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Functional Magnetic Resonance Imaging: The Hemodynamic Inverse Problem

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Abstract

Neuronal activity demands glucose and oxygen supplies, which are delivered by circulating blood. Averaged neuronal activity can predict temporally prolonged hemodynamic responses as described by linear transform models. Inferences in the opposite direction, though, from hemodynamic responses to neuronal activity, are made in the case of functional magnetic resonance imaging (fMRI). The validity of these inferences is under debate and constitutes the "hemodynamic inverse problem". The present review briefly describes the properties of the fMRI technique and continues to present experimental evidence supporting the view that the underlying neuronal activity can be successfully captured in the fMRI signal in a roughly linear way and in a timescale down to a few hundred milliseconds.

Keywords: fMRI, hemodynamic inverse problem, BOLD response, brain imaging

Over the past two decades the field of cognitive neuroscience has experienced an explosive growth. New imaging techniques have been introduced and researchers have been given an unprecedented opportunity to examine the neurobiological correlates of human cognition and behaviour –positron emission tomography, magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), transcranial magnetic stimulation, and more. However, perhaps none of these methods

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has done more to excite cognitive neuroscientists as the development of functional MRI (fMRI). Functional MRI combines the high spatial resolution and anatomic imaging capabilities of conventional MRI with dynamic imaging, allowing the spatially accurate mapping of human brain function to the underlying anatomy.

Functional MRI measures changes in blood oxygenation and blood volume that result from neural activity and its subsequent energy demands (Ogawa et al., 1990,

