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Clinical Article

Functional neuronavigation combined with intra-operative 3D ultrasound: Initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data

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Summary

Objective. The aims of this study were: 1) To develop protocols for, integration and assessment of the usefulness of high quality fMRI (functional magnetic resonance imaging) and DTI (diffusion tensor imaging) data in an ultrasound-based neuronavigation system. 2) To develop and demonstrate a co-registration method for automatic brain-shift correction of pre-operative MR data using intra-operative 3D ultrasound.

Methods. Twelve patients undergoing brain surgery were scanned to obtain structural and fMRI data before the operation. In six of these patients, DTI data was also obtained. The preoperative data was imported into a commercial ultrasound-based navigation system and used for surgical planning and guidance. Intra-operative ultrasound volumes were acquired when needed during surgery and the multimodal data was used for guidance and resection control. The use of the available image information during planning and surgery was recorded. An automatic voxel-based registration method between preoperative MRA and intra-operative 3D ultrasound angiography (Power Doppler) was developed and tested postoperatively.

Results. The study showed that it is possible to implement robust, high-quality protocols for fMRI and DTI and that the acquired data could be seamlessly integrated in an ultrasound-based neuronavigation system. Navigation based on fMRI data was found to be important for pre-operative planning in all twelve procedures. In five out of eleven cases the data was also found useful during the resection. DTI data was found to be useful for planning in all five cases where these data were imported into the navigation system. In two out of four cases DTI data was also considered important during the resection (in one case DTI data were acquired but not imported and in another case fMRI and DTI data could only be used for planning). Information regarding the location of important functional areas (fMRI) was more beneficial during the planning phase while DTI data was more helpful during the resection. Furthermore, the surgeon found it more user-friendly and efficient to interpret fMRI and DTI information when shown in a navigation system as compared to the traditional display on a light board or monitor. Updating MRI data for brain-shift using automatic co-registration of preoperative MRI with intra-operative ultrasound was feasible.

Conclusion. In the present study we have demonstrated how both fMRI and DTI data can be acquired

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and integrated into a neuronavigation system for improved surgical planning and guidance. The surgeons reported that the integration of fMRI and DTI data in the navigation system represented valuable additional information presented in a user-friendly way and functional neuronavigation is now in routine use at our hospital. Furthermore, the present study showed that automatic ultrasound-based updates of important pre-operative MRI data are feasible and hence can be used to compensate for brain shift.

Keywords: Functional magnetic resonance imaging; diffusion tensor imaging; intra-operative 3D ultrasound; multimodal imaging; brain shift; image registration; neuronavigation; minimally invasive surgery; image guidance.

Introduction

New and existing imaging modalities make an increasing amount of potentially important information available for any given patient. Furthermore, image guidance is now commonly used during many neurosurgical procedures. Essential questions in multimodal neuronavigation are: What information is needed for optimal surgical planning and guidance in the operating theatre? How should all this multimodal information be presented to the surgeon? And how can technology ensure that information displayed in the navigation system represents an accurate picture of the intra-operative anatomy throughout the operation?

The possibility to preoperatively acquire high quality images of eloquent grey matter and important white matter tracts is an excellent example of additional information potentially important for the safe surgical resection of brain tumors.

Mapping of the cerebral cortex using ultra-fast MR-imaging is a maturing science, and is increasingly being used as the preferred method for identifying specific eloquent cortices for surgical planning due to its non-invasive nature and easy implementation. Functional MRI (fMRI) is a four-dimensional MR-imaging modality, relying on the temporal change in blood oxygenation in small vessels in cortical areas during activation experiments performed inside the MRI-scanner [24]. The method can reliably predict the location and aid the display of the sensorimotor cortices, the visual cortices and the main language-specific cortices [8].

Furthermore, the structure of white matter in the brain may be visualized with diffusion tensor imaging (DTI). This method uses magnetic gradients to induce directionally constrained water diffusion along the axons of the brain [31] and can thus infer the directionality of the main axonal bundles within the brain [2].

Integration of functional MR images (fMRI) into neuronavigation systems, termed functional neuronavigation, is still in its infancy, but is promising for performing tailor-made surgical procedures, allowing for better planning [23, 34] as well as more optimal guidance and resection. Especially in the presence of cerebral masses distorting anatomical landmarks, knowing the exact location of important functional areas might be essential for optimal surgical outcome.

However, the movement of brain tissue (i.e. brain shift), mainly caused by CSF drainage and tumor tissue removal, severely reduces navigation accuracy [13, 20, 27, 33] and represents a big challenge in neuronavigation based only on pre-operative images. To fully rely on the images in the navigation system during surgery, brain shift must be monitored and corrected for. Frequently the surgeon tries to track the changes visually and mentally. This can be a rather challenging task as the direction and extent of brain shift may vary considerably [21]. Furthermore, the tissue shift is most likely non-uniform in nature and implies a deformation of the image data that is difficult to predict and model. In these cases pre-operative images may only be trusted for overview and approximate orientation during surgery.

Alternatively, an intra-operative imaging modality can be used to track the anatomical changes that occur during surgery. With MR as the intra-operative modality [35], both intra-operative fMRI and DTI based tractography have already been demonstrated to be feasible with the right equipment [17, 22]. But fMRI requires the patient to be awake and perform certain tasks inside the scanner and the quality of the generated data is often not as good as what can be achieved pre-operatively using MR scanners with high field strengths. In addition, the time needed to acquire and process data into a format suitable for presentation to the surgeon is often substantial. An alternative approach is therefore to acquire fMRI and DTI pre-operatively, track the anatomical changes that occur during surgery using intra-operative structural MRI (sMRI) and apply the changes found to the preoperative data. Also, for intra-operative monitoring of the location of eloquent areas, cortical electrostimulation may be used [25]. This technique of brain mapping does not suffer from inaccuracy due to brain shift as it may be performed at any time during surgery. However, cortical electrostimulation requires an awake patient, and may generate epileptic seizures.

Intra-operative ultrasound has been available in neurosurgery for several years [6, 10]. Advances in ultrasound technology have made the image quality of ultrasound comparable to intra-operative MRI. The integration of intra-operative ultrasound with neuronavigation enables acquisition of 3D ultrasound data for direct image guidance, and represents an efficient and inexpensive tool for intra-operative imaging and surgical guidance [36]. Furthermore, brain shift detected with intra-operative ultrasound could be used to update pre-operative image data (e.g. fMRI and DTI) in order to increase the value of this information throughout the operation. This update could be done mentally (i.e. in the surgeons mind), manually (i.e. landmark tracking) [5, 32] and automatically. In a stressing clinical situation a robust, accurate and automatic method would be preferred. But the automatic registration of images from modalities like MRI and ultrasound is a challenging task and no solutions for this have been demonstrated in the operating theatre using real patient data.

Neuronavigation systems are continuously being refined in order to minimize invasiveness and post-surgical morbidity at the same time as the radicality is maximized [7, 12, 38]. Numerous challenges exist in the registration and optimal visualization of the complementary and supplementary multimodal information available before and during surgery [14]. In the present paper we demonstrate solutions which may solve some of these challenges, and which we believe indicate future directions in neuronavigation: 1) The integration and use of a full range of structural and functional MR information in an ultrasound-based system for image guided surgery and 2) an automatic method for brain-shift correction of relevant pre-operative MR images based on high quality intra-operative 3D ultrasound data, which may improve the usefulness of these data during surgery.

