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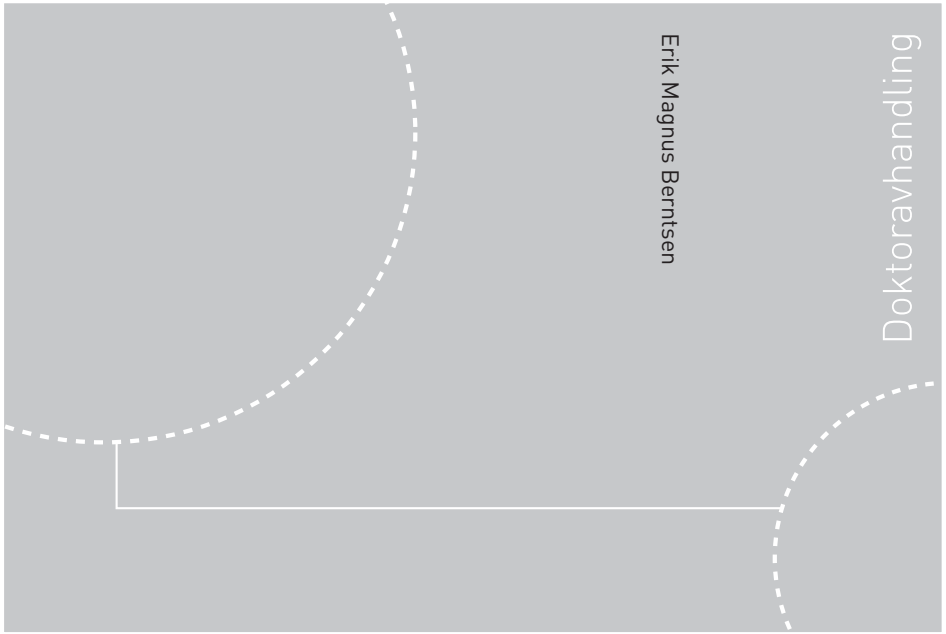

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Trykt av Tapir Uttrykk

Preoperativ planlegging og funksjonell nevronavigasjon med funksjonell MR og diffusjon tensor traktografi i pasienter med hjernesvulster

Funksjonell MR er en populær forkortelse på MR-teknikken Blood-Oxygenation-Level-Dependent functional-Magnetic-Resonance-Imaging som kan brukes til å kartlegge hjernens grå substans. Her sitter nevronene som styrer viktige funksjoner som f.eks. språk, kroppsbevegelser, hukommelse og personlighet.

Diffusjon tensor traktografi er en MR-teknikk som kan brukes til å framstille hjernens hvite substans, som er nerveledningene mellom ulike deler av grå substans i hjernen.

Hos pasienter med hjernesvulster nært viktige områder i grå og hvit substans, kan man bruke disse teknikkene til å kartlegge hvordan disse områdene sitter i forhold til svulsten. Denne informasjonen kan brukes både til å planlegge inngrepet før operasjonen, men også til navigere og kontrollere fjerningen av svulsten under operasjonen. Under operasjonen gjøres dette ved å integrere bildene i et nevronavigasjonssystem, som er en enhet hvor man på bilde-data kan se posisjonen på kirurgens instrumenter i forhold til hjernen og svulsten. Disse bildedataene kan være tatt opp før operasjonen (f.eks. MR) eller under operasjonen (f.eks. ultralyd).

Hovedfunnene i denne avhandlingen er:

- for å best kartlegge det primære motoriske området bør man benytte bevegelse av fingre, tær og tunge under MR-undersøkelsene

- for å best kartlegge det fremre språkområdet bør man benytte en oppgave hvor man på kommando skal generere ord, mens for det bakre språkområdet bør man benytte en oppgave hvor man skal finne navnet på det som blir beskrevet (f.eks. ”høy rosa fugl”)

- ved å benytte en oppgave hvor man både skal løse en oppgave og produsere et svar, kan man kartlegge det fremre og bakre språkområdet i en og samme undersøkelse (f.eks. svare ”Hva er ku” på utsagnet ”Dyr som sier mø”)

- ved å bruke funksjonell MR og diffusjon tensor traktografi kombinert med et nevronavigasjonssystem som benytter seg av oppdatert anatomisk informasjon fra 3D ultralyd under operasjonen, får nevrokirurgene en fordel når de opererer som muliggjør et kompromiss mellom å fjerne så mye svulstvev som mulig uten å samtidige risikere nye nevrologiske utfall

Candidatus medicinae Erik Magnus Berntsen
Institutt for sirkulasjon og bildediagnostikk
Veiledere: Asta Kristine Håberg
& Olav Haraldseth

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Sammendrag

Blood-Oxygenation-Level-Dependent functional Magnetic-Resonance-Imaging (BOLD fMRI) og Diffusion Tensor Imaging (DTI) er spesialiserte MR-teknikker for avbildning av henholdsvis funksjonelle områder i grå substans og nevronale forbindelser i hvit substans. Ved å bearbeide BOLD fMRI bildene kan man kartlegge funksjonelle områder i hjernen og visualisere dem i form av fargekart for eksempel overlagt på anatomiske MR-bilder. Ved å bearbeide DTI bildene med en teknikk som heter Diffusion Tensor Tractography (DTT) kan man kartlegge nevronale forbindelser i hjernen og visualisere dem som "fiber-bunter". Resultatet fra disse undersøkelsene kan være til hjelp ved planlegging og reseksjon av hjernesvulster fordi disse metodene gir informasjon om funksjonen i grå og hvit substans som ligger i nærheten av svulsten. Dermed kan man operere bort mest mulig av svulsten uten å skade disse viktige funksjonelle områdene under operasjonen. Slik funksjonell informasjon fra BOLD fMRI og DTT kan integreres i nevronavigasjons-systemer og brukes under selve operasjonen. Det overordnede målet med arbeidet bak denne avhandlingen har vært å utvikle, implementere og evaluere BOLD fMRI og DTT ved 3 Tesla for rutinemessig bruk i forbindelse med prekirurgisk planlegging og funksjonell nevronavigasjon kombinert med minimal invasiv nevrokirurgi.

En første tilnærming til å utvikle BOLD fMRI oppgaver for bruk til kartlegging av viktige områder i hjernebarken hos pasienter er å samle inn normgivende funksjonelle data i friske individer. Vi undersøkte derfor et utvalg motoriske oppgaver med BOLD fMRI i friske forsøkspersoner, for deretter å evaluere hvilke som var best egnet for funksjonell kartlegging og framstilling av det primære motoriske området. Bevegelse av fingre, tær og tunge var de oppgavene med høyest suksses-rate i friske frivillige og viste seg også å fungere med like stor grad av suksses for pasienter med hjernesvulster.

Vi har også undersøkt et utvalg språkoppgaver i friske forsøkspersoner for å evaluere reproduserbarhet og grad av lateralisering av språkaktiveringene i de enkelte oppgavene, for å bestemme hvilke oppgaver som er best egnet til å kartlegge de fremre og bakre språkområdene. Vi fant at en ordgenererings-oppgave var best egnet for kartlegging av

det fremre språkområdet, mens en navngivings-oppgave var best egnet for det bakre området.

Vi har også utviklet en ny språkoppgave med potensialet for samtidig kartlegging av både det fremre og bakre språkområdet i en og samme undersøkelse. Denne oppgave har i tillegg fordelen av å være mer engasjerende å utføre, noe som kan hjelpe personen som utfører oppgaven til å beholde konsentrasjonen og motivasjonen gjennom hele undersøkelsen.

Vi har også evaluert bruken av BOLD fMRI og DTT i ultralyd-veiledet funksjonell nevronavigasjon ved å retrospektivt gå igjennom et 3-års materiale med pasienter operert på denne måten. Her fant vi at fjerning av hjernesvulstvev ga en signifikant forbedring i klinisk status etter 3 måneder sammenlignet med før operasjonen. For gliomene fant vi et gjennomsnittelig gjenværende svulst volum på 11% etter operasjonen. Vi fant også en signifikant korrelasjon mellom avtagende avstand mellom tumor og funksjonelt område og økende gjenværende svulstvolum etter operasjonen. Dette tyder på at operasjonene er gjennomført som et kompromiss mellom å fjerne så mye svulstvev som mulig uten å samtidige risikere nye nevrologiske utfall. Det var imidlertid noen pasienter med avstand mellom tumor og funksjonelt område på mindre enn 2 mm som ble radikalt operert uten nye nevrologiske utfall etter operasjonen. Dette tyder på at funksjonell nevronavigasjon med oppdatert anatomisk informasjon fra 3D ultralyd under operasjonen gir nevrokirurgene en fordel når de opererer, samt muliggjør så mye fjerning av svulsten som mulig uten å påføre nye nevrologiske utfall.