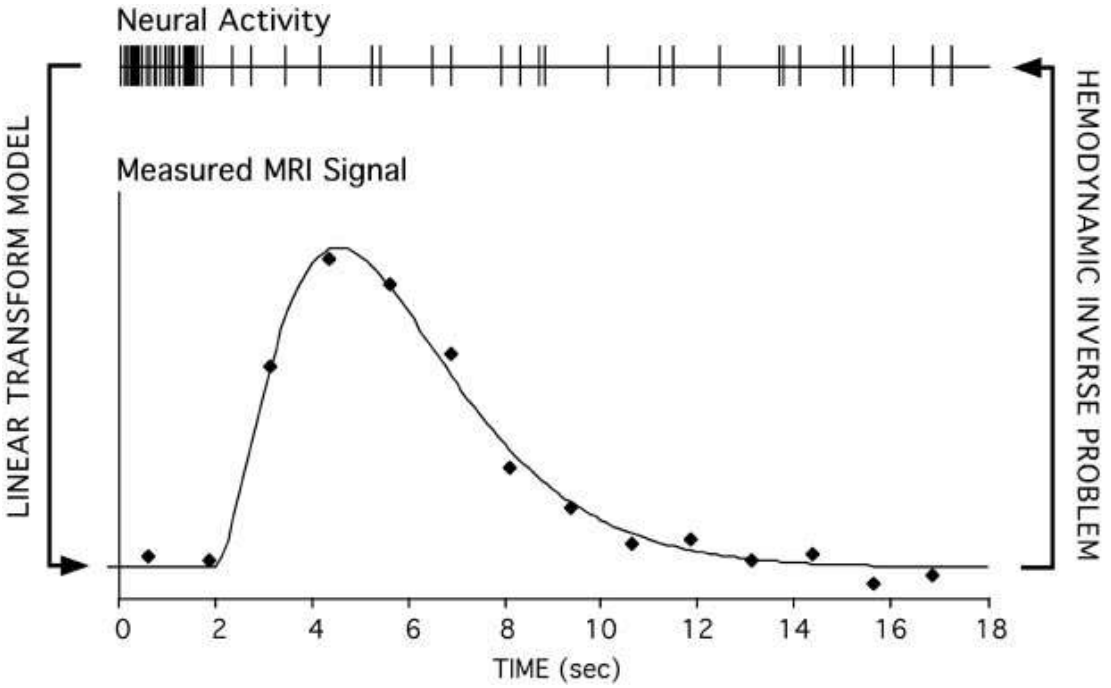

Fig. 1. A schematic illustrating the linear transform model that specifies the relation between averaged neural activity and the temporally prolonged hemodynamic response measured by fMRI. The inverse transformation presents the hemodynamic inverse problem. From "The Hemodynamic Inverse Problem: Making Inferences about Neural Activity from Measured MRI Signals", by R.L. Buckner, 2003, *Proceedings of the National Academy of Sciences, 100*(5), p. 2178. Copyright 2003 by National Academy of Sciences, U.S.A. Reprinted with permission.

1992; Bandettini et al., 1992; Blamire et al., 1992; Kwong et al., 1992; Logothetis et al., 2001). Yet, that very principle of the fMRI technique has been questioned for its validity and has set the stage for the formulation of the "hemodynamic inverse

problem". "The hemodynamic inverse problem refers to the challenge of making valid and precise estimates of the underlying neural activity from the measured hemodynamic response" (Buckner, 2003, p. 2177) (see Fig.1). Thus, while linear transformation models specify the relation between averaged neural activity and the temporally prolonged hemodynamic response measured by fMRI, inferences in the opposite direction, from the measured hemodynamic responses to the underlying neuronal activity, might not lead to accurate estimations.

The blood-oxygen-level-dependent (BOLD) signal

As its name implies, fMRI is a technique based on MRI. The latter provides images of the distribution of hydrogen atoms in tissue water. The technique relies on the use of magnetic fields to distort the behaviour of atoms, and the information gained on how long the atoms take to recover from this distortion is used to create an anatomical image of the brain (see Brown & Semelka, 2011, for an overview of the basic principles and applications of MRI).

An opening for MRI in the area of functional brain imaging emerged when it was discovered by Fox and colleagues (Fox & Raiche, 1986; Fox, Raiche, Mintum, & Dence, 1988) that during changes in neural activity there are local changes in the amount of oxygen in the tissue. As neurons become active, they increase their use of oxygen causing a temporary dip in the amount of oxygen in the blood. At the same time, the neurons signal the blood vessels to dilate to increase blood flow. The resulting increase in cerebral blood flow (CBF) brings more oxygen to the area than the neurons can actually use and thus produces a relative increase in local oxygen. Thus, the amount of oxyhemoglobin (hemoglobin that contains bound O_2) is higher than the amount of deoxyhemoglobin (hemoglobin without bound O_2), whereas before the neural activation

they were about equal. By combination of this observation with a much earlier observation made by Pauling and Coryell (1946), that changing the amount of oxygen carried by hemoglobin changes the degree to which hemoglobin disturbs a magnetic field, Ogawa et al. (1990) were able to demonstrate that in vivo changes of blood oxygenation could be detected by MRI, introducing fMRI. The fMRI method is therefore based on the blood-oxygen-level-dependent (BOLD) signal (see Buxton, 2009, for a comprehensive introduction on the principles and techniques of fMRI). Of note, fMRI scanners can be tuned to acquire images that measure different phenomena, such as the diffusion process of molecules, mainly water, in biological tissues, but the principal acquisition mode used nowadays to study cognitive events is the BOLD signal.

The hemodynamic inverse problem: linear transformation

The neural basis of cognitive events, which is what is typically explored in experiments using fMRI, is inferred by measuring the correlation between the BOLD signal and a stimulus. Properties of the relation between the neural activity and the hemodynamic response are still being explored, such as whether the hemodynamic response reflects averaged neural spiking, synaptic events, the metabolic interactions between neurons and astrocytes, or a combination thereof (e.g., Magistretti & Pellerin, 1999; Lauritzen, 2001; Logothetis et al., 2001; Logothetis, 2003; Attwell et al., 2010; Bélanger, Allaman, & Magistretti, 2011; Sheeringa et al., 2011; Magri et al., 2012). Interrelated factors further include the type of neural activity involved, the cell groups generating this activity, the link between this activity and energy demands, and the processes ultimately coupling the energy demand to the supply of energy to the brain (Logothetis, 2003). Whichever the relation, the critical point remains the same: the BOLD signal is an indirect measure of neural activity. This brings us back to the

question in debate: can we make valid inferences about neural activity from the measured hemodynamic response? A number of studies using a variety of different techniques have tackled the question of how well the fMRI response relates to neural activity.