Methods

Patients and data

Image guided surgery based on a full set of multimodal image data, including pre-operative MRI (sMRI, fMRI ($n = 12$) and DTI-based tractography ($n = 6$)) and intra-operative 3D ultrasound, was applied in twelve patients undergoing primary cerebral tumor resections. Informed consent was given by each patient before treatment.

Patients and procedures are presented in Table 1.

The intended use of the proposed framework for brain shift correction of important pre-operative information was tested postoperatively using patient data from two tumor cases and additional data from three patients undergoing cerebrovascular surgery.

Pre-operative MRI acquisition and processing

All MR images were acquired with a Philips Intera 3 Tesla scanner (Philips Medical Systems, Best, the Netherlands) with Quasar Dual gradients (maximum gradient strength 80 mT/s/m) using a six-channel sensitivity encoding (SENSE) head-coil (In vivo, Orlando FL, US). Before scanning the patients were equipped with five skin-fiducials for pre-operative registration of MR-images into the neuronavigation system. A full presurgical MR imaging session consisted of two whole brain high-resolution 3D gradient echo T1-weighted se-

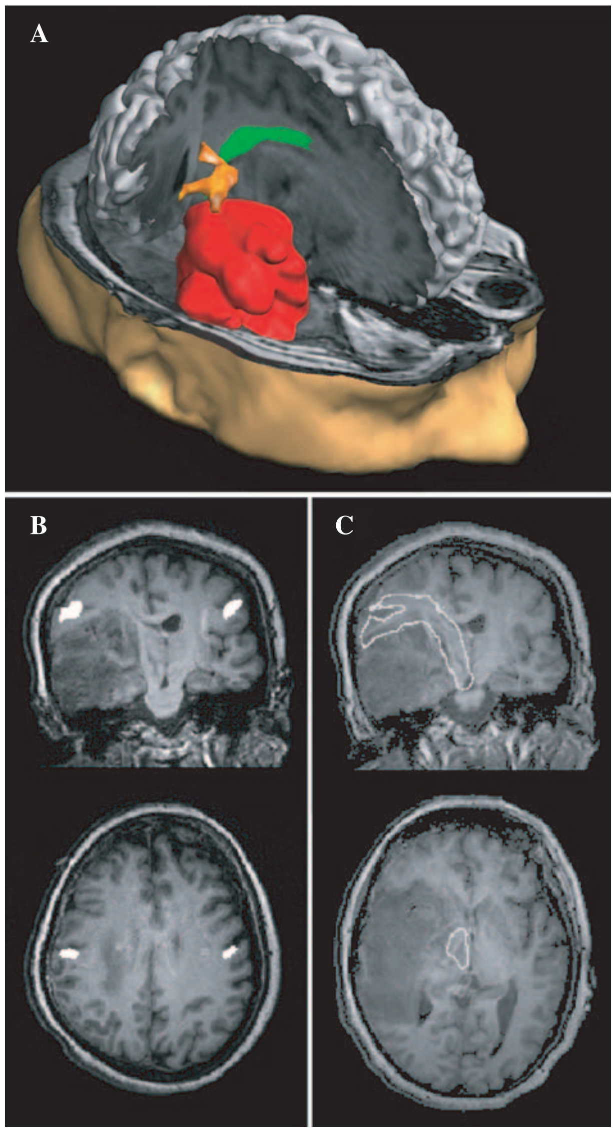

Fig. 1. Image fusion between functional and structural MRI data (patient #3). (A) All MR information fused in a 3D view (tumor in red, tongue activations in yellow and lateral corticospinal tracts in green). (B) Tongue activations (bright white islands). (C) Lateral corticospinal tracts (bright white outlines)

ries (MP-RAGE) in the transverse plane, one before and one after the administration of an intravenous gadolinium contrast agent, one 3D T2-weighted series, one time-of-flight MR-angiography series, two to six functional MR time-series and diffusion tensor data.

fMRI: For all functional imaging, a single shot echo-planar-imaging (EPI) [18] sequence was used to image the whole brain at a voxel-resolution of $1.72 \times 1.72 \times 2.3\,mm^3$ with $TR = 3000\,ms$, $TE = 35\,ms$ and with a SENSE-reduction factor of 2.2. A wide range of different motor- and language paradigms were used to activate and identify the primary motor cortex and the main language cortices. Paradigms were presented visually on a LCD-screen behind the magnet bore that was seen by the patient in a mirror mounted on top of the head-coil. Mapping paradigms were individually chosen from the location of the tumor, and included movement of fingers, toes and tongue, several tests for activating the frontal language areas (the inferior frontal gyrus including Broca's area) and the posterior language areas (Wernicke's area, angular gyrus and supramarginal gyrus). Language tests included word generation (WG), responsive naming task (RST), object naming (ON), antonym production (AP), sentence reading (SR) of varying difficulty and jeopardy. All paradigms used were block-designed, with four 27 second periods of activity interleaved with five equally long resting periods. Post-processing of the functional series was done using the Brain Voyager QX software (Brain Innovation, Maastricht, the Netherlands) and included head movement correction, linear trend removal and high-pass filtering to remove physiological noise and sometimes conservative spatial smoothing. The functional series were co-registered to the post-gadolinium T1-weighted images. Signal-changes in the EPI time-series on a voxel-by-voxel basis were fitted to a Boynton-type hemodynamic response function [3] where the condition effects were estimated according to the general linear model. The resulting statistical maps were thresholded by the image analyst for statistical significance and optimal surgical visualization purposes. The T1-images were routinely segmented into white and grey segments from which rendered models of the brain were reconstructed (Fig. 1A). The functional images overlaid the contrast-enhanced T1-weighted images were then locked together and exported in DICOM-format, with the resulting images appearing as a normal T1-weighted image stack with the functional clusters appearing as bright white areas (Fig. 1B).

DTI: DT imaging was done using a spin-echo EPI sequence utilizing maximum gradient strength, collecting full-brain volumes at a voxel resolution of $(1.72\,mm)^3$, a b-factor of 700 in 32 spatially independent gradient directions, utilizing cardiac triggering, $TE = 50\,ms$, and a SENSE reduction factor of 1.5. Geometric distor-

