Improving the Efficiency of Task-based Functional Magnetic Resonance Imaging

PhD thesis

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I. INTRODUCTION

The thesis starts with a short introduction, where I describe the motivation and the fundamental concepts of Magnetic Resonance Imaging (MRI) and functional magnetic resonance imaging (fMRI). In the first part I concentrate on conventional task-based fMRI (t-fMRI) for presurgical planning then I describe a recent MRI sequence, namely simultaneous multislice imaging (SMS). In the second part I describe the effects of physiological artefacts (breathing and pulse) and state-of-the-art algorithms to reduce them in fMRI data are described.

1. Simultaneous multislice imaging

Simultaneous multislice (SMS) or – in Siemens nomenclature – multiband (MB) imaging accelerates the acquisition along the slice direction using parallel image reconstruction. A significant advantage of SMS that is does not cause sensitivity reductions – unlike other acceleration techniques. SMS leads to a reduction in acquisition time by factor of N (that is equal to the number of simultaneously excited slices), without a significant decrease of signal to noise ratio (SNR).

Due to the simultaneously excited slices, residual aliasing often arises from different slices and hence may cause artefacts, a phenomenon termed “slice leakage”. These residual artefacts are prominent in accelerated acquisitions and they may cause false positive results, however this may be remedied with the so-called *blipped CAIPI* reconstruction approach.

Several studies show that SMS imaging is suitable with the increased amount of data points to reach higher statistical values (t-scores). Nevertheless, it is difficult to predict whether SMS-based sampling acceleration would change the required scanning time substantially to achieve a certain statistical power.

2. Physiological artefacts at fMRI

Physiological noise is one of the major confounds in fMRI. It modifies the BOLD signal, resulting in extra variance of the data. It can seriously influence statistical sensitivity, resulting in false negative results. The two types physiological noise relevant in fMRI analysis are those induced by the cardiac and respiratory cycles.

Cardiac pulsation modulates cerebral blood flow, cerebral blood volume and modifies the arterial pulsatility. Higher heart rate may also increase the amplitude of the arterial pulse wave and can lead to vessel dilatation, also leading pulsatile flow of the cerebrospinal fluid. Heart-rate variability changes local T2* values. Respiration may induce modulation of the B_0 magnetic field and many also cause signal fluctuations: changes is respiratory volume in time modifies the concentration of blood CO_2, and the exhalation and inhalation induce magnetic field changes, leading to sub-voxel shifts.

Several studies showed the relevance of physiological noise and the impact of physiological noise correction in fMRI. However, most of the published studies applied noise correction to resting-state fMRI.

There are two main types of correction methods: data-driven (or exploratory) which rely on noise-like properties of the fMRI data (e.g. Principal component analysis, Independent component analysis, CORSICA, etc.) and model-based, which are based on independent external measures of physiological signals (e.g. RETROKCOR, RETROICOR, etc.). PhysIO toolbox is a well-documented open source software which contains the most of model-based methods, with its inputs being the peripheral recordings and its outputs being regressors representing the physiological noise components. Most of these techniques are used only at resting-state fMRI, and there a few studies used them at task-based fMRI.

Despite the existence of several noise reductions techniques, temporal filtering is one of the most used physiological “correction method”, albeit it is not as straightforward as it seems to be. Usually, in fMRI, the repetition time (TR) is long, which leads to under-sampling and thus potential aliasing of physiological signals.

II. OBJECTIVES

1. The relevance of simultaneous multi-slice (SMS) EPI sequence in task-based functional MRI

1.1. Compare results obtained with a conventional EPI sequence at 0.5Hz sampling rate to those obtained with a simultaneous multi-slice sequence at 1Hz sampling rate

Investigate the efficiency of a four-times accelerated simultaneous multi-slice (SMS) sequence. Compare the conventional EPI and SMS sequences using region of interest analysis in three pre-defined brain areas (Extrastriate Body Are- EBA; Fusiform Face Area-FFA; Parahippocampal Place Area-PPA). Determine the optimal scan length with SMS sequences, where the same- or better statistical results (t-values) are obtainable.