Utfordringene i den videre bruken av disse teknikkene består i å etablere standardiserte oppgaver og analyser for tolkning av disse undersøkelsene, samt å planlegge og utføre kontrollerte kliniske forsøk, enten i form av prospektive oppfølgings studier eller randomiserte studier, for å evaluere effekten av prekirurgisk BOLD fMRI og DTT på morbiditet og mortalitet i pasienter med hjernelesjoner.

Summary

Blood-Oxygenation-Level-Dependent functional Magnetic-Resonance-Imaging (BOLD fMRI) and Diffusion Tensor Imaging (DTI) are specialized MRI-techniques for imaging of eloquent cortices and neural tracts in gray and white matter, respectively. By processing of the BOLD fMRI images, it is possible to map eloquent cortices and visualize them as statistical parametric color coded maps to be overlain on for instance anatomical MRI-images. Processing of the DTI images using a technique called Diffusion Tensor Tractography (DTT), makes it possible to map important neural tracts and visualize them as fiber bundles. The results from these examinations may be helpful during planning and resection of brain lesions, by providing information on functional eloquent cortices and important white matter tracts in close proximity to the lesion, as the goal of surgery is to maximize resection without inflicting new neurological deficits. This functional information may also be incorporated into neuronavigation systems and utilized during surgery. The overall aim of this thesis was to develop, implement, and evaluate BOLD fMRI and DTT at 3 Tesla for routine use in preoperative planning and 3D ultrasound-guided functional neuronavigation combined with minimal invasive neurosurgery.

Obtaining normative functional data in healthy subjects is a first step in the development of clinical useful tasks. Thus, we investigated different motor tasks in a group of healthy subjects to evaluate which combination was best suited for functional mapping and delineation of the primary motor cortex. Movement of fingers, toes, and tongue yielded the highest success rates in healthy subjects and proved equally successful in patients with brain lesions.

We also investigated a set of language tasks and the reproducibility of the activation size and location for these. We found that a word-generation task and a responsive naming task should be preferred for mapping of the frontal and temporal language area, respectively.

A novel language task with the potential to map both the frontal and temporal language areas was also established. This task has the advantage of being more engaging, which may help the subjects to maintain concentration and stay motivated throughout the scanning session.

We have also evaluated the use of BOLD fMRI and DTT in 3D ultrasound-guided functional neuronavigation by retrospectively reviewing patients operated during a three-year period. We found that surgery gave an overall significant improvement in clinical status compared to preoperatively, and for gliomas we found a median residual tumor volume of 11%. We also found a significant correlation between decreasing lesion-to-eloquent-area distance and increasing residual tumor percentage in gliomas, indicating that the resections were performed as a compromise between removing as much tumor tissue as possible without jeopardizing eloquent areas. Furthermore, some glioma patients with lesion-to-eloquent-area distance less than 2 mm also had radical resections without post-operative neurological deficits. Thus indicating that guided functional neuronavigation with updated anatomical information using 3D ultrasound gives the surgeon an advantage when resecting brain lesions, as well as facilitates maximal tumor resection with minimal deficit.

The challenges ahead lie in establishing standardized tasks and analysis for processing of these investigations, as well as carrying out prospective outcome studies or clinical randomized trials in order to produce evidence for effect of presurgical BOLD fMRI and DTT on morbidity and mortality in patients with brain lesions.

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Finally, I am grateful for the patience and support of my girlfriend Marianne.

Erik Magnus Berntsen

Trondheim, June 2009

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Abbreviations

AVM	Arteriovenous Malformation
BOLD	Blood Oxygenation Level Dependent
Deoxy-Hb	Deoxygenated-Hemoglobin
DTI	Diffusion Tensor Imaging
DTT	Diffusion Tensor Tractography
EPI	Echo Planar Imaging
FACT	Fiber Assignment by Continuous Tracking
FMRI	functional Magnetic Resonance Imaging
Hb	Hemoglobin
LEAD	Lesion-to-Eloquent-Area Distance (LEAD)
MRI	Magnetic Resonance Imaging
Oxy-Hb	Oxygenated-Hemoglobin
PET	Positron Emission Tomography
SENSE	SENSitivity Encoding
TMS	Transcranial Magnetic Stimulation

List of Publications

1. Integrated pre- and intraoperative imaging in a patient with an arteriovenous malformation located in eloquent cortex**. Berntsen EM, Gulati S, Solheim O, Kvistad KA, Lindseth F, Unsgård G;** ***Minimally Invasive Neurosurgery, 2009 Apr; 52 (2): 83-5***

2. Mapping the primary motor cortex in healthy subjects and patients with peri-rolandic brain lesions before neurosurgery**. Berntsen EM, Samuelsen P, Lagopoulos J, Rasmussen jr. IA, Håberg A.K, Haraldseth O;** ***Neurological Research 2008 Nov; 30 (9): 968-73***

3. Reproducibility of functional MRI activations in language areas with three language tasks. **Berntsen EM, Rasmussen jr. I.A, Håberg A.K, Haraldseth O;** ***Submitted to the American Journal of Neuroradiology***

4. Putting the brain in Jeopardy: a novel comprehensive and expressive language task? **Berntsen EM, Rasmussen jr. IA, Samuelsen P, Xu J, Haraldseth O, Lagopoulos J, Malhi GS;** ***Acta Neuropsychiatrica 2006 Apr; 18 (2): 115-119***

5. Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative navigated 3D ultrasound. **Gulati S, Berntsen EM, Solheim O, Kvistad KA, Håberg A, Selbekk T, Torp SH, Unsgård G;** ***Minimally Invasive Neurosurgery 2009 Feb; 52 (1): 17-24***

6. BOLD fMRI and diffusion tensor tractography incorporated into a 3D ultrasound-based intra-operative imaging navigation system: impact on therapeutic strategies, extent of resection and clinical outcome. **Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T, Unsgård G, Håberg A;** ***Submitted to Neurosurgery***

1. Introduction

Magnetic Resonance Imaging (MRI) is today a key stone in imaging and differentiation of intra-cranial soft tissue masses with a high degree of anatomical detail, thus offering valuable information prior to neurosurgery. The last two decades has conceived additional MRI-techniques such as Blood-Oxygenation-Level-Dependent functional-MRI (BOLD fMRI) which may be used for mapping of eloquent cortices visualized using color-coded statistical parametric maps overlaid on for instance the anatomical images of the brain. Another novel MRI-technique is Diffusion Tensor Imaging (DTI) which may be used for mapping of neural tracts in the white matter, which through an analysis called Diffusion Tensor Tractography (DTT) can visualize the neural tracts as three-dimensional fiber bundles. Together with conventional anatomical imaging, functional imaging with BOLD fMRI and DTT may be helpful during planning and resection of brain lesions, as the goal of neurosurgery is to maximize resection without inflicting new neurological deficits. This functional information from the MRI images may also be incorporated into neuronavigation systems and utilized during surgery, thus named functional neuronavigation. Preoperative mapping and functional neuronavigation during neurosurgery are currently the best-established clinical application of BOLD fMRI and DTT [1]. The overall aim of this thesis was to develop, implement, and evaluate BOLD fMRI and DTT at 3 Tesla for routine use in preoperative planning and 3D ultrasound-guided functional neuronavigation combined with minimal invasive neurosurgery.

1.1 Magnetic Resonance Imaging

The following chapter will give a qualitative description of MRI, while the subsequent chapters will describe the basics of fMRI and DTI in more detail. For a more thorough description of the theoretical basis of MRI the book *"MRI – The Basics"* by Hashemi, Bradley and Lisanti is recommended [2].

MRI is an imaging technique able to depict inner organs of the human body based on the physical properties of unpaired atomic nuclei. As the two major components of the

human body, water and fat, are abundant with hydrogen atoms (^{1}H), this is the nuclei most commonly used for medical imaging. By placing the hydrogen atoms in a large static magnetic field and manipulate them with electromagnetic fields, one is able to derive information about tissue properties at specific spatial localizations and thereby produce images of the organ examined. Different tissue properties may be derived and used for image production. The static magnetic field is typically 1.5 Tesla, 30.000 times earth's magnetic field, and the electromagnetic field is then 63.87 megahertz. The first MRI-image of *in vivo* human anatomy was acquired in 1977 by sir Peter Mansfield and Andrew A. Maudsley and was a cross section through Maudley's finger revealing "considerable anatomical detail, particularly of the soft tissue regions" taking 23 minutes to produce [3].

In clinical practice today, MRI is primarily used to identify tissue pathology in a range of disease processes, especially in the central nervous system and soft tissues using a variety of structural imaging techniques. Other MRI techniques depicting tissue function and metabolism are, however, rapidly evolving and increasingly used in the clinic.