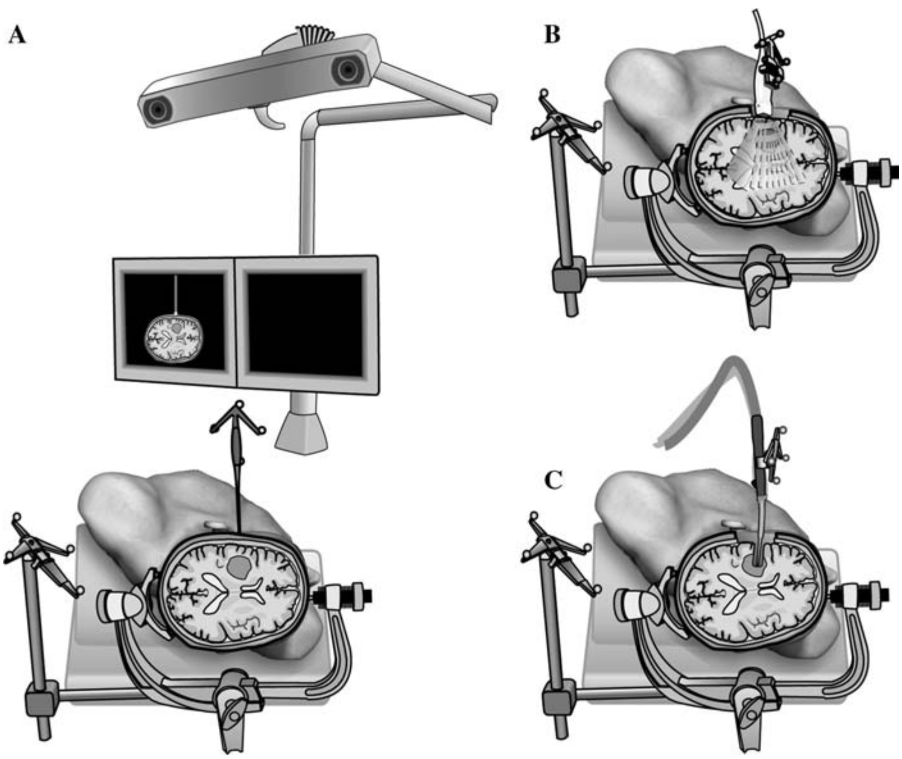

Fig. 2. Ultrasound-based neuronavigation. (A) Navigated pre-operative planning in the operating theatre using a tracked pointer. All surgical instruments are tracked by an optical camera system and the surgeon steers the instruments by looking at the navigation monitor to the left. (B) Freehand 3D ultrasound acquisition using a tracked ultrasound probe (real-time 2D ultrasound can be viewed on the right monitor). (C) Navigated resection using a tracked CUSA

tions in the DTI-images were partially unwarped using B0-field mapping-techniques [9], using the FUGUE/PRELUDE-algorithms in FSL-software (Analysis Group, FMRIB, UK), while intra-session head-movements and eddy-currents were corrected with the FLIRT-algorithm, also in FSL. Fractional anisotropy (FA) maps and tensors were estimated using DTI-studio (S. Mori, John Hopkins University, US), and main white matter tracts were identified with a fiber assignment by continuous tracking algorithm (FACT) [19] using two or three separate regions of interest (ROI's) to be traversed. Medial corticospinal tracts (CST) and corpus callosum (CC) were usually easily visualized using this procedure. For visualizing the pyramidal tracts, activated clusters from motor experiments provided one ROI to be traversed, together with the posterior horn of the internal capsule (PLIC) and the pyramid of the brain stem. The tracts were co-registered and overlaid as bright white contours on the contrast-enhanced T1-weighted images (Fig. 1C). The size of the contours was slightly expanded to accommodate for residual co-registration errors and geometric distortions. Image sets were locked and exported as a DICOM-stack. Neither the fMRI results nor the DTI results were subjected to intra-operative electrophysiology experiments for validation during surgery.

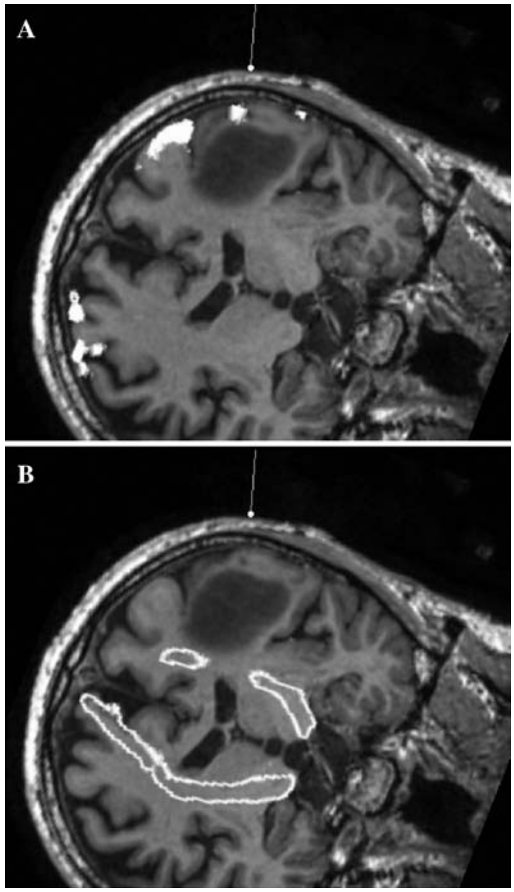

Fig. 3. Navigated preoperative planning based on corresponding any-planes (oblique slices) that show sMRI, fMRI and DTI-based tractograms (patient #9). (A) The functional areas appearing as white islands above the lesion (tongue movements) should be avoided on the surgical path down to the lesion. (B) The corticospinal tracts appearing as white outlines below the lesion should be avoided during the final stages of a radical tumor resection

Surgical neuronavigation and intra-operative 3D ultrasound acquisition

Prior to surgery, the fused MR images (functional/anatomical and tractogram/anatomical) were imported into an ultrasound-based neuronavigation system (SonoWand, MISON A/S, Trondheim, Norway) [6], together with the T1- and T2-weighted images and the MRA data

All pre-operative MRI-data were registered to the patient using a fiducial-based corresponding point technique. The craniotomy was then planned in detail (Fig. 2A) using image guidance based on both structural and functional MRI data (Fig. 3). After the craniotomy, but before opening the dura, one or more 3D ultrasound acquisitions were performed (Fig. 2B). In order to generate ultrasound volumes, an optically tracked 4–8 MHz Flat Phased Array (FPA) ultrasound probe with optimal focusing properties at 3–6 cm was tilted and/or translated by free hand movement over the anatomical area of interest. The pyramid-shaped 3D data sets (Fig. 2B) were transferred to the navigation computer and reconstructed into a regular 3D volume (i.e. similar to the MRI volumes). The time required to perform the free-hand scan, transfer the images and reconstruct the volume was between 30 and 60 s depending on the resolution of the final ultrasound volume. Both 3D ultrasound tissue data and 3D ultrasound angiography (Power Doppler) data were acquired. Tumor tissue was then removed using a tracked CUSA™ (Cavitron Ultrasound Surgical Aspirator, Valleylab, US) (Fig. 2C). Additional ultrasound data were acquired when needed due to suspected brain shift (Fig. 5). For resection control, a final ultrasound scan was acquired at the end of the operation so that complete removal of the tumor could be verified [36].

Postoperatively, both pre- and intra-operatively acquired image data could be exported with the same spatial mismatch (shift) as experienced during surgery. This made it possible to develop and test new image co-registration techniques using real patient data before the algorithms were adapted and approved for intra-operative use.

