificity for individual disorders<sup>56</sup>, consistent with the notion that current diagnostic distinctions are not biologically realistic categories.

Another approach to the discovery of therapeutic targets is the use of genetic association studies to identify sets of genes that are associated with a disorder and that together may indicate particular molecular pathways underlying the disorder. Although the numbers of subjects needed to establish reliable genetic associations is daunting, progress has been made through large international collaborations. For example, Psychiatric Genomics Consortium has to date identified more than 100 common genetic variants reliably implicated in schizophrenia<sup>57</sup>. Imaging can also be used to develop endophenotypes (or intermediate phenotypes) that may bear a closer relation to the effect of a gene variant than does disease diagnosis, as well as to mitigate the problem of heterogeneity within conventional diagnostic categories (see Box 1).

It may be less surprising that the methods developed for human neuroscience research have been applied in the diagnosis and treatment of neurological diseases, but at least two recent developments deserve mention here. Studies of Alzheimer's disease at mechanistic levels from molecules to systems have improved diagnostic accuracy and have enabled a degree of prediction before clinical signs of the disease<sup>58</sup>. Molecular biomarkers from blood and CSF, and patterns of brain activity and structure have revolutionized clinical research in this area by facilitating trials of preventive treatment and by providing intermediate phenotypes as early gauges of effectiveness. Disorders of consciousness following severe brain damage are another area of clinical neuroscience for which neuroimaging shows promise. Some patients who have been diagnosed as being in the vegetative state can follow commands to imagine actions that activate specific areas of the brain in much the same way as healthy control subjects do, and can even use these imagined actions to answer questions (for example, "Do you have any brothers? If yes, imagine playing tennis, if no, imagine walking through your house.")<sup>59</sup>. Thus, neuroimaging offers new insights into the assessment of consciousness, as well as the distinct problem of prognosis, in severely brain-damaged patients.

## Predicting behaviour

The ability to predict future behaviour is of value in almost every sphere of human activity. Although it has often been said that "the best predictor of future behaviour is past behaviour," in some cases brain imaging can improve our ability to predict future behaviour, over and



above what we can do with behavioural history. Marketing professionals were among the first to attempt to predict behaviour using brain imaging. Recognizing the limitations of focus groups and other traditional methods to discern what consumers want, they have used functional neuroimaging to predict the effects of different advertising campaigns, packaging, and other factors on consumer behaviour, based on the premise that activity in the brain's reward or motivation centres may be a more direct measurement of wanting than are verbal self-reports<sup>60</sup>. Although most of this work is conducted by and for corporations aiming to improve sales rather than share scientific knowledge, published academic studies have begun to lend some credence to the potential of neuromarketing. For example, when teenage subjects were scanned while listening to unfamiliar songs, the reward system activity evoked by the songs, but not the subjects' ratings of their likeability, was predictive of sales of the songs over the subsequent three years<sup>61</sup>.

Prediction is also important outside of business. Falk and colleagues have adapted neuromarketing methods for the purpose of creating more effective public service announcements. They showed that brain responses (but not ratings) to an anti-smoking advertisement were predictive of subsequent call volume to an anti-smoking hotline<sup>62</sup>. Gabrieli *et al.*<sup>63</sup> recently summarized evidence concerning neuroimaging-based prediction in domains ranging from healthful eating to criminal recidivism, including numerous examples of prediction of educational outcomes. Indeed, neuroimaging can predict future academic skills over and above traditional behavioural predictors, thus enabling earlier and more appropriate interventions to address individual children's reading and math difficulties. These authors also pointed out a number of methodological challenges in neuroimaging-based prediction of behaviour, including the need to develop and test predictions with different samples, to avoid the 'optimism bias' that occurs when predictions are tested in the same population from which they were generated.

### Human neuroscience in the courtroom

In recent years the methods of human neuroscience have found their way into the courtroom. Perhaps the most obvious, but also the most misunderstood, role for neuroscience is in helping to determine criminal responsibility. Proving that a criminal act may have had a neural cause is not in itself exculpatory, as every human act is caused by the brain<sup>64</sup>. However, to the extent that neuroscience can provide evidence of mental dysfunction (for example, a tumour in the frontal cortex that may have impaired the ability to control behaviour), immaturity or other psychological grounds for reduced criminal responsibility, it is potentially relevant and has been used. For example, the Supreme Court explicitly cited neuroscience evidence in its decision in *Graham v. Florida* to abolish life in prison without parole for juveniles who commit non-homicidal offences. It is more difficult to make legal arguments for applying neuroimaging evidence to individual cases because most findings from neuroimaging research are generalizations based on groups of people and may therefore not allow reliable inferences regarding individuals<sup>65</sup>. Nevertheless, neuroimaging scans from defendants are sometimes presented in the sentencing phase of criminal trials as grounds for mitigation of the sentence, as weaker evidentiary standards apply in the sentencing phase.

