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Functional MRI today

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Abstract

Most brain imaging researchers would agree with the assertion that functional MRI (fMRI) is progressing. Since fMRI began in 1991, the number of people, papers, and abstracts related to fMRI has been increasing; the technology and methodology has shown advances in robustness and sophistication; the physiology of the signal is better understood; and, even though it hasn't yet made significant headway into the clinical setting, applications are widening. Questions that stem from this optimistic and perhaps overly general set of observations include those that ask what the ultimate theoretical and practical limits of fMRI are and how close are we to approaching these limits. In this commentary, I attempt to provide a snapshot of fMRI as it exists at the end of 2005, and to give a clear impression that not only are we progressing by "dotting the i's and crossing the t's" but that fundamental changes in fMRI methodology and processing are being put forth as the field matures.
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1. Numbers

As a field, fMRI continues to grow and is continuously being redefined in subtle ways as the status quo is repeatedly challenged. More people with more novel ideas are invigorating the field. Fundamentally new pulse sequences and processing methods are still being put forth as the numbers of people using the established method also grows. It appears that with regard to fMRI research, there is just as much scientific "low hanging fruit" today as there was in the first few heady years. Regarding numbers, the Organization for Human Brain Mapping meeting, one of the primary international fMRI/neuroimaging meetings, has had a steadily increasing attendance, which now exceeds 2000. Next year is the first year that the meeting will branch into parallel sessions, reflecting not only the size but the inevitable specialization that is occurring. Fig. 1 shows the number of papers published in fMRI. It was obtained by a simple search using Medline on "fMRI" or "Functional MRI" as key words or words in the title or abstract of the paper. The trend, as shown in this figure appears to be tapering a bit from a purely exponential growth, but is at least linear and shows no signs of a plateau.

The main journals publishing fMRI results, and their corresponding fraction of publications relative to the total number of fMRI publications for both this past year, 2005, and for the period of 1992–2005, are shown in Fig. 2. This figure was obtained using the "Scopus" online search engine. On first glance, one point is clear: the journal, NeuroImage, leads the pack by a large margin. It should be noted that this figure is not weighted by impact factor, not that impact factor would significantly change the distribution. Also, on first glance, it does not appear that the distribution in 2005 has deviated much from the overall average distribution of fMRI papers since 1992, but a closer look reveals a hint of some general trends that are further clarified in Fig. 3, which shows the fractional *change* in the relative proportion of fMRI papers published by each journal between 2005 and the average from 1992 to 2005. While there are exceptions, there appear to be increases in the publication fraction of papers from journals which mostly emphasize basic neuroscience or cognitive neuroscience applications of fMRI. The decreases in publication fraction have been in journals mostly emphasizing methodology. While not drawing any premature conclusions from this, I think that this can be seen as an indication that the field is maturing in that the fraction of applications is growing relative to the fraction of methodology advances.

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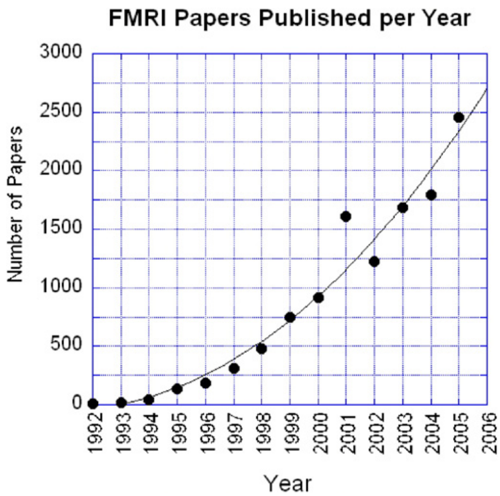

Fig. 1. Number of papers with keyword, title, or abstract containing “fMRI” or “functional MRI” published per year.

This is not at all suggesting that the novelty or significance of the methodological advances are diminishing, but that more of the novel methodologies are directly tied in with significant applications, and therefore less appropriate for methodology journals. More people are actually using the technique to ask interesting questions related to human brain function.

