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Future trends in Neuroimaging: Neural processes as expressed within real-life contexts

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Abstract

Human neuroscience research has changed dramatically with the proliferation and refinement of functional magnetic resonance imaging (fMRI) technologies. The early years of the technique were largely devoted to methods development and validation, and to the coarse-grained mapping of functional topographies. This paper will cover three emerging trends that we believe will be central to fMRI research in the coming decade. In the first section of this paper, we argue in favor of a shift from fine-grained functional labeling toward the characterization of underlying neural processes. In the second section, we examine three methodological developments that have improved our ability to characterize underlying neural processes using fMRI. In the last section, we highlight the trend towards more ecologically valid fMRI experiments, which engage neural circuits in real life conditions. We note that many of our cognitive faculties emerge from interpersonal interactions, and that a complete understanding of the cognitive processes within a single individual's brain cannot be achieved without understanding the interactions among individuals. Looking forward to the future of human fMRI, we conclude that the major constraint on new discoveries will not be related to the spatiotemporal resolution of the BOLD signal, which is constantly improving, but rather to the precision of our hypotheses and the creativity of our methods for testing them.

Keywords

natural stimuli; social neuroscience; functional labeling; inter-subject correlation

Introduction

Functional magnetic resonance imaging (fMRI) has revolutionized the field of human neuroscience. It opened a new window into the human brain by allowing researchers to non-invasively measure activity with an unprecedented combination of spatial coverage and spatiotemporal resolution while subjects perform a rich variety of cognitive tasks. The steady supralinear growth of fMRI papers from 1994 to the present (Figure 1) is one measure of how this versatile technique has contributed to our substantive knowledge about the brain. Many of the most influential discoveries in the field are reviewed in this special issue, “20 Years of fMRI NeuroImage.”

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In this paper, we review the state of the field, and propose that now is the time to defer debates about the functional labeling of different regions, and to devote our resources to characterizing underlying neural processes. We highlight a range of new methods that enable fMRI researchers to characterize neural processes. Finally, we challenge researchers to increase the ecological validity of fMRI studies by studying human cognition within natural contexts, and we highlight the importance of the mechanisms by which two (or more) brains interact.

Mapping the territory—Beginning in the early 1990s, fMRI provided researchers with a new and powerful tool to explore unknown cortical territories. The surge in mapping cognitive functions in different cortical and subcortical regions was comparable to the “Age of Exploration” during the 16th century, when many explorers toured and charted the world, establishing direct contacts with Africa, the Americas, and Asia. Neuroscientists' explorations have produced a wealth of new discoveries. One very productive line of research, for example, is the mapping of retinotopic areas in the visual system, which has revealed many new retinotopic areas (Arcaro et al., 2009; Engel et al., 1997a; Larsson and Heeger, 2006; Sereno et al., 1995; Silver and Kastner, 2009; Wandell et al., 2007). A similar line of research led to a more refined mapping of the tonotopic belt areas that surround the primary auditory cortex (Bilecen et al., 1998; Engelien et al., 2002; Formisano et al., 2003). Many papers have also mapped the functional responses associated with cognitive functions, including visual perception (Grill-Spector et al., 1998b; Heeger, 1999; Kourtzi and Kanwisher, 2000), language (Poeppel and Hickok, 2004; Salmelin and Kujala, 2006), attention (Corbetta and Shulman, 2002), working memory (Rajah and D'Esposito, 2005), and theory of mind (Saxe et al., 2004; Siegal and Varley, 2002).

The wealth of discoveries was accompanied by a tendency to assign functional labels to different brain areas based on the category of stimuli that produced the largest changes in aggregate activity. Perhaps the most well-known functionally-labeled areas are high-level visual areas such as the fusiform face area, or FFA (Kanwisher et al., 1997), the parahippocampal place area, or PPA (Epstein and Kanwisher, 1998), and the extrastriate body area, or EBA (Downing et al., 2006; Downing et al., 2001).