Neuroimaging can be applied in ways other than determining degree of responsibility. Lie detection is one example that has been pursued in legal contexts, although it has not so far been admitted into US courts and has yet to demonstrate validity, reliability or resistance to countermeasures outside of the laboratory<sup>66</sup>. Another application concerns pain: brain-based biomarkers for pain would help discriminate real suffering from malingering—a pivotal issue in many lawsuits—and have been admitted as evidence in at least one US case<sup>67</sup>.

### Challenges and future directions for neuroimaging

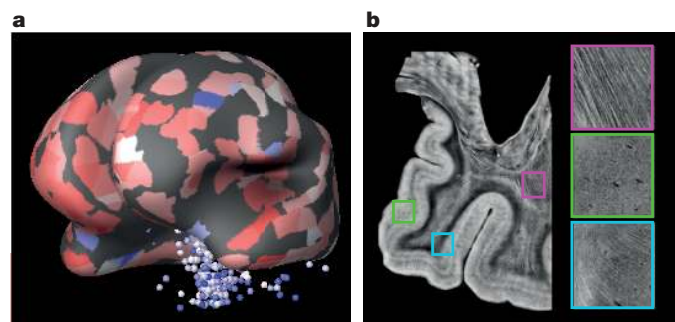
The field of neuroimaging is growing rapidly, and there are a number of exciting new directions on the horizon.

### New technologies for imaging and manipulating the human brain

Rapid advances in non-human neuroscience have been driven by the development of technologies that measure and manipulate brain function with increasing precision. Human neuroscience has lagged in this respect, in part because of the ethical challenges associated with direct manipulation and neuronal recording of the human brain. However, in response to the urgent need for better treatments for psychiatric disorders, research is underway with the aim to design implantable systems for sensing and modulating human brain networks<sup>68</sup>. The development of optogenetic and 'opto-fMRI' approaches in non-human primates<sup>69</sup> suggests that these methods may one day become feasible for use in human studies, and it is likely that electrical brain stimulation will be supplemented in the near future with optogenetic approaches. Although such invasive techniques will likely only be used in rare clinical cases (that is, patients are undergoing implantation for medical reasons), they have the potential to provide much greater specificity in circuit mapping.

fMRI will probably remain the principal neuroimaging method in humans in the foreseeable future. However, the ongoing BRAIN initiative in the United States<sup>70</sup> is providing substantial funding to develop entirely new techniques for imaging of brain function, and a significant proportion of this funding will go specifically towards the development of new methods for imaging the human brain. In addition, new developments in MRI have greatly increased the utility of standard MRI systems. For example, multiband imaging techniques<sup>71</sup> have enabled a several-fold increase in the temporal resolution of fMRI acquisitions, and higher MRI field strengths (7 tesla and higher) hold promise to enable improvements in spatial resolution as well (for example, ref. 72). There is thus great reason to be optimistic that methodological limits will continue to be pushed in the future.

Additional insight into human brain function will likely come from the study of postmortem human brains, which has long been a staple method for the characterization of anatomical structure and study of brain disorders. New techniques have enhanced the ability to visualize the structure of human brain tissue (Fig. 3). For example, optical coherence tomography has been used to image *ex vivo* human cortical tissue, providing high-resolution imaging of cytoarchitecture with less distortion than standard microscopy techniques<sup>73</sup>. The first whole-brain atlas of genome-wide gene expression in postmortem human brains<sup>74</sup> has provided an important resource for understanding how gene expression relates to brain function; for example, the maps from this project have