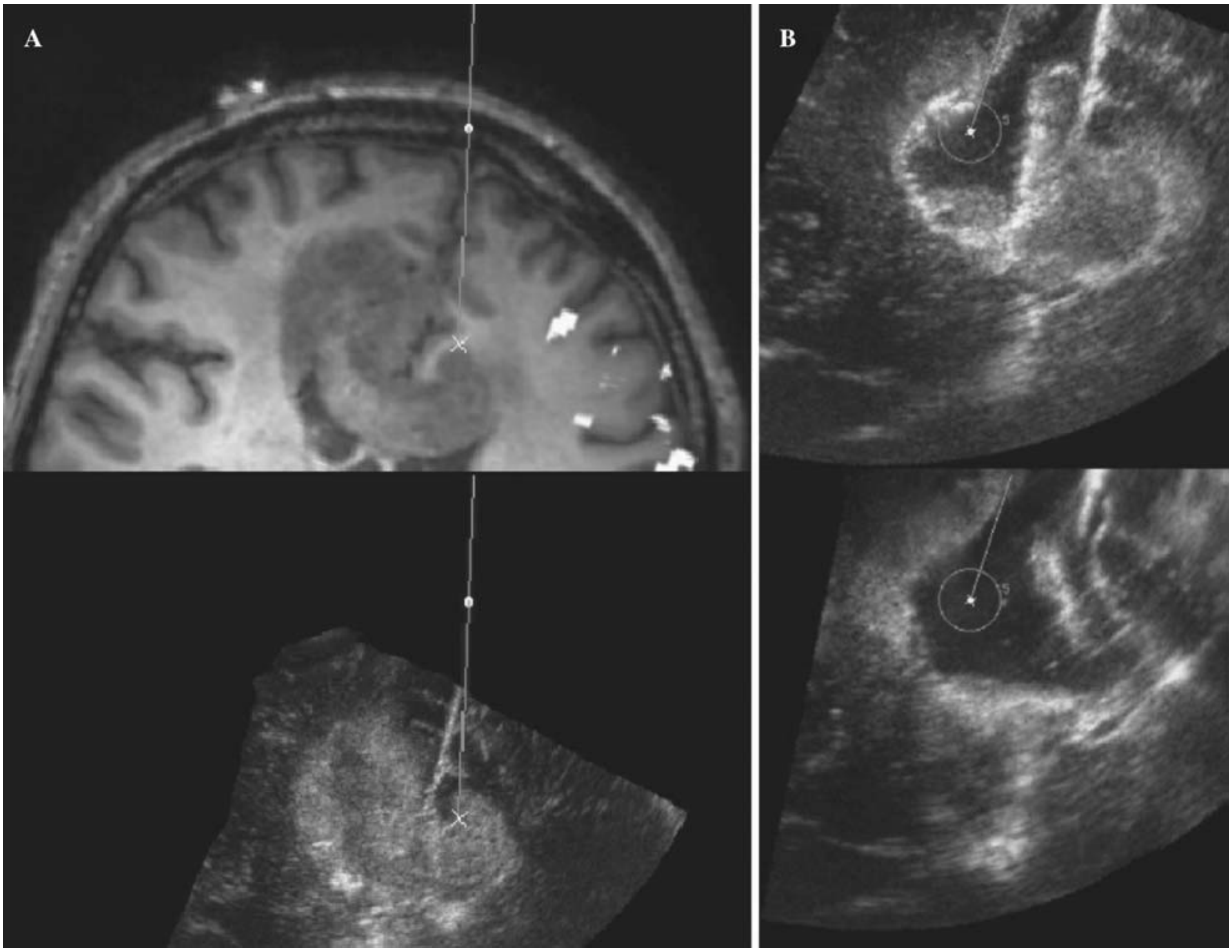

Fig. 4. Intra-operative navigation and resection control (patient #2). (A) Corresponding anyplanes from MRI and ultrasound. The ultrasound data had been acquired from dura before surgery had started. (B) Later in the operation CUSA navigated resection was performed based on intra-operative ultrasound alone as the MR data became inaccurate due to brain shift. The top ultrasound anyplane shows a small resection cavity, which is enlarged towards the end of the resection as shown in the bottom anyplane

Multimodal volume-to-volume registration

A software module for co-registration of pre-operative MRI data and intra-operative ultrasound data was developed and used postoperatively in a three-step approach. First, all the pre-operative MRI volumes were registered to a single MRI volume to be used in the next step (i.e. the master MRI volume). Secondly, the master MRI volume was registered to one of the ultrasound volumes acquired from dura mater (initial ultrasound volume). In addition, the software module offers the possibility for tracking the changes that occur during surgery by co-registration of subsequent ultrasound volumes and use this information to further update the pre-operative data. For each of the three steps a specific registration method was built by putting together three key components: a transform (rigid or non-rigid), a metric (a measure of how similar the two volumes are under the current transform) and an optimization algorithm to get from the initial transform to the final optimal transform [38]. Different combinations of the key components were tried for each of the three steps. The present study focused on the second step: MR to ultrasound registration. For this step a rigid transformation (translation and rotation), a mutual information based metric [16, 37] and a gradient descent optimizer was applied [39].

The automatic multimodal co-registration between pre-operative MR (master volume) data and intra-operative 3D ultrasound data (initial volume) was tested using both tissue and angiography data (i.e. either MR-tissue to US-tissue registration or MR-angio (MRA) to Power Doppler-based US-angio (USA) registration (see Fig. 6). The transformation found by the registration method was then applied to all relevant pre-operative MR data for brain shift correction.

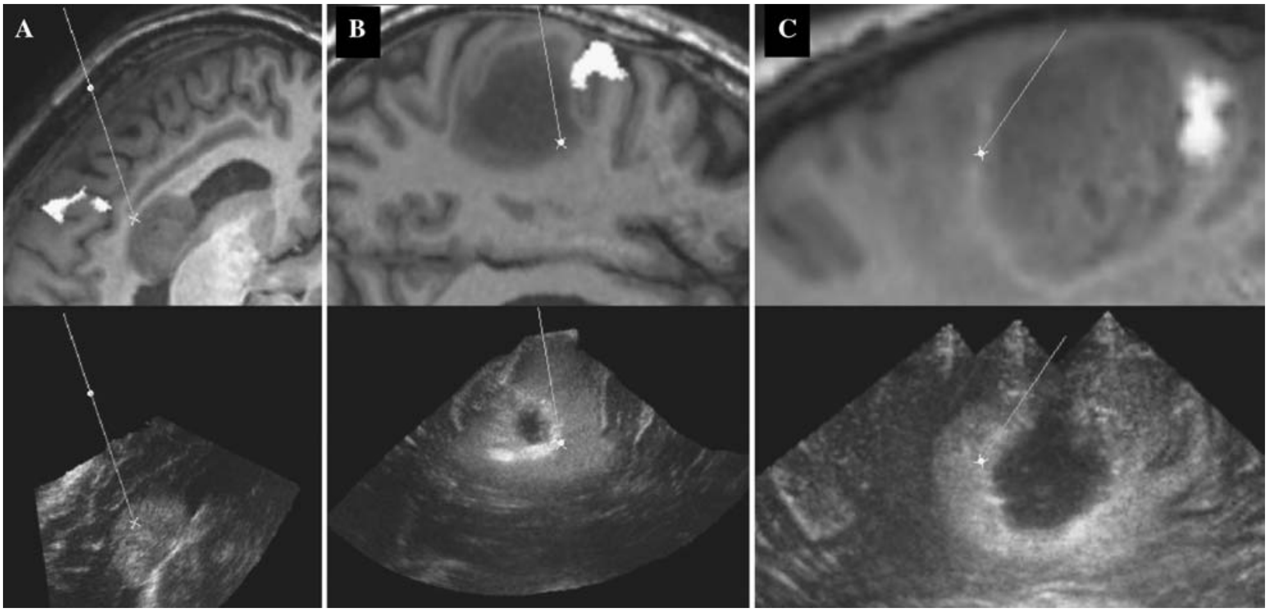

Fig. 5. Brain shift detection using corresponding anyplace slices from MRI (top row) and ultrasound (bottom row). Examples taken from different stages are shown; (A) immediately after the first ultrasound volume was acquired (patient #1), (B) when some tumor tissue had been removed (patient #9) and (C) towards the end of the operation when the central part of the tumor had been removed (patient #11)

