Simultaneous Multi-Slice Imaging for Resting-State fMRI

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Background

Functional MRI (fMRI) is a primary tool in neuroscience that enables non-invasive detection and characterization of brain activity. fMRI is often described in terms of spatial 'mapping'; importantly, however, fMRI experiments encode information about brain activity in the temporal domain. Echo-planar imaging (EPI) has therefore been crucial to this development by enabling temporal resolution (TR) of several seconds per whole-brain image volume. Nevertheless, the encoding of activity in the temporal domain means that fMRI data quality is fundamentally tied to temporal resolution. It is therefore notable that a typical fMRI experiment with TR = 3 s may encode hundreds of thousands of voxels, but can only achieve 200 time points in 10 minutes. The advent of parallel imaging has enabled reduction of image distortions in EPI; however, unlike many structural MRI techniques, parallel imaging 'acceleration' has little effect on volume scan times in fMRI.

Temporal resolution in fMRI has until recently remained directly proportional to the number of slices (TR = 2-3 s). The explosion of simultaneous multi-slice (SMS, also known as multiband) technology in the past 5 years, described in detail elsewhere in this issue, has now removed the strict coupling between the number of slices and the temporal resolution. The dense temporal sampling enabled by SMS techniques can enormously benefit our ability to identify which voxels are activated by a task or define regions that spontaneously co-activate in resting-state fMRI, provided other aspects of data quality are not unduly compromised.

The source of these gains is somewhat complex, and we therefore go into some detail on this point below.

In this article, we will focus in particular on the benefits SMS has to offer for resting-state fMRI. In resting-state fMRI [1, 3], intrinsic signal fluctuations are used to identify connectivity patterns in the brain under the (now well-established) hypothesis that connected brain regions will co-fluctuate in activity level even in the absence of an experimentally imposed task (Fig. 1). A given neural network would thus be characterized by a common time course of activity that is shared within the network and largely independent of activity outside the network[1]. Many resting-state studies aim to capture the dynamics of a rich set of networks, placing even greater demand on the temporal domain than simple tasks with predefined timings. Moreover, dense temporal sampling has the potential

[1] This simplistic description of independent time courses would only strictly hold if the brain was composed of isolated networks. In practice, the picture is more one of networks that are more and less tightly coupled, representing a hierarchy of connectivity that is reflected in the degree to which time courses are shared.

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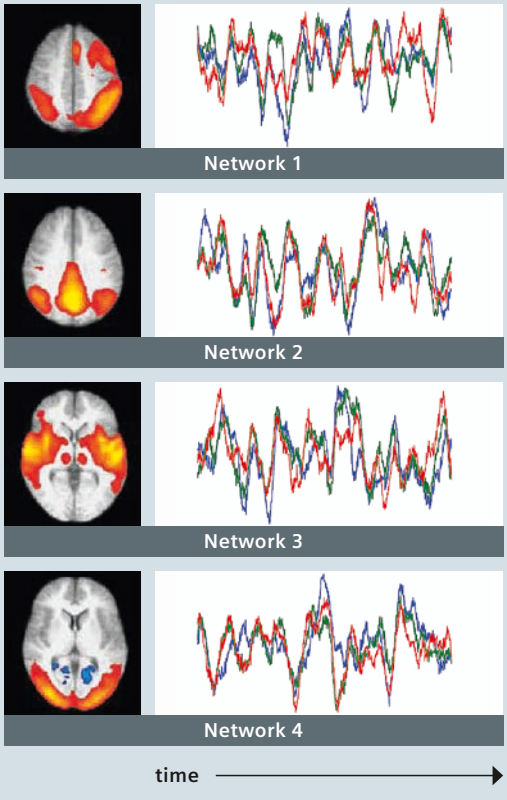


1 Resting-state fMRI identifies patterns of connectivity across the brain based on spontaneous fluctuations of the BOLD signal (in the absence of an experimentally-induced mental or cognitive state). Each map represents the spatial distribution of one brain network, with example voxel time courses depicted in the color plots to the side. Brain networks are inferred by identifying voxels that share a common time course (e.g. are temporally correlated), as simulated here. The centrality of the time domain for identifying networks makes SMS acquisition a powerful technology for resting-state fMRI.

to reveal subtle aspects of these networks, such as transient connectivity. We discuss the role that SMS has to play in achieving these goals.