2. The four basic parts of fMRI

It is useful to think of fMRI as being comprised of four interacting, co-evolving parts: hardware, methodology, signal interpretability, and applications. Each drives and feeds off advancements of the others. Hardware includes the primary magnet, shim coils, radiofrequency coils, receivers, and subject interface devices. Methodology includes pulse sequences, post processing, multi-modal integration techniques, and paradigm designs. Signal interpretability includes advancements in understanding the relationship between underlying neuronal activity and BOLD. Applications include not only those directed at understanding brain organization but also towards complementing clinical diagnoses, characterizing neurological and psychiatric disorders, and even towards providing therapy. Other non-medical applications include behavior prediction, lie detection, and brain−computer interfaces.

In this commentary, I will focus on the first three parts and only mention specific applications as they relate to novel hardware, methodology, and interpretation. I realized that agreeing to write this commentary put me in an awkward position in that while I'm to mention what I consider the most interesting advances in the past year or few years, my perspective is perhaps biased towards what papers I pay most attention to—methodological papers. In addition, on average, 6–7 fMRI papers are published a day, and, in a (very) good

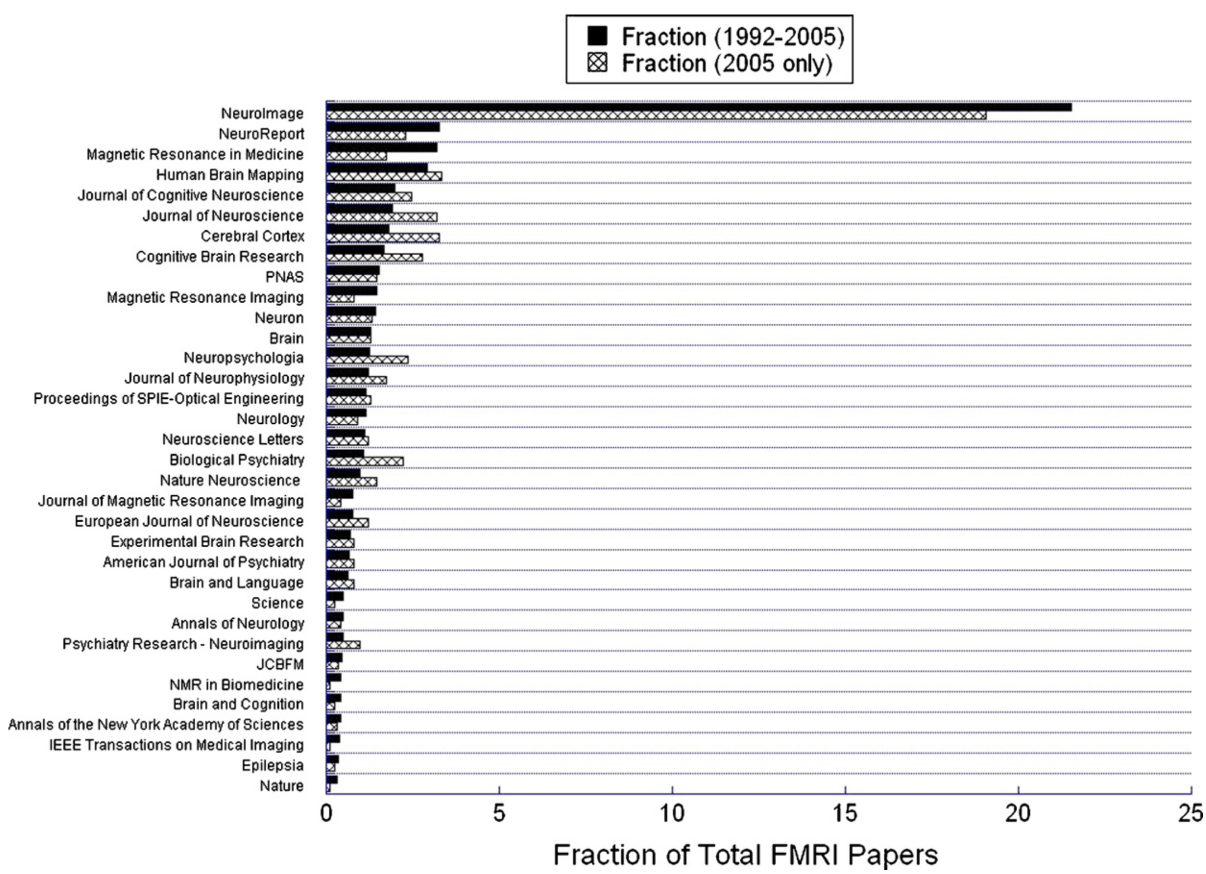

Fig. 2. The fraction of total functional MRI papers published by each journal. Black bars indicate the distribution for the period from 1992 to 2005, and the hatched bars indicate the distribution for only the period during 2005.