Assessment of preoperative MR image acquisition and processing, intra-operative navigated use of fMRI and DTI data and automatic brain shift correction of important pre-operative information

For each patient the image quality as well as technical and practical problems, logistics and benefits linked to the different steps in the combined protocol for fMRI and DTI were registered. Different strategies for fusing functional and anatomical image data were tried in order to make it easier for the surgeon to interpret the important information using fewer images. For every operation, the surgeon reported if and in what way the acquired data was useful in the different phases of the operation. As no gold standard exists for the registration of real patient data, visual inspection was used as an initial assessment of the results achieved by the automatic method for pre-operative MRI to intra-operative ultrasound registration based on angiographic data. In each case where the registration framework was applied ($n = 5$) the surgeon was presented with three volumes (pre-operative MRA, intra-operative USA and corrected MRA) in an in-house application for volume rendering of multiple overlapping volumes where the 3D scene could be zoomed and rotated and the different volumes could be turned on and off. The clinician reported whether the registration looked "acceptable" or "not acceptable" taking into account that the MRA and USA volumes in general do not look exactly the same due to the fact that different physical properties are imaged.

Results

Image acquisition, analysis and visualization were successfully performed in all patients (sMRI and fMRI: $n = 12$, DTI: $n = 6$). All fMRI language mappings gave clear lateralized activations in the major language areas. Mapping of the motor cortices also gave strong and unambiguous signals. DTI-based tractography enabled valuable visualizations of the corpus callosum and the corticospinal tracts. Using fMRI-activation-clusters as a ROI to search for fibers connecting into the posterior limb of the internal capsule (PLIC) and the pyramid of the brain stem made the tracking easier and presumably more correct. The use of B0-field-mapping techniques reduced geometric distortions in the acquired DTI-sets by correcting a 1–2 mm voxel-shift, measured in the genu of the corpus callosum. This made the co-registration between DT images and T1-weighted images easier and more correct.

All the available MR data was successfully imported into the neuronavigation system (fMRI: $n = 12$, DTI: $n = 5$, for patient #2 the DTI data acquired could not be exported to the navigation system as this option was not ready at the time). Both fMRI and DTI-based information were made available pre- and intra-operatively, and could be consulted at any time during surgery. The surgeons reported that the integration of fMRI and DTI data in the navigation system represented valuable additional information presented in a user-friendly way. It enabled the surgeon to find the best location for the

Table 1. *Patient demographics including tumor type and localization, the kind of fMRI and DTI data acquired, in what way these data were useful during the treatment process and outcome*

Patient no.	Sex	Age (yr)	Diagnosis	Tumor localization	fMRI	DTI	Useful for	Outcome
1	M	53	astrocytoma WHO III	left temporal lobe	tongue, fingers, SR	x	planning, intra-operative identification of eloquent cortex	good (neurologically unchanged)
2	M	65	glioblastoma	medial frontal lobe, left side, extending through corpus callosum to right side.	fingers, SR	CC	planning; (DTI data could not be exported to the navigation system at this time)	fair (paresis in right arm and aphasia)
3	F	68	glioblastoma	right temporal lobe	tongue, fingers, SR	CST	planning; not used during surgery due to system failure early in surgery.	good (slight worsening of function in right arm)
4	M	69	glioblastoma	left occipitotemporal region	tongue, fingers, SR	CST	planning; confirmation of no adjacent eloquent cortex.	good (neurologically unchanged)
5	M	45	glioblastoma	right frontal lobe	tongue, fingers, toes, SR	x	planning; confirmation of no adjacent eloquent cortex.	good (neurologically unchanged)
6	F	47	glioblastoma	left temporal lobe, extending medially	fingers, ON	x	planning	poor (edema and hemorrhage during surgery. Paralysis in right arm and leg postop.)
7	F	52	cavernous haemangioma	left frontal lobe	WG, RNT, AP, ON	CC, CST	planning	good (neurologically unchanged)
8	M	56	glioblastoma	left frontal lobe	fingers, RNT, SR, WG	CC, CST	planning; intra-operative localization of CST.	good (neurologically unchanged)
9	M	47	glioblastoma	left parietal region	fingers, tongue, SR, RNT, jeopardy	CST	planning; intra-operative localization of CST.	good (slight worsening of function in right arm)
10	M	46	gemistocytic astrocytoma	occipital, frontal, parietal lobe	fingers, SR, WG, jeopardy	x	planning; intra-operative idendification of eloquent cortex.	good (neurologically unchanged)
11	M	47	glioblastoma	left temporal lobe	tongue, WG, RNT	x	planning; confirmation of no adjacent eloquent cortex	good (neurologically unchanged)
12	F	43	cavernous haemangioma	left central sulcus	fingers, tongue, RNT	x	planning; intra-operative identification of eloquent cortex.	good (neurologically unchanged)

The following abbreviations are used: *fMRI*: *WG* Word generation, *RNT* responsive naming task, *ON* object naming, *AP* antonym production, *SR* sentence reading and *DTI*: *CST* corticospinal tracts, *CC* corpus callosum, *x* no DTI data acquired.

craniotomy and a satisfying trajectory that avoided unnecessary injury to important white and grey matter. The surgeon did not find it difficult to distinguish between the overlay (activations or tracts) and high intensity structures in the anatomical images. Integrating overlay information about the gray and white matter areas closest to the tumor in the dataset with the highest lesion-to-normal tissue contrast was found beneficial as it enabled the surgeon to interpret the important information using fewer images.

The use of fMRI and DTI data in the surgical procedures is summarized in Table 1. Navigation based on fMRI data was found to be important for pre-operative planning in all twelve procedures. In five out of eleven cases the data was also found useful during the resection. DTI data was found to be useful for planning in all five cases where information about white matter tracts was imported into the navigation system. In two out of four cases DTI data was also considered important during the resection (for patient #3 the fMRI and DTI data imported and used for planning could not be used during surgery due to a system failure while testing an experimental module for stereoscopic visualization). Information regarding the location of important functional areas (fMRI) was more beneficial during the planning phase while the location of white matter tracts (DTI) seemed to be more helpful during the resection. The main reason for not finding the available data more useful intra-operatively was that the visualized areas were too remote from the surgical area. In addition, the surgeon found it hard to make effective use of uncorrected pre-operative data during surgery.