**Figure 3 | New methods for characterizing the postmortem human brain.**

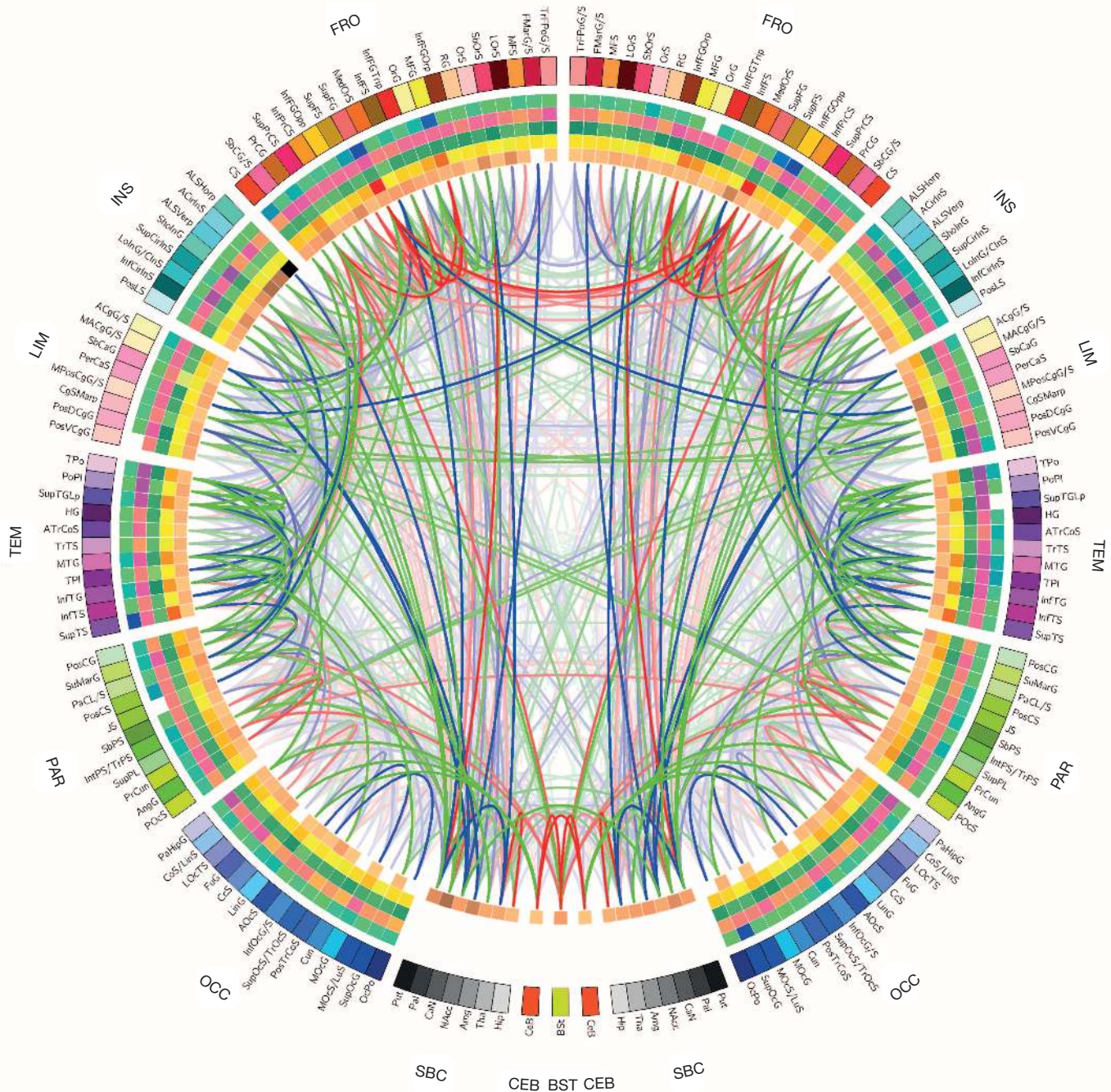
**a**, A map of expression of the serotonin receptor 3B displayed on the reconstructed cortical surface in one individual from the Allen Brain Atlas Human Brain data set (generated using data from <http://human.brain-map.org/>). **b**, Optical coherence tomography imaging of the human brain (2.9 in-plane resolution). Large panel presents an average intensity projection in depth over 300; inset zooms are maximum intensity projections over 300, showing fibres in the white matter (pink inset), fibres arcing through the subcortical junction to insert into the cortex (cyan inset), and neurons in the cortex (bright spots in the green inset). Image courtesy of Bruce Fischl, Caroline Magnain and David Boas, Massachusetts General Hospital.

been used to identify expression differences across different resting-state networks<sup>75</sup>. Continued development of such resources will be essential for progress in understanding the genetic architecture of brain function and their relation to mental health disorders.

**Connectomics**

The Human Connectome Project<sup>76</sup> is nearing completion, and has already provided a rich database for the modelling of functional and anatomical connectivity of the human brain. However, fundamental challenges remain. For example, diffusion MRI provides the means to track white matter pathways (Fig. 4) and has been used to identify white

matter connectivity disruptions associated with cognitive disorders such as dyslexia<sup>77</sup>; however, diffusion imaging has inherent biases that limit its ability to accurately track connections across the entire brain<sup>78,79</sup>. The last decade has seen a proliferation of approaches to model functional connectivity on the basis of functional MRI data, though the dust has yet to settle regarding which methods are most effective (for example, ref. 80). To determine this, the analysis methods must be validated, which is challenging to do in humans but may be achieved using direct measurements of functional connectivity from invasive human approaches and non-human animals to validate the neuroimaging results. There is increasing evidence that at least in non-human primates



**Figure 4 | A ‘connectogram’<sup>90</sup> for an example healthy adult female subject.** The outermost ring shows the various brain regions arranged by lobe (fr, frontal; ins, insula; lim, limbic; tem, temporal; par, parietal; occ, occipital; nc, non-cortical; bs, brain stem; CeB, cerebellum) and further ordered anterior (top) to posterior (bottom). The colour map of each region is lobe-specific and maps to the colour of each regional parcellation as determined using FreeSurfer.