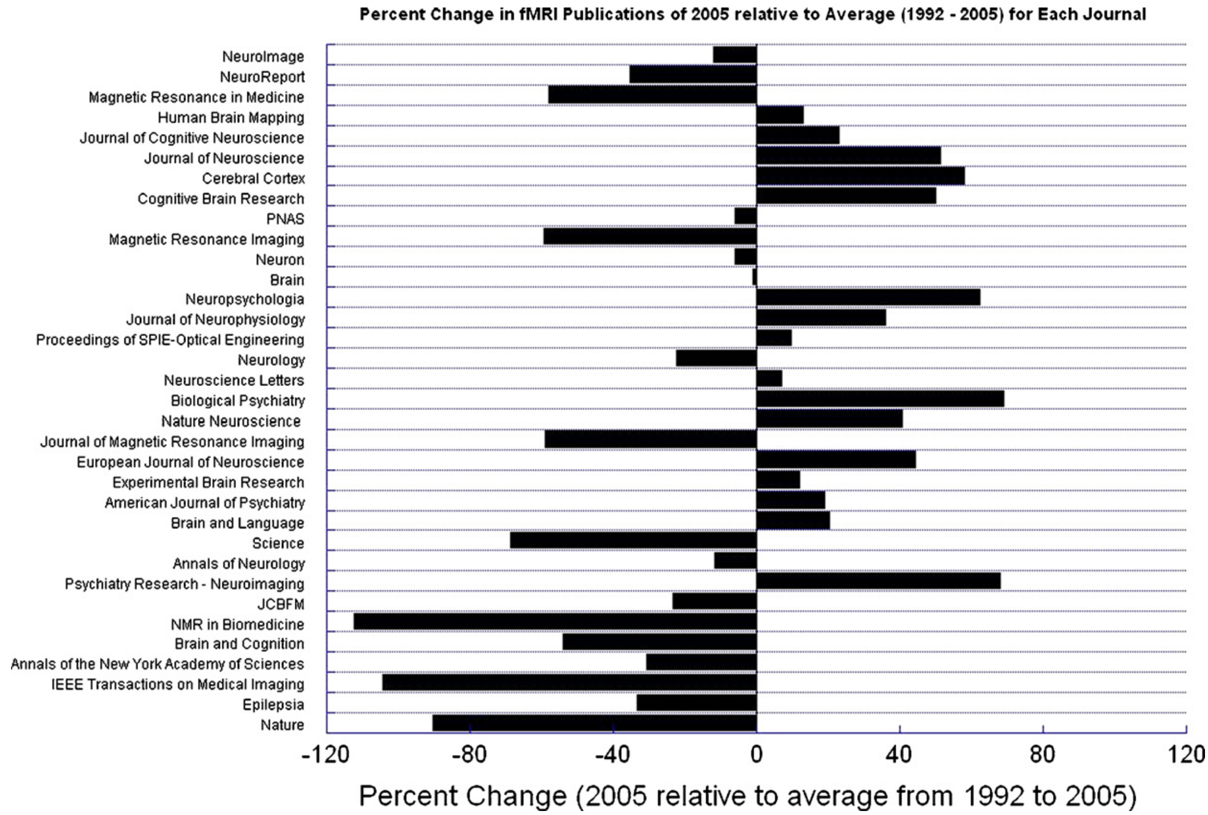

Fig. 3. The difference in the fraction of total Functional MRI papers for each journal between 1992 and 2005 and just 2005. Negative difference indicates a decline for 2005 and positive difference indicates a growth for 2005.

week, I read about 5 papers. Therefore, I'm going to miss a significant amount of new information. Hopefully, I've been in contact with enough people who would alert me to all the most interesting advances. It's of course, impossible in these few pages to provide a comprehensive, in depth, or even balanced view of the latest developments. Therefore, admittedly, this is a biased, oversimplified overview of the highlights of the highlights.

Most of us collect fMRI data as we did 5, 10, or even 15 years ago. It is only a little easier now. The scanner crashes a bit less and there's a bit less "spiking" in the time series data. Today, and since the beginning, images of 64×64 matrix size are typically collected using T2∗-weighted EPI. This is somewhat of a shame since we can do much better, but it's changing. The cutting edge advances, as they become more robust and stable and easy to use (stability and robustness are of course fundamentally important for applications), are steadily making their way into the protocols of the average user. The people developing cutting edge hardware and imaging techniques remain quite busy, as the growing community collectively screams out for more signal, less noise, more information in the signal, higher resolution, higher speed, and more stability.

Let's go into the standard practice a bit more: The standard practice today is to collect T2* weighted EPI data at about 3 mm^3 resolution, with each "volume" consisting of about 30 slices, which takes about 2.5 s to obtain. The typical field strength is 3 Tesla and the typical coil configuration is still a single channel quadrature of coil. Time series of images are collected. These time series are about 5 min in duration. For a study on an individual