Benefits of high temporal resolution for resting-state fMRI

Statistical benefits of fast sampling
One fundamental characteristic of fMRI is that the blood oxygenation level-dependent (BOLD) response to neural activity is relatively sluggish, as described by the blurred hemodynamic response function used to model the BOLD response to a task. It may seem at first as if there is little to be gained from sampling a slowly-varying signal faster than is necessary to characterize its basic temporal features. This intuition would seem to be supported if one compares the size of BOLD signal change to the standard deviation of the measurement noise (the contrast-to-noise ratio), for which the density of samples has little effect.

Critically, however, the statistical tests used to identify brain activity as 'above threshold' depend on both the noise level *and* the number of independent measurements. Increasing the number of time points reduces the influence of noise on estimates of BOLD signal change in much the same way that averaging of repeated measurements reduces noise. That is, an increased number of time points drives an improved estimate of the *noise*, even if the *signal* is much smoother than the temporal sampling rate. From this perspective, it is clear that the achievable benefits depend on the specific properties of the noise, which is inextricably linked to signal modeling.

fMRI analysis most typically decomposes the measured data into modeled 'signal' and noise 'residuals' (defined as the component of the measured data that is unexplained by the signal model). A simple regression analysis of task fMRI might fit one regressor time series matching a pre-defined task to each voxel's measured time course. More sophisticated analyses can include multiple regressors to account for independent cognitive processes, as well as artifactual fluctuations such as physiological variations or movement. In all cases, a voxel's residuals would be given by the difference between the complete model fit (including all regressors) and the measured data.

Inclusion of a larger number of regressor time courses by definition reduces the 'noise' residuals; but intuitively, there is a limit to the number of regressors that can be usefully fit. This intuition is partly quantified by the temporal 'degrees of freedom', which is essentially the number of data points available to the regression[2]. SMS can directly increase the degrees of freedom by enabling more time points in a given experimental duration, thereby boosting statistical significance.

This is a key insight into the role of SMS in fMRI: Acquiring more samples per unit time increases degrees of freedom and supports fitting of an increased number of regressors; conversely, experiments with a small number of regressors are intrinsically high degrees-of-freedom and therefore have less to gain from SMS in a statistical sense.

Resting-state fMRI analysis
In task fMRI, the timing of a given cognitive, sensory or motor process is controlled. By comparison, resting-state fMRI analyses must empirically determine the time course of any resting-state network (RSN) of interest. There are broadly two approaches to this problem: 'seed' analyses extract the desired time course based on pre-specified anatomy, whereas data-driven 'multivariate' analyses decompose the data set as a whole into network components based on certain criteria of interest.

Seed analysis is at heart similar to the regression described above for task fMRI. Investigators specify a seed voxel or region that they know to be part of a network of interest, from which a characteristic time series is extracted. This time series is then used in the same way as a task regressor to identify voxels that share this time course, representing brain areas with connectivity to the seed (i.e. RSNs) [3]. This concept can be extended to multiple networks by defining a set of seed regions and extracting the unique time series from each region using multiple regression. For example, in the 'dual regression'[3] approach [5], network maps from a population brain atlas are used to extract subject-specific time courses, which are then used in a multiple regression to define subject-specific spatial maps for each RSN (typically 10s of networks).

Multi-variate analyses, most notably independent component analyses (ICA), are fundamentally different from regression. Rather than analyzing each voxel independently with a seed-derived time series, the entire 4-dimensional data set (3D space x 1D time for one subject) is decomposed simultaneously. This analysis aims to holistically identify RSNs as 'modes' (or 'components') of variation in the 4-dimensional data that are in some sense independent. Each mode represents an RSN and is characterized by a canonical time course and its associated spatial map. Temporal ICA aims to identify components based on temporal independence, which this fits with the characterization of networks based on temporal co-fluctuation; alternatively, spatial ICA require that the modes are spatially independent, i.e. non-overlapping. In practice, the fact that most fMRI protocols achieve several orders of magnitude more samples in space than time means that spatial ICA is far more robust than temporal ICA. For ICA, the number of networks that are identified is set by the investigator, and typically in the range of 10-100.