In order to maintain accurate guidance, 2–5 3D ultrasound updates were acquired during surgery. The lesion was clearly depicted by 3D ultrasound in all twelve cases. At the start of the operation brain shift in the range of 0–10 mm were observed by 3D ultrasound as compared to preoperative MRI (see Fig. 5). Additional shifts were usually observed during surgery as a result of progressive removal of tumor tissue. The value of uncor-

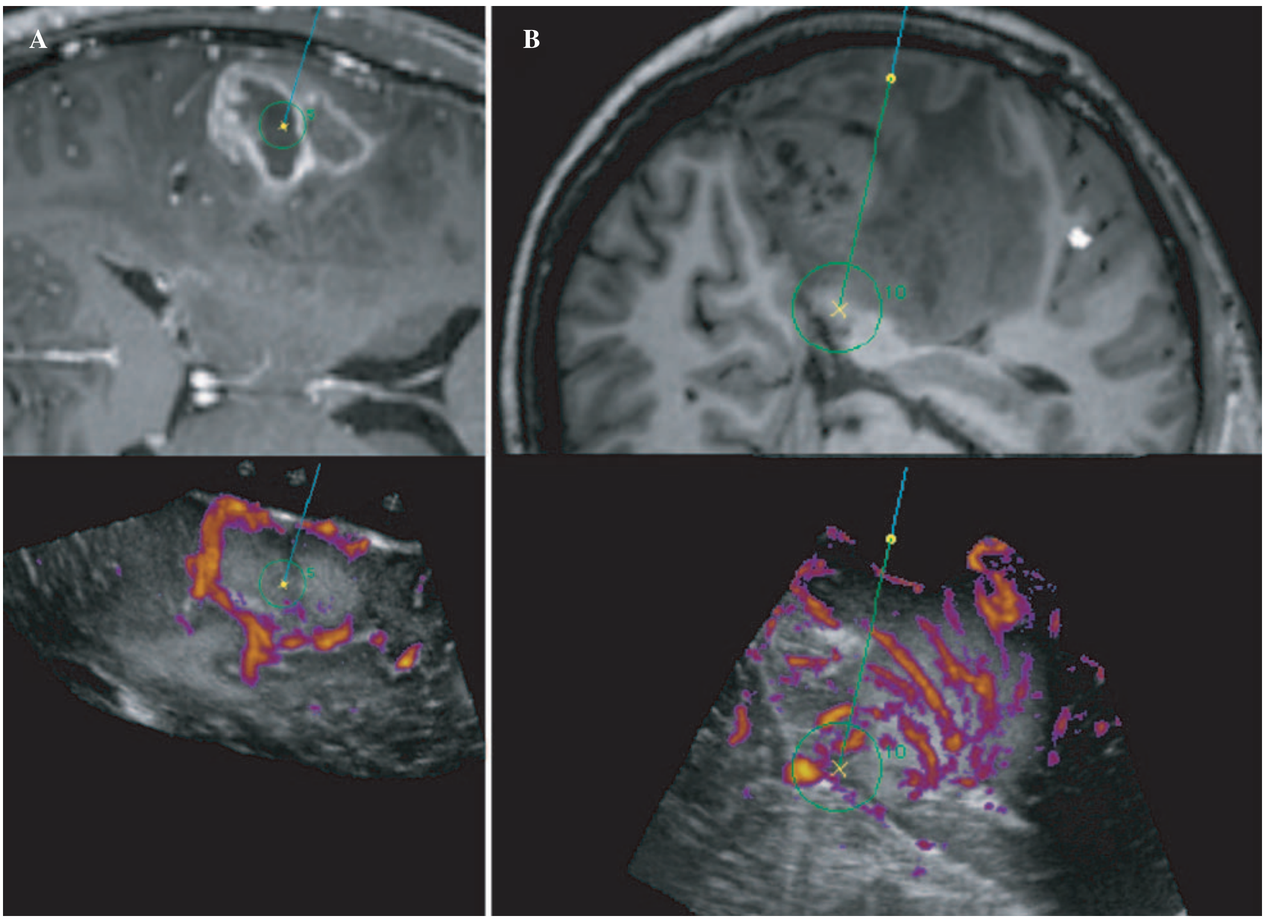

Fig. 6. Brain tumors close to vessels (A, patient #1) and infiltrated by vessels (B, patient #10). Intra-operative 3D ultrasound angiography (Power Doppler) was useful for both detecting important vessels near the tumor (bottom row) and for updating pre-operative MR data for brain shift

rected pre-operative MRI data in the navigation system was strongly reduced when considerable brain shift occurred throughout the surgery. Based on the movement of imaged anatomical landmarks, the surgeon had to mentally transform the localization of the functional areas and white matter tracts in these cases.

Postoperative trials showed that automatic multimodal co-registration between pre-operative MRI data and intra-operative 3D ultrasound data is feasible (Fig. 7). Multimodal MRI to ultrasound registration based on angiography data gave better results than using tissue data. Using angiography data ($n = 2$ tumor cases, $n = 3$ vascular cases) the performance was reported to be satisfactory in all cases, both in terms of accuracy (as determined by visual inspection) and due to running time (less than 5 minutes). In the region of interest, vessels were visible in both modalities in all five cases. The intended future intra-operative use of the registration framework is shown in Fig. 8. As can be seen from the figure, updated pre-operative information will probably make it easier for the surgeon to locate the exact position of eloquent areas.

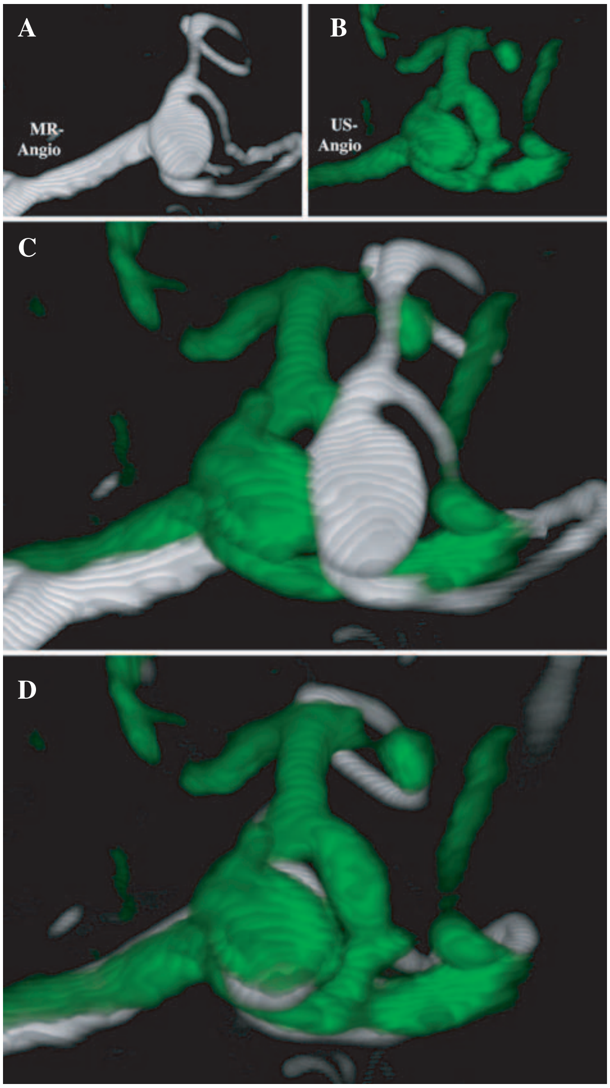

Fig. 7. Automatic multimodal volume-to-volume registration between (A) MR angiography data (MRA, gray) and (B) Power Doppler based ultrasound angiography data (USA, green) of a middle cerebral artery aneurysm. (C) Before registration: the mismatch between the MRA volume and USA volume is the same as the shift experienced during surgery in the navigation system. (D) After automatic MRA to USA registration the match is satisfactory, but as we can see the two volumes are not completely identical as the two modalities image different physical properties

Discussion

Structural and functional pre-operative MRI in combination with intra-operative 3D ultrasound is a powerful tool for optimal surgical planning and radical tumor resection at the same time as the probability for postoperative deficits are minimized. Still, many problems and challenges must be addressed before navigation systems and acquisition protocols are functioning correctly and flawlessly in everyday surgical practice.