1.2 Blood-Oxygenation-Level-Dependent fMRI

Blood-Oxygenation-Level-Dependent fMRI, hereafter referred to as fMRI, is a specialized MRI-technique using a T_2*-weighted gradient echo sequence. The basis for this technique was first reported by Ogawa et al. in 1990. They discovered that this special MRI-sequence was sensitive to changes in the concentration of de-oxygenated hemoglobin (deoxy-Hb) in blood [4]. Furthermore, they reported signal changes around the vessels in the rat brain at different levels of blood oxygenation, and based on this suggested that this sequence could be used to study regional brain activity, similar to Positron Emission Tomography (PET) [5]. These discoveries were the foundation for functional neuroimaging with fMRI and in 1992 three separate groups published functional studies with fMRI in humans [6-8].

The physical basis for the BOLD signal lay in the physical properties of deoxy-Hb, being paramagnetic, and thus having the ability to influence the MRI signal [4, 9]. Changes in the level of deoxy-Hb compared to oxy-Hb will therefore give a variation in the measured MRI signal, known as the BOLD signal [5]. The neurophysiological basis for the BOLD signal lay in changes of blood flow, volume, and level of oxygenation following neuronal activity, the so-called neurovascular coupling [10]. The complex mechanism of this neurovascular coupling is not fully understood and several models are proposed, but none of these fully explain all aspects of the biophysics giving rise to the BOLD signal [11, 12]. The most intuitive and simplified explanation is that local neuronal activity requires an increased local metabolism with an increased need for glucose and oxygen [13]. This is achieved by a local increase in blood flow and concomitant increase in blood volume, supplying the extra glucose and oxygenated hemoglobin (oxy-Hb) needed. The amount of oxy-Hb delivered is, however, greater than the amount of oxygen extracted, giving a paradoxical local increase in oxy-Hb and thus a local decrease in the concentration of deoxy-Hb. Even though the neurovascular coupling is not understood in detail, it has been shown that fMRI activations do reflect increase in neural activity and mostly the input and intra-cortical processing in a given cortical area [14, 15]. Furthermore, it has been shown that fMRI has good concordance with other brain mapping techniques such as intraoperative motor evoked potentials and intraoperative electrocortical mapping [16-19].

While fMRI has been an invaluable research tool to non-invasively study the brain at work at high spatial resolutions in healthy human brains, its primetime in clinical practice is yet to come. The use of fMRI in clinical research has been applied to some extent in different patients groups to better understand recovery of stroke, progression of multiple sclerosis, Parkinson's and Alzheimer's disease, as well as schizophrenia, bipolar disorder, attention deficit disorder, depression and obsessive compulsive disorder [20]. Some of the earliest examples of fMRI used in clinical practice is for preoperative mapping prior to surgery of epileptic foci, neoplastic brain tumors and arteriovenous malformations (AVMs) [21-23]. Other areas of clinical use have also been explored, such as imaging of auditory cortex prior to cochlear implantation [24, 25].

1.2.1 fMRI in practice and methodological considerations

An fMRI investigation consist of several steps, starting with a subject lying inside an MRI-scanner performing a particular task at given times, while MRI-images are acquired. After scanning these images need to be pre-processed before statistical analysis is performed, in order to produce color-coded statistical parametric activation maps. Thereafter, these activation maps need to be interpreted. Obviously the process from image acquisition to interpreted functional maps consists of several steps each vulnerable to different sources of error. Thus, expertise in fMRI acquisition, analysis and functional neuroanatomy is required to performed these investigations accurately [26].

The T_2*-weight sequence used for fMRI is very sensitive to inhomogeneities in the magnetic field, giving signal distortions. This is especially a problem in regions where there is crossing between tissues (e.g. air filled sinuses) and metal shavings from prior operations [27]. There exists strategies for overcoming these problems, e.g. alternative MRI-sequences, such as spin echo BOLD fMRI or arterial spin labeling, and also methods for mapping of B0-field variations to warp distortions after acquisition [28]. The extent of these inhomogeneities varies with the strength of the static magnetic field, which also affects the BOLD signal. It has been shown that an increased proportion of the BOLD signal arises from the brain tissue (and thus the active neurons) rather than draining veins at higher field strengths [29]. Furthermore, the contrast-to-noise also increases with higher field strength, giving a stronger BOLD signal [29].

The task itself is usually presented visually either through MRI-compatible goggles or by using a liquid crystal display (LCD) located behind the scanner opening and viewed via a mirror mounted on the head coil. The task is traditionally presented as a block design, event-related design or as resting-state experiment. In a block design the task is usually presented in blocks between 15-30 seconds interleaved with equally long or longer blocks of rest, e.g. 4 blocks of 30 seconds with finger movement interleaved with 5 blocks of 30 seconds of rest. In an event-related design the task will be presented for a briefer period of time at random intervals, e.g. usually 30 or more events lasting from under a second to 10-15 seconds randomly presented with periods of rest with longer duration, usually 5-30

seconds. In both the block-design and event-related-design the analysis is based on convolving the hemodynamic response function (see later) with the signal in the periods of activity. For resting state fMRI, however, there is no task or stimuli to respond to. For these experiments one is interested in spontaneous fluctuations of the BOLD signal in a low-frequency range (< 0.1 Hz), which are proposed to represent spontaneous neuronal activity and used for functional connectivity analysis [30]. For clinical purposes, such as preoperative mapping, block-design is most often chosen as it yields strong and robust activations. The specific task(s) the subject is to perform depends on the cortical area to be mapped. In presurgical planning the most frequently used paradigms are different motor and language tasks. For motor tasks the subjects are instructed to do for instance finger-tapping when a finger is presented on the screen. For language tasks the subjects are instructed to do for example word generation covertly without moving the tongue or mouth when a letter is presented. Covert language generation is done in order to avoid artifacts related to movement and also due to differences in the amount of air in the mouth in relation to vocalization.

It is important that the subjects undergoing the fMRI investigation are able to perform the given task, i.e. that he/she performs the task at the right time so the statistical analysis has the correct contrast when analyzing. This may be controlled fairly well by observing the subject if a motor task is performed, or by using some sort of response to indicate start or end of task performance within each block. However, controlling a covertly executed language task is more difficult. One possibility is to ask the patients afterwards how it went and also to perform the task again outside the scanner to get an impression of performance, but such post-scanning evaluations will be subjective and may be biased. Another possibility is to have the subjects pushing a response button each time they solve the task (i.e. produce a new word). This will, however, make the task much harder to perform, and recruit both motor cortex and cortical areas for dual tasking in addition to the language cortex, making the analysis and interpretation of activation maps much more complicated [31]. This exemplifies that for some fMRI investigations it is difficult to know with absolute certainty how well the task was performed. It is also important that the subject is able to lie still when solving the task, as movement of the head during

scanning gives rise to signal distortions. This is usually solved to a certain degree with physical constraints of the head. The ability to correctly perform the task solving with the head still are factors that may vary with age, cognitive function and intracranial pathology in the subjects. These factors are therefore important to consider when performing an fMRI investigation in order to pick the paradigms best suited to delineate the cortical regions close to the lesion and at the same time ensure patient compliance.

After image acquisition the fMRI data has to be pre-processed to correct for head movement during scanning and remove cardio-respiratory artifacts and other cyclical related noise. These pre-processing steps have many variables which may provide different results if adjusted. Furthermore, preprocessing is heavily dependent on the algorithms used, which may differ slightly between the different software packages, exemplifying the lack of standardized pre-processing methods for fMRI data [32]. In order to anatomically localize the eloquent cortex mapped with fMRI, the functional images have to be co-registered to anatomical images, which have greater anatomical detail. This procedure is usually partial automatic and partial manual. In the current work, where fMRI images where to be overlain on each individual's anatomical scan for export into the neuronavigation system, careful registration between the fMRI and anatomical T_1 weighted images is of vital importance. In order to ensure the best possible fit a manual procedure was used and followed the automatic alignment. This manual procedure consisted of careful inspection of the proposed automatic alignment at several different anatomical localizations and if necessary fine tune the alignment manually, thus making the co-registration user dependent. As the functional images and anatomical images are not identical, there will always be some discrepancy between them. The user can, however, ensure as good as possible co-registration within the regions of interest, being the areas with anticipated activations for the function investigated. After co-registration, statistical analysis has to be applied in order to identify activated brain areas. This is done using assumptions about temporal properties of the BOLD signal, the so-called hemodynamic response function, which may be modeled according to different functions, for instance by either a single gamma or a double gamma function [33, 34]. For visualization of activity, statistical activation maps is then calculated using the

General Linear Model with conditions modeled according the (block) paradigm, and convolved with the hemodynamic response function [35]. These activation maps then represent brain-activity which subsequently needs to be thresholded statistically and their functional significance interpreted.