SMS for resting-state fMRI
As in task fMRI, both seed and multivariate analyses decompose fMRI data into 'signal' (corresponding to RSNs) and noise residuals. Hence, we can apply similar arguments regarding the benefits of SMS for

[2] More precisely, degrees of freedom is the number of independent time points in the model-fitting residuals, reduced by the model complexity (i. e. the number of regressors).
[3] While dual regression is not typically described as a seed-based technique, it is useful and appropriate to characterize it as such for our purposes.

resting-state fMRI based on the degrees of freedom, considering both the complexity of the model (number of RSNs) and the number of independent noise measurements. For example, the most common seed-based analysis includes only a few regressors, and thus has intrinsically high degrees of freedom even without SMS. Seed-based analyses will therefore have little to gain from SMS in many situations, although SMS may be beneficial to seed-based analyses in clinical applications if it can confer reduced scan times.

The potential of SMS is at its greatest when a large number of RSNs are considered, for example in dual regression. As originally defined [5], the first stage of dual regression uses ICA to derive a group-wide atlas of RSN spatial maps, potentially parcellating the entire cerebral cortex. Alternatively, the dual regression approach can utilize a network atlas that is derived from another data set or resource, such as the Human Connectome Project. In either case, the limiting degrees of freedom is at the individual subject level, since it is at this stage that a multiple regression is used to refine each RSN to its subject specific spatial map. The degrees of freedom for this multiple regression is thus determined by the number of time points in each subject's scan and the number of RSNs being studied. In dual regression, the increased degrees of freedom offered by SMS acquisition directly enable consideration of a richer set of networks.

Intrinsically multi-variate analyses like ICA have the potential to decompose fMRI data into hundreds of brain parcels representing a detailed network hierarchy, although more commonly 20-50 RSNs might be identified. The loss of degrees of freedom implied by this relatively large number of components would require a proportionate increase in the number of time points to robustly identify RSNs. Previously, this increase in time points could only be achieved by combining at a group level across a large cohort of subjects (requiring the assumption that brain regions co-align across subjects) or acquiring long time series from a given subject. Increasing the density of temporal sampling using SMS within a more modest experimental duration for a single subject (5-20 minutes) can therefore directly enable a more detailed analysis of a network hierarchy, such as the temporal functional modes [6] and clinical applications described below.

Resting-state fMRI in practice

The gains described above can be leveraged in several ways to improve the quality of resting-state fMRI data. First, for a fixed duration of experiment, the increased degrees of freedom confers statistical benefit, which may be useful for detecting subtle differences between networks or for a more fine-scale differentiation of a given network. Alternatively, one can leverage this statistical advantage to combat the reduced SNR associated with smaller voxels to achieve gains in spatial resolution. Finally, one could reduce scan time in the face of limited subject compliance, with clinical applications in particular having much to gain. This final goal is directly enabled by SMS up to a point; however, resting-state fMRI acquisitions must be long enough to observe brain networks in a broad range of its repertoire of 'states'.

Large-scale population studies

Several neuroimaging initiatives have been launched in recent years that aim to distribute large-scale databases of resting-state fMRI. These resources share the hypothesis that certain insights into brain function and connectivity can only be gained from a large number of subjects. Resources like the 1000 Functional Connectomes Project [7] achieve large numbers by aggregating many smaller existing studies, with the benefit of low additional cost but requiring researchers to account for heterogeneity across study protocols. An alternate approach is to explicitly acquire large cohorts with a single protocol to maximize data homogeneity and quality. We will briefly highlight the role of SMS in two such prospective studies representing different extremes of data acquisition: the Human Connectome Project (HCP) and the UK Biobank Project.

The HCP Consortium is focused on characterizing connectivity in the brain [8], with the WashU-UMinn consortium focusing on healthy adults and acquiring a range of modalities including resting-state fMRI in 1200 subjects [9]. SMS has been a central technology to the HCP from the outset, and a number of technical developments have arisen from this project in addition to the data resource (see articles by Uğurbil and Yacoub in this issue). Within the HCP, the benefits of SMS have been intensely optimized to achieve both high spatial and temporal resolution fMRI (2 mm, TR = 0.72 s), with individual subjects undergoing four 15-minute resting-state scans. Subjects undergo a total of 4 hours of imaging, which additionally includes task fMRI, diffusion imaging and anatomical scans, as well as intense non-imaging phenotyping. Data are acquired on a single scanner (representing a pre-cursor to the MAGNETOM Prisma 3T platform) that was designed specifically for this study. The use of state-of-the-art SMS fMRI has enabled the HCP to achieve exquisite data quality for individual subjects, as well as protocol homogeneity over a relatively large, extensively phenotyped cohort.