Boynton et al. (1996), in their seminal work, explored the hypothesis that fMRI responses are proportional to the local neural activity, averaged over a small region of the brain and averaged over a period of time. Three empirical tests on the temporal averaging of neural activity provided support to the hypothesis. First, fMRI responses in the human primary visual cortex (V1) were found to depend separably on stimulus timing and stimulus contrast. Second, responses to shorter stimuli were found to predict responses to long-duration stimuli, and third, the noise in the fMRI data was found to be independent of stimulus contrast and temporal period. Thus, a linear transform model was suggested, according to which neural activity is a nonlinear function of the contrast of a (visual) stimulus, while the fMRI response is a linear transform of the neural activity of V1 averaged over time. Even though noise might be introduced at each stage of the process, the effects of these individual noises on the fMRI response can be summarized by a single noise source. Observations made by DeYoe et al. (1994), Savoy et al. (1995), and Tootell et al. (1995) are also consistent with the linear transform model. With regards to the spatial averaging of neural activity in V1, Engel, Glover, and Wandell (1997) presented findings showing that the spatial precision of the fMRI signal is consistent with a line spread function with a full width at half maximum amplitude of 3.5 mm. Of note, since the vasculature is specialized in different brain areas (Zheng, LaMantia, & Purves, 1991), these models might not account for areas other than the V1.

A number of studies have combined fMRI measurements with measurements taken by means of other brain imaging techniques, such as EEG (e.g., Bonmassar et al.,

1999; Krakow et al., 2000; Musso et al., 2011; Kirino et al., 2013), MEG (e.g., Robitaille et al., 2010), or optical imaging recording of intrinsic signals (e.g., Hess et al., 2000). However, these comparisons suffer from important methodological problems; EEG is a measure of electrical activity in the brain that originates mainly from action potentials (Niedermeyer & da Silva, 2005), while MEG measures magnetic fields produced by this electrical activity (Hämäläinen et al., 1993). Both techniques have poor spatial resolution and a rather imprecise localization of the electromagnetic field patterns associated with neural current flow. Optical recordings, on the other hand, rely on the measurement of hemodynamic responses themselves (Bonhoeffer & Grinvald, 1996), thus not offering an opportunity for validation (Logothetis et al., 2001).

Rees, Friston, and Koch (2000) tried to couple BOLD signal modulation directly with spiking activity. They compared human fMRI responses with electrophysiological data from single cell recordings in monkeys previously made by Britten et al. (1993). The monkey data were collected from the middle temporal visual area (MT or V5), known to be specialized for visual motion processing. The human measurements were localized in human MT complex, a motion-responsive cortical region that is held to be homologous with monkey MT along with adjacent motion-sensitive areas. On the basis of the analysis of this set of data, Rees et al. (2000) concluded that the BOLD signal is directly proportional to the average neural firing rate, with a 1% increase in BOLD signal representing an average of nine additional spikes per second.

However, successfully coupling the BOLD signal with spiking activity has not always been the case. Mathiesen et al. (1998), for example, took direct measurements of CBF and extracellular recordings of single unit activity and local field potentials (LFP) in the rat cerebellar cortex. They modulated the spiking activity from Purkinje cells,