The utility and validity of assigning functional labels to brain areas has long been debated, with views on each side of the issue reflecting different perspectives on the general functional architecture of the brain. Some argues for strong modularity, whereby different functions are compartmentalized within small, well-defined brain areas e.g. (Kanwisher, 2010; Pitcher et al., 2009). Others argue for a distributed architecture in which each brain area can be involved in several different functions, e.g. (Haxby et al., 2001; McIntosh, 2004). Functional localization may ultimately be found to apply much better to some brain regions than to others. The only way, however, to conclusively resolve this debate is by characterizing the underlying neural processes performed in each area. We therefore propose that the debate on functional localization can be deferred, and that the greatest progress can be made by studying underlying neural processes (for similar arguments see (Donaldson, 2004; Poldrack, 2010). To clarify what we mean by this, we detail below the types of scientific questions whose answers inform us about neural processes, and we describe neuroimaging methods that can answer those types of questions.

To characterize the neural processes is to provide a detailed description of (i) the range of available response properties of neurons in local circuits and (ii) the circuit wiring that gives rise to those response properties. Thus, questions that help characterize the underlying neural processes include the following:

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1) What is the ***range of response properties*** of neurons in the circuit? For example, within the visual system, one can ask what are the spatial receptive field sizes of neurons within a given area (Dumoulin and Wandell, 2008) and how they are modulated by context (Kourtzi et al., 2003; Li et al., 2006)? Do neurons in a given brain area respond to local features or to global configuration (Andrews et al., 2010; Thompson et al., 2005), how sharp and selective are their response tuning curves (Engel et al., 1997b; Grill-Spector et al., 1998a; Piazza et al., 2004) and how does attention change their tuning curves (Spitzer et al., 1988)? In which coordinate systems can spatial information be represented in each brain region (Golomb and Kanwisher, 2011; Pertzov et al., 2011)?

2) How are such response properties **implemented within a *neural circuit***? For example, is shunting inhibition used as a means to normalize neuronal responses in visual cortex (Heeger, 1992; Reynolds and Heeger, 2009)? Which aspects of local wiring within the retina enable the computation of object-specific motion while suppressing global image motion due to head movement (Baccus et al., 2008)? Which aspects of global wiring enable path integration and, more generally, spatial cognition (Doeller et al., 2010)? Do spatial groupings of functional properties within an area correspond to patches of anatomical connectivity (Bosking et al., 1997)?

Characterizing the range of response properties and their relation to a neural circuit can provide us with a more nuanced understanding of a brain region's functional roles. First, characterizing the neural processes can better define the functional properties of an area. For example, some response properties that are implemented in a local network (e.g. holistic representation) may be necessary for the execution of multiple functions (e.g. face processing and reading). Second, the same network may support more than a single process. For example, even if 80% of the neurons within a given area (e.g. the FFA) are recruited for a particular function (e.g. face detection or face recognition), it may still be the case that 20% of the neurons in this area are recruited for a different process (e.g. object recognition).

The practice of assigning functional labels to brain areas is very fruitful if it serves as a starting point for generating hypotheses as to the neural processes in an area. On the other hand, if the scientific community hastily adopts a functional label as a fact, rather than as a hypothesis, this may misdirect or hinder future studies in that area. For example, the name of the premotor cortical region known as the frontal eye field (FEF) contributed to the widespread belief that the FEF is a low-level motor area specialized for the initiation of saccades (Bruce et al., 1985). Recent studies, however, indicate that the FEF may also be involved in other processes such as spatial attention (Moore and Fallah, 2001) and spatial working memory (Curtis, 2006), and that its local processes require integration of information over long time scales (Hasson et al., 2008b). Thus, we must take care that existing functional labels (e.g. the FEF) do not prevent scientists from testing and publishing ideas that are difficult to reconcile with that label. Moreover, we note that the danger of premature functional labeling is not specific to contiguous brain regions; equal care must be taken in labeling spatially distributed sites that compose a (putative) functional network.

An interim approach may be to employ anatomical labels for reference purposes until one has convincingly characterized the underlying neural processes within a region or network of regions. Regardless of the preferred style of scientific investigation, we suggest that debates about functional labeling of a region be deferred for the present, in favor of discussions about local circuit architecture and the range of neural processes that each region may subserve.

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New perspectives require new designs and analytic methods

Using fMRI to characterize neural processes—The challenge of understanding brain function at the level of neural processes can guide and motivate future studies. But can fMRI be used to characterize neural processes? This question is pointed, in light of the spatiotemporal limitations of the blood-oxygenation-level-dependent (BOLD) signal. The spatial resolution of fMRI is typically around 1–3mm; therefore the BOLD signal sums responses across millions of neurons. The 1–3 second temporal resolution of fMRI is also low relative to the milliseconds-long temporal resolution of the underlying neural responses. Nevertheless, if used properly, fMRI can aid us enormously in characterizing particular aspects of the underlying processes within a neural circuit.