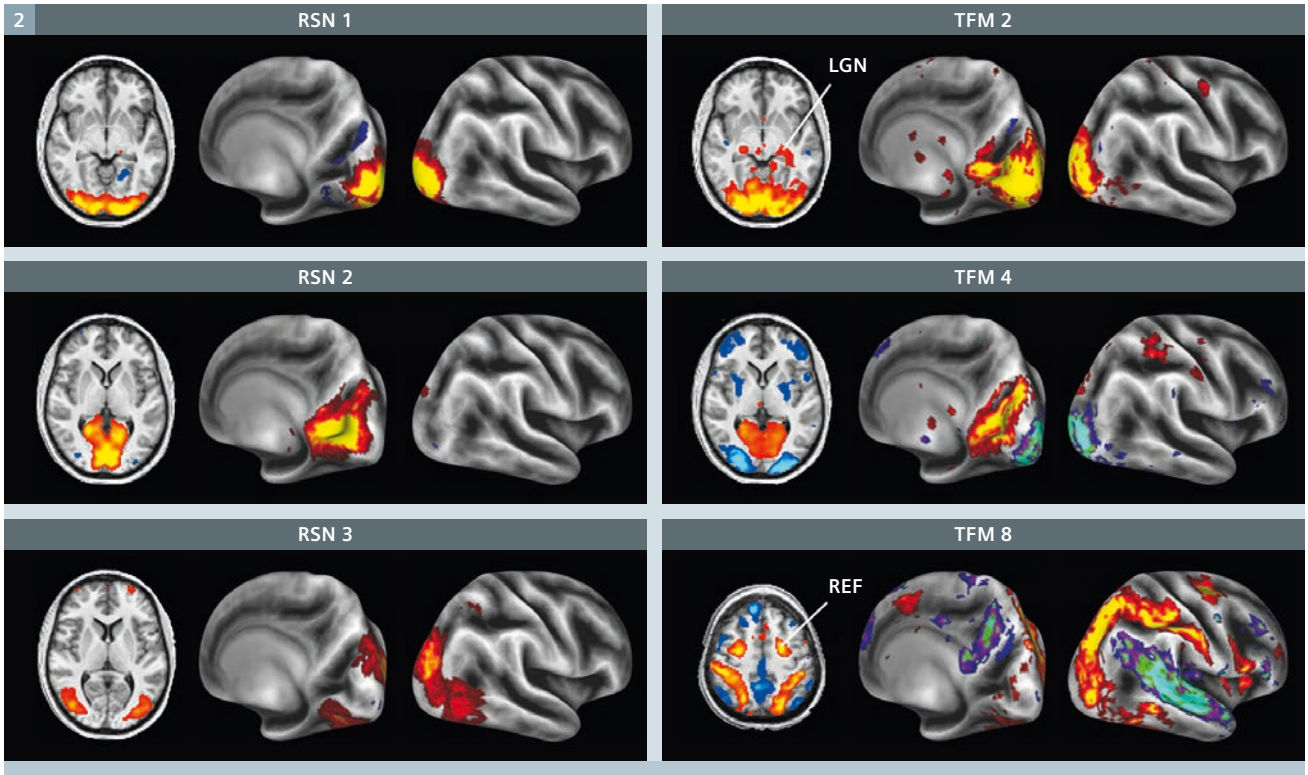
UK Biobank is an established epidemiological cohort of 500,000 subjects aged 45-75 that has undergone (non-imaging) phenotyping, behavioral/lifestyle measures and genotyping, and will be followed for long-term health outcomes via the UK National Health Service. An Imaging Enhancement study is currently in the pilot phase, and ultimately aims to enlist 100,000 of the existing cohort for imaging, including brain, cardiac and body scans. Successfully scanning of this cohort over five years corresponds to extremely high throughput: three dedicated centers running 7 days per week, each accumulating 18 subjects per day. The resulting brain imaging protocol is limited to 35 minutes, during which several imaging modalities are acquired (task and resting-state fMRI, diffusion imaging and multiple anatomical modalities). SMS imaging techniques developed for the HCP [10]

have been critical to achieving this highly-ambitious goal without requiring significant compromise relative to conventional data quality. The resting-state fMRI protocol achieves 2.4 mm resolution with sub-second sampling (TR = 0.73 s) using an SMS acceleration of 8, enabling 500 time points per subject in just 6 minutes.