which are the principal cerebellar cortex output neurons, at the same time they measured CBF. They used the laser Doppler flow technique for neural stimulation, which causes monosynaptic excitation of the Purkinje cells and a disynaptic inhibition of the same neurons. Stimulation of the monosynaptic system evoked long-lasting complex spikes and extracellular field potentials. Stimulation of the disynaptic system inhibited spiking activity, while the postsynaptic activity increased as indicated by the simultaneously recorded LFPs. Mathiesen et al. (1998) were able to demonstrate that suppression of the Purkinje cell spikes was further accompanied by an increase in CBF, that is an increase in blood flow at the same time that spiking activity ceased. They, therefore, concluded that increases in CBF responds to all synaptic excitation, even if it is the case that the excitation acts through inhibitory neurons to reduce the net number of action potentials on Purkinje cells. In a subsequent paper, Mathiesen, Caesar, and Lauritzen (2000) further demonstrated temporal coupling between the hemodynamic response and the monosynaptic excitation system, but not the disynaptic system, where coupling was clearly observed only at low stimulation frequencies. Thus, it could be the case that the spiking activity of the main output neurons, the pyramidal cells, is not the main determinant of the BOLD signal.

Logothetis et al. (2001), in another influential study, simultaneously measured intracortical electrophysiological and fMRI data in anaesthetized macaque visual cortex. Their experiments were designed to investigate which component of the microelectrode signal – single-, multi-unit spiking activity, or LFPs – best predicts the BOLD response. Local FPs relate to spiking activity, but also to subthershold integrative processes in areas such as dendrites that cannot be captured otherwise, and multi-unit activity represents the weighted sum of spiking activity. Logothetis et al. (2001) demonstrated that LFPs were the only signal that significantly correlated with the hemodynamic

response at recording sites characterized by transient responses. Importantly, findings showed that a spatially localized increase in the BOLD contrast directly and monotonically reflects an increase in neural activity. This correlation between firing rate and BOLD was also confirmed in studies combining MRI and magnetic resonance spectroscopy in cats conducted by both Hyder, Rothman, and Shulman (2002) and Smith et al. (2002). A number of subsequent studies further report a good correlation between evoked field potentials and hemodynamic response (e.g., Leopold, Murayama, & Logothetis, 2003; Sheth et al., 2004; Mukamel et al., 2005; Franceschini et al., 2008; Ojemann, Ramsey, & Ojemann, 2013). Taken together, the above findings do provide evidence in support of the BOLD signal being representative of the underlying neuronal – spiking or non-spiking – activity in response to a stimulus.

The hemodynamic inverse problem: temporal resolution

The finding that the BOLD signal does indeed reflect the neural responses elicited by a stimulus in a roughly linear way solves only part of the hemodynamic inverse problem. An even greater challenge surrounds the temporal orchestration of information processing: the BOLD signal reflects changes in blood vasculature that accompany neural activity. Yet, these changes are temporally slow, beginning seconds after a neural event and lasting for tens of seconds. Therefore, for isolated cognitive acts, which can often be completed in under a second, the sluggish nature of the measured BOLD response means that the signal is detected after the neural event has subsided. This might leave little room for making judgments about important aspects of the brain function such as the time differences between the activation of different neural substrates of the brain or the determination of which neural substrates are involved in task-related processing and which ones are constants of the task.

In the initial experiments that used fMRI to study cognitive processes, temporal resolution was sacrificed by the use of the block-design paradigm. Block designs involve “on” and “off” periods. The experimental manipulation takes place during “on” periods while the “off” periods resemble the “on” periods in all aspects apart from the experimental manipulation. Essentially, many trials of the same type are presented in immediate succession. The functional activation images obtained on the “on” periods are then subtracted from those acquired during the “off” periods. These periods might be up to minute-long, collecting averaged brain activity. By relying on this time-blocked averaging, these methods do not take advantage of the high temporal resolution fMRI has to offer. Possible reasons for following these methods could have included a historical precedent from positron emission tomography, readily available data analysis strategies, and the power of such paradigms (Buckner, 2003).

