Simultaneous Multi-Slice (SMS) Imaging for Pre-Surgical BOLD fMRI and Diffusion Tractography: Case Illustrations

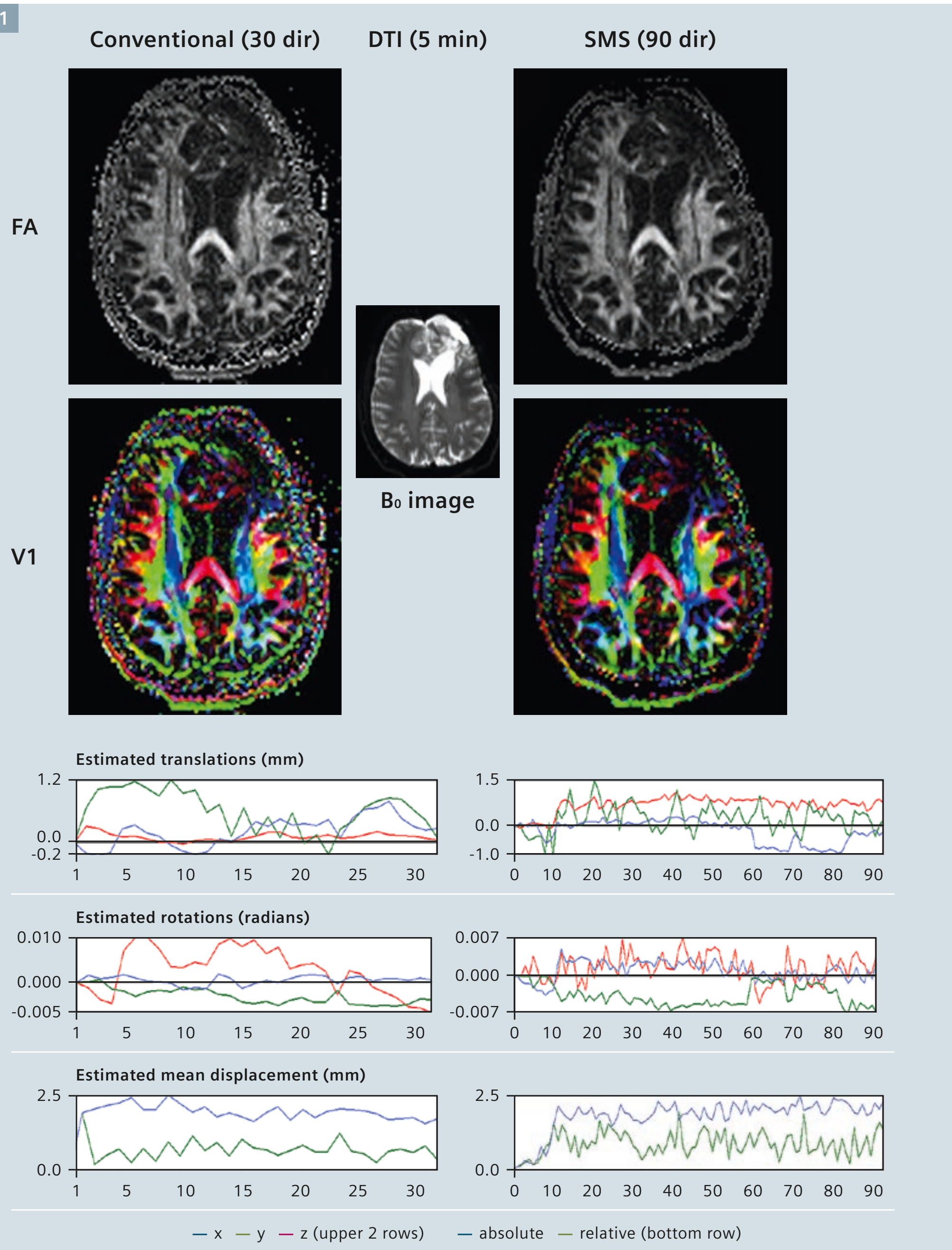
Andreas J. Bartsch[1,2,3]

[1] Radiologie Bamberg, Germany
[2] Departments of Neuroradiology, Universities of Heidelberg and Wuerzburg, Germany
[3] Oxford Centre for Functional MRI of the Brain (FMRIB), University of Oxford, UK

Introduction

Simultaneous multi-slice (SMS) imaging accelerates the temporal sampling of MRI and enables unprecedented increases in temporal resolution. This is of interest not just for research, but for various clinical applications that are currently emerging.

Dense temporal sampling by SMS offers new insights into temporal dynamics when time-series are studied and has been shown to improve the sensitivity of resting-state fMRI, for example (cf. the corresponding article by Miller et al. in this issue; [15, 19]). At the same time, it can be used to encode more information in diffusion MRI (e.g., by recording more diffusion directions; Fig. 1), to shorten acquisition times, or to increase spatial image resolution and / or coverage [8, 10, 18].