The set of five rings (from the outside inward) reflect grey matter volume, area, thickness, curvature, and connectivity density. The lines inside of the circle represent the computed degrees of connectivity between segmented brain regions using diffusion tractography, with colour representing the relative fractional anisotropy of the connection (from blue to red). Image courtesy of Jack Van Horn, University of Southern California.

functional connectivity reflects anatomical connectivity as measured using either diffusion MRI<sup>81</sup> or anatomical tract-tracing<sup>82</sup>; but it remains an important challenge to establish the ways in which functional and diffusion connectivity measures converge or diverge.

### Reproducibility of neuroimaging research

Large-scale meta-analyses have made it clear that neuroimaging results can be highly convergent across studies, to the degree that cognitive processes can be accurately inferred from individual subject data using decoders trained on meta-analytic data based on reported activation coordinates<sup>83</sup>. However, the last few years have also seen increasing concern regarding the reproducibility of research findings in neuroscience, paralleling more general concerns about reproducibility of scientific results<sup>84</sup>. These issues are particularly acute for neuroimaging given the high dimensionality of the data, relatively low statistical power of many studies<sup>85</sup>, high degree of analytic flexibility in data analysis procedures<sup>86</sup>, and potential for questionable research practices such as circular analysis procedures<sup>87</sup>. The field of neuroimaging has been at the forefront of a number of developments that aim to improve reproducibility and the sharing of data are increasingly being embraced. The Alzheimer's Disease Neuroimaging Initiative (ADNI), International Neuroimaging Data Sharing Initiative (INDI), ENIGMA, and the Human Connectome Project together have shared thousands of neuroimaging data sets and this has enabled a number of novel discoveries. For example, data sharing by the ENIGMA consortium has enabled the first well-powered genome-wide association study of brain volume<sup>88</sup>, identifying replicated associations between brain volume and several common genetic variants. In addition, nearly all of the main software packages for neuroimaging data analysis are free and open source, providing transparency and reproducibility in data analysis across groups, and the publication of fully reproducible analysis workflows has begun (for example, ref. 89). The increasing use of machine learning methods, with their focus on out-of-sample generalization rather than statistical significance, is also leading to a greater emphasis on achieving reproducibility.

### Outlook

The use of new tools for imaging and manipulating the brain will continue to advance our understanding of how the human brain gives rise to thought and action. The combination of myriad methods with different and complementary strengths and weaknesses will allow neuroscientists to develop a multilevel understanding of the brain, spanning from molecules to large-scale networks. New analysis methods have advanced fMRI beyond 'blobology' and will provide direct insight into the mapping of mental and neural representations, while newer analysis and acquisition newer methods will offer other novel insights into the relation of mind and brain. fMRI and other human neuroscience methods will continue being applied to solve real-world problems, within medicine and beyond. Although some of these applications are currently premature relative to the demonstrated capabilities of the methods, it is clear that the new methods of human neuroscience will have much to offer science and society.

Received 31 May; accepted 4 September 2015.

Published online XX 2015.

- Buckholtz, J. W. *et al.* Dopaminergic network differences in human impulsivity. *Science* **329**, 532 (2010).
- Plichta, M. M. & Scheres, A. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci. Biobehav. Rev.* **38**, 125–134 (2014).
- Schilling, C. *et al.* Common structural correlates of trait impulsiveness and perceptual reasoning in adolescence. *Hum. Brain Mapp.* **34**, 374–383 (2013).
- Legon, W. *et al.* Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nature Neurosci.* **17**, 322–329 (2014).
- Chamberlain, S. R., Müller, U., Robbins, T. W. & Sahakian, B. J. Neuropharmacological modulation of cognition. *Curr. Opin. Neurol.* **19**, 607–612 (2006).