1.2. Compare results obtained with a conventional EPI sequence at 0.5 Hz sampling rate to those obtained with a simultaneous multi-slice sequence at 2.5Hz sampling rate

Investigate the efficiency of six times accelerated simultaneous multi-slice sequence. Compare the conventional EPI and SMS sequences with region of interest analysis at three pre-defined brain areas (Extrastriate Body Are- EBA; Fusiform Face Area-FFA; Parahippocampal Place Area-PPA). Determine the optimal scan length with SMS sequences, where the same- or better statistical results (t-values) are obtainable.

2. Role of physiological noise correction in pre-surgical functional MRI

2.1. Effects of physiological noise (breathing and pulse) on whole brain fMRI activation maps

Compare the standard (non-corrected) and physiological artefact corrected whole brain fMRI activation maps to reveal the effects of physiological noise on fMRI mapping.

2.2. Effects of physiological noise at the eloquent brain areas in pre-surgical fMRI

Determine the role of physiological noise at the eloquent brain areas, by means of region of interest (ROI) analyses to identify differences between the non-corrected and physiological corrected maps.

III. METHODS

1. Comparison of simultaneous multislice imaging and conventional EPI sequence

1.1. Subjects

21 healthy volunteers participated in this study. All participants were right-handed, without any known history of psychiatric or neurological disorders, or head injury. Every subject had normal vision and gave informed written consent in accordance with protocols approved by Health Registration and Training Centre (ENKK 006641/2016/OTIG).

1.2. Image acquisition

Data were acquired on a Siemens Magnetom Prisma 3T MRI scanner at the Brain Imaging Centre, Research Centre for Natural Sciences, Hungarian Academy of Sciences. Functional measurements were done with three different parameter sets in a balanced (across subjects) pseudo-random order: one with conventional EPI sequence and two measurements with SMS technique with two acceleration factors: four and six. The total acquisition times were the same in every run of the EPI measurements.

1.3. fMRI stimuli and experimental design and fMRI data analysis

During the fMRI scanning session, grayscale images of human faces, houses, and headless bodies were presented. In each run, we used 30 seconds long periods, where faces (F), houses (H), and bodies (B) were presented in a randomized order. In each block 6 stimulus per category per block were presented. In a rest period (25 s long) only a fixation dot was presented.

Standard preprocessing (motion correction, co-registration, segmentation, normalization, and spatial smoothing) and analysis of the data were performed using the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, University College London, UK) and custom MATLAB codes. We calculated voxelwise contrasts (t-scores) to determine differences in the evoked BOLD signals between different stimulus conditions (e.g. face vs. houses).

Finally, within the functionally defined regions similar contrast statistics were assessed using the data acquired with different MB factors during the main experiments: mean t-scores within a 6 mm radius sphere centred at the peak voxel of the defined ROIs were averaged across hemispheres and used in the comparisons.

1.4. ROI selection for data analysis

Category-selective regions were defined based on statistical maps and anatomical images – using independent functional localizer scans. The fusiform face area (FFA), the parahippocampal place area (PPA) and the extrastriate body area (EBA) were selected for the comparison.

1.5. Comparison of the statistical power of different combinations of scan length and sampling rates

We truncated the acquired data at 4 different time points (124, 254, 384 and 515 seconds) to get activity time-courses with 5 different lengths.

We used the following consistent notations: 1/5FL, 2/5FL, 3/5FL and 4/5FL representing the approximate duration ratio relative to the non-truncated full scan length (FL). We also truncated data acquired with MB4 and MB6, then compared the shortened scans with the full-length 11 mins standard (TR=2sec) scans to establish the efficiency of the acceleration technique and reveal the accidental differences.

2. Physiological artefact correction for pre-surgical language fMRI

2.1. Subjects

14 patients with primary brain tumour participated in this study. Data were analyzed retrospectively after the fMRI examination. We mapped the primary language and motor areas.

2.2. Image acquisition

All data were acquired on a Siemens Magnetom Verio 3T scanner at the Department of Neuroradiology, National Institute of Clinical Neurosciences, Budapest, Hungary. 2D EPI sequences were used to perform functional measurements with GRAPPA parallel imaging.

Physiological parameters (breathing and pulse) were recorded with the built-in MRI compatible devices.