A major advance in fMRI’s temporal resolution was the introduction of event-related fMRI, when Buckner et al. (1996) demonstrated that individual measurements in fMRI can be made without a need to perform a block of repeated tasks. In their first experiment whole brain fMRI was used to detect single-trial responses in prefrontal regions within single subjects, whereas in their second experiment higher temporal sampling of a more limited spatial field was used to measure temporal offsets between regions. The activation maps that were produced solely from the single-trial data were comparable to those produced from blocked runs. Their findings allowed them to conclude that single-trial paradigms can be used to exploit the high temporal resolution of fMRI. Such paradigms thus provide experimental flexibility and time-resolved data for individual brain regions on a trial-by-trial basis. The most important implication of this breakthrough work was that fMRI, when using event-related designs, can reliably explore rapidly occurring cognitive functions.

Several other laboratories have also developed methods for analyzing event-related fMRI paradigms, with a review already published by 1998 (Rosen, Buckner, & Dale 1998) and new methods are constantly being developed (e.g., Lindquist & Wager, 2007; Mumford et al., 2012). McCarthy et al. (1997), for example, have explored how infrequent target events are processed by the brain. They presented continuous strings of characters with a target string appearing unpredictably once every 20 or so trials. The results revealed that detection of infrequent target stimuli elicited a small, transient BOLD signal that began 1.5 s after target onset and peaked within 4.5-6 s, in line with the known P300 event-related potential known to be elicited by infrequent target events. Again, this study demonstrated that fMRI can provide a sensitive measure of cognitive processes engendered by brief and unpredictable stimuli on a trial-by-trial basis, a paradigm design that can only be analyzed by using event-related procedures. Unpredictable stimuli are also used in go/no-go paradigms that have been also studied successfully using event-related fMRI designs (e.g., Konishi et al., 1997; Durston et al., 2002; Ahmadi et al., 2013).

Another example of event-related fMRI comes from the field of memory research, where it is crucial to be able to sort trials based on subject response. For example, widely used memory paradigms ask participants to indicate on a trial-by-trial basis whether they remember a stimulus or not by pressing a key or recalling an item. It is clear that in such memory paradigms it is essential to be able to sort trials based on participant response. The extent of the use of event-related fMRI designs in memory research is illustrated by the fact that a number of meta-analyses of findings are to be found (e.g., Spaniol et al., 2009; Murty et al., 2010; Kim, 2011). To report but one example of such work, a recent study by Klaassen et al. (2013) investigated the effect of caffeine on working memory (WM) load-related brain activation. For this study,

participants were scanned in a non-withdrawal state during encoding, maintenance, and retrieval phases of a WM maintenance task, specifically, a parametric version of the letter Sternberg task, with trial string length organized in a fast event-related design and presented in a fixed pseudorandom order. Using this paradigm, researchers were able to show a detrimental effect of caffeine on WM at higher levels of WM load.

In addition to the advert of the event-related design, Menon, Luknowsky, and Gati (1998) developed another technique to analyze fMRI data, named latency-resolved fMRI. Menon et al. (1998) studied mental chronometry, which stands for the temporal analysis of mental events into their hierarchical processing stages, by using rapid fMRI of single trials of two simple tasks. These tasks involved a hemifield checkerboard presentation and a visually cued motor task. Menon et al. (1998) were able to demonstrate that while microvascular response to the onset of neural activity is delayed consistently by several seconds, the relative timing between the onsets of the fMRI responses in different brain areas appears to be preserved. Moreover, they found that fMRI onset latencies correlate well with independently measurable parameters of the task, such as reaction time or stimulus presentation time. Thus, they showed that fMRI onset latencies can be used to study the relative onset of activity in different brain regions during cognitive or perceptual tasks with a temporal accuracy of tens of milliseconds. The technique therefore further allows for the determination of which brain areas are involved in task-related processing and which brain areas are constants of the task.