- Parvizi, J. *et al.* Electrical stimulation of human fusiform face-selective regions distorts face perception. *J. Neurosci.* **32**, 14915–14920 (2012).  
**This study uses the combination of fMRI and intracranial electrical stimulation to demonstrate the causal role of fusiform regions in face perception.**
- Chen, A. C. *et al.* Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proc. Natl Acad. Sci. USA* **110**, 19944–19949 (2013).
- Bandettini, P. A. Twenty years of functional MRI: the science and the stories. *Neuroimage* **62**, 575–588 (2012).
- Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412**, 150–157 (2001).
- Attwell, D. *et al.* Glial and neuronal control of brain blood flow. *Nature* **468**, 232–243 (2010).
- Hillman, E. M. C. Coupling mechanism and significance of the bold signal: a status report. *Annu. Rev. Neurosci.* **37**, 161–181 (2014).
- Sirotnin, Y. B. & Das, A. Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. *Nature* **457**, 475–479 (2009).
- Thomsen, K., Offenhauser, N. & Lauritzen, M. Principal neuron spiking: neither necessary nor sufficient for cerebral blood flow in rat cerebellum. *J. Physiol. (Lond.)* **560**, 181–189 (2004).
- Einenvoll, G. T., Kayser, C., Logothetis, N. K. & Panzeri, S. Modelling and analysis of local field potentials for studying the function of cortical circuits. *Nature Rev. Neurosci.* **14**, 770–785 (2013).
- Farah, M. J. Brain images, babies, and bathwater: critiquing critiques of functional neuroimaging. *Hastings Cent. Rep.* **44**, S19–S30 (2014).
- Poldrack, R. A. & Yarkoni, T. From brain maps to cognitive ontologies: informatics and the search for mental structure. *Annu. Rev. Psychol.* <http://dx.doi.org/10.1146/annurev-psych-122414-033729> (in the press).
- Norman, K. A., Polyn, S. M., Detre, G. J. & Haxby, J. V. Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends Cogn. Sci.* **10**, 424–430 (2006).
- Kriegeskorte, N., Mur, M. & Bandettini, P. Representational similarity analysis—connecting the branches of systems neuroscience. *Frontiers Syst Neurosci* **2**, 4 (2008).
- Naselaris, T., Prenger, R. J., Kay, K. N., Oliver, M. & Gallant, J. L. Bayesian reconstruction of natural images from human brain activity. *Neuron* **63**, 902–915 (2009).
- Cowen, A. S., Chun, M. M. & Kuhl, B. A. Neural portraits of perception: reconstructing face images from evoked brain activity. *Neuroimage* **94**, 12–22 (2014).
- Mitchell, T. M. *et al.* Predicting human brain activity associated with the meanings of nouns. *Science* **320**, 1191–1195 (2008).  
**An outstanding example of the use of fMRI along with a model of word meaning derived from a large text corpus to predict activation patterns associated with words.**
- Huth, A. G., Nishimoto, S., Vu, A. T. & Gallant, J. L. A continuous semantic space describes the representation of thousands of object and action categories across the human brain. *Neuron* **76**, 1210–1224 (2012).
- Sprague, T. C., Saproo, S. & Serences, J. T. Visual attention mitigates information loss in small- and large-scale neural codes. *Trends Cogn. Sci.* **19**, 215–226 (2015).
- Lewis-Peacock, J. A. & Norman, K. A. Competition between items in working memory leads to forgetting. *Nat. Commun.* **5**, 5768 (2014).
- Charest, I., Kievit, R. A., Schmitz, T. W., Deca, D. & Kriegeskorte, N. Unique semantic space in the brain of each beholder predicts perceived similarity. *Proc. Natl Acad. Sci. USA* **111**, 14565–14570 (2014).
- Davis, T. & Poldrack, R. A. Quantifying the internal structure of categories using a neural typicality measure. *Cereb. Cortex* **24**, 1720–1737 (2014).
- Mack, M. L., Preston, A. R. & Love, B. C. Decoding the brain's algorithm for categorization from its neural implementation. *Curr. Biol.* **23**, 2023–2027 (2013).
- Xue, G. *et al.* Greater neural pattern similarity across repetitions is associated with better memory. *Science* **330**, 97–101 (2010).
- Kriegeskorte, N. *et al.* Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron* **60**, 1126–1141 (2008).  
**This paper applies representational similarity analysis to human fMRI and monkey electrophysiology data to demonstrate similar representational spaces in the inferior temporal cortex across species.**
- Wager, T. D. *et al.* An fMRI-based neurologic signature of physical pain. *N. Engl. J. Med.* **368**, 1388–1397 (2013).
- Davis, T. *et al.* What do differences between multi-voxel and univariate analysis mean? How subject-, voxel-, and trial-level variance impact fMRI analysis. *Neuroimage* **97**, 271–283 (2014).
- Todd, M. T., Nystrom, L. E. & Cohen, J. D. Confounds in multivariate pattern analysis: theory and rule representation case study. *Neuroimage* **77**, 157–165 (2013).
- Dubois, J., de Berker, A. O. & Tsao, D. Y. Single-unit recordings in the macaque face patch system reveal limitations of fMRI MVPA. *J. Neurosci.* **35**, 2791–2802 (2015).
- Schultz, W. Predictive reward signal of dopamine neurons. *J. Neurophysiol.* **80**, 1–27 (1998).
- McClure, S. M., Berns, G. S. & Montague, P. R. Temporal prediction errors in a passive learning task activate human striatum. *Neuron* **38**, 339–346 (2003).
- O'Doherty, J. P., Dayan, P., Friston, K., Critchley, H. & Dolan, R. J. Temporal difference models and reward-related learning in the human brain. *Neuron* **38**, 329–337 (2003).