The more we learn about the origin of the BOLD signal, the more confident we become about its validity and usefulness. Recent studies have revealed that, in most cases, the BOLD signal correlates with modulations of the broadband high-frequency (65–150 Hz) power of local field potentials (LFP) (Hermes et al., 2011; Logothetis et al., 2001). Moreover, it has been shown that the BOLD signal and the power of high-frequency LFPs are usually correlated with the mean local firing rate in a region (Manning et al., 2009; Mukamel et al., 2005; Nir et al., 2007), establishing a link between the BOLD signal and the local average firing rate. These findings indicate that the BOLD signal can, in most circumstances, be treated as a low-pass-filtered version of the instantaneous population firing rate. Despite the blurring and delay induced by convolution with the hemodynamic response function (HRF), isolated and transient changes in the overall firing rate can still be detected using fMRI, and in many cases this enables us to characterize aspects of the underlying processes that are shared across all neurons within a voxel. For example, with the use of innovative analysis methods, such as fMRI adaptation, researchers can extract information about the characteristics of the underlying neural representations at sub-voxel resolution (Dinstein et al., 2007; Grill-Spector and Malach, 2001; Montaser-Kouhsari et al., 2007). Moreover, while techniques such as two-photon microscopy and optical imaging provide superior spatial resolutions to fMRI, they also have much narrower fields of view. Thus fMRI provides a bird's-eye view of neural circuits that is not available with other methods.

Improving sensitivity of fMRI to spatial patterns—The characterization of underlying processes requires more sophisticated experimental designs and analytic methods with improved sensitivity to spatial and temporal patterning of the BOLD signal. One new analysis method that is already changing the way we analyze imaging data is multivariate pattern analysis (MVPA). The insight behind MVPA is that examining voxels in isolation ignores the information contained in the spatial patterning of neural signals (Norman et al., 2006). MVPA methods have increased sensitivity relative to individual-voxel-based methods, which tend to average responses across voxels and ignore fine-grained spatial patterns that may convey information. Although the MVPA results must be interpreted with care (Freeman et al, 2011), the increased sensitivity of these methods can be valuable for characterizing underlying functional properties of neurons in an area (Haynes and Rees, 2005; Kamitani and Tong, 2005; Miyawaki et al., 2008) as well as large scale organization principles (Freeman et al., 2011; Haxby et al., 2001). In addition, the method can be used to characterize the underlying neural processes over time. For example, researchers used MVPA to demonstrate that early visual areas can retain specific information about visual features in working memory for many seconds after the physical stimulus was removed (Harrison and Tong, 2009). Similarly, MVPA methods were used to show that higher-order visual areas reinstate evoked activation patterns during retrieval of information in a free recall task (Polyn et al., 2005). Both studies reveal working memory-related processes in visual areas, and thereby helping to characterize the underlying response properties of these areas.

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Improving the sensitivity of fMRI to temporal patterns—The practice of averaging the BOLD signal across short time-windows triggered at event boundaries has many of the same drawbacks as averaging over regions of space. The two central assumptions of event-related designs are (i) that the brain processes events in isolation and (ii) that these independent processing events are characterized by a short, stereotyped burst of activity. In addition, given the relatively low signal-to-noise ratio associated with the BOLD response to any single event (e.g. a sentence), the responses are usually averaged across many instances of the same event category (“sentences”). However, these assumptions may not be valid for natural temporally extended sequence of events. First, the responses to a class of natural stimuli (e.g. “sentences”) may not have a canonical response profile which is shared across members of the class. Second, in some cases it may not be possible to define a prototypical response profile, even for an individual stimulus, because the neural response to each stimulus depends on temporal context (e.g. prior sentences). In such cases, the response timecourse to a concatenated series of natural stimuli (e.g. sentences) may be reliable and stimulus-specific, even while the average response across stimuli (e.g. average sentence response) will be effectively flat. Thus, there are some aspects of neural processing which may be invisible to event-related averaging, but which can be detected by examining temporal response profiles and by not averaging across individual stimuli.