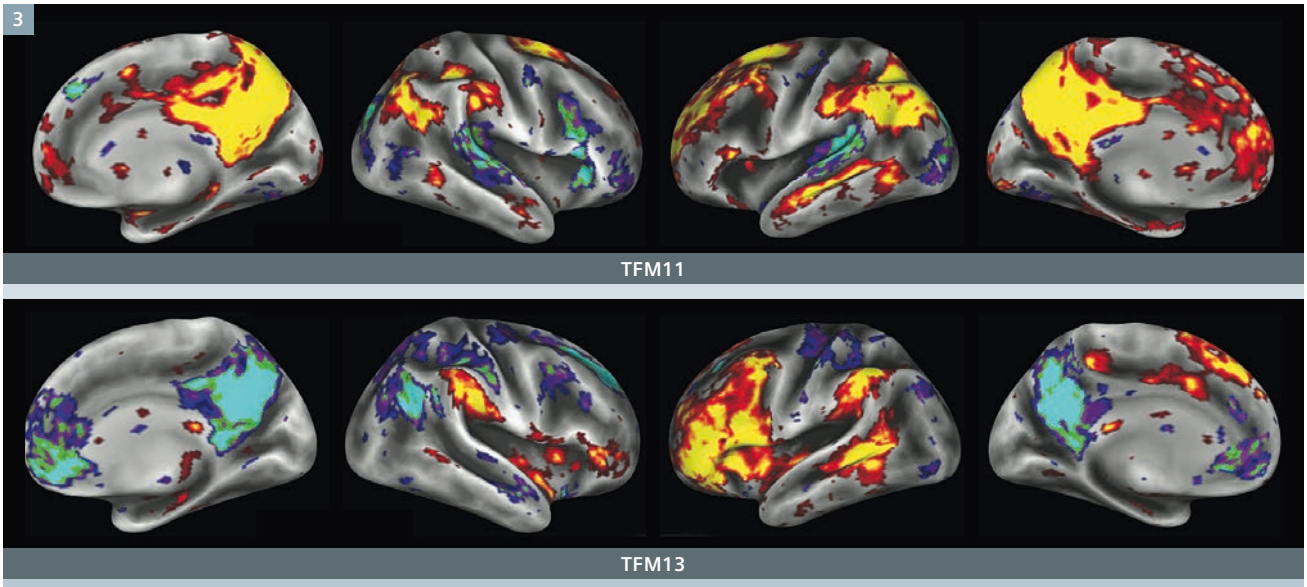
Revealing novel aspects of functional connectivity

Coincident with the development of SMS acceleration for fMRI has been an explosion of ambitious resting-state research with respect to both sophisticated data analysis techniques and attempts to probe increasingly subtle aspects of brain function. The benefit of high temporal resolution for resting-state fMRI is likely to extend beyond boosted statistics or improvements in spatial resolution. Here, we highlight one example from our research where SMS has directly enabled novel methodology and preliminary insights into functional connectivity, namely the identification of temporally independent modes of functional activity.

The goal of most resting-state studies is to derive estimates of apparent connection strength between brain regions. While many potential measures of connection strength exist, the most common are based on temporal correlation. Standard approaches parcellate the brain into regions and associated time courses, and estimate the connection strength between a pair of regions based on the correlation between regional time series. Regardless of how the regions are derived (seed- or ICA-based), this approach is underpinned by some problematic assumptions. Temporal correlation is only able to capture the time-averaged behavior of the connectivity between two regions, which would conceal neuroscientifically interesting variations in connection strength over time ('non-stationarities'). Examples include independent networks with spatial overlap (due to interdigitation of neural populations or simply limited spatial resolution), or temporal modulation of physical connections due to processes like attention. In the case of multiple networks that contain a common (overlap) region but are largely independent, the 'networks' identified by both spatial ICA and seed-based approaches are unsatisfying: spatial ICA requires components to be non-overlapping, whereas seed-based analysis identifies all correlated areas as a single network, even if the extended regions do not significantly correlate with each other. These assumptions are problematic, both with respect to basic neuroscience investigations and



2 Components of the visual system identified from resting-state data using ICA. On the left, spatial independence breaks the occipital lobe into non-overlapping 'resting-state networks' corresponding to early stages of processing of information at the centre and periphery of vision (RSN 1 and RSN 2, respectively), and higher-level visual processing (RSN 3). On the right, temporal independence combines across these areas to identify extended visual networks that correspond to known anatomical support for processes such as low-level visual processing (TFM 2), high vs low visual eccentricity (TFM 4) and the dorsal visual stream (TFM 8). *Reproduced with permission from [2].*



3 High-level cognitive networks identified from resting-state fMRI data on the basis of temporal independence, both including overlap with the well-established 'default mode network' [1]. The network on the top (TFM 11) is reasonably symmetric across hemispheres and involves a set of regions that are involved semantic processing. The network displayed below (TFM 13) contains significant overlap with this semantic network, but is strongly lateralized and includes language regions. *Reproduced with permission from [2].*

for clinical applications, particularly pre-surgical planning, as described below.