Bellgowan, Saad, and Bandettini (2003), in another seminal work, reported how voxel-wise characterization of the hemodynamic response with regards to delay and width, in addition to amplitude, enriches the information conveyed by the fMRI signal. Bellgowan et al. (2003) studied single word processing using a lexical decision task,

whereby participants were asked to decide whether letter strings presented to them correspond to words or non-words. The stimuli were further rotated 0°, 60°, and 120° to cause variation in perceptual processes. Results suggested that the BOLD signal tracked the timing of the task variables. For example, delays in the onset of the activation in areas such as the prefrontal cortex and the inferior frontal gurus were proportionate to the rotation of the stimuli. Moreover, word processing resulted in activations that were shorter in duration compared to non-word processing. These findings demonstrate not only that hemodynamic delay and width in addition to amplitude are informative, but also that the estimation of timing differences of a few hundred milliseconds is plausible.

Another route to further improve the temporal ability of fMRI down the millisecond scale involves combining measurements from different brain imaging techniques, predominantly EEG and MEG, with fMRI (Bonmassar et al., 1999; Krakow et al., 2000; Robitaille et al., 2010; Musso et al., 2011; Kirino et al., 2013). These kinds of comparisons are of great interest, since the fMRI signal provides information with good spatial resolution (Buxton, 2009), whereas both EEG and MEG have excellent temporal resolution (Dale, 1999; George et al., 2001). Hence, the combining of fMRI with EEG/MEG provides a noninvasive unified view of human brain activity with high spatial and temporal resolution. Thus, even though – as discussed in the previous section – these comparisons might not appear to be suitable when exploring the question of the neural underpinnings of the BOLD signal, they do present researchers with an excellent tool for pushing the limits of fMRI's temporal resolution.

A fine example of this approach has been demonstrated by Ogawa et al. (2000), who conducted fMRI in human participants and fMRI as well as intra- and extra-cranial EEG recordings from the somatosensory cortex in rats. For the human participants, Ogawa et al. (2000) used a preparatory task and a sampling task to probe the response

characteristics of somatosensory and visual systems. In rats forepaw electrical stimulation was applied. Responses measured by EEG and fMRI were found to be reasonably well correlated for brief stimuli. This finding suggests that by controlling the temporal relation of input tasks, it is possible to study temporal evolution of certain neural events at the time scale of their evoked electrical activity by noninvasive fMRI methodology. In other words, the fMRI signal can be used to extract information about neuronal events down at the time scale of tens of milliseconds. Overall, the above-described advances in fMRI design and analysis illustrate the great strides neuroscientists have made in challenging the problem of the sluggishness of the BOLD response compared to the rapid neural events that underlie cognition, allowing fMRI to be used both for the spatial and for the temporal orchestration of cognitive processing in the brain.

Conclusions

Making inferences about the underlying neuronal activity based on the hemodynamic responses that are captured in the BOLD signal by fMRI technology has been the epicenter of a debate – a debate on whether the hemodynamic inverse problem is solvable. The outcome of this debate will determine the validity of all research findings based on the BOLD response and with them the very usefulness of the fMRI technique. A number of studies presented in the present review, using a variety of methodologies, have successfully demonstrated that there is indeed a forward relation between stimulus, neuronal activity, and the hemodynamic response. Thus, the hemodynamic inverse problem appears to be solvable, as the BOLD response does represent, even if in a rough way, neuronal activation in response to experimental stimuli. Furthermore, the BOLD response has been shown to allow for inferences not only about the amplitude of the underlying neuronal activity, but also about the timing

of such activity, at a time scale down to a few hundred milliseconds. The BOLD response might be time-shifted, due to its very nature, but these shifts seem to be proportionate to timing delays in the underlying neuronal activity.

Absolute limitations of the methodology do exist and are due to technical limitations of the imaging devices and to a number of artifacts, such as the pulsation of the human brain that causes temporal blurring. The properties of the hemodynamic signal itself present another limitation; the vascular origin of the signal imposes physiological constraints on temporal and spatial resolution. Moreover, the local vasculature' architecture does confound measurements from different sites across the brain. On the other hand, due to both the drive to ever-higher magnetic field strengths and improvements in radio frequency receiver coil technology, MRI signal-to-noise ratio shows no evidence of plateau. In addition to that, new and more sophisticated data analytic methods offer greater understanding of the data's true sensitivity and specificity and are very likely to continue to improve the researcher's ability to address questions about the underlying mechanisms of brain function. In addition, other techniques, such as EEG or MEG, have and will continue to be used in combination with hemodynamic measures, pushing the limits of the temporal resolution of fMRI. Lastly, animal models that allow single-, multi-unit spiking activity, and LFPs to be measured are likely to contribute to future progress.