There is no consensus on how to threshold statistical parametric activation maps for fMRI investigations, except that there is a general agreement that some kind of correction for multiple comparison should be performed, especially when analyzing group studies. Some fMRI studies use anatomical defined regions of interest to limit the area of interest when analyzing the data, e.g. functional studies of the hippocampus [36]. Furthermore, many studies evaluating and comparing different fMRI tasks use such regions of interest based on anatomical landmarks or Brodmann's or other maps of cytoarchitecture [37, 38]. For presurgical mapping, however, the statistical activation maps are individually thresholded for each subject and each task, in order to produce activation maps unequivocally delineating the cortical area of interest. This is a pragmatic way of analyzing fMRI for presurgical mapping. Another issue is that fMRI investigations do not necessarily differentiate between essential and participating brain areas unless the task has been specifically designed to do so [39, 40]. Thus, single subject fMRI analysis for presurgical mapping is inherently a user dependent process, heavily dependent on the user's competence, comprehension of functional neuroanatomy and interpretation of the activations.

As stated previously, there are no standardized tasks, scanning procedures, administration of tasks, pre-processing or interpretation of activations for clinical applications of fMRI, something that is desirable and needed in order to obtain objective and comparative information between the centers engaged in this activity [40]. This is one of the main challenges for clinical fMRI in the future.

1.3 Diffusion Tensor Imaging and Tractography

Diffusion Tensor Imaging (DTI) is developed from Diffusion Weighted Imaging which uses a spin-echo sequence combined with two gradient pulses, depending on the ability of water molecules in tissue to diffuse randomly, i.e. Brownian motion [41]. When applying the diffusion gradients, water molecules, which have moved in a direction along the gradient, will give rise to signal loss. When applying the diffusion gradients in the X, Y and Z direction, diffusion weighted images can be made representing diffusion in a given voxel. DTI is an advanced form of diffusion weighted imaging, where the gradients are applied in at least three more directions (combinations of the X, Y and Z direction), making it possible to create a mathematical model of diffusion in three-dimensional space, known as the diffusion tensor [42]. From this diffusion tensor it is possible to calculate the direction of maximum diffusivity, which has been shown to coincide with the fiber orientation in the white matter of the brain [43]. The more directions the gradients are applied in, the more accurate the estimate of the tensor becomes. At least six directions are needed to accurately describe the tensor. Thus, by using DTI it is possible to map the anatomical location of neural tracts in the brain, e.g. the corticospinal tracts, the optic radiations of the optic tract, and the arcuate fasciculus [41, 42, 44].

Several different parameters can be derived from the DTI images, such as maps of fractional anisotropy (FA maps) which is a measure of the magnitude of anisotropic diffusion ranging from 0 (isotropic diffusion i.e. non-directional) to 1 (anisotropic diffusion i.e. strongly directional) [45]. Another frequently derived property of DTI is the direction of maximum diffusivity modulated with the FA-value and represented as color coded maps, thus representing both the magnitude and direction of diffusion [46]. The accepted convention for color coding is with blue representing the superior/inferior direction, red the left/right direction, and green the anterior/posterior direction. A third way of presenting the DTI images is through fiber tracking or tractography, which is a visualization technique for neural tracts in three dimensions [42, 47, 48]. These three-dimensional tracts are constructed based on different algorithms such as the TENsor Deflection (TEND) algorithm or the Fiber Assignment by Continuous Tracking (FACT) algorithm [49, 50]. By using such algorithms one is able to calculate which voxels in the

different sequential slices that are connected with each other based on the diffusion tensor. These algorithms automatically suggest tracts which have to be virtually dissected using a region-of-interest tool to produce plausible tracts. Thus, if the corticospinal tracts are to be visualized one has to postulate that this tract runs through the posterior limb of the internal capsule and the precentral gyrus.

DTI and DTT are the only non-invasive methods of detecting and visualizing white matter tracts in vivo, thus having a great potential for both clinical research and practice. Some of the areas where DTI, and properties derived from DTI, have been used, are in studies of brain development, schizophrenia, Alzheimer's disease, epilepsy and for neurosurgical planning [51].

1.3.1 DTI and DTT in practice and methodological considerations

A DTI investigation consists of several steps, but unlike fMRI the subject being scanned is not required to perform a task and thus only needs to lie still, while the images are being acquired. After scanning the images has to be processed using different algorithms before tractography is performed as a final step.

The MRI-sequence used for DTI is even more sensitive to inhomogeneities of the magnetic field and head-movement than the sequence used for fMRI, causing greater distortions of the signal. Thus the importance of minimizing the head movement becomes even more important and cardiac gated synchronization of scan acquisition has been demonstrated useful in order to minimize brain pulsations following cardiac beats [52].

A fundamental problem for DTT is the lack of an in vivo gold standard for tractography, thus making it difficult to validate the different algorithms as well as the method itself. It has however been shown that DTT has good concordance with intraoperative subcortical mapping [53-56]. Furthermore, DTT processing consists of several steps with the potential of introducing error(s). For example, the user has to choose limit values for fractional anisotropy and maximum allowed angulations of tracts for use in the tracking

algorithms. White matter regions where there are several fiber bundles with different orientations or where they “kiss”, cross, merge or diverge, are particularly troublesome for the tracking algorithms. In such regions the algorithm can either not track the fiber bundles present or track pathways that do not exist [47, 57]. Similar problems arise in the presence of tumor and edema, but here some of these problems have been overcome using novel tracking algorithms or more advanced processing procedures [58, 59]. Nevertheless, the suggested tracts have to be manually and individually processed with a region-of-interest tool to virtually dissect plausible tracts of interest, by choosing anatomical localization these tracts are known to run within. If one is to visualize for example the corticospinal tracts, some potential region-of-interests to use are the cerebral peduncles, posterior limb of the internal capsule, and the superior part of the precentral gyrus. This process heavily depends on the user performing the tractography where detailed knowledge of neuroanatomy is a prerequisite, thus making also DTT a user dependent process.

1.4 Functional Brain Mapping in Neurosurgery

The goal of neurosurgery in lesions located in or near eloquent cortex is to maximize resection without inflicting new neurological deficits, posing a difficult challenge even for experienced neurosurgeons. There is growing evidence that more extensive surgical resection is correlated to prolonged survival for both low- and high-grade gliomas and the National Comprehensive Cancer Network has acknowledged this in the recent guidelines [60, 61]. Therefore, accurate localization of eloquent cortices, as well as the white matter tracts connected to these areas, is an essential adjunct to successful surgical excision in these patients. Functional mapping of the brain has, however, been pursued for decades and with the advent of new imaging techniques new ways of functional mapping has arisen. In the 1930s Otfrid Forster used electrical probes to map the motor cortex of awake patients undergoing brain surgery [62]. This work was continued by Wilder G. Penfield in collaboration with Theodore B. Rasmussen, who mapped different cortical areas during surgery, i.e. motor and language cortices, in awake patients [63]. This

method of direct electrocortical stimulation has been the gold standard for functional brain mapping, but it requires large craniotomies and is limited by the difficulty of examining in the sulcal depths and deep structures, and thus alternative mapping techniques have been sought [39]. The Wada test, which is an injection of sodium amytal in the internal carotid artery leading to temporarily anesthetizing of one hemisphere, has been used for determine lateralization of language and memory in epilepsy patients prior to lobectomy [64]. The drawback with this test is its invasive nature of the combined with the limited spatial resolution, being hemispherical. Furthermore, the procedure is cumbersome to repeat and fraught with the risk of stroke [39]. Thus non-invasive techniques have been pursued and with the advent of positron emission tomographic (PET) imaging, detecting local increase in blood flow or cerebral metabolism during task performance using radioisotopes, one was able to preoperatively depict functional cortices and their relation to brain lesions with relatively high temporal resolution [65, 66]. With the development of BOLD fMRI in the 1990s, preoperative functional mapping become easier accessible, as these investigations could be performed in regular MRI-scanners, facilitating its use. Furthermore, fMRI is even less invasive than PET, as no injection of radioisotopes is needed, and provides even better temporal and more importantly spatial resolution. A drawback with both PET and fMRI is that they do not differentiate between essential and participating brain areas when performing a task [39, 40]. This may, however, be accomplished with transcranial magnetic stimulation (TMS), a technique where a magnetic field is transmitted through the skull inducing an electric current within the cortex leading to activation or inhibition of the underlying cortical area, depending on the frequency used [67]. By applying TMS to the primary motor cortex movements will be produced, thus identifying the cortex activated as essential for production of movements. Similarly, TMS may be applied to language cortex and through inhibition produce temporary aphasia and identify cortices essential for language production. TMS may be especially useful in cases where it is not possible to perform fMRI but also in cases where the fMRI investigations are inconclusive [68]. The usefulness of TMS for functional mapping has been demonstrated in brain tumor patients, preoperative TMS has been integrated into neuronavigation systems, and clinical experience with it is emerging [68-70].