37. Badre, D. & Frank, M. J. Mechanisms of hierarchical reinforcement learning in cortico-striatal circuits 2: evidence from fMRI. *Cereb. Cortex* **22**, 527–536 (2012).
38. Daw, N. D., Gershman, S. J., Seymour, B., Dayan, P. & Dolan, R. J. Model-based influences on humans' choices and striatal prediction errors. *Neuron* **69**, 1204–1215 (2011).
39. LaRocque, K. F. *et al.* Global similarity and pattern separation in the human medial temporal lobe predict subsequent memory. *J. Neurosci.* **33**, 5466–5474 (2013).
40. Raichle, M. E. The brain's default mode network. *Annu. Rev. Neurosci.* **38**, 433–447 (2015).
41. Shulman, G. L. *et al.* Common blood flow changes across visual tasks: II. decreases in cerebral cortex. *J. Cogn. Neurosci.* **9**, 648–663 (1997).
42. Greicius, M. D., Krasnow, B., Reiss, A. L. & Menon, V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc. Natl Acad. Sci. USA* **100**, 253–258 (2003).
43. Vincent, J. L. *et al.* Intrinsic functional architecture in the anaesthetized monkey brain. *Nature* **447**, 83–86 (2007).
44. Becerra, L., Pendse, G., Chang, P.-C., Bishop, J. & Borsook, D. Robust reproducible resting state networks in the awake rodent brain. *PLoS ONE* **6**, e25701 (2011).
45. Buckner, R. L. *et al.* Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J. Neurosci.* **25**, 7709–7717 (2005).
- This paper presents a multimodal analysis implicating the default mode network in cognitive decline associated with Alzheimer's disease.**
46. Smith, S. M. *et al.* Correspondence of the brain's functional architecture during activation and rest. *Proc. Natl Acad. Sci. USA* **106**, 13040–13045 (2009).
- This paper demonstrates that resting state networks are systematically associated with cognitive functions.**
47. Laumann, T. O. *et al.* Functional system and areal organization of a highly-sampled individual human brain. *Neuron* **87**, 657–670 (2015).
48. Murphy, K., Birn, R. M. & Bandettini, P. A. Resting-state fMRI confounds and cleanup. *Neuroimage* **80**, 349–359 (2013).
49. Power, J. D., Schlaggar, B. L. & Petersen, S. E. Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage* **105**, 536–551 (2015).
50. Tagliazucchi, E. & Laufs, H. Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. *Neuron* **82**, 695–708 (2014).
51. Morcom, A. M. & Fletcher, P. C. Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage* **37**, 1073–1082 (2007).
52. Nestler, E. J. & Hyman, S. E. Animal models of neuropsychiatric disorders. *Nature Neurosci.* **13**, 1161–1169 (2010).
53. Insel, T. R. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am. J. Psychiatry* **171**, 395–397 (2014).
54. Mayberg, H. S. Targeted electrode-based modulation of neural circuits for depression. *J. Clin. Invest.* **119**, 717–725 (2009).
55. Sulzer, J. *et al.* Real-time fMRI neurofeedback: progress and challenges. *Neuroimage* **76**, 386–399 (2013).
56. Goodkind, M. *et al.* Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* **72**, 305–315 (2015).
- This paper examines a large structural imaging dataset and finds that brain abnormalities linked to mental illness are shared across diagnostic categories.**
57. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427 (2014).
58. Sperling, R. A., Karlawish, J. & Johnson, K. A. Preclinical Alzheimer disease—the challenges ahead. *Nature Rev. Neurol.* **9**, 54–58 (2013).
59. Owen, A. M. Detecting consciousness: a unique role for neuroimaging. *Annu. Rev. Psychol.* **64**, 109–133 (2013).
60. Ariely, D. & Berns, G. S. Neuroimaging: the hope and hype of neuroimaging in business. *Nature Rev. Neurosci.* **11**, 284–292 (2010).
61. Berns, G. S. & Moore, S. A neural predictor of cultural popularity. *J. Consum. Psychol.* **22**, 154–160 (2012).
62. Falk, E. B., Berkman, E. T. & Lieberman, M. D. From neural responses to population behavior: neural focus group predicts population-level media effects. *Psychol. Sci.* **23**, 439–445 (2012).
63. Gabrieli, J. D. E., Ghosh, S. S. & Whitfield-Gabrieli, S. Prediction as a humanitarian and pragmatic contribution from human cognitive neuroscience. *Neuron* **85**, 11–26 (2015).
64. Morse, S. J. Brain overclaim syndrome and criminal responsibility: A diagnostic note. *Ohio State J. Criminal Law* **3**, 397–412 (2006).
65. Jones, O. D., Wagner, A. D., Faigman, D. L. & Raichle, M. E. Neuroscientists in court. *Nature Rev. Neurosci.* **14**, 730–736 (2013).
66. Farah, M. J., Hutchinson, J. B., Phelps, E. A. & Wagner, A. D. Functional MRI-based lie detection: scientific and societal challenges. *Nature Rev. Neurosci.* **15**, 123–131 (2014).
67. Reardon, S. Neuroscience in court: the painful truth. *Nature* **518**, 474–476 (2015).
68. Underwood, E. DARPA aims to rebuild brains. *Science* **342**, 1029–1030 (2013).
69. Gerits, A. *et al.* Optogenetically induced behavioral and functional network changes in primates. *Curr. Biol.* **22**, 1722–1726 (2012).
70. Insel, T. R., Landis, S. C. & Collins, F. S. The NIH Brain Initiative. *Science* **340**, 687–688 (2013).