subject, about 10 time series are collected. The pararadigms are either event-related or blocked design. The data are subsequently analyzed using one of the common platforms such as SPM, AFNI, Brain Voyager, or FSL using linear regression or a variant. The activation maps for each individual are smoothed, transformed into a normalized space and averaged across subjects. At least 12 or so subjects are averaged to make an average activation map, which the researcher then spins a story aboutthe results are typically in agreement with or slightly different than some other set of findings using the same or another imaging technique with a slightly different paradigm or perhaps a behavioral study.

Of course, this approach has been very effective towards furthering the understanding of functional brain organization, and many very clever paradigms and novel conclusions have been developed in this context. At the same time, more people are realizing that this is not necessarily the only or the best, or, for many questions, even a good way to perform fMRI. Improvements in technology, interpretation, and methods all are pushing us out of our standard approaches.

3. Technology

How has technology improved fMRI in recent years? Three advances are worth mentioning: Higher field strength (Yacoub et al., 2001; Norris, 2003; Duong et al., 2002; Di Salle et al., 2004), parallel imaging techniques (Yang et al., 2004; Schmidt et al., 2005; Lin et al., 2005; Preibisch et al., 2003; Golay et al., 2004), and high resolution imaging in general.

3.1. High field strength

Increasing field strength increases (a) signal to noise ratio (SNR), in a linear manner, (b) BOLD contrast in approximately linear or super linear manner, and (c) arterial spin-labeling derived perfusion contrast. The increase in perfusion contrast is achieved because blood longitudinal relaxation (T1) values increase, causing the rf-tagged blood signal to provide signal for a longer period after it has been excited, therefore contributing to the signal.