1.4.1 fMRI, DTI and DTT in Preoperative Planning

One of the first papers reporting the use of fMRI in a patient population is the one of Jack et al. in 1994, where they used both fMRI and invasive cortical mapping to map the motor cortex of two patients having epileptic seizures, due to neoplastic brain tumors located in close proximity to the primary motor cortex [21]. They found a correlation between the two techniques, and suggested that preoperative mapping was a potentially useful clinical application of fMRI. This was followed shortly thereafter by Morris et al. in 1994, who mapped the language and motor areas of three patients with epilepsy syndromes [23]. In 1995 Latchaw et al. demonstrated the same in patients with AVMs [22]. Following these reports, there was a dramatic increase in the use of fMRI in preoperative planning before neurosurgical procedures, focusing mostly on motor and language functions [71].

In 2002 Witwer et al. demonstrated the use of DTI in nine patients with neoplastic brain tumors [72]. Same year Mori et al. presented the use of DTT to visualize neural fiber tracts in close proximity to neoplastic brain tumors in two patients, and in 2004 Yamada et al. demonstrated DTT in a patient with an AVM [73, 74]. These reports have been followed by studies demonstrating the technique in larger number of patients both with neoplastic brain tumors and AVMs [75-79].

Since the brain consists of both white and grey matter, fMRI and DTI can together provide valuable information prior to neurosurgery. Combined, both techniques provide additional information for the surgeon in the preoperative planning of the neurosurgical procedure [40]. Some studies have investigated the combination of fMRI and DTI prior to neurosurgery. In 2004 Ulmer et al. demonstrated that twice as many functional systems were localized within 5 mm of the tumor borders when DTI and fMRI were combined compared to fMRI alone in 28 patients [80]. The functional systems taken into consideration were language, speech, vision, motor and pre-motor functions. Furthermore, only one out of the 24 operated patients (4%) encountered unplanned surgically-induced deficit. The study of Hendler et al. from 2003 based on 20 patients with brain lesions made use of fMRI, DTI and DTT, concluding that the combination of

fMRI and DTI provided valuable information that could not be extracted using either method alone [81]. Furthermore, the use of DTT seemed crucial and invaluable for visualization and understanding the complicated spatial relationship between the lesion, gray matter, and white matter fiber bundles.

1.4.2 fMRI, DTI and DTT in Functional Neuronavigation

During the last two decades several neuronavigation systems for performing frameless stereotactic neurosurgery have been developed, where anatomical data can be used intraoperatively to navigate in the brain during surgery [82-86]. Thus the need for integration of functional information from fMRI and DTI into the navigation systems has emerged, in order to take advantage of this functional information also during surgery. Given the functional nature of the information this has been named functional neuronavigation. Some of the first papers on functional neuronavigation are the ones of Malidjan et al. and Shulder et al. in 1997, where they integrated fMRI into a neuronavigation system, allowing functional identification of eloquent cortex [87, 88]. This was followed by several others in the years to come, either in larger number of patients or combined with other mapping techniques such as direct cortical stimulation [89, 90]. The information from DTI and DTT has also been integrated into such neuronavigation systems, as demonstrated by Nimsky et al. in 2005, where fiber tract data from patients with brain lesions were reliably integrated into the navigation system [91, 92]. As a natural consequence, integration of combined fMRI and DTT images into neuronavigation systems has been demonstrated and used for functional neuronavigation [93, 94]

There have been a number of clinical papers suggesting that the additional information provided by functional imaging (fMRI and/or DTT) is highly valuable and enables safe resection [19, 73, 77, 79, 95-99], especially when incorporated into a neuronavigation system [91, 94, 100-103]. In previous studies, either integrating fMRI data into neuronavigation systems [103, 104] or based on clinical demonstration of fMRI data and structural pathology [97, 105] a minimal distance between 5 to 15 mm for feasible

surgical resection has been suggested. A few papers have also focused on functional navigation using intraoperative 3D ultrasound for intraoperative guidance as well as correction of brain shift [93, 106]. To our knowledge only one prospective randomized trial examining the clinical impact of DTI-data on degree of tumor resection, clinical outcome and survival has been published. Wu and colleagues demonstrated that high-grade glioma patients benefit both in terms of increased tumor resection, improved postoperative outcome and time of survival when DTI-data was used to navigate during surgery, compared to those operated with conventional neuronavigation [107]. This is supported by other non-randomized uncontrolled studies [101, 102].

1.4.3 Considerations regarding Functional Neuronavigation

A big challenge for navigation based on preoperative images is the presence of brain shift during surgery [93, 108]. The extent of brain shift for white matter tracts in patients undergoing tumor resection has been shown to vary from an inward shift of 8 mm to an outward shift of 15 mm, and this shift needs to be compensated for throughout the operation [109]. Brain shift correction can be done mentally (i.e. in the surgeons mind), manually (i.e. landmark tracking) or preferably automatically as the shift may be non-uniform and difficult to predict. Several methods have been suggested, such as intraoperative MRI [110] and 3D ultrasound [106]. Our group has previously shown that it is feasible to update MRI data correcting for brain-shift using automatic co-registration of preoperative MRI with intra-operative ultrasound [93]. Kamada et al. demonstrated in 2005 the use of white matter stimulation for real-time reliable white matter mapping, thus adjusting any brain shift discrepancy between preoperative DTT and shifted positions of brain structures [55, 110]. Another suggested solution is to use intraoperative MRI to acquire new anatomical and DTI images during surgery, when a marked brain shift necessitates updating the neuronavigation system [109, 111]. Intraoperative MRI does, however, require an MRI-compatible operating theatre and equipment, which is not needed for the ultrasound-based navigation system.

The navigation accuracy of the neuronavigation system is another potential source of error as there may be a registration error between the patient and the images. This has, however, been evaluated to be below 2 mm for the neuronavigation system used at St. Olavs Hospital [112].

Even though the literature is full of illustrative case reports and studies demonstrating the usefulness of fMRI and DTT before and during neurosurgery, the two techniques have not yet reached the status of full clinical acceptance. There are two main reasons for this. Firstly, there is no consensus as to standardization of image acquisition, pre-processing, post-processing or interpretation of the statistical activation maps [40]. Secondly, there is to our knowledge only one prospective randomized trial or outcome study that definitively shows benefits to the final outcome, such as improved neurological status or survival of the patient, when applying fMRI and DTT preoperatively [113]. In spite of this, fMRI and DTT have gained wide popularity, probably due to the promising prospects of further development and the usefulness of knowing where the functional cortices and their white matter connections are located.

It is, however, important to remember that such imaging techniques is an helpful adjunct to the neurosurgeons toolbox and that good resection of pathological lesions eventually will depend on the operating surgeon, thus neurosurgical skill will be the determining factor in the end [114].

2. Aims

The overall aim of the work in this thesis was to develop, implement, and evaluate fMRI and DTT at 3 Tesla for routine use in preoperative planning and functional neuronavigation during 3D ultrasound guided minimal invasive neurosurgery. The overall hypothesis is that information yielded by combining these techniques will improve the planning of the surgical intervention, lead to a more radical resection and at the same time avoid damaging important eloquent cortices and neural fiber tracts during surgery. If accomplished, post-surgical morbidity such as severe functional impairments and neurological deficits may be avoided. Furthermore, the combination of these techniques also holds the potential of reducing time spent in the operating theater, as it facilitates the identification of eloquent brain areas and safe resection of the brain lesions.

The aim of the first paper was to demonstrate the usefulness of fMRI and DTT together with intra-operative imaging techniques in an illustrative patient with an AVM harbored in the middle part of the primary motor cortex close to the finger area.

The aims of the second and third paper was to establish robust motor and language tasks, respectively, for precise and reproducible mapping of motor and language areas at 3 Tesla, for use in preoperative planning and functional neuronavigation.

The aim of the fourth paper was to develop a new more engaging language task that was able to produce robust activations in both frontal and temporal language areas for mapping of language areas and determination of hemispheric language dominance.

The aims of the fifth and sixth paper were to assess the use of presurgical mapping and functional neuronavigation in the clinic. This was done by investigating the extent of tumor resection, distance between lesions and eloquent areas, impact on patients overall clinical and neurological status before and after surgery, and the practical usefulness of fMRI and DTT integrated into a 3D ultrasound-based intra-operative imaging navigation system.