2.3. fMRI stimuli and data analysis

We used 4 different language fMRI tasks (picture naming, synonym task, auditory decision and speech comprehension) in order to map the eloquent brain areas. Every paradigm contained 6 active and 6 passive blocks, every block was 24 seconds long.

Standard preprocessing and analysis of the data were performed using the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, University College London, UK) and custom MATLAB (The Mathworks) codes. In order to decrease the physiological artefacts we used the convolution based RETROICOR/RVHR, which identifies and eliminates breathing and pulse related artefacts.

Task-based fMRI were analysed both with and without RETROICOR/RVHR. The Jaccard coefficient was used to quantitatively compare the activation maps obtain with and without physiological artefact correction.

We performed Region of Interest analysis by placing ROIs in the relevant eloquent brain areas (Broca-, Wernicke- and primary sensory-motor areas).

Paired t-test was applied to determine the significant differences between ROIs. Levene’s test was used to reveal the homogeneity of ROIs’ variance. fMRI activations’ extension in the eloquent brain areas are also analysed. We used two-sample t-test to determine the differences between the ROIs’ extensions.

3. Results

3.1. Comparison of simultaneous multislice imaging and conventional EPI

We found significant ($p < 0.0014$) differences in the PPA ROI analysis, when compared 4/5FL and FL measurements in the case of MB4 with MB1 FL values. We also found significant differences ($p < 0.0056$) in EBA ROI analysis, when compared to 4/5FL and FL measurements with MB1 t-values.

We found non-significant differences ($p > 0.09$) – in EBA ROI analysis – between the full scan length MB1 and the extremely truncated MB4 sequences (1/5FL, 2/5FL). Note, that a substantial decrease in t-scores ($p < 0.001$) are detected when compared the full scan length MB1 measurement with MB4 sequence, when only 20% (1/5FL) of the full scan time was used. We did not recognize any significant differences at any truncated scan length in the FFA ($p > 0.18$) when the acceleration factor was 4.

The multiband sequence with acceleration factor of 6 definitely overperformed the full scan length MB1 measurements in all ROIs when we used at least 60% (3/5FL) of the total scan length ($p < 0.001$). In the FFA and EBA regions multiband measurements with acceleration factor of 6 even at 2/5FL reached significantly higher t-scores compare to FL, non-accelerated measurement ($p < 0.008$ for FFA and EBA).

We analysed the sampling rate effects in ROIs (PCC, lMPF and rMPF) where no relevant stimulus related activations were expected during the fMRI sessions. Neither significant differences in activation levels ($t_{max}<2.5$, $p_{min}>0.21$) nor significant differences in t-scores ($t_{max}<2.4$, $p_{min}>0.54$) between on MB1 and higher sampling rate (MB4 and MB6) scans could be found.

We analysed the results of higher sampling rate measurements at the single subject level based on a representative sample around the FFA region. Our general conclusion was that peak t-scores were higher and the spatial extent of FFA activations were larger when using 1Hz or ~2.5Hz sampling rate compared to 0.5 Hz. Note, that there were several subjects whose activation statistics did not follow a clear positive trend with higher temporal resolution in case of very short scanning duration (e.g. 1/5FL, 2/5L or 3/5FL yielded lower t-scores compared to FL with MB1).

The results showed that the simultaneous multislice acquisition technique helps reducing the overall scanning time while maintains or improves the robustness of functional area localization. This could be very helpful in clinical practice. Indeed, by selecting appropriate acceleration factors the increase in temporal resolution counteracts the degradation of SNR caused by the change in “g-geometry factor” and T1 relaxation effects. While FFA has a small activated volume, it can be found close to areas with high magnetic susceptibility, whereas PPA, with its deep location, is expected to have lower SNR characteristics.

3.2. Results of physiological noise correction in pre-surgical fMRI

3.2.1. Whole brain activation results

Jaccard coefficients were more than 0.5 in five cases while lower Jaccard values were found in other patients, the mean ± standard deviation was 0.27 ± 0.16. So, the uncorrected and corrected statistical maps were significantly different. In order to better understand these differences and to determine how the model-based RETROICOR/RVHR modifies the statistical maps, we analysed the number of significant ($p < 0.001$) and non-significant ($p > 0.001$) voxels. We found significant differences between the original and physiological corrected activation maps in both cases ($p = 0.009$ and $p < 0.001$).