With regard to BOLD contrast, higher field strength brings with it additional problems. These problems include (a) increased susceptibility-related temporal fluctuations due to breathing and even BOLD fluctuations in the brain, (b) increased signal dropout effects, (c) increased rf power deposition, (d) decreased rf homogeneity, (e) somewhat greater acoustic noise (the torque generated by gradient switching is higher), and (f) increased subtle physiologic effects that are caused by movement near the magnet bore—including peripheral nerve stimulation, seeing phosphenes, vertigo, nausea, metallic taste in the mouth. It is important to note that none of these effects are considered to be lasting or dangerous—just slightly uncomfortable for some people who are sensitive to this.

With standard protocols, like those mentioned above, increasing field strength may not be of significant benefit, since at the spatial resolutions used, the gain in temporal signal to noise is diminished as the magnitude of non-thermal, or rather physiologic, fluctuations increases (Kruger and Glover, 2001). Temporal signal to noise ratio (TSNR) and image signal to noise ratio (SNR) are somewhat proportional at low levels of SNR (about 60 and lower), but at an SNR value of about 100, TSRN plateaus and increases no further because of physiologic noise.

For performing *standard* resolution EPI (3 mm^3 voxel volume), it may turn out that 3 Tesla is optimal since not much more is gained by higher field strengths and much more is potentially lost, as mentioned above, but for *higher* resolution EPI or functional MRI in general, higher field strengths appear to be critical for providing the necessary signal to compensate for the reality that signal to noise ratio (SNR) is directly proportional to voxel volume. The SNR of a voxel volume of 1 mm^3 is 9 times less than that of a voxel volume of 3 mm^3. If the SNR is 100 at the low resolution it will be about 11 at the high resolution. Anything under about 50 is considered not high enough for most fMRI applications which can only acquire images for about an hour per session. Under ideal conditions, a doubling of field strength at least doubles the SNR. More signal is required still… hence the need for improvement with regard to rf coils.

3.2. Parallel imaging

A smaller, localized rf coil also increases SNR over that of a large coil since the SNR is approximately proportional to the coil's sensitive region. To perform whole brain imaging with local rf coils, an array of multiple coils is of course necessary. Localized rf coil arrays and field strengths above 4 Tesla may be critical for imaging with sufficient SNR at sub-millimeter resolution. It is noteworthy that the only studies which have successfully imaged ocular dominance columns as of yet are all at or above 4 Tesla, even though it is possible to image at higher resolution at the lower field strengths. The SNR necessary for imaging at columnar resolution seems only to be achievable at 4 Tesla or above and with the use of local rf coils.

Arrays of rf coils are coming into more common use for fMRI (Bodurka et al., 2004; Beauchamp et al., 2004) and for clinical anatomical imaging. Currently, all three of the main vendors are selling parallel arrays ranging from 4 to 32 channels. Parallel rf coil arrays can serve at least two purposes. The first is to increase SNR by simple addition of each coil signal (Ledden et al., 2001). The second is to use the spatially unique coil sensitivity to aid in spatial encoding (Golay et al., 2004), at some cost in SNR (de Zwart et al., 2002). While arrays of up to 96 channels have been demonstrated, it appears that, for brain geometry, 16–32 channel arrays are optimal (de Zwart et al., 2002). These techniques have allowed higher resolution for single shot EPI and spiral imaging (Weiger et al., 2002).

One further advantage of parallel imaging techniques such as sensitivity encoding (SENSE) is that, if one wants to image at the same resolution as with conventional EPI, the necessary readout window duration, or the time to acquire each image, is significantly reduced. For example, at a typical resolution EPI, the readout window is 25–40 ms. When using multiple rf coils and SENSE reconstruction, the readout window necessary can be reduced to about 5 ms. This decrease in readout window time can translate to more images in a volume per unit time or a shorter TR for a given number of images in a volume. Reduction in TR, assuming noise which is mostly uncorrelated over time, improves temporal signal change detectability (Constable and Spencer, 2001). Reduction of the readout window time can also allow performance of multi-echo EPI, in which several separate images (now able to be spaced closer together in time because of the shorter readout window) are collected at different echo times. Lastly, reduction of the readout window time also reduces off-resonance related distortions in the EPI phase encode direction, thus reducing the distortion of the images.