In the present study we have shown fMRI and DTI images of good quality in acceptable agreement with the underlying anatomical image information. However, for all ultra-fast MR-imaging modalities like EPI-based fMRI and DTI, geometric distortions may be present due to susceptibility effects close to air-filled spaces in the head and through the introduction of strong magnetic gradients [29, 30]. Thus, the high signal-to-noise that is obtained using 3T MR-scanners may come at the expense of increased geometric distortions, which may only partially be corrected for using B0-mapping strategies. Geometric distortions can displace fMRI-activations and DTI based tracts relative to high-resolution T1-images, and spatial mismatches in the order of several millimeters may occur. In this study, we experienced that susceptibility artifacts were not a practical problem as the eloquent cortices in question had some distance to air-filled sinuses, and co-registration errors did not affect the identification of central sulcus or Broca's/Wernicke's area significantly. Thus, for mapping these functional cortices, we did not apply B0-inhomogeneity corrections. For DTI, the white matter of interest was closer to the sphenoid and frontal sinuses than grey matter of interest, and spatial shifts, were easier to notice. We found that without using B0-mapping based correcting schemes, the position of these tracts could be displaced by several millimeters, and did not combine well with activated clusters found by fMRI nor be well co-registered to the T1-images. The correction of B0-inhomogeneities was therefore essential for DTI. Furthermore, in the present study we found reliable BOLD-signals in all performed experiments, although functional imaging using BOLD-fMRI is based on statistical modelling, and does not claim 100% sensitivity and specificity in delineating cortical areas responsible for a function [26]. Individual differences in activation patterns and signal intensity were seen. These differences also varied as a function of the proximity between the tumor masses and the investigated cortex [1, 28]. EPI-based fMRI also suffers from issues of patient compliance and head movements during experiments [11], and we found that training even the most trivial task was important for achieving satisfying results. It is important that the surgeon is aware of these methodological limitations in image quality and consistency, and acts accordingly.

In the present study we have demonstrated how both fMRI and DTI data can be integrated into a neuronavigation system for improved surgical planning and guidance. Surgical planning based on pre-operative MRI data has been done for many years with good results [38]. Recently, also others have shown that fMRI and diffusion tensor data can be integrated into navigation systems [4, 5], and that the additional information is important for optimal planning of the surgical procedure. However, by using intra-operative ultrasound we experienced that the value of high-quality pre-surgical MR images for guidance dropped considerably immediately after the craniotomy. To some extent the surgeon could mentally correct for this, especially at the very beginning of the operation. But brain shift is a challenging problem and the lack of intra-operative updates have made many of the commercial neuronavigation systems into planning tools instead of technology improving surgical guidance. Still, direct benefits for the patient have been documented also for these systems [38]. Although various modalities for intra-operative structural imaging have been demonstrated, important pre-operative data like fMRI that is hard to acquire intra-operatively still need to be positioned correctly during the operation for optimal use. Both intra-operative MR and intra-operative ultrasound can be used to reposition these data and thus obtain the best possible clinical accuracy when guiding the procedure based on both pre- and intra-operative information.

For navigation based on pre-operative MRI the main sources of error are the image to patient registration and the fact that the data is not updated in order to compensate for brain shift. In contrast, image to patient registration is not needed for navigation based on intra-operative ultrasound as acquisition is performed in the same co-ordinate system as navigation is executed. The clinical navigation accuracy of the ultrasound based neuronavigation system SonoWand has previously been evaluated to be below 2 mm based on slicing a recently acquired ultrasound volume [15]. It should be noted that the observed mismatch between pre-operative MRI data and intra-operative ultrasound data can only be interpreted as brain shift if 1) the independent MR and ultrasound navigation accuracy measured in a controlled environment (lab) is very low, 2) the MR to patient registration is verified to be small and 3) the ultrasound navigation is based on a recent ultrasound acquisition. Moreover, if intra-operative ultrasound is used to update pre-operative MRI data, the accuracy of the corrected MR images can be improved towards the ultrasound navigation accuracy. However, multimodal registration between MRI and ultrasound is complex and may introduce additional error sources.

The present study shows that automatic ultrasound-based updates of important pre-operative MRI data are feasible and hence can be used to compensate for brain shift. However, further refinements are needed in order for the MRI to ultrasound step of the proposed registration scheme to work fully automatically in a robust and stable manner. Also, the use of a rigid transform in the co-registration between a master MR volume and an initial ultrasound volume acquired from the dura was reasonable. Though the rigid mismatch sometimes was substantial (patient registration errors and shift included), the deformation in the target area was relatively small. Besides, refining this step of the algorithm with an additional deformable registration method is possible but may introduce new model parameters making the algorithm less robust and more time consuming. Moreover, it is also likely that multimodal deformation detection at this stage might be triggered by differences between the two modalities just as much as actual tissue deformations (Figs. 7 and 8). Vessels imaged by ultrasound tend to be more smeared out and appear thicker than the same vessels imaged by MRA. Ultrasound is more sensitive to small vessels and ultrasound Power Doppler shows both arteries and veins whereas MRA usually shows one or the other. Furthermore, whereas the master MRA to initial USA registration step is multimodal, the tracking of brain shift during surgery can be made unimodal using USA (at time t1) to USA (at time t2) registration. This will increase the robustness for both the linear and