1 Comparison of conventional (30 diffusion encoding directions) vs. SMS DTI (90 directions; SMS factor 3), both recorded with whole-brain coverage at 1.8 mm isotropic in 5 min, in a patient with a partially resected, left frontal oligodendroglioma (same slice position but scans not coregistered). Online-generated FA **(top)** and color-coded V1 maps **(middle)** illustrate less noisy estimates from more sampled diffusion directions by SMS. Between-volume motion tends to be slightly lower for SMS compared to conventional DWI **(bottom)**. A subdural hygroma abutting the left frontal lobe is apparent in the middle image with no diffusion but T2-weighting.

While SMS imaging is applicable to different pulse sequences such as echo-planar imaging (EPI) and turbo spin echo (TSE), it has gained particular attention for BOLD fMRI and diffusion EPI. While SMS-accelerated EPI may be able to increase statistical confidence and / or to reduce experimental scan duration of clinical BOLD fMRI (see Fig. 2 in this article; Figs. 4, 5 of the article by Miller et al. in this issue), the benefit of fast temporal sampling becomes particularly apparent for diffusion EPI. Here, multidirectional (MDDW) and high-angular resolution diffusion-weighted imaging (HARDI), possibly across multiple b-value shells, are instrumental for diffusion-tensor (DTI; Fig. 1) or -kurtosis imaging (DKI) and tractography (Figs. 2, 3, 5, 6). For example, recording 3 times more unique diffusion directions by SMS within the same period of time compared to conventional DTI can reduce the noise in fractional anisotropy (FA) and color-coded first eigenvector (V1) maps (Fig. 1, top).

For DWI requiring just 3 diffusion-encoding directions (e.g., stroke or epidermoid imaging), there is, in terms of acquisition speed, relatively little to gain: Here, SMS reduces the default imaging time only by a fraction and in the magnitude of 15 to 20 seconds for each whole-brain average. In a busy practice scanning up to 40 neuroradiological patients in 10 hours, this may enable the examination of one additional patient per day.

For DTI or tractography studies investigating structures with rather uniformly directed diffusion and few crossing fibers, such as in the peripheral nervous system, potential gains offered by SMS are probably less related to sampling more diffusion directions and more to extend the coverage and facilitate isotropic recordings.

For structures in the central nervous system with lots of crossing fibers or tractography into low FA areas, such as perifocal tumor edema [6], sampling more diffusion directions can considerably improve the tracking of the fiber pathways of interest (Fig. 2, bottom). Diffusion tractography nowadays regularly supplements fMRI for pre-surgical planning and intra-operative neuronavigation, and here SMS allows us to record high-resolution (1.8 mm isotropic) diffusion-weighted (e.g., at b = 1500 s/mm^2) whole-brain data of, for example, 160 unique encoding directions in less than 10 minutes while comparable conventional recordings without SMS would normally exceed the scanning tolerance of clinical patients, especially if fMRI is conducted in the same session.

Additionally, faster scanning by SMS imaging may, at least in theory, reduce motion artifacts. Other than motion between consecutive volumes, within-volume motion is usually not correctable. In our experience, estimated motion between EPI volumes tends to be slightly lower for SMS recordings (Fig. 1, bottom). Thereby, SMS may increase the quality of the scans recorded.

For fMRI, SMS changes the autocorrelation structure and 'spin history' effects of the data. Statistical modeling and inference can account for the former, while dense temporal sampling in SMS fMRI makes the data more amenable to denoising procedures to remove effects of the latter. SMS fMRI is attractive for clinical applications considering potential gains in 'functional' signal-to-noise ratios (SNR) that can be achieved at the individual patient level. Assuming that the detected functional signal adds up linearly with each measurement and that the random noise increases with the square root of the number of measurements, the 'functional SNR' would increase by the square root of the number of samples. In other words, if we measure the same functional signal four times and sum up the measurements, we increase the SNR by a factor of two compared to a single measurement. Even though these assumptions are certainly simplistic, SMS is able to boost statistical confidence, and these gains can be invested

I) to render first-level FMRI results more robust (see Fig. 2 in this article; Figs. 4, 5 in the article by Miller et al. in this issue),

II) to increase the spatial resolution of the measurements (see Fig. 4 in the article by Miller et al. in this issue) and / or

III) to shorten the experimental acquisition time (see Fig. 5 in the article by Miller et al. in this issue).

Increasing the spatial resolution of fMRI and diffusion tractography is relevant for clinical applications to improve spatial accuracy, including registration to anatomical scans, but penalized by a loss in SNR because the measured signal decreases approximately linearly with the voxel size. Additionally, the relative contribution of thermal noise increases nonlinearly at higher spatial resolutions. This is also the reason why task-based SMS fMRI data tend to require a similar amount of smoothing like low-resolution recordings to achieve comparable results [11]. However, recent statistical advances specifically addressing pre-surgical fMRI indicate that the potentially detrimental effects of smoothing (blurring of larger or elimination of smaller activations, leading to false-positive or -negative detections in space) can be avoided [16].