3.3. High resolution fMRI

Higher resolution fMRI is of course inevitable. As high resolution fMRI comes into more common usage (Beauchamp et al., 2004; Kim and Ogawa, 2002; Ugurbil et al., 1999), several unique imaging, post processing, and data handling challenges and opportunities will be brought to the forefront. The highest robustly fMRI-usable resolution at 3 Tesla is about 1.5 mm^2, and at 7 Tesla is about 1 mm^2. The use of this high resolution has several tradeoffs aside from the lower SNR discussed above. Higher resolution decreases signal dropout yet increases warping due to the generally longer readout window duration. The functional resolution, imposed by the vascular point spread function, has been shown to be between 3 and 1.5 mm^2, and with the development of sequences and other techniques allowing greater vascular specificity, is certain to be reduced somewhat. In addition, processing methods are emerging which are focusing more on information content in the pattern of activation rather than on mapping per se, perhaps altering somewhat how the concept of spatial resolution is considered. For instance, a smoothed and distorted functional map still may contain all the essential information related to the task at hand but may not correspond spatially to the underlying regions of activation.

A major challenge to high resolution fMRI is that this high spatial frequency information is lost in the procedures that involve normalization and averaging of fMRI maps across subjects. Spatial smoothing and transformation to normalized space reduces the effective functional resolution to about 10 mm^3. For fMRI to advance, the use of high resolution imaging needs a robust method for multi-subject averaging. This currently does not exist.

In summary, high field strength buys an increased SNR to perform higher resolution imaging. High resolution can be achieved with single shot EPI using rf coil arrays and parallel imaging techniques. Coil arrays, when not being used for parallel imaging, help further increase SNR, which may be critically necessary for imaging at sub-millimeter resolutions. Functional brain information at sub-millimeter resolution may be unique to that mapped at low resolution, and therefore certainly worth pursuing. High signal to noise achieved with coil arrays and high field strength also allows more close scrutiny of temporal fluctuations that may contain unique and relevant neuronal and physiological information.

4. Interpretation

It is clear from the growing number and range of applications that fMRI users have an established confidence that the fMRI signal changes reliably reflect meaningful underlying neuronal activity. Recent work has established that BOLD signal change and flow changes are more correlated with synaptic activity (local field potentials) than to spiking (Logothetis and Pfeuffer, 2004; Logothetis and Wandell, 2004; Logothetis et al., 2001). Flow and BOLD increases and decreases have been shown to correspond to respective increases and decreases in neuronal activity. It has also been established that the sources of the variability across the brain in fMRI magnitude and dynamics (latency differences) are likely dominated by variations in the vasculature rather than underlying neuronal activity (Muller et al., 2005; Formisano and Goebel, 2003). Nevertheless, modulations in behavioral timing, and therefore neuronal activity timing, as small as 100 ms have been shown to correspond to similar modulations in fMRI signal latency (Bellgowan et al., 2003; Henson et al., 2002) in specific regions. In addition, modulations of the degree of neuronal activity are clearly reflected through changes in the magnitude of the fMRI signal.

The post-undershoot remains controversial. Some groups argue that it is a result of a perseveration of an increased oxidative metabolic rate (keeping blood oxygenation below baseline; Lu et al., 2004a), while other groups believe that it is due to a perseveration of an increased venous blood volume (keeping the amount of deoxyhemoglobin below baseline even though the blood oxygenation or the *fraction* of deoxyhemoglobin in the blood, has returned to normal levels; Buxton et al., 2004).