One method of detecting reliable response patterns over extended time scales is the inter-subject correlation (inter-SC) analysis. This analysis assesses response reliability of a given brain region by quantifying the similarity of the response time courses across different subjects who are engaging with the same stimulus (e.g. a movie or audiobook) (Hasson et al., 2009; Hasson et al., 2004). The inter-SC method differs from conventional fMRI data analysis methods in that it circumvents the need to specify a model for the neural processes in any given brain region. Instead, the inter-SC method uses the subject's brain responses to naturalistic stimuli as a model to predict brain responses within other subjects who perform the same task. The inter-SC analysis is also a time-varying analysis that compares the temporal response patterns across subjects. This contrasts with conventional trigger averaging methods, which compare changes in the peak signal amplitude relative to a pre-determined baseline while averaging out meaningful temporal variations in the signal.

Combining methods is necessary for studying processes that span spatiotemporal scales—Combining fMRI with other neuroimaging techniques can improve our understanding of neural processes. Each technique has strengths and limitations, and thus to characterize neural processes within or across areas it is essential to harvest information from multiple methods and thus multiple spatiotemporal scales. A few research centers now have the capacity to record single-unit electrophysiological data in monkeys and rats while the animals are being scanned in an fMRI scanner (Logothetis et al., 2001; Maier et al., 2008). Similarly, it is now possible to simultaneously combine EEG recording and TMS with fMRI scanning (Mullinger and Bowtell, 2011; Ruff et al., 2008; Ruff et al., 2006; Sajda, 2009; Zanto et al., 2011). Magnetic resonance imaging (MRI) and positron emission tomography (PET) systems have recently been combined in a single scanner (Judenhofer et al., 2008). Animal researchers have started to combine fMRI imaging with optogenetics methods, and one of their objectives is to more precisely characterize the relationship between local firing rate and the BOLD signal (Lee et al., 2010; Logothetis, 2010; Palmer, 2010). The existence of grid-like cells in human entorhinal cortex was recently demonstrated via a combination of elegant experimental design, convergent electrophysiological evidence, and the non-invasive spatiotemporal resolution of BOLD (Doeller et al., 2010). This study provides another example of how fMRI, when used to its potential, can reveal fine-grained functional properties of neural circuits.

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New perspectives facilitate new questions

The shift from functional labeling to the investigation of underlying neural processes widens the scope of investigations that fMRI researchers can pursue. Descriptions in terms of neural processes are often more general, and thus identify commonalities across networks of regions with different functional specializations. For example, the spatial receptive field (SRF) sizes of neurons in area V3A are similar to the SRFs sizes in area V4, while the functional properties of these areas are distinct. The SRF size of an area constrains the set of computations that this area can perform. Similarly, we have proposed that neurons accumulate information not only across space but also over time (Hasson et al., 2008b; Lerner et al., 2011). We defined the ***temporal receptive window*** **(*TRW*)** of a neuron as the length of time prior to a response during which sensory information may affect that response. We found that, as with SRFs, the topographical organization of the TRWs is distributed and hierarchical. TRW organization is *distributed* in the sense that each brain area has the capacity to accumulate information over time. The processing is *hierarchical* because the capacity of each TRW increases from early sensory areas to higher-order perceptual and cognitive areas. Early sensory cortices such as the primary auditory or visual cortex have relatively short TRWs (up to hundreds of milliseconds), while the TRWs in higher-order areas can accumulate information over minutes.

Mapping the time scale of processing within each brain area revealed an organizing principle for large-scale topography, reflected in an orderly and gradual change in the time scale of processing along the cortical surface. This topographic organization scheme is independent of the functional selectivity of the particular area. That is, two different areas with apparently different response profiles (e.g. areas involved in processing music or speech) can have similar processing time scales even though they process different types of information (Rogalsky et al., 2011). Although the temporal receptive window of an area will not determine its functional roles, it does constrain its potential roles. For example, areas with short TRW (e.g. 20–150 msec) may be most sensitive to transient input such as an individual phoneme. However, a longer TRW (150–1000 msec) is necessary to combine single phonemes into whole words, and a much longer TRW (1–12 seconds or longer) is necessary to integrate word-level information with sentence-level information.