3. Materials and Methods

3.1 Participants and Patient Populations

The healthy volunteers in the different papers are subjects recruited from NTNU campus or people employed at NTNU or St. Olavs Hospital. They all gave their written informed consent after the procedures had been carefully explained and had the opportunity to ask questions. All subjects were given the choice to withdraw from the studies at any time.

The patients in the different papers are all neurosurgical patients referred to preoperative mapping with fMRI and DTT at St. Olavs Hospital in the period between October 2004 and March 2007. All imaging of patients was done clinically as a part of the surgical procedures.

3.2 Ethical Approval

All studies were approved by the local ethical committee for clinical research and adhered to the Declaration of Helsinki. Storage of data was approved by the Norwegian Social Science Data Services.

3.3 MRI Scanning

Both functional and structural MRI scanning was performed on an Intera 3 Tesla MRI Scanner (Philips Medical, Best, the Netherlands), with a Quasar Dual gradient system yielding a maximum of 80 mT/m and a SENSE head coil using parallel imaging (MRI Devices/InVivo, Orlando, Florida, USA). Preceding anatomical and functional scans, scout imaging with nine images in three orthogonal planes was performed for planning of plane orientation, followed by a SENSitivity Encoding (SENSE) head-coil calibration scan.

Anatomical images were acquired using a whole brain three-dimensional T_1-weigthed Magnetization-Prepared Rapid Gradient Echo sequence (MPRAGE) [115]. For scanning

of healthy subjects in the different studies a transversal sequence consisting of 182 slices, each 1.20 mm thick, was used. For scanning of patients with brain lesions, an isotropic 1.00 mm^3 transversal sequence consisting of 180 slices was used, due to prerequisites of the functional neuronavigation system used [83].

fMRI images in all studies were acquired using a single shot echo-planar-imaging (EPI) sequence, with the following scan parameters in common: TR = 3000 ms, flip angle = 90º, TE = 35 ms, and SENSE-factor varying between 2.0 and 2.2. Preceding each functional scan four dummy scans for magnetization stabilization were acquired and discarded before analysis. We aimed at using relatively thin slices and high acquisition matrices, in order to obtain functional images with good spatial resolution. For patients with brain lesions, all functional scans were block-designed consisting of 81 volumes of 41 contiguous transversal slices with a voxel-resolution of 1.80 x 1.80 x 2.3 mm^3. For the healthy subjects in the second paper functional scans were block-designed consisting of 81 volumes of 33 contiguous coronal slices tilted parallel to the primary motor cortex, giving a voxel-resolution of 1.64 x 1.64 x 1.64 mm^3. For the healthy subjects in the third paper the parameters were identical to those used in the neurosurgical patients, in order to make the results as comparable as possible. For the healthy subjects in the fourth paper the functional scans were event-related consisting of 195 volumes of 40 contiguous transversal slices with a voxel-resolution of 2.40 x 2.40 x 2.30 mm^3.

DTI images were acquired using a diffusion weighted spin-echo EPI sequence with a voxel-resolution of 1.80 x 1.80 x 1.72 mm^3, a b-factor of 700 in 32 spatially independent gradient directions, and a SENSE reduction factor of 1.5.

3.4 Analysis

All analysis of structural and functional images on both individual and group levels were performed using the BrainVoyager QX software package (Brain Innovation, Maastricht, Netherlands) [116]. This software has the option of pre-processing and statistical analysis

of functional data, as well as having the option to export fMRI and DTT data as superimposed white areas of activations and white outlines, respectively, to conventional T_1-images for use in the neuronavigation system. The BrainVoyager QX software also has the possibilities to perform advanced segmentation and three-dimensional reconstructions of gray and white matter boundaries, as well as brain lesions. Furthermore, it enables the use of cortex based alignment, a procedure utilizing the curvature information from the each individual's hemisphere, minimizing the spatial dis-concordance between the subjects when performing group analysis [116-118].

Thresholding of the statistical activation maps in the different papers differ according to the type of study. The first, fifth and sixth paper describe patients undergoing presurgical mapping where the activation maps were individually thresholded for each subject and each task, in order to produce activation maps unequivocally delineating the area of interest. In the second paper, evaluating motor tasks, activation maps were also individually thresholded for each subject and each task, in order to produce activation maps unequivocally delineating the area of interest. Further analyses were performed, where the tasks were required to yield activation within specific predefined regions of interest, in order to be characterized as successful. These pre-defined regions of interests were constructed by dividing the central sulcus along with the pre- and post-central gyri into three different areas based on the hand-knob in the pre-central gyrus, also known as the inverted omega [119]. In the third paper, evaluating language tasks, the statistical activation maps were thresholded at a fixed p-value corrected for multiple comparisons, followed by further analysis based on the size of activations within pre-defined anatomical regions of interest. These regions of interest were frontal and temporal language regions defined from Brodmann's map of cortical cytoarchitecture, thus the frontal region covered Brodmann's area 44, 45 and 47, while the temporal region covered Brodmann's area 22 [37]. The fourth paper is a group study where the statistical activation maps were produced using a random effects model, thus making the results in this group transferable to the population at large.

Analysis of DTI images was performed using different softwares at different steps in the process. First pre-processing was done using the software FSL (Oxford Centre for Functional MRI of the Brain, Oxford, United Kingdom) [120]. Then DTI-Studio was used to analyze the DTI images, and subsequent DTT was done utilizing the Fiber Assignment by Continuous Tracking (FACT) algorithm (Laboratory of Brain Anatomical MRI, John Hopkins Medical Institute, Baltimore, USA) [49, 121]. In-house python software for integration of DTT with BrainVoyager QX was written by Jian Xu.

All statistical analysis outside BrainVoyager QX has been done using the SPSS software package (SPSS Inc., Chicago, Illinois, USA).

3.5 Surgery

All patients were operated at the neurosurgical department at St. Olavs Hospital between November 2004 and September 2007. Patients underwent anatomical and functional MRI scanning within 72 hours before surgery. In these pateints preoperative fMRI was aimed at identifying motor and/or language cortices and DTT performed to identifying the corticospinal tract. The preoperative data was imported into the ultrasound-based navigation system (SonoWand®, SonoWand AS, Trondheim, Norway) and used for surgical planning and guidance [93]. Intraoperative 3D ultrasound volumes were acquired when needed during surgery and the multimodal data was used for guidance and resection control. Thus, detection of brain shift was done using intraoperative 3D ultrasound and correction on preoperative structural and functional MRI images was done mentally by the neurosurgeon. All tumors were histological classified and graded by a neuropathologist according to the World Health Organization's classification system [122].

4. Summary of Papers

4.1 Paper 1

Integrated pre- and intraoperative imaging in a patient with an arteriovenous malformation located in eloquent cortex

Berntsen EM, Gulati S, Solheim O, Kvistad KA, Lindseth F, Unsgård G

Minimally Invasive Neurosurgery, 2009 Apr; 52 (2): 83-5

The aim of the first paper was to demonstrate the usefulness of fMRI and DTT together with intra-operative imaging techniques in one illustrative case where an AVM was harbored in the middle part of the right primary motor cortex close to the finger area.

fMRI and DTT were used for preoperative mapping of primary motor areas and the corticospinal tracts, respectively. The fMRI-activations and DTT-tracts were integrated into a neuronavigation system and visualized intraoperatively throughout the operation, thus utilizing functional neuronavigation. Furthermore, stereoscopic visualizations of the angioarchitecture based on 3D MRI-angiograms were used to plan the surgical approach to the feeder vessels. Finally, intraoperative ultrasound was used to locate and clip the feeding vessels. The AVM was carefully resected with the aid of the above-mentioned imaging techniques and the intuitive usefulness of the techniques was further substantiated by the rewarding postoperative outcome. Seven weeks after surgery the patient had regained full preoperative strength in her left upper extremity, and did not suffer any major limitations in activities of daily living.

These results demonstrate the usefulness of preoperative mapping with fMRI and DTT, together with intraoperative ultrasound, which was further substantiated by the postoperative course.

4.2 Paper 2

Mapping the primary motor cortex in healthy subjects and patients with peri-rolandic brain lesions before neurosurgery

Berntsen EM, Samuelsen P, Lagopoulos J, Rasmussen jr. IA, Håberg AK, Haraldseth O

Neurological Research 2008 Nov; 30 (9): 968-73

The aim of the second paper was to establish a robust set of motor tasks for precise functional mapping and subsequent functional delineating of the primary motor cortex for use in preoperative planning and functional neuronavigation.