Given that patients (especially children[1], elderly, neuropsychologically impaired, mentally handicapped and those suffering from intractable epilepsies) often have a limited tolerance for long scan durations, the potential benefits of SMS-accelerated scanning to obtain high-quality data are substantial. At the same time, there is no obvious drawback: Auditory noise characteristics are the same for conventional and SMS EPI (with the fundamental frequency peak being determined by the echo spacing of the read-out gradient, [5]), and the risk for peripheral nerve stimulations (due to rapid read-out gradient switches) should not be increased. In fact, we have *not* observed an increased number of such incidents with SMS over the past three years.

Therefore, pre-surgical BOLD fMRI and diffusion tractography are prime examples of where the use of SMS-

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[1] MR scanning has not been established as safe for imaging fetuses and infants under two years of age. The responsible physician must evaluate the benefit of the MRI examination in comparison to other imaging procedures.

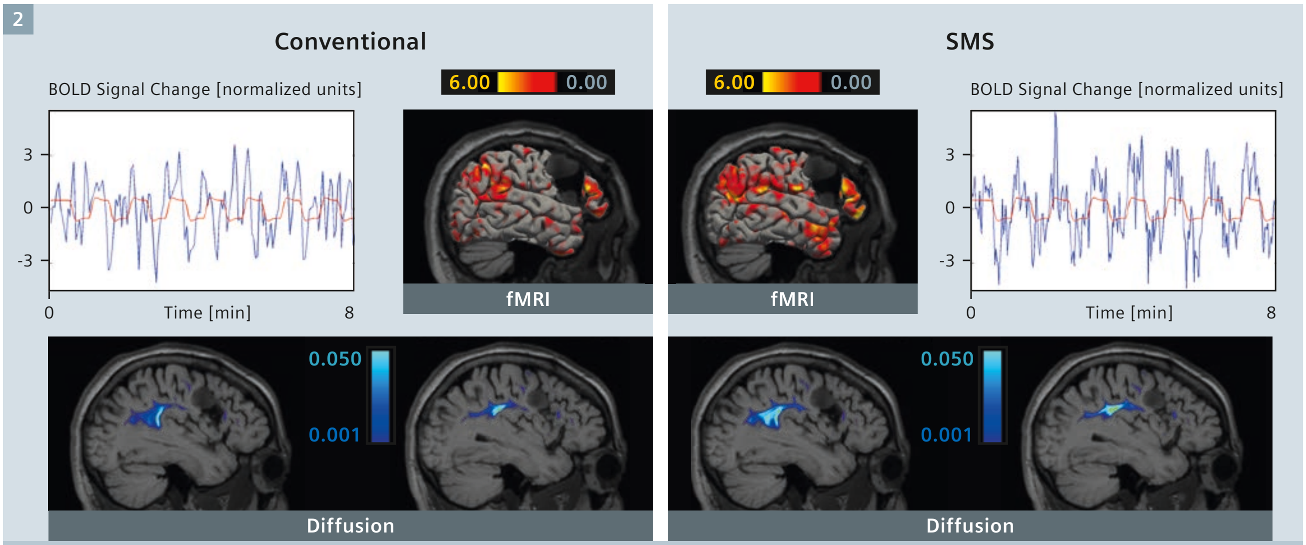
accelerated EPI is expected to translate into obvious clinical advantages, and we have decided to share our experience with this new technology in this context based on selected cases.

Case-based illustrations of SMS benefits

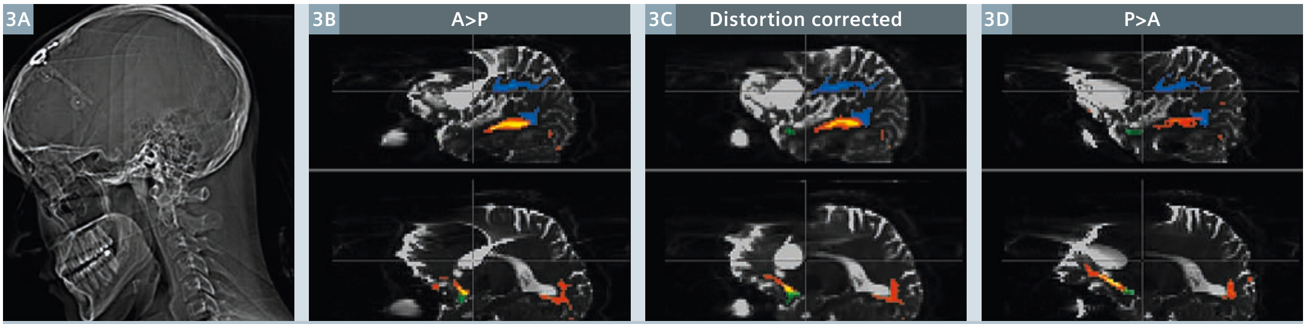
Head-to-head comparisons of conventional vs. SMS fMRI and diffusion-weighted EPI were performed in Figures 4 and 5 of the article by Miller et al. in this issue and in Figures 1 and 2 of this presentation. Figure 2 illustrates the core findings:

Recording more time points and more diffusion directions by SMS acceleration is able to enhance the statistical confidence of fMRI and diffusion tractography results. Such improvements may lead to increased spatial extent and maximum height probabilities to detect functional activations and structural connectivities. In other words, SMS can improve the sensitivity of functional and diffusion MRI. Sensitivity is crucial for pre-surgical fMRI and tractography applications because most of these aim to avoid infliction of new clinical deficits to the patient by minimizing false-negative detections.

For the patient shown in Figure 2, right-brain speech had already been confirmed by intra-operative electrical stimulation mapping (ESM) during the primary, partial tumor resection. However, ESM was, at the time, complicated by a series of intra-operative seizures, and the current fMRI examination prior to secondary resection was considered helpful in supporting a sufficient safety margin between the recurrent, low-grade glioma and cortical fMRI activations (Fig. 2, top). Probabilistic diffusion tractography revealed the proximity of the arcuate fasciculus (AF) to the upper medial tumor nodule, with SMS suggesting



2 Comparison of conventional vs. SMS BOLD fMRI (**top**; TR 3.0 vs. 1.5 secs) and diffusion tractography (**bottom**; 60 vs. 180 directions; distortion-corrected by phase reversal – cf. Fig. 3) in a left-hander with a recurrent, right frontal low-grade glioma prior to second surgery. Doubling the temporal fMRI resolution by SMS increased the statistical confidence (red-to-yellow Z-statistics obtained by independent component analysis ICA / dual regression) of the activations correlated with the language paradigm and improved the temporal correlation of the respective time-courses (blue) with the model (red; r = 0.2 vs. 0.7; **top**). Similarly, tripling the number of diffusion directions by SMS increased conditional probabilities to reconstruct streamlines of the superior longitudinal / arcuate fascicle (blue-to-light blue, thresholded at 1 ‰ of the number of samples making it from seed to target [6]; **bottom**).



3 Distortion correction by SMS SE-EPI using alternate phase encodings (A>P **(3B)** vs. P>A **(3D)**). Patient with a left fronto-opercular cystic ganglioglioma, craniofix and Ommaya reservoir **(3A)**. Probabilistic tractography of SMS DWI with the arcuate **(blue-to-lightblue)**, inferior longitudinal **(red-to-yellow)** and uncinate **(green-to-lightgreen)** fascicle. Note distortion of the tumor cyst depending on the phase-encode direction and the resulting neuro-navigation error as indicated by the cross hairs.

a smaller safety margin than conventional diffusion tractography (Fig. 2, bottom). We regularly provide these data to the operating neurosurgeon for transfer into the neuro-navigation system. It is useful to define ESM points and to tailor the neurosurgical approach to the functionally relevant anatomy.

Figures 3 – 6 further illustrate the application of SMS to pre-surgical fMRI and tractography. Distortion correction of BOLD and diffusion-weighted EPI is essential for accurate pre-surgical planning and intra-operative neuro-navigation, particularly in patients with **I)** lesions close to the skull base and

II) previous surgery, craniofix and metallic implants (Fig. 3). SMS spin-echo (SE-) EPI is currently the fastest means to acquire field map data for distortion correction by alternate phase encodings. Figure 3 illustrates the profound neuro-navigation error that may result if geometric distortions are not adequately corrected for.

Figure 4 depicts the same patient as in Figure 4 of the article by Miller et al. in this issue. Here, SMS BOLD fMRI was used for cerebrovascular reactivity mapping (CVRM) [17].

The incidentally detected, left supramarginal focal cortical dysplasia (FCD) without transmantle sign, which was initially mistaken for a low-grade glioma but then shown to lack any spectral tumor pattern, revealed reduced BOLD signal changes in response to hypercapnic fluctuations evoked by simple breath holding.

Abolished or decreased cerebrovascular reactivity may increase false-negatives of cognitive task-based and resting-state fMRI results. Based on SMS mapping of speech and language functions, however, the lesion was considered to occupy an eloquent location in the dorsal stream [12], a conclusion indeed primarily supported by SMS but not conventional BOLD fMRI (cf. Fig. 4 of the article by Miller et al. in this issue). Follow-up of the lesion with reduced mechanical compliance established by MR elastography [7, 9] over the past two years was stable and resection was therefore not recommended.