Identification of more subtle temporal features like the non-stationarities described above, places a strong demand on the temporal domain of the acquired data, which is typically several orders of magnitude smaller than the spatial domain of image voxels. We explored the potential to identify extended brain networks using temporal independence (temporal ICA), in which a brain network would be recognized based on having a unique temporal signature [2]. Unlike spatial ICA, this analysis does not penalize spatial overlap between networks, but it does require a large number of temporal samples to robustly identify these independent time processes. This approach was demonstrated using pilot resting-state SMS data acquired by the HCP. We combined data across five subjects with TR = 0.8 s to accumulate 24,000 time points over 360 minutes. Following careful data clean up (see below), the data was parcellated into 142 regions using spatial ICA, which were then fed into temporal ICA to identify 21 temporally independent functional modes (TFMs).

The resulting TFMs contained significant spatial overlap, with most of the spatial ICA parcels contributing significantly to multiple modes. Encouragingly, most of the TFMs also corresponded to extended networks of known functional anatomy. The visual system was decomposed into well-established streams of visual information processing (Fig. 2), while other TFMs capture high-level cognition such as semantic processing or language (Fig. 3).

Clinical fMRI at the individual patient level

The use of resting-state fMRI in the clinical domain is fairly recent, but has begun to attract attention for clinical applications in general, and for pre-surgical mapping in particular [11, 12]. Resting-state fMRI does not depend on task performance and is less contingent on patient compliance. It is also less demanding with respect to experimental setup than task-based fMRI and can be more easily acquired by MRI technicians. In some instances, such as when probing orofacial motor functions, task-based fMRI is prone to task-correlated head motion. Furthermore, there is initial evidence that resting-state fMRI data may establish intra- and perilesional BOLD reactivity and thereby serve as a less stressful substitute for cerebrovascular reactivity mapping by experimentally induced hypercapnia [13]. Clinical applications can benefit directly from the increase in statistical significance conferred by SMS, or can leverage statistical gains to increase spatial resolution or reduce scan durations – all of which are extremely desirable for clinical applications.

Increasing the spatial resolution of fMRI improves spatial accuracy, including registration to anatomical scans, but incurs a reduction in SNR proportionate to voxel volume. In some contexts, data quality can be improved through the combined use of high spatial resolution with edge-preserving smoothing to increase SNR, reducing partial volume and signal dropout compared to data acquired at the filtered resolution. However, smoothing can artificially extend or eliminate true activations, both of which are problematic for pre-surgical mapping and intra-operative neuro-navigation. Sophisticated data analysis strategies will thus be required to translate the potential improvements in spatio-temporal resolution with SMS fMRI into clinical applicability [14, 15].

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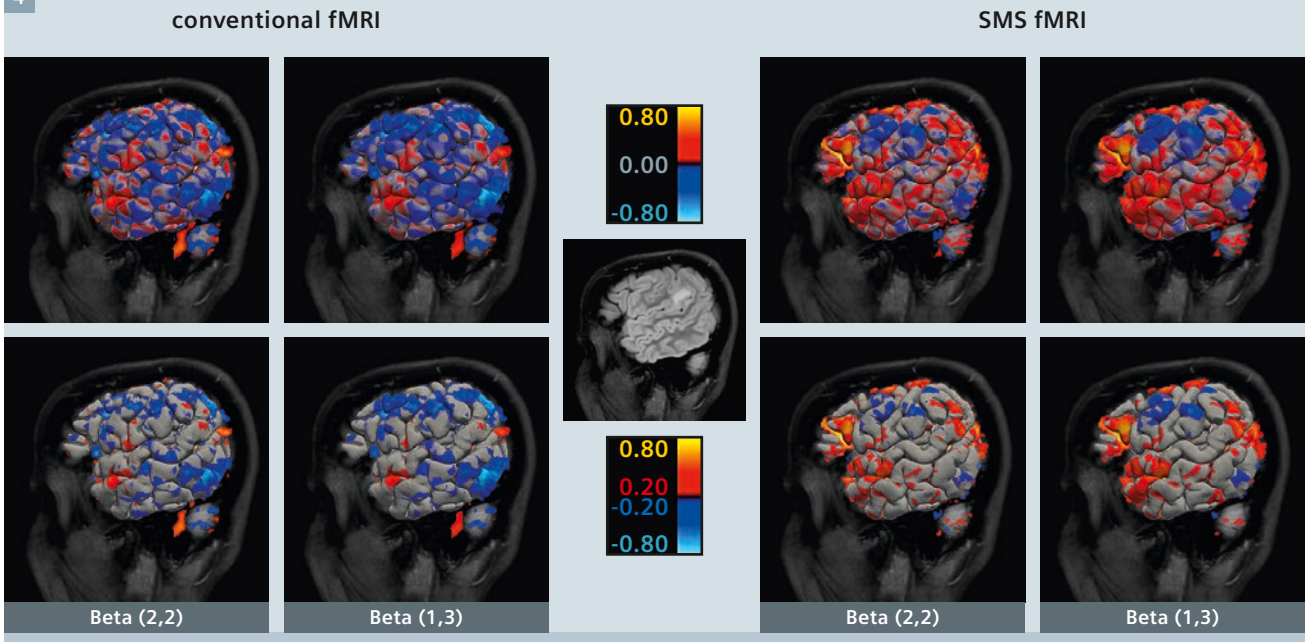