In this study we examined six different motor tasks in healthy volunteers, which were finger-, tongue-, lip- and toe-movements, as well as isometric upper-arm and thigh contraction tasks. We found that the finger-, toe- and tongue-motor tasks were the most robust in identifying their respective primary motor area, with a success rate of 88%, 88% and 81% respectively. Moreover, all three tasks activated regions at regular intervals along the convexity of the hemisphere making it possible to functionally delineate the entire primary motor cortex. We also reviewed patients that previously had performed these three motor tasks during fMRI, to evaluate whether this set of tasks were successful in patients with brain lesions. Also in this population these tasks had a high success rate, 100%, 100% and 78% respectively.

The results from this study showed that finger-, toe- and tongue-motor tasks were the most effective at localizing the primary motor cortex for the purposes of neurosurgical planning. These three tasks produced the highest success rate and resulted in activations at regular intervals along the convexity of the hemisphere allowing the delineation of the entire motor strip even in the presence of edema and anatomical distortions.

4.3 Paper 3

Reproducibility of functional MRI activations in language areas with three language tasks

Berntsen EM, Rasmussen jr. IA, Håberg AK, Haraldseth O

Submitted to the American Journal of Neuroradiology

The aim of the third paper was to investigate the intra-subject reproducibility of activation size and location for three different language tasks used for presurgical mapping at 3 Tesla, in order to establish which tasks should be used for presurgical mapping.

In this study we examined eleven healthy volunteers undergoing fMRI examinations at 3 Tesla while performing a responsive-naming task, an object-naming task and a word-generation task. The task reproducibility together with probabilistic maps showing the spatial consistency of activations across the subjects were calculated. For the frontal language region it was the word-generation task that showed the best reproducibility, produced the largest area of activation and had the best spatial consistency across subjects. For the temporal language region the responsive-naming task showed good reproducibility, produced the largest activations and the best spatial consistency across the subjects.

The results from this study show that the word-generation task should be used for mapping of the frontal language area in the clinics, as it is easy to perform and produces spatially consistent activations across many subjects with high reproducibility of activation size and localization. For the temporal language region the responsive-naming task should be preferred as it produces spatially consistent activations across many subjects with good reproducibility of activation size and localization.

4.4 Paper 4

Putting the brain in Jeopardy: a novel comprehensive and expressive language task?

Berntsen EM, Rasmussen jr. IA, Samuelsen P, Xu J, Haraldseth O, Lagopoulos J, Malhi GS

Acta Neuropsychiatrica 2006 Apr; 18 (2): 115-119

The aim of the fourth paper was to develop a new engaging language task that was able to produce robust activations in both frontal and temporal language areas for the mapping of language and determination of hemispheric language dominance.

In this study ten healthy volunteers were presented to language tasks inspired by the popular television game 'Jeopardy' in which the subject is presented with an 'answer' and is required to respond by generating the corresponding 'question' the answer would normally follow. Subjects were instructed to read the prompt (the answer to a question) and then once they had formulated a suitable response (the question) press a keypad button to indicate successful completion of the task. Participants were instructed to begin their response with the phrase 'What is?' when formulating questions. A typical example of the task is the prompt 'Drink we get from a cow' the response to which should be 'What is milk?' The Jeopardy task produced robust left hemisphere activation in regions corresponding to both frontal and temporal language areas and showed that it is potentially useful in language localization investigations by mapping both language areas in one experiment.

The results from this study show that the novel language task yielded activations in both the frontal and temporal language areas and lateralized to the language dominant hemisphere. It is therefore suited to language localization investigations and is efficient in that it maps both language areas in one experiment.

4.5 Paper 5

Surgical resection of high-grade gliomas in eloquent regions guided by blood oxygenation level dependent functional magnetic resonance imaging, diffusion tensor tractography, and intraoperative navigated 3D ultrasound

Gulati S, Berntsen EM, Solheim O, Kvistad KA, Håberg A, Selbekk T, Torp SH, Unsgård G

Minimally Invasive Neurosurgery 2009 Feb; 52 (1): 17-24

The aims of the fifth paper were to assess the postoperative functional outcome, determine the extent of tumor resection and evaluate the practical usefulness of fMRI and DTT solely in patients with high-grade gliomas undergoing functional neuronavigation guided by fMRI and DTT with intraoperative 3D ultrasound.

In this study 25 consecutive patients were included, and fMRI and DTT were performed in 23 and 18 patients, respectively. The patients' pre- and post-operative gross functional neurological status, degree of tumor resection and the quality of the fMRI/DTT investigations were determined. There was a significant improvement in the patients' functional status within three months after surgery and the mean percentage of residual tumor was calculated to 16±22% of original tumor volume (median 8%). Preoperative fMRI successfully delineated probable functional cortex in 91% of the paradigms, whereas 94% of the DTT sessions yielded potential valuable information. The tongue task failed in four cases and the language investigation failed in one case due to failure of task performance, while the rest of the examinations were successful.

The present study demonstrated that most patients with high-grade gliomas were capable of successfully performing the fMRI tasks without excessive head motion disturbance. This study indicates that the combination of fMRI, DTT, and 3D ultrasound facilitated maximal tumor resection of high grad gliomas with minimal deficits, as it may aid the preservation of motor and language function even in patients with highly malignant tumors.

4.6 Paper 6

BOLD fMRI and diffusion tensor tractography incorporated into a 3D ultrasound-based intra-operative imaging navigation system: impact on therapeutic strategies, extent of resection and clinical outcome

Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T Unsgård G, Håberg AK

Submitted to Neurosurgery

The aims of the sixth paper were to explore a possible relationship between lesion-to-eloquent-area distance (LEAD) and the extent of lesion resection, occurrence of new postoperative deficits and patients' postoperative clinical outcome in all patients operated with assistance of 3D ultrasound based navigation system with imported fMRI and DTT data. Also, the impact of fMRI and DTT on therapeutic strategies and any additional value of performing DTT together with fMRI were assessed.

51 consecutive patients with lesions in proximity to eloquent areas mapped with fMRI and/or DTT were included, of which 45 underwent surgery. Thirty-three patients had histological verified gliomas, both high and low grade, while twelve patients had other lesions including AVMs, cavernomas, metastasis and meningiomas. The LEAD, extent of resections, patients' clinical outcome and new postoperative neurological deficits were retrospectively assessed. The median residual percentage for gliomas (n=33) was 11% and 0% for other lesions (n=12). For gliomas there was a significant correlation between decreasing LEAD and both increasing residual tumor percentage and range of residual tumor percentage. However, the variance in residual tumor volume was large in the glioma group and some of the patients with LEAD less than 2mm also had radical resections. Compared to preoperative status, there was an overall significant improvement in clinical status with no significant change in neurological status after 3 months in both the glioma group and the other lesion group.

The use of the functional images preoperatively was retrospectively assessed and shown to have a direct consequence on preoperative therapeutic strategies for four patients (8%). Two patients declined operation due to the intimate relationship between functional cortices and lesion. The two others cases were biopsied instead of resected as the corticospinal tract was engulfed by the tumor in one case and the fMRI was unsuccessful in the other.

The additional value of DTT was assessed in those 21 cases where both corticospinal DTT and motor fMRI were acquired. In 14 cases (67%) the shortest LEAD decreased when DTT was taken into account. In four cases (19%) the functional areas delineated with fMRI and DTT were equally close to the lesion, while in three cases (14%) the fMRI activation was the closest. This constitutes a significant decrease in LEAD when taking the DTT into account.

The positive correlation between decreasing LEAD and increasing residual tumor indicate that resections were performed as a compromise between removing as much tumor as possible and not jeopardizing eloquent areas. The results also show that functional neuronavigation with intraoperative 3D ultrasound makes it possible to radically resect lesions in immediate proximity of functional areas without inflicting neurological deficits and improve the overall clinical status, even when the LEAD is less than 2 mm. Furthermore, we found that the functional imaging had a direct consequence on preoperative therapeutic strategies for four patients (8%), and that there was a significant decrease in the LEAD when taking DTT into account, compared to fMRI alone.

5. Discussion

fMRI and DTT are now in use for presurgical mapping and functional neuronavigation, and therefore the need for robust and reproducible activations together with accurate fiber tracts has become of imperative importance. It is important to investigate the fMRI tasks used and develop new ones with respect to reproducibility and ability to identify the cortices in question. Three of the papers in this thesis aim at doing this. It is also essential to investigate whether fMRI and DTT have any effect on degree of resection, clinical outcome and/or survival, which two of the papers in this thesis aimed at doing.