Figure 4 also illustrates the usage of advanced physiological signal monitoring: Respiration, pulse and ECG can all be recorded along with SMS, and Siemens' proprietary implementation logs these signals in precise temporal synchronization with each acquired slice and volume to (pseudo-) DICOM series. From these, the recorded signals can be read out for physiological noise modeling to 'regress out' effects of physiological noise in fMRI, for example. This feature makes physiological signal monitoring very convenient and easy to handle without the need for any third-party equipment.

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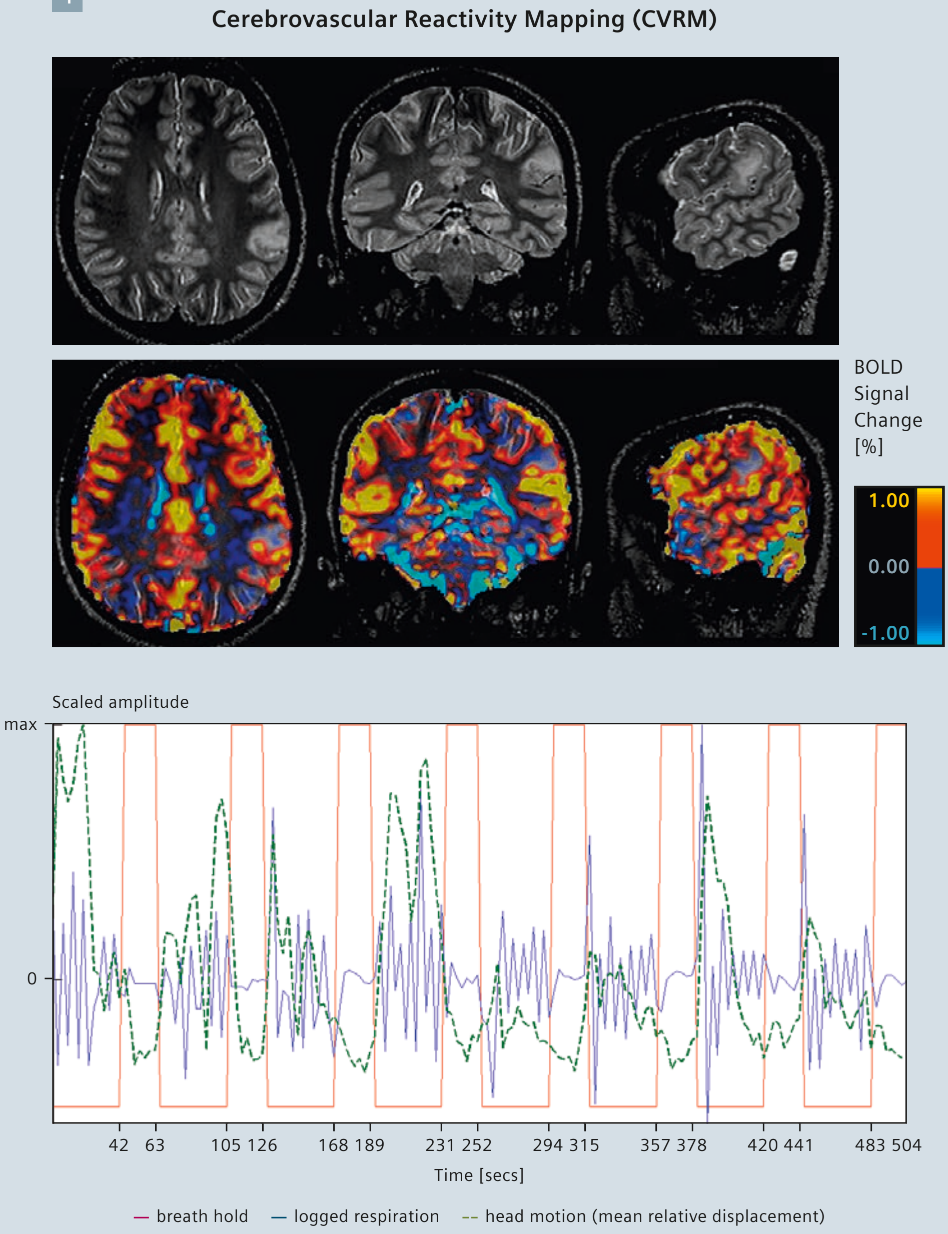
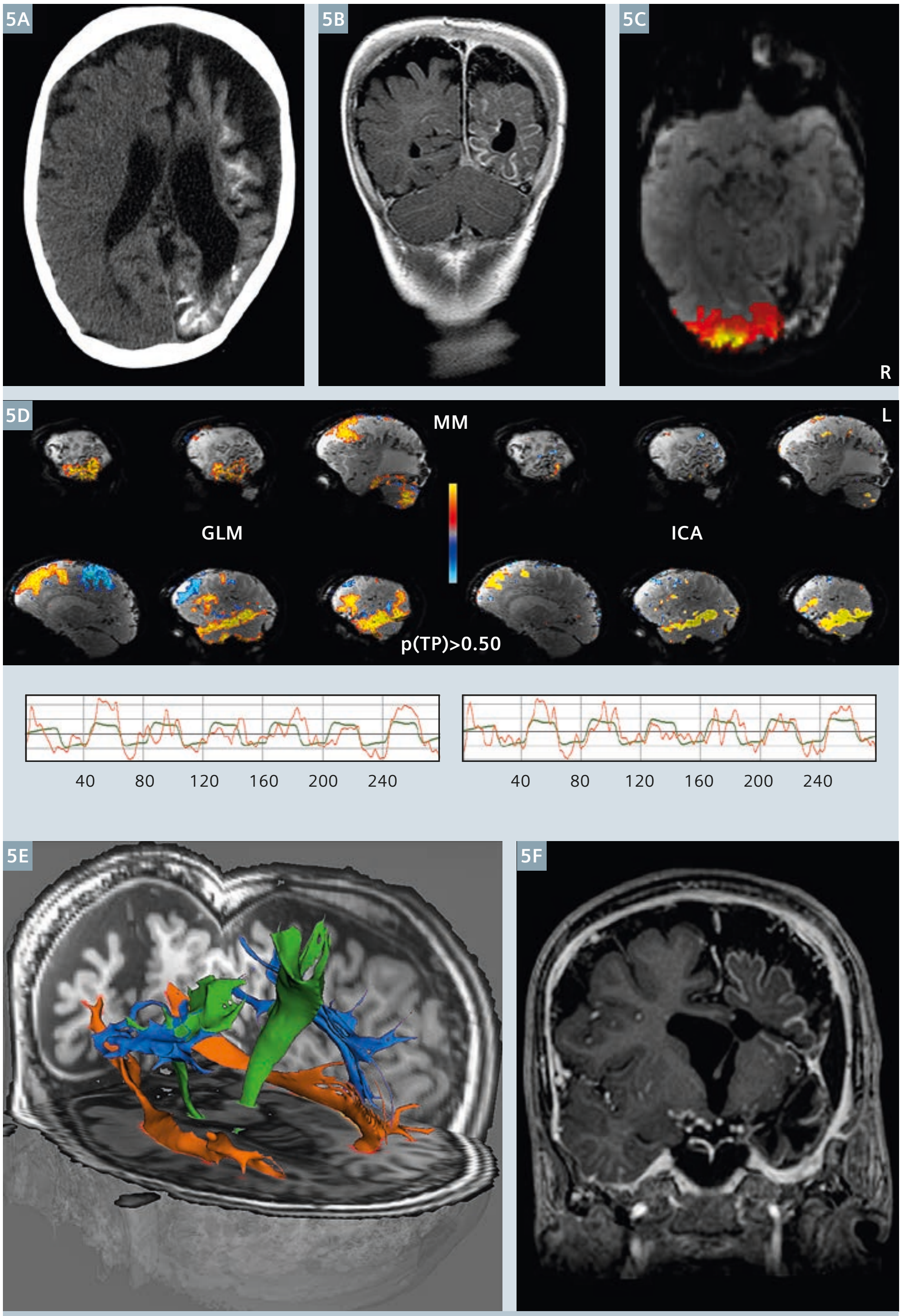