The validity of fMRI measurements cannot be showcased more convincingly than by successful attempts at decoding brain activation, that is matching mental content to brain activation (for a review, see LaConte, 2011). Decoding has been demonstrated in the case of simple stimuli (e.g., gratings) or images depicted fixed categories (e.g., faces, houses) with regards to their orientation (Haynes & Rees, 2005· Kamitani & Tong, 2005), position (Thirion et al., 2006), and object category (Cox & Savoy, 2003;

Haxby et al., 2001). The procedure involves measuring the activity in the visual cortex and comparing it with brain activity evoked by those same stimuli or categories in previous scanning sessions. What is more, recently even more complex stimuli, such as novel natural images, have been successfully decoded (e.g., Kay, 2008). Decoding novel images does not rely on the comparison of brain activation with previously recorded activation, but is based on quantitative receptive field models that characterize the relationship between visual stimuli and fMRI activity in early visual areas, making a single measurement suffice. These findings suggest the possibility of decoding pictures of one's visual experience from brain activation measurements alone. Again, evidence is to the direction that fMRI signals contain a considerable amount of stimulus-related information.

In conclusion, the hemodynamic inverse problem seems to be coming to a solution: there are solid experimental results that allow us to believe that we can indeed be making valid and precise estimates of the underlying neural activity from the measured hemodynamic response. These advances in fMRI methodology enable researchers to correlate neuroanatomical markers with cognitive processes and test cognitive neuroscience models of brain function. One of the most exciting challenges of contemporary neuroscience would be to turn this wealth of data into a unified explanation of how this magnificent instrument, our brain, works.

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Λειτουργική απεικόνιση μαγνητικού συντονισμού: Το αντίστροφο πρόβλημα της αιμοδυναμικής

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Περίληψη

Η νευρωνική δραστηριότητα απαιτεί αποθέματα γλυκόζης και οξυγόνου τα οποία μεταφέρονται μέσω του κυκλοφορικού συστήματος. Η μέση νευρωνική δραστηριότητα μπορεί να προβλέψει τη χρονικά παρατεταμένη αιμοδυναμική αντίδραση με βάση γραμμικά μοντέλα μετασχηματισμού. Εκτιμήσεις προς την αντίθετη κατεύθυνση, όμως, από τις αιμοδυναμικές αποκρίσεις στη νευρωνική δραστηριότητα, γίνονται στην περίπτωση των πειραμάτων με τη χρήση λειτουργικής απεικόνισης μαγνητικού συντονισμού (fMRI). Η εγκυρότητα των εκτιμήσεων αυτών είναι υπό συζήτηση και στοιχειοθετούν το «αντίστροφο πρόβλημα της αιμοδυναμικής». Η παρούσα ανασκόπηση περιγράφει εν συντομία τις ιδιότητες της τεχνικής fMRI και στη συνέχεια παρουσιάζει πειραματικά ευρήματα που υποστηρίζουν την άποψη ότι η υποκείμενη νευρωνική δραστηριότητα μπορεί να «συλληφθεί» με επιτυχία από το σήμα fMRI με έναν περίπου γραμμικό τρόπο και με χρονική ανάλυση που πλησιάζει μέχρι και τις μερικές εκατοντάδες χιλιοστών του δευτερολέπτου.

Λέξεις-κλειδιά: λειτουργική απεικόνιση μαγνητικού συντονισμού, αιμοδυναμική αντίδραση, απεικόνιση εγκεφάλου

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