The primary motor cortex controls voluntary movements and is strongly somatotopic organized along the precentral gyrus. Damage to this region during surgery has severe consequences for the patients and has thus been subject to intra-operative mapping since the 1930's [62, 63]. With the advent of fMRI various motor tasks have been used for preoperative mapping, including finger tapping, hand clenching, elbow and shoulder movement, as well as tongue, lip, foot and toe movement [71]. We have evaluated a set of motor tasks in healthy volunteers and reviewed patients with brain lesions undergoing the same tasks, finding movement of the fingers, toes and tongue to be best suited for outlining of the entire motor strip. These tasks activate regions at regular intervals along the convexity of the hemisphere making it possible to functionally delineate the primary motor cortex, even in the presence of edema and anatomical distortions. These motor tasks are used routinely in the clinics and are the same tasks which the patients in the clinical studies (papers 1, 5 and 6) underwent. These three tasks should also be used in the future for preoperative mapping of the primary motor cortex. Whether they should be used alone or in combination depends on the individual pathology and clinical status. Factors that will influence the choice of motor tasks are for instance how difficult it is to identify the primary motor cortex anatomically, i.e. how gross the anatomy is distorted, and the location and size of the tumor with regard to the expected eloquent areas, and the clinical status of the patient. The final decision on choice of tasks should be decided by the neurosurgeon and neuroradiologist in collaboration.

Mapping of cortical language areas prior to neurosurgery heavily reflects the classical brain-language model derived from the works of Broca and Wernicke in the 19th century [123-126]. This model consists of an inferior frontal region for speech production (Broca's area) and a posterior superior temporal region for speech comprehension (Wernicke's area) in the left hemisphere. In modern linguistic and cognitive neuroscience it is uncontroversial that this model is empirically wrong, as it does not explain the range of aphasia syndromes, it is linguistically underspecified, as language is not merely production and comprehension, and it is anatomically underspecified, as also other areas contribute to language processing [127]. Furthermore, recent MRI studies of the preserved brains of Broca's two historic patients indicate inconsistencies between what is now called Broca's area and the area originally identified by Broca [128]. Therefore new models for cortical organization of language have been presented and are continuously being developed [129, 130]. However, the classical model is a useful simplification of language distribution for clinical purposes such as presurgical mapping, where the main purpose is to determine the localization of language areas definitively yielding speech disturbances and aphasia if damaged. It is therefore of outmost importance to choose a language task which will activate and unequivocally define the language regions in proximity of the brain lesion with a high degree of reproducibility. We have evaluated a set of language tasks with respect to reproducibility of activation size and location in healthy subjects (paper 3) and developed a novel language task with the potential to map both the frontal and temporal language areas at once (paper 4). We found that a word-generation task should be preferred for mapping of the frontal language area and a responsive naming task for the temporal language region. These were the tasks with the best spatial consistency across a group of subjects and good reproducibility of activation size and localization. These are two of the tasks used routinely in the clinics, but also an object naming task has been used clinically. Our results show that word generation and responsive naming should be preferred. Furthermore, the novel "Jeopardy" task is a candidate for future clinical use if shown to have reproducible activation and LI in individual subjects. Future research should be directed towards comparing new language tasks, such as the Jeopardy task, with the word generation and responsive naming task in

order to verify or falsify the assumption that these tasks are the best fitted for language mapping.

Since functional neuronavigation with fMRI and DTT has become part of clinical routine it is critical to carefully examine its impact on therapeutic strategies, extent of resection and postoperative outcome. This should preferably be done through randomized clinical trials or well-designed long-term outcome studies [1, 40, 131]. However, in lack of such evidence, important information may be obtained from evaluating clinical and technical data which has been systematically collected and thoroughly analyzed, and two of the papers in this thesis were aimed at doing just that.

Our studies (paper 1, 5 and 6) demonstrate the usefulness of fMRI and DTT in patients with brain lesions on both an individual as well as a group level. In the first paper, the combination of fMRI and DTT together with intraoperative ultrasound and careful resection of the AVM resulted in a rewarding postoperative outcome. This successful result on the individual level was further substantiated by our two studies in patients with brain lesions undergoing functional neuronavigation. Here we found an overall significant improvement in both clinical and neurological status 3 months after surgery in patients with both gliomas and non-gliomas. Furthermore, we found a significant correlation between decreasing lesion-to-eloquent-area distance (LEAD) and increasing residual tumor, indicating that the resections were performed as a compromise between removing as much tumor as possible and not jeopardizing eloquent areas. Moreover, we found that functional neuronavigation with intraoperative 3D ultrasound makes it possible to radically resect lesions in immediate proximity of functional areas without inflicting neurological deficits and improve the overall clinical status, even when the distance between eloquent area and tumor is less than 2 mm.

The challenges ahead lie in carrying out prospective outcome studies or clinical randomized trials in order to document the potential effect of fMRI and DTT in combination with navigated minimal invasive on morbidity and mortality in patients with primary brain tumors as well as other brain lesions. Detailed information on each patient

and operation should be collected, such as pre- and post-operative clinical and neurological status, in order to detect any improvement or additional neurological deficits. Also any effect on overall mortality should be investigated. Moreover, the distance from lesion to eloquent cortex and white matter tracts needs to be collected, as well as whether the neurosurgeons are able to identify the eloquent cortices and white matter tracts based on conventional neuronavigation images. Data should be collected with regard to the use of functional information during planning and also during the resection, and whether the functional information leads to any changes in the surgical plan. Finally, the extent of the brain shift during surgery and how this affected the functional information requires further investigation, and technical approaches on solutions to solve the brain shift's impact on image registration should the sought. Carrying out such a study raises many challenges. Firstly, the process of integrating functional information into the neuronavigation system and getting acquainted with the techniques possibilities and limitations, both preoperatively and during surgery, require significant time (years). Here St. Olavs Hospital has an advantage, having several years of experience with functional mapping and neuronavigation, which already is clinical routine. Secondly, the problems of brain shift during surgery still remain unsolved. This should ideally be solved, or at least taken into consideration and compensated for, before normative prospective randomized clinical trials or outcome studies can be performed. Our group has previously shown that it is feasible to update MRI data correcting for brain-shift using automatic co-registration of preoperative MRI with intra-operative ultrasound, but this was done offline and still remains to be implemented into the neuronavigation system for intraoperative real time use [93]. A third challenge is that patients with brain lesions are very heterogeneous with respect to preoperative neurological deficits, tumor localization, histology, size, proximity to eloquent cortices, surrounding edema and mass effects, thus making general inferences based on small numbers of cases very difficult. Thus, the need for larger populations of patients is pivotal in order to perform clinical studies. The number of patients operated at St. Olavs Hospital is possibly too small to perform prospective randomized clinical trials, where one group would be subjected to functional neuronavigation and the other receive conventional neuronavigation. In the previously mentioned study by Wu et al., showing

improved postoperative outcome and time of survival when DTI-data was used compared to conventional neuronavigation, there was 120 patients in each group enrolled over 4 years [107]. This in comparison with the 51 patients enrolled at our hospital over 3 years. One solution to this problem may be to design a national multi-center study including all hospitals in Norway performing these investigations and functional neuronavigation. However, the equipment for functional neuronavigation differs between the hospitals. An ethical dilemma is whether one possibly could deny one group of patients functional neuronavigation if they according to today's clinical practice normally would be operated using it. As mentioned, to our knowledge there is only one prospective randomized study showing benefit from functional neuronavigation, thus further studies are warranted. An alternative solution may be to perform a prospective long-term outcome study either as multi-center study or only at our hospital.

The results from the papers in this thesis suggests that the use of fMRI and DTT for preoperative mapping and functional neuronavigation is beneficial for both the neurosurgeon and patient as it enables localization of eloquent areas, increased resection of the brain lesions and prevention of new neurological deficits. It is my opinion that the next logical step for evaluation of these techniques is either a national prospective randomized clinical trial or a prospective long-term outcome study at St.Olavs Hospital for evaluation of effect on morbidity and mortality.

6. Conclusion

The papers constituting this thesis demonstrate developments, evaluation and implementation of fMRI and DTT at 3 Tesla for preoperative planning and functional neuronavigation. We have evaluated and proposed motor and language tasks which should be used as standardized paradigms for preoperative mapping in the future. Our clinical results indicate that guided functional neuronavigation with updated anatomical information using ultrasound gives the surgeon an advantage when resecting brain lesions by facilitating maximal tumor resection with minimal deficit. Furthermore, functional neuronavigation benefits the patient as fMRI and DTT maps eloquent cortices in the brain which subsequently may be avoided during surgery, thus avoiding new post-operative neurological deficits. The challenges ahead lie in establishing standardized tasks and analysis for processing of these investigations, as well as carrying out prospective outcome studies or clinical randomized trials in order produce evidence for effect on morbidity and mortality in patients with brain lesions.

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