There is a significant growing interest in “resting state” data and in its relationship to what is known as the “default network” of the brain (Biswal et al., 1995). Since 1995, it has been known that low frequency temporal correlations exist in fMRI data. There is growing evidence that these regions that show correlated low frequency fluctuations are functionally related and not simply due to physiologic phenomenon such as vasomotion. Research to robustly map and establish the source and utility of low frequency correlated fluctuations is rapidly increasing (Wu and Li, 2005; Kiviniemi et al., 2005a; Fransson, 2005; Fox et al., 2005; Kiviniemi et al., 2000, 2004, 2005b; Laufs et al., 2003a,b; Lowe and Sorenson, 1997).

In addition to characterizing ongoing correlated fluctuations, research aimed at characterizing the “default network” has also focused on the network of regions that demonstrate a consistent signal decrease during an array of cognitive tasks (Binder et al., 1999; McKiernan et al., 2002, 2003; Raichle et al., 2001). There is growing evidence that there is spatial overlap between the resting state network demonstrated by low frequency fluctuation correlation and the resting state network demonstrated by observing the signal decreases during a cognitive task (Raichle et al., 2001; Fox et al., 2005).

5. Methods

Methodological advancements fall into the categories of pulse sequences, paradigm designs, and processing methods. In this last section, I discuss some of the more interesting advancements related to these categories.

5.1. Pulse sequences

For the past 15 years, fMRI has been performed using essentially the same basic pulse sequence: T2* weighted EPI. The reason for this is because BOLD contrast provides the highest functional contrast to noise ratio, is the most time efficient, is temporally stable (relative to multi-shot imaging), and provides for whole brain coverage in about 2 s. Arterial spin labeling (ASL) based perfusion imaging, while achieving perhaps greater capillary specificity and long term temporal stability (i.e. minimal signal drift relative to BOLD contrast), remains less useful for typical activation studies due to its lower functional contrast to noise, additional time required (for the tagging pulse), and typically incomplete brain coverage with a single rf pulse “tag.” Nevertheless, for studies involving extremely long duration activation and/or rest periods, ASL based perfusion contrast to noise ratio has been shown to be superior to that of BOLD (Aguirre et al., 2002). In addition, recent studies have even demonstrated that cross-subject variability, as reflected in the quality of group activation maps, is less than that of BOLD contrast, suggesting that perhaps ASL based perfusion maps are better for multi-subject studies. More work needs to be performed in order to confirm this finding.

For over 14 years, perfusion and oxygenation have been noninvasively – and even simultaneously – measurable with fMRI. Recently, a technique called "vascular space occupancy" (VASO) has been put forward as being non-invasively sensitive to blood *volume* changes (Lu et al., 2003, 2004b; Lu and van Zijl, 2005). It involves the application of an inversion pulse, waiting until blood signal passes through the null point, and then applying the imaging pulse. In this manner, blood signal is nulled. An increase in blood volume (more nulled signal) would then increase the signal void in the active voxel, thus reducing the signal. This technique remains to be fully established and verified, but given recent data suggesting that blood volume changes are potentially more localized to brain activation areas than perfusion or blood oxygenation changes, it has potential for greater spatial specificity at a comparable functional contrast to noise ratio as BOLD contrast techniques.

While BOLD contrast remains the functional contrast of choice, the following functional contrasts can currently be detected using MRI in humans: Baseline blood volume (with gadolinium), changes in blood volume (VASO and invasively with gadolinium), baseline and changes in perfusion (ASL), changes in $CMRO_2$ (Davis et al., 1998; Hoge et al., 1999a,b), diffusion coefficient, temperature, and potentially, neuronal current changes (Bandettini et al., 2005), with activation.

5.2. Paradigm design

An interesting development in fMRI is that which involves having the subject either freely performing a task, resting in the scanner doing nothing, or being presented with a natural stimulus (Hasson et al., 2004). In effect, the subject is either performing a task in a spontaneous manner, with simultaneous, time-registered, recording of their behavioral or physiological state using electrophysiological or behavioural measures (Goldman et al., 2002; Patterson et al., 2002; Laufs et al., 2003a,b), or is given a task such as viewing a movie, in which the changes in brain state are dictated by the sequence of events as they occur based on what the subject is looking at during each moment of time. Of course the analysis for these paradigms is not as straightforward as with more standard paradigm designs such as blocked and event-related, but the information is potentially unique and more robustly obtainable, justifying this approach in many situations. This type of approach additionally emphasizes the utility of multi-modal integration. Having at least two objective measures (i.e. either electrophysiological and fMRI or repeated fMRI studies with an identical stimulus timing) and precise temporal registration allows determination of meaningful information (to the extent that it correlates with the physiologic or behavioral measures) from fMRI signal that otherwise appears noise-like.