4 Improved single-subject fMRI results with SMS fMRI. Speech mapping data in the same patient, using non-SMS low spatio-temporal resolution (3 mm, TR = 3s) vs. SMS high spatio-temporal resolution (1.8 mm isotropic, TR = 1.5 s, SMS factor 3). Statistical confidence of the SMS results increases remarkably (*top*: unthresholded, *bottom*: thresholded using different Beta priors [14] instead of smoothing kernels), demonstrating that doubling the temporal resolution by SMS over-compensated the reduced SNR at higher spatial resolution. The lesion was an incidentially detected, left supramarginal focal cortical dysplasia (small center image), initially mistaken for a low-grade glioma, with reduced intra- and perilesional cerebrovascular reactivity.

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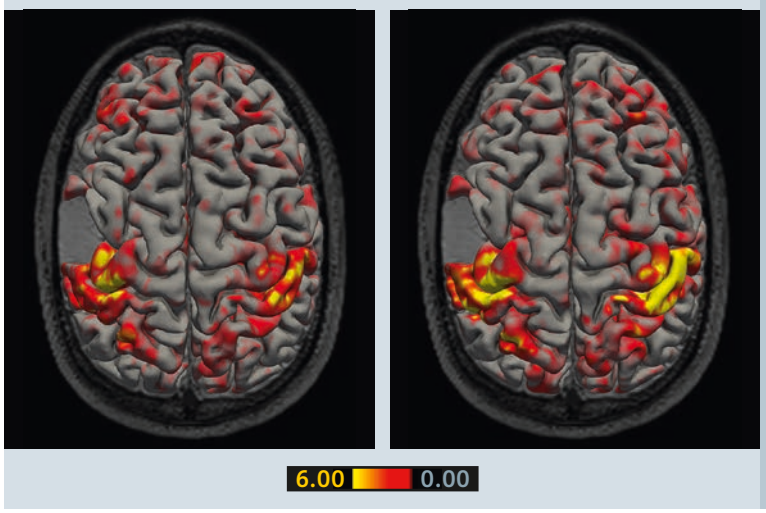

5 Improved (sensori-)motor mapping by SMS resting-state fMRI in a left precentral low-grade glioma prior to resective surgery. The patient suffered from focal motor seizures involving both eyebrows (bilateral N.VII innervation), the contralateral mouth corner (contralateral N.VII innervation), chewing, vocalizations and speech arrest (N.V, IX, X and XII innervation), corresponding to the motor humunculus representation below the handknob. Task-based fMRI would have been confounded by stimulus-correlated head motion potentially causing false-positive detections primarily at the tumor border. Resting-state fMRI reveals statistical gains (color-coded Z-statistics) of SMS high (TR = 1.56 s, SMS factor 3) over non-SMS low (TR = 3.33 s) temporal resolution fMRI, despite the shorter acquisition time (6.5 vs. 14 min).

An example of the benefits of increased spatio-temporal resolution by SMS fMRI for language mapping in a patient is given in Figure 4.

Shorter experiments are desirable not only because scan time is precious in the clinical domain, but also considering limitations in task performance and/or compliance in patients.