We detected moderately strong, significant positive correlation between the Jaccard index and heart rate ($R^2 = 0.31$, $p = 0.002$). However, we did not find significant correlations between the Jaccard index and respiration ($R^2 = 0.0052$, $p = 0.711$).

3.2.2. Results of ROI analysis

The ROIs’ mean t-values were decreased after the physiological correction in every patient. We found significant differences ($p < 0.0015$) between the non-corrected and corrected region of interests at 5% significance level. The ROIs’ standard deviations were also decreased, albeit – using Levene-test –significant differences have not been detected ($F = 0.28$). However, with the decreased standard deviations, we can determine, that more reliable activation maps are available after physiological noise correction. Accordingly, physiological noise correction provided more precise functional MRI activations at the eloquent brain areas.

We analyzed the extension of eloquent brain area activations and found significant differences between the uncorrected and physiological corrected maps ($p = 0.012$). Physiological correction decreased the extent of activations in all patients. These findings corroborate the relevance of physiological noise correction.

4. Conclusion

4.1. Simultaneous multislice imaging for task-based functional MRI

One of the major problems in clinical functional MRI is long scanning time. In this study, we analysed the beneficial effects of the simultaneous multislice based acceleration technique quantitatively. We examined the performance of the standard fMRI analysis method in relation to three different sampling frequencies in three target ROIs: EBA, FFA, PPA. We showed that the same statistical power can be reached using SMS sequences (increasing temporal resolution) even with serious scan time reduction using appropriate MB sequences with proper acceleration. Based on our experiments an 11 min long classical (unaccelerated) localizer scan can be replaced safely with a 4 min accelerated acquisition with multiband factor 6 using ~2.5Hz sampling rate. It could be very helpful, especially when patient cooperation is a real problem even within this relatively short time-frame. With accelerated scans very similar statistical results can be reached compared to those of a standard-length protocol – without acceleration.

So far, the usage of the MB sequences in the clinical routine is still not widespread despite the many advantages of the accelerated acquisitions. This may be due to the relative novelty of the technique and the challenges posed by the different implementations across vendors. Note, that there are several vendors, who provide original, built-in SMS sequences without any manual installation/intervention. It is worth noting that false-positive activations could appear in case of one slice leaking into other simultaneously exited slices when using MB sequences, albeit these artefactual activations can be controlled with new reconstruction techniques e.g. blipped-CAIPI.

In this study we used a special paradigm based on complex visual stimuli to demonstrate the efficiency of higher temporal resolution (with lower scan time) obtained with difference acceleration factors at higher order visual areas, namely EBA, FFA and PPA. Importantly SMS sequences can be used not only for research studies with complex cognitive paradigms and questions, but clinical practice can also benefit from introducing SMS based acceleration in the daily routine, especially cases where patient cooperation is restricted.

4.2. Retrospective physiological noise correction at presurgical task-based functional MRI

In this study we demonstrated the efficiency of a model-based physiological correction technique, which works in the image space and uses the hear-rate and cardiac variability to reduce the physiological based artefacts. We analysed the effect of physiological noise in a special case, namely presurgical task-based fMRI.

RETROICOR/RVHR reduced the false-positive results and provided more reliable statistical maps. Although ROI analysis revealed that the calculated activation amplitudes decreased after physiological correction, the spatial specificity of the eloquent brain activations increased. These findings need further validation using other modalities, like invasive electrocorticography.

The primary concern in presurgical fMRI is having false negative results. In principle, applying this retrospective, model-based correction technique the statistical activation threshold can be lowered – increasing the sensitivity of the analysis – without introducing excessive false positive activations.

We can conclude, that RETROICOR/RVHR can reduce the physiological artefacts. Physiological correction can significantly improve fMRI activation maps, while reducing the false positive results. This in turn leads to more reliable statistical maps and helps to characterize eloquent brain activations and to improve the efficiency of presurgical planning.

LIST OF OWN PUBLICATIONS

Publications related to the thesis

1. **Kiss M.**, Hermann P., Vidnyánszky Z., Gál V.: Reducing task-based fMRI scanning time using simultaneous multislice echo planar imaging. Neuroradiology (2018) Mar;60(3):293-302. **IF: 2.504**
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