Another recently developed paradigm design in fMRI of note has been named fMR-adaptation(Grill-Spector and Malach, 2001). This approach relies on the rapid adaptation and recovery properties of specific neuronal pools, and the reflection of these properties in fMRI signal, to characterize and differentiate sub-voxel populations of neurons that are sensitive to subtle differences in stimulus or general paradigm properties. Grill-Spector and Malach (2001) described this methodology well in that the paradigm proceeds in two stages: first, a neuronal population is adapted by repeated presentation of a single stimulus; second, a property of the stimulus is varied and the recovery from adaptation (manifest as an increase in fMRI signal) is assessed. If the signal remains adapted, it indicates that the neurons are invariant to that attribute. However, if the fMRI signal recovers from the adapted state it implies that the neurons are sensitive to the property that was varied.

This clever approach is growing in its applications from low level to higher level and semantic processing. At the same time, there remain several unknowns as to how to properly interpret these signal changes in the presence of variable hemodynamic effects, inhibition and excitation effects on fMRI signal changes, and unknown and likely variable adaptation dynamics as a function of stimulus timing (inter stimulus interval and stimulus duration).

5.3. Processing methods

One of the most exciting directions to recently emerge in fMRI processing is the use of multivariate analysis (Haynes and Rees, 2005b; Formisano et al., 2004; Strother et al., 2004; Cox and Savoy, 2003; Kriegeskorte et al., 2006), machine learning (Davatzikos et al., 2005; Mitchell et al., 2004), and pattern classification techniques. Early work by Haxby et al. (2001) helped pioneer this approach. It was demonstrated in the Haxby et al. study that while spatial maps did not necessarily reveal statistically significant maps that differentiated the brain activation associated with viewing different object categories, the *pattern* of activation within the overlapping active regions corresponded well with each of the categories. In essence, this was somewhat of a breakthrough in brain mapping techniques along two avenues: (a) this was among the first methods which used spatial correlation between two halves of the time series data as a measure of the *information* contained in the activation maps rather than using a univariate measure to map function and then compared statistically, assuming each voxel was independent, the corresponding maps, and (b) this was among the first to turn brain mapping on its ear. Rather than determining the place in the brain that showed activation in correspondence to a stimulus, the activation map or rather the unique voxel-wise pattern of activation was used to provide information as to what the subject was viewing.

Since then, several papers have developed on this theme. One paper went so far as to call the technique "brain reading" (Cox and Savoy, 2003). In 2005, two of the more fascinating fMRI papers of the year were published in Nature Neuroscience (Kamitani and Tong, 2005; Haynes and Rees, 2005a), both delving into the application of machine learning algorithms to characterize and use the unique and spatially distributed information (undetectable using standard univariate approaches) about the type of stimulus a subject was observing, either consciously or unconsciously. It is certain that there will be significant growth, refinement, and applications of this approach to fMRI in the very near future. Lastly, it should be emphasized that this type of approach would benefit significantly from high resolution imaging.

6. Conclusion

Functional MRI is certainly still progressing. It is progressing not only in small increments as more groups try to apply current techniques to novel applications but is also progressing on a fundamental level, as we develop novel methods of collecting, pooling, comparing, and analyzing data. By all measures, the field is extremely healthy and continues to surprise. In this very brief commentary, I have attempted to highlight at least a few of the novel advancements in technology, interpretation, and methodology over the past few years.

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