More human, more natural, more social

Studying specifically human faculties—In the coming decade we will see more studies focused on the neural processes that distinguish humans from other species on the planet. Neuroimaging methods are ideal for this purpose, because they enable us to noninvasively study the human brain.

Conducting experiments with human subjects has practical advantages. First and foremost, the scope of processes that can be studied is far wider in humans than in animal models. Many processes – such as verbal and nonverbal communication, tool use, decision-making, and complex social interaction – reach unparalleled complexity in humans. Second, training animals to perform even simple tasks is highly challenging, while human subjects learn complicated tasks quickly and can follow complex verbal instructions. Finally, human subjects can report their mental states, allowing researchers to study the neural correlates of phenomena such as emotion and awareness. Because of these advantages some studies that would be impossible with non-human animals are relatively simple to conduct with human subjects.

Indeed, in recent years, new studies have emerged on the neuroscience of human behaviors for which we lack good animal models. These include the fields of neurolinguistics (Joanette et al., 2008; Poeppel et al., 2008), music perception (Hannon and Trainor, 2007; Janata et

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al., 2002; Levitin and Tirovolas, 2009), storytelling and narrative processes (Lerner et al., 2011; Mar, 2011), neuroaesthetics (Cela-Conde et al., 2011; Chatterjee, 2011; Cinzia and Vittorio, 2009), the perception of art (Ishizu and Zeki, 2011) and film (Hasson et al., 2008a), human social interaction (Adolphs, 2009; Ochsner and Lieberman, 2001; Stephens et al., 2010; Zaki and Ochsner, 2009) and the perception of self (Goldberg et al., 2006; Jenkins et al., 2008).

At the same time as we study these more particularly human behaviors, we encourage the mutually beneficial interaction between studies of human and non-human animals. For example, animal studies have used experimental designs borrowed from human imaging studies to map responses in the macaque brain to the same set of stimuli (Arcaro et al., 2011; Orban et al., 2006; Peeters et al., 2009). Inter-species homologies and differences have also been studied using fMRI, for example in the domain of face processing (Ku et al., 2011; Tsao et al., 2008). In addition, the localization of face-selective responses in the macaque brain using fMRI has been used to guide the implantation of single unit electrodes in the animal brain; electrophysiological measurements then assessed the functional properties of neurons within each area to validate the fMRI findings (Freiwald and Tsao, 2010; Tsao, 2006). Thus, after twenty years of neuroimaging research we are entering a period where, on the one hand, complex and particularly human faculties are being directly studied, and on the other hand, information shared across animal and human disciplines is facilitating research in each subfield.

Real life cognition—Another important trend in neuroimaging research is the shift from studying cognitive functions in isolation within controlled laboratory environments to studying the same functions within the context of more natural settings. There is an inherent tension in any scientific investigation between the generality and tractability of research questions. On the one hand, scientists strive to explain how we process information and interact with the environment in natural contexts. The complexity of such situations, however, can hinder our attempts to isolate and manipulate independent variables. Therefore, it is customary to create simplified experimental setups in which the experimenter strips the environment of most of its dimensions, fixes or controls the remaining independent variables, and observes the changes in few dependent variables. While this practice has served us well – as evidenced by the knowledge accumulated over the years – it also has some weakness. First, the ecological validity of any finding discovered within a controlled laboratory setup is not clear until tested in real-life contexts. In many cases, however, adding real-life parameters changes the results and forces us to redefine our concepts. On the other hand, the multidimensionality and lack of experimental control that is sometimes associated with natural stimuli can make it harder to isolate the intervening parameters. Thus, a cooperative approach is necessary, specifically one in which “reductionists” start to gradually modify their experimental setups in an attempt to test the generalizability of their findings, while those concerned with ecologically valid are careful to generate hypotheses that can be tested in controlled settings.

Second, moving into real life situations brings new experimental questions to the table, which are ignored or forgotten within the confines of controlled experimental settings. One example, already discussed above, is the time scale of processing. Although most real-life events (e.g. listening to a lecture, watching a movie, or engaging in a conversation) unfold over many minutes, there is surprisingly little research on the neural processes that underlie the brain's capacity to accumulate information over these long time scales. For the purposes of experimental control, many laboratory experiments reduce the temporal complexity of their visual or auditory stimuli, presenting stimuli for 1000 milliseconds or less. Yet in order to sense and act in real-life circumstances, the brain gathers information over both long and short time scales. In light of the limitations of traditional paradigms described above,

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neuroscientists increasingly study brain responses to natural, real-life events (Felsen and Dan, 2005; Hasson et al., 2009; Kayser et al., 2004; Reinagel, 2001; Simoncelli, 2003; Spiers and Maguire, 2007), while developing complementary paradigms to study the neural activity that drives human behavior under realistic conditions.