71. Moeller, S. *et al.* Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. *Magn. Reson. Med.* **63**, 1144–1153 (2010).
72. Yacoub, E., Harel, N. & Ugurbil, K. High-field fMRI unveils orientation columns in humans. *Proc. Natl Acad. Sci. USA* **105**, 10607–10612 (2008).
73. Magnain, C. *et al.* Optical coherence tomography visualizes neurons in human entorhinal cortex. *Neurophotonics* **2**, 015004 (2015).
- A demonstration of the power of optical coherence tomography to image neural structure in ex vivo human brain tissue.**
74. Hawrylycz, M. J. *et al.* An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* **489**, 391–399 (2012).
75. Richiardi, J. *et al.* Correlated gene expression supports synchronous activity in brain networks. *Science* **348**, 1241–1244 (2015).
76. Van Essen, D. C. *et al.* The WU-Minn Human Connectome Project: an overview. *Neuroimage* **80**, 62–79 (2013).
- This paper presents a broad overview of the Human Connectome Project.**
77. Saygin, Z. M. *et al.* Tracking the roots of reading ability: white matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *J. Neurosci.* **33**, 13251–13258 (2013).
78. Van Essen, D. C. *et al.* *Mapping Connections in Humans and Non-human Primates: Aspirations and Challenges for Diffusion Imaging 2nd edn*, Ch. 16 (Elsevier, 2013).
79. Evely, C. *et al.* Superficial white matter fiber systems impede detection of long-range cortical connections in diffusion MR tractography. *Proc. Natl Acad. Sci. USA* **112**, E2820–E2828 (2015).
80. Smith, S. M. *et al.* Network modelling methods for fMRI. *Neuroimage* **54**, 875–891 (2011).
81. Honey, C. J. *et al.* Predicting human resting-state functional connectivity from structural connectivity. *Proc. Natl Acad. Sci. USA* **106**, 2035–2040 (2009).
82. Shen, K. *et al.* Information processing architecture of functionally defined clusters in the macaque cortex. *J. Neurosci.* **32**, 17465–17476 (2012).
83. Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C. & Wager, T. D. Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods* **8**, 665–670 (2011).
84. Ioannidis, J. P. A. Why most published research findings are false: author's reply to Goodman and Greenland. *PLoS Med.* **4**, e215 (2007).
85. Button, K. S. *et al.* Power failure: why small sample size undermines the reliability of neuroscience. *Nature Rev. Neurosci.* **14**, 365–376 (2013).
86. Carp, J. On the plurality of (methodological) worlds: estimating the analytic flexibility of fMRI experiments. *Frontiers Neurosci.* **6**, 149 (2012).
87. Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S. F. & Baker, C. I. Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neurosci.* **12**, 535–540 (2009).
88. Stein, J. L. *et al.* Identification of common variants associated with human hippocampal and intracranial volumes. *Nature Genet.* **44**, 552–561 (2012).
- This paper presents the first well-powered genome-wide association study of brain structure.**
89. Waskom, M. L., Kumaran, D., Gordon, A. M., Rissman, J. & Wagner, A. D. Frontoparietal representations of task context support the flexible control of goal-directed cognition. *J. Neurosci.* **34**, 10743–10755 (2014).
90. Irimia, A., Chambers, M. C., Torgerson, C. M. & Van Horn, J. D. Circular representation of human cortical networks for subject and population-level connectomic visualization. *Neuroimage* **60**, 1340–1351 (2012).
91. Blokland, G. A. M. *et al.* Heritability of working memory brain activation. *J. Neurosci.* **31**, 10882–10890 (2011).
92. Glahn, D. C. *et al.* Genetic control over the resting brain. *Proc. Natl Acad. Sci. USA* **107**, 1223–1228 (2010).
93. Barnett, J. H., Scoriels, L. & Munafo, M. R. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biol. Psychiatry* **64**, 137–144 (2008).
94. Nickl-Jocksch, T., Janouschek, H., Eickhoff, S. B. & Eickhoff, C. R. Lack of meta-analytic evidence for an impact of COMT Val158Met genotype on brain activation during working memory tasks. *Biol. Psychiatry*, (2015).
95. Farah, M. J. Neuroethics: the ethical, legal, and societal impact of neuroscience. *Annu. Rev. Psychol.* **63**, 571–591 (2012).
96. Illes, J. & Racine, E. Imaging or imagining? A neuroethics challenge informed by genetics. *Am. J. Bioeth.* **5**, 5–18 (2005).
97. Farah, M. J. & Gillihan, S. J. The puzzle of neuroimaging and psychiatric diagnosis: technology and nosology in an evolving discipline. *AJOB Neurosci.* **3**, 31–41 (2012).
98. Conrad, P. *The Medicalization of Society: On the Transformation of Human Conditions into Treatable Disorders* (Johns Hopkins Univ. Press, 2007).
99. Sahakian, B. & Morein-Zamir, S. Professor's little helper. *Nature* **450**, 1157–1159 (2007).
100. Fitz, N. S. & Reiner, P. B. The challenge of crafting policy for do-it-yourself brain stimulation. *J. Med. Ethics* **41**, 410–412 (2015).
101. Horvath, J. C., Forte, J. D. & Carter, O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). *Brain Stimul.* **8**, 535–550 (2015).