4 Cerebrovascular reactivity mapping (CVRM) by SMS BOLD fMRI, same patient as in Fig. 4 of the article by Miller et al. in this issue. **Top:** SMS identified reduced cerebrovascular BOLD reactivity of the left supramarginal focal cortical dysplasia (FCD). **Bottom:** Logged respiration (blue) by Siemens' proprietary physiological monitoring confirmed patient compliance with breath-hold commands (red), motion correction estimates reveal increased head motion (green) during free breathing.

Figures 5 and 6 spotlight the application of SMS fMRI and diffusion tractography to patients with drug-resistant seizures evaluated prior to invasive electrocorticography and epilepsy surgery.

Epilepsy differs from tumor surgery in that patients with intractable seizures but with no identifiable brain lesions and no pre-surgical neurocognitive impairments (such as the case in Fig. 6) are at particular risk to develop new postsurgical deficits. In contrast, for patients who undergo surgical resections of brain tumors or other intra-axial lesions, those with no pre-surgical deficits generally fare best (such as the case in Fig. 2).

The patient shown in Figure 5 is the case of a 9-year-old, handicapped boy with classical Sturge-Weber syndrome (Figs. 5A, B) evaluated prior to left hemispherotomy considered for surgical treatment of refractory seizures. Absent visual resting-state fMRI signal fluctuations in the primarily affected left hemisphere (Fig. 5C) reflected right visual field hemianopsia of the patient. Speech mapping (passive story listening vs. scrambled sounds) with SMS BOLD fMRI detected predominantly right hemispheric activations (Fig. 5D), using both general linear modeling (GLM; model time-course in green) and independent component analysis (ICA) with spatial mixture modeling (MM) for statistical inference [20]. Right-brain speech was later confirmed by left intra-carotid WADA testing and corresponded to degeneration of the left arcuate fasciculus (AF), especially in the posterior segment, detected by probabilistic SMS diffusion tractography (Fig. 5E). Similarly, the left corticospinal tract showed signs of degeneration that corresponded to the patient's right hemiparesis (and impeded unbiased handedness evaluation). Left hemispherotomy was successfully performed (Fig. 5F), effectively eliminating the previous frequent seizures, and did not result in aphasic complications but just slight worsening of the hemiparesis. Rapid temporal sampling by SMS was instrumental to minimize the acquisition time for BOLD fMRI and diffusion tractography (< 30 min) obtaining high-quality data (280 fMRI time-points, 320 diffusion directions) without exceeding the scanning tolerance of the patient.



5 SMS BOLD fMRI and diffusion tractography in a boy with Sturge-Weber syndrome prior to surgical treatment of refractory seizures. Pathognomonic CAT **(5A)** and contrast-enhanced T1-weighted MRI **(5B)** scans revealing left leptomeningeal angiomatosis and intra-axial calcifications. SMS BOLD fMRI detected no signal fluctuations of visual resting-state networks in the degenerated left occipital lobe, corresponding to a right visual field hemianopsia of the patient **(5C)**. Speech mapping by SMS BOLD fMRI suggested right hemispheric language lateralization **(5D)**. SMS diffusion tractography **(5E)** indicated degeneration of the left arcuate (AF; **blue**) and pyramidal (**green**) tract, while the left inferior fronto-occipital fasciculus (IFOF; **orange**) seemed largely intact. Subsequent left hemispherotomy was successful **(5F)** without aphasic deficits.

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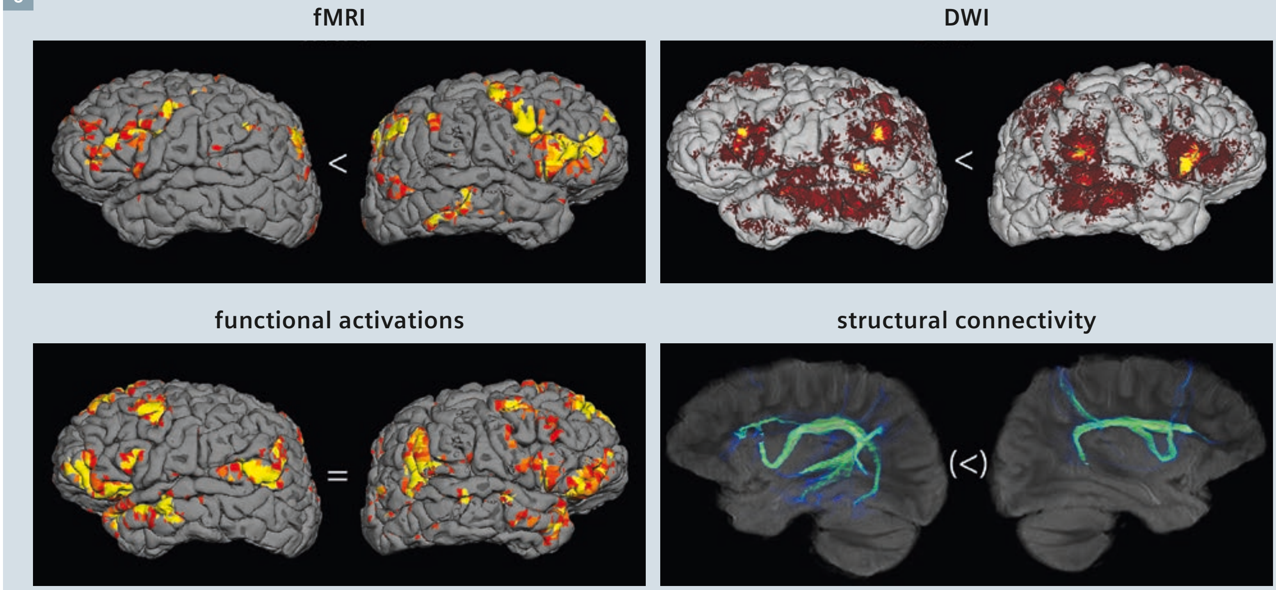

6 SMS BOLD fMRI and diffusion tractography in a left-handed boy with no apparent lesion (according to structural MRI) but drug-resistant, left frontal lobe seizures. Speech mapping by SMS BOLD fMRI **(left)** detected two paradigm-correlated components: one right-lateralized **(top left)** and another bilateral **(bottom left)**. SMS diffusion tractography **(right)** revealed spatial cross-correlation of right triangular activation probabilities with association fiber projection probabilities of the arcuate fasciculus **(top right)**. Its anterior segment was hypoplastic on the left **(bottom right)**. Right Broca's dominance was considered likely, invasive left frontal electrocorticography (ECoG) was recommended to further localize the seizure focus.