Figure 5 illustrates corresponding gains that can be achieved by SMS for pre-surgical fMRI, exemplified by sensorimotor mapping. These benefits have to be substantiated and systematically explored by future studies. Note that motor mapping is, even in the case of space-occupying lesions, rarely indicated because the sensori-motor strip can be identified in most patients by pure anatomic criteria. The real challenge to transfer resting-state fMRI into pre-surgical practice lies in the mapping of 'eloquent' functions with no absolute cortical representation. That is, the meaningful pre-surgical mapping of essential functions whose cortical

representations cannot be predicted by anatomic criteria alone, such as speech and language in particular. While it is intrinsically difficult to avoid a circularity of assumptions about the hemispheric representation and dominance of speech and language in this context, recent attempts to relate connectivity gradients from SMS resting-state fMRI to language lateralization in non-clinical samples of the HCP project have been promising [16]. However, task-based pre-surgical fMRI mapping can be performed in 3 to 8 minutes while the recording of these high-quality SMS resting-state data took one hour (see above), and initial efforts to translate such sophisticated analyses to real pre-surgical tumor patients using clinically acceptable scan times of 6 to 13 min have proven difficult. Generally, acquiring high-quality resting-state fMRI data that provide access to subtle information in the spatio-temporal domain (such as robust functional connectivity gradients or TFMs; see above) will continue to require longer scan times than simple task-based fMRI even if SMS acceleration is used.

Cautions, challenges and confounds

Achieving the benefits of SMS in fMRI does require some additional care to protocol design and data analysis. Here we review several common challenges and strategies to overcome them.

High temporal resolution using SMS requires careful consideration of standard analysis pipelines. Residuals are generally assumed to be 'white noise' (with each time point independent of other time points), making any source of structured noise problematic. Violation of this assumption (for example, temporally smooth noise) can cause the residuals to have lower degrees of freedom than anticipated and thereby inflate the apparent statistical significance. At high temporal resolution, it is therefore crucial to account for any structure in the residuals [4]. Most fMRI software packages enable suitable noise corrections, although this may not be a default option.

Fast temporal sampling with SMS will typically reduce the repetition time down to the second or sub-second range, such that the magnetization will not recover fully from one RF excitation to the next. This results in some loss of signal in each individual volume relative to more typical temporal sampling at a rate of 2-3 seconds. Reducing the excitation to the Ernst angle can mitigate these effects, but some signal loss is inevitable. Nevertheless, it is straightforward to demonstrate that the signal loss in a given image volume is more than compensated by the statistical gains described above [17].

Despite the benefits described above, fast sampling is not a panacea for overcoming some limitations of functional MRI based on the *BOLD response*. Neurovascular coupling, which determines BOLD signal delays, is dependent on region, physiological state and neurovascular pathology. Hence, while faster sampling enables detection of the BOLD response to *neural* activity with greater temporal precision, uncertainties in the hemodynamic response mean that it is unlikely to provide the ability to infer neural timings with greater precision [18]. It may, however, enable the detection of subtle temporal features of the hemodynamic response, such as an initial signal reduction (known as the 'initial dip') that has been long hypothesized to provide improved spatial specificity to the locus of neural activity [19].

Another challenge associated with short repetition time is signal instability from 'spin history' effects that disturb the signal steady state, such as caused by subject motion. Motivated in part by recent innovations in SMS technology, machine learning techniques have been developed to automatically 'clean' data by removing these artifacts [20]. These techniques, which have been extensively evaluated within the HCP, can remove much of the signal fluctuations due to physiological noise, hardware instabilities and motion. Indeed, the fact that methods for cleaning data often are based on the same analytical techniques (multivariate analysis [20] or regression [21]) suggests that SMS data may be more intrinsically amenable to clean-up than conventional non-SMS data.

Conclusions

Simultaneous multi-slice imaging offers enormous potential benefits to functional MRI in general, and resting-state fMRI in particular. These benefits derive primarily from the statistical advantage of increasing the experimental degrees of freedom. For simple tasks, this could enable shorter experiments, but the primary benefit is expected when estimating a number of separate time courses reflecting different aspects of brain function. In resting-state fMRI, experiments that probe a rich hierarchy of brain networks are limited by the degrees of freedom. SMS fMRI can therefore be expected to have particular impact in this area. Several examples of such benefit have been highlighted here, including deployment in large cohorts, unique insights into connectivity and clinical applications.

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