Two-brain neuroscience—A very recent trend is the conceptual shift from a single-brain perspective towards a multi-brain, social perspective on primate cognition and behavior (Dumas, 2011; Hari and Kujala, 2009; Hasson et al., 2012). Cognitive neuroscience experiments typically isolate human or animal subjects from their natural environment by placing them in a quiet sealed room where interactions occur with a computer screen. There is no place here for modeling the influence of one brain on the responses of another. In everyday life, however, we spend most of our time interacting with other individuals. These interactions are crucial for shaping our minds. Indeed, many of our cognitive faculties (e.g. conversing, doing calculus, reading, playing musical instruments, or using tools) were learned through interactions with other individuals. Moreover, human societies function by distributing knowledge and allocating tasks across different group members. Institutions such as financial markets, political systems, and educational systems evolve through the interaction of many individuals over many generations. Such distribution of knowledge makes the system robust and stable. With so many of our cognitive faculties emerging from interpersonal space, a complete understanding of the cognitive processes within a single individual's brain cannot be achieved without examining and understanding the interactions among individuals (Hari and Kujala, 2009; Hasson et al., 2012). Indeed, recent studies have started to examine the neural interaction across two brains engaged in a game of charades (Schippers et al., 2010), or transmitting and reading facial expressions (Anders et al., 2011), or producing and comprehending natural speech (Stephens et al., 2010). The shift to the multi-brain frame will bring new insights about the processes occurring within the borders of individuals' brains and may shed light on the mechanisms by which our brains interact in social contexts (Hasson et al., 2012; Stephens et al., 2010).

Conclusion

Neuroimaging studies were initially regarded with suspicion by those in other fields of neuroscience. After twenty years of intensive research, these reservations have been replaced by a more balanced understanding of the advantages and limitations of fMRI relative to other techniques. Many researchers now agree that progress will be made only by integrating knowledge across different levels of analysis and across disparate disciplines. Moreover, as the field of neuroimaging matures, our goals have evolved from the initial mapping of brain functions to an attempt to understand more deeply the underlying computations that subserve these functions. We are also more aware that a comprehensive understanding of the brain must situate its function within the context of a whole organism in its habitat. Given that our natural environment is composed of a network of interconnected brains, studying the ways in which brains couple together will enable us to usefully re-conceive the functions of the individual brain. We look forward to the future of neuroimaging, which promises to be increasingly creative and interdisciplinary in its approach, increasingly mechanistic in its explanations, and more relevant than ever before to the understanding of complex human behaviors.

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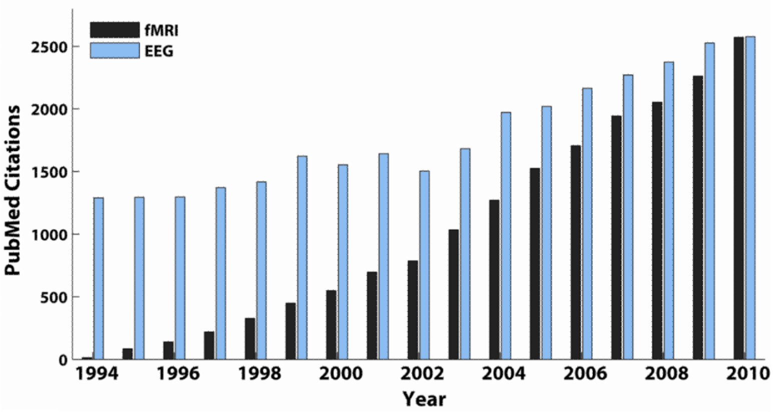

Figure 1.

Estimates of fMRI and EEG literature growth, 1994–2010. Bar height indicates the number of PubMed search results for the term “fMRI” (black bars) or “EEG” (blue bars) appearing in the title or abstract of papers published in each calendar year.