**Acknowledgements** Thanks to I. Eisenberg, D. Glahn, R. Raizada, and M. Shine for comments on an earlier draft of this manuscript, and N. Logothetis for helpful discussions.

**Author Contributions** R.P. and M.F. planned and wrote the paper.

**Author Information** Reprints and permissions information is available at [www.nature.com/reprints](http://www.nature.com/reprints). The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to R.P. ([poldrack@stanford.edu](mailto:poldrack@stanford.edu)).

# Author Queries

Journal: **Nature**

Paper: **nature15692**

Title: **Progress and challenges in probing the human brain**

Query Reference	Query
1	AUTHOR: A PDF proof will be produced on the basis of your corrections to this preproof and will contain the main-text figures edited by us and the Extended Data items supplied by you (which may have been resized but will not have been edited otherwise by us).
2	When you receive the PDF proof, please check that the display items are as follows (doi:10.1038/nature15692): Figs 0 (black & white); 1–3 (colour); Tables: 1; Boxes: 2; Extended Data display items: 0.
3	Please check the edits to all main-text figures (and tables, if any) very carefully, and ensure that any error bars in the figures are defined in the figure legends. If you wish to revise the Extended Data items for consistency with main-text figures and tables, please copy the style shown in the PDF proof (such as italicising variables and gene symbols, and using initial capitals for labels) and return the revised Extended Data items to us along with your proof corrections.
4	<ul style="list-style-type: none"> <li>A single sentence summarizing your paper (websum), which will appear online on the table of contents and in e-alerts, has been provided below. Please check this sentence for accuracy and appropriate emphasis.</li> </ul>
5	Author: first sentence revised slightly. OK?
6	<del>Author: this reference is not cited in the text, please cite or remove</del>
Web summary	This Review evaluates current techniques used to investigate human brain function, discusses the successes and limitations of these techniques to test hypotheses about causal mechanisms, and looks to future directions and implementation of these techniques in real-world problems.



## For Nature office use only:

Layout	<input type="checkbox"/>	Figures/Tables/Boxes	<input type="checkbox"/>	References	<input type="checkbox"/>
DOI	<input type="checkbox"/>	Error bars	<input type="checkbox"/>	Supp info	<input type="checkbox"/>
Title	<input type="checkbox"/>	Colour	<input type="checkbox"/>	Acknowledgements	<input type="checkbox"/>
Authors	<input type="checkbox"/>	Text	<input type="checkbox"/>	Author contribs	<input type="checkbox"/>
Addresses	<input type="checkbox"/>	Methods	<input type="checkbox"/>	COI	<input type="checkbox"/>
First para	<input type="checkbox"/>	Received/Accepted	<input type="checkbox"/>	Correspondence	<input type="checkbox"/>
		AOP	<input type="checkbox"/>	Author corr	<input type="checkbox"/>
		Extended Data	<input type="checkbox"/>	Web summary	<input type="checkbox"/>
				Accession codes link	<input type="checkbox"/>