Figure 6 illustrates the case of a nonlesional, drug-resistant epilepsy patient, not eligible for WADA testing. He was transferred for best possible non-invasive assessment of language organization / lateralization prior to invasive electrocorticography (ECoG). ECoG was considered to better localize the seizure focus. The 13-year-old left-handed boy suffered from refractory seizures originating in the left frontal lobe (according to scalp EEG) during which he maintained the ability to speak. Using independent component analysis (ICA), speech mapping by SMS BOLD fMRI detected two paradigm-correlated independent components – one lateralized to the triangular part of the *right* inferior frontal gyrus and another with largely bilateral activations – presumably corresponding to the dorsal and ventral stream of speech and language processing, respectively [12]. Lateralization of the dorsal stream fMRI component suggested *right*-brain speech dominance for articulation, consistent with preservation of expressive speech during *left* frontal seizures. However, an important limitation is that fMRI cannot discriminate essential from dispensable (co-)activations by itself. Therefore, we sought to substantiate right-brain speech dominance by relating the functional to structural connectivity profiles [6, 13]. Probabilistic SMS diffusion tractography revealed a highly significant correspondence of right-lateralized fMRI activations with right triangular projections of the arcuate fasciculus (AF) which was not significant on the left. On the left, the anterior segment of the AF was hypoplastic. This case exemplifies a sophisticated clinical application of joint fMRI and diffusion analysis. SMS was essential to generate the underlying high-resolution data (1.8 mm isotropic) at a minimal scan time (25 min) adjusted to reduced scan compliance of the patient.

Conclusions

The case studies presented here make it evident that SMS is ready to be transferred into clinical practice. We have illustrated that SMS can increase the statistical confidence of fMRI and diffusion tractography results. This is in itself very valuable. These gains may also be used to increase spatial image resolution and coverage, to improve spatial coregistration to high-resolution anatomical scans for intra-operative neuro-navigation, and / or to shorten acquisition times. Eventually, SMS may allow us to better tailor pre-surgical fMRI and tractography to individual limitations of task performance and scanning tolerance of the patients we care for.

Pre-surgical fMRI and diffusion tractography will take advantage of this exciting new technology. In terms of auditory scan comfort, despite an increased specific absorption rate (SAR), or unwanted peripheral stimulations, no penalties are involved. Dense temporal sampling of SMS may also be of clinical interest for real-time fMRI applications, where the gains could be substantial, and potentially to better differentiate vegetative from minimally conscious states or locked-in patients. However, benefits for such clinical applications have yet to be evaluated.

Over the past decade, pre-surgical fMRI and diffusion tractography have hardly kept up with the rapid methodological advancements in the field. Pre-surgical tractography, for example, often continues to rely on 6 or 12 diffusion directions only – even though it has been demonstrated that at least 30 unique sampling orientations are required for a robust estimation of diffusion tensor orientations [14]. Current guidelines of the American Society for Functional Neuroradiology (ASFNR) do not specify a firm minimum of unique diffusion encoding directions for clinical DTI and tractography or provide a recommended set of pre- and post-processing algorithms to be used [2]. Similarly, Current Procedural Terminology (CPT) codes of the American Medical Association (AMA) for clinical fMRI [2] and practice guidelines for fMRI by the American College of Radiology (ACR) [1] make no reference to recommended data acquisition and analysis strategies to assure appropriate conduct for fMRI exams. Unfortunately, clinical settings tend to strongly favor speed over sensitivity and accuracy in data acquisition and analysis. SMS seems a perfect tool to overcome exactly these shortcomings.

Overall, SMS provides a showcase for capitalizing on recently developed, advanced data acquisition and analysis strategies that lead to tangible benefits in research [10, 15, 19] and clinical practice. It is able to facilitate patient-specific applications to optimize clinical decision-making [4] and to translate technological cutting-edge progress into medical practice. In this regard, SMS is a versatile 'kick' for functional and diffusion MRI to finally become much more than just fashionable merely by virtue of 'colored brain images'.

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... to Optoacoustics', Israel (http://www.optoacoustics.com/), supreme Active Noise Cancellation (ANC) system to cancel out EPI read-out noise making both fMRI as well as diffusion scanning much more comfortable. For fMRI it also greatly improves auditory stimulus transmission. Data shown in Figures 5, 6 were recorded using ANC (and these patients would have hardly tolerated unattenuated EPI noise).

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Contact

Andreas Joachim Bartsch, M.D.
Radiologie Bamberg
http://www.radiologie-bamberg.de/
Heinrichsdamm 6
96047 Bamberg
Germany
bartsch@radvisory.net