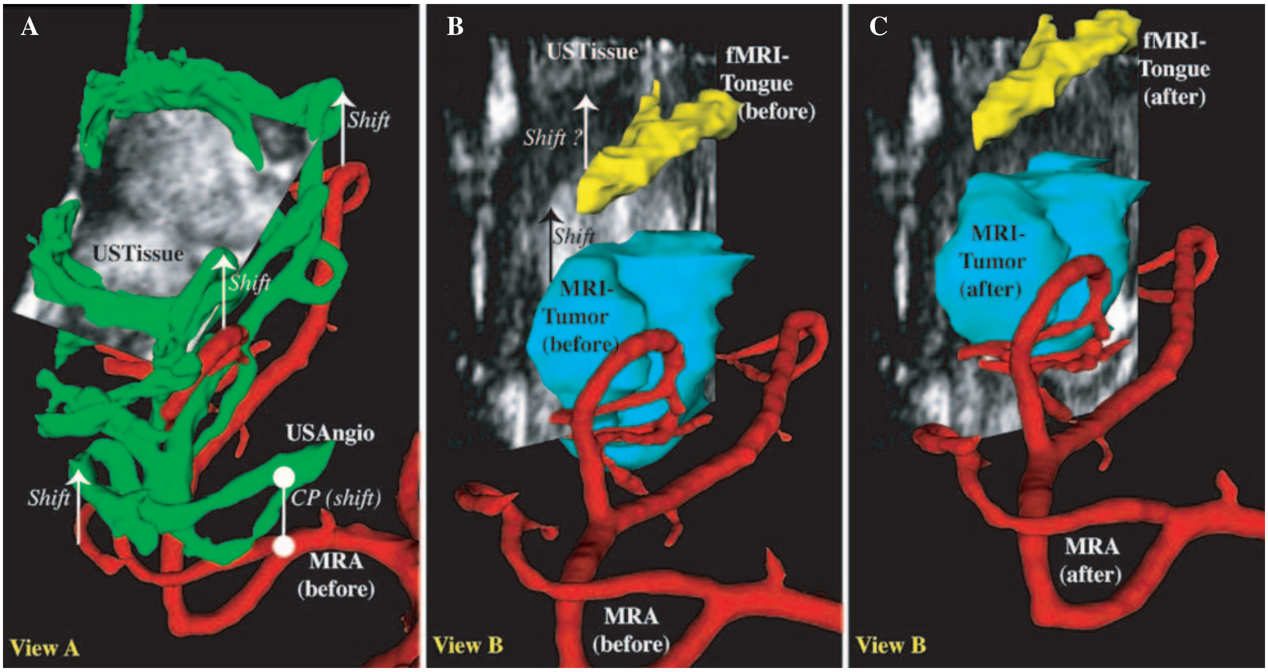

Fig. 8. The use of intra-operative 3D ultrasound to update essential pre-operative data due to anatomical changes that occur during surgery (patient #1). (A) Even before surgery starts, considerable shift between pre-operative MRA (red) and intra-operative ultrasound angiography (green) can clearly be observed by looking at identical structures in the two datasets. (B) Before brain shift compensation ultrasound tissue data disclosed a mismatch when compared with the segmented MRI tumor border (blue). Furthermore, the tongue activation appeared to be inside the tumor as depicted by ultrasound. Obviously this is not the case as can be seen in (C) where both structural and functional MR data have been moved according to the mismatch detected by the automatic registration algorithm

the non-linear part of the registration, which is important as surgical manipulation and resection probably will increase the need for the deformable step. Additionally, brain shift does not seem to occur uniformly in different tissues. It is well known that deep-seated midline brain structures shift less than brain tissue closer to the cortical surface [5]. The proposed framework should be able to handle such complex deformations. In the future a rigid registration may be applied first to find the global translation and rotation followed by a non-rigid registration to find the local deformation in the area covered by the ultrasound probe. If only angiography data is used in the registration we must assume that enough vessels exist in the target area and that these vessels move with the surrounding tissue. This assumption is probably correct in most cases. If not, tissue data can be used in addition to the angiography data in the registration. Registration of subsequent ultrasound volumes using tissue data will probably give far better results than the tissue based multimodal MR to ultrasound registration that have been investigated in this paper, especially when we do not image high contrast structures like the ventricles. Still, challenges do exist. For example the problem with ‘‘user induced deformations’’ sometimes experienced when freehand 3D ultrasound is used [15], particularly for angiography data as flash artifacts and different acquisition directions and hand movements can lead to small variations in the volumes. However, the repeatability issues could be eliminated completely if a 3D ultrasound probe (motorized or 2D array based) that imaged from the same location during the procedure was used. Also, the proposed framework would be more robust if combined with additional options to manually initiate the co-registration in cases with large shifts or correct the automatic registration results if needed. Vessel bifurcations are well-defined and easily accessible image landmarks that would make such an additional manual step relatively straightforward in most cases (Fig. 8A).

Though updating pre-operative MRI data based on intra-operative 3D ultrasound data faces many challenges, we have demonstrated a method that may pinpoint future directions in navigated surgery. Still, the method for updating relevant information must be further refined for practical clinical use. In addition a clinical study evaluating the effect on patient outcome for guiding surgical procedures based on additional information like fMRI and DTI should be performed, both with and without brain shift correction. This will probably disclose important knowledge of the true value of this information in surgical guidance.

Conclusions

In the present study we have shown that high quality functional MRI data can be acquired, imported and used in an ultrasound-based neuronavigation system on a routine clinical basis. Functional neuronavigation was found to be helpful to the surgeon for both pre-operative planning and intra-operative navigation and control. Furthermore, we have developed and postoperatively demonstrated a vessel-based method for brain shift correction of pre-operative MRI data. Automatic co-registration based on intra-operative 3D ultrasound makes it possible to display relevant and important information correctly, which is needed for accurate, safe and efficient neurosurgical resections. The full integration of fMRI, DTI and structural MRI into an ultrasound-based neuronavigation system is a powerful combination as it enables tailor-made pre-surgical planning as well as navigation based on updated multimodal information during surgery.

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Comments

In their study Rasmussen and co-workers report on a combination of techniques for the implementation of functional MRI data (fMRI, fibre tracking with DTI) in a 3D-Ultrasound neuronavigation system. They report a series of 12 patients operated with this technique.

The idea of this is to intra-operatively present brain regions of functional activity (eloquent tissue) to the neurosurgeon, which is called "functional neuronavigation", and to test the feasibility of ultrasound updates to restore spatial information of functional data and by this to compensate brain shift.

The concept is intriguing. However, the idea is not new. Our group has earlier proposed and elaborately shown the use of 3D ultrasound for the update of functional image data that is used intra-operatively on the basis of landmark tracking [1]. This development is a logical step in the evolution of more sophisticated neuronavigation systems which allow to work with multimodal data sets that combine structural and functional information in a time where not every neurosurgical unit can use intra-operative MRI.

The merit of the presented study is the combination in one machine (SonoWand, Mison, Trondheim, Norway). However, brain shift compensation and the investigation of the effects on functional data again is done purely off-line. The automated algorithm that is based on angio-architecture which is acquired intra-operatively and used (off line) to realign intra-operative structural and preoperative functional information appears straightforward. However, the authors will have to prove in a larger series if non-uniformity of tissue shift – which we know to occur e.g. in the midline – has an effect on the robustness of the proposed technique.

To be of real help for the operating neurosurgeon, brain shift and its effects on a functional environment (be it dislocation or deformation) has to be detected, compensated for and to be displayed intra-operatively. The presented study – like previous one – goes a further step into this direction.

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The study proposes to integrate functional MRI and Diffusion Tensor Imaging with an Ultrasound based navigation system and also address the issue of brain shift correction. A neuronavigation system like this would definitely prove to be an inexpensive and convenient modality for surgical guidance than the cumbersome and costly intra operative – MRI systems, However, standardization and accurate reproducibility of volume data is challenging and would hold the key in determining success of this system. The tool holds promise as it compensates for brain shift and if it achieves technical finesse, would definitely be a strong candidate for becoming the neuronavigation system in near future.

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