Research report

"Neuronal current imaging – Clinical application of a non-invasive MR-based investigation method to detect local epilepsy-related magnetic field inhomogeneities after first-time epileptic seizure"

Dear members of the research council,

Enclosed please find the final report on our research activities related to the topic. Within support of the research award granted by the Swiss Epilepsy League we conducted a neuroimaging study that investigated a newly, in-house developed MRI-based method based on neuronal current imaging (stimulus induced rotatory saturation/SIRS) in patients with focal and general epilepsies. Off-resonance spin locking (SL) has been recently suggested as a MR imaging method to study low-frequency motional processes in biological tissues. Recently, we have suggested this method to detect weak transient magnetic field oscillations generated by neuronal currents excited by epileptogenic tissue in human beings (1). Using the spin lock technique, we evaluated the performance of this new contrast proposed to observe oscillating fields induced by neural currents. Since measurable effects in epilepsy patients are many times higher than in physiological neuronal activity we were able to perform experiments with the new technique in humans. These experiments have been conducted during my stay at the Medical University in Vienna in 2019.

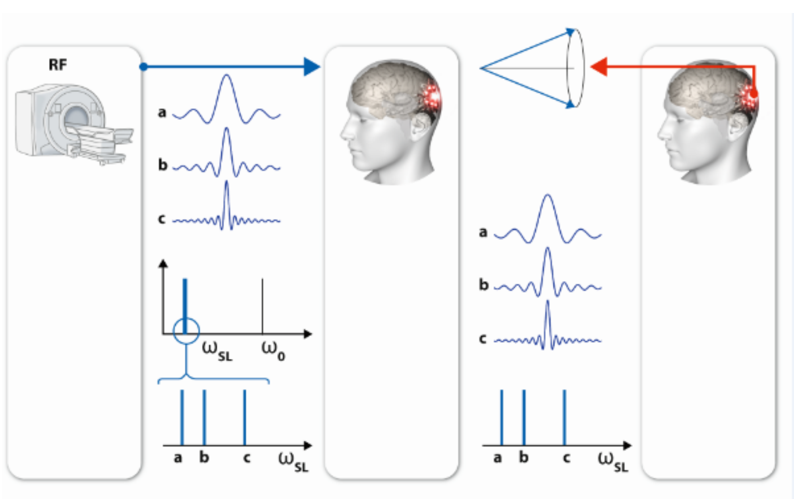

Figure 1: Schematic description of the spin-locking experiment: local neuronal currents produce weak transient magnetic fields that attenuate focal magnetic resonance signal intensity. The key approach of the proposed method is a nonhemodynamic resonant saturation effect, whereby epilepsy-related oscillations in the high and ultrahigh frequency domain (80–600Hz) are overlaid with processing spins in the magnetic field of the magnetic resonance scanner. The spins synchronize with oscillations in preselected frequency domain, which – if present – generate a weak signal attenuation in the magnetic field.

1) We applied Bloch simulations and phantom experiments to study and observe induced fields and the influences of external factors such as field inhomogeneities and relaxation phenomena. From the phantom experiments, we conclude that the SL on / SL off contrast can be used to detect oscillating neural fields and we have identified new methods to reduce the effect of external influences on the signal.

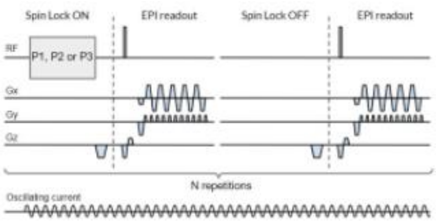

Figure 2a: SL on and SL off preparations are applied alternately between each EPI readout. The oscillating current is kept constant during the acquisition time.

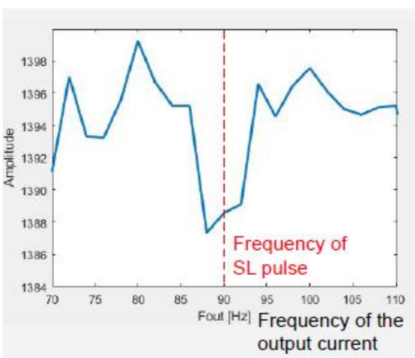

Figure 2b: Signal amplitude as a function of the frequency of the output current using the SIRS sequence: For the exemplary measurement, the spin-lock frequency is set to 90 Hz. The effect on the presaturation can be observed within a small frequency band of ± 3 Hz around the selected frequency.

2. We have conducted a study in 25 healthy volunteers. All studies were performed on a clinical Siemens Magnetom Prisma Scanner with a 64-channel head coil. All volunteers underwent two MR SL experiments with a preselected frequency at 120 and 240 Hz, as suggested previously for examinations in patients with epilepsy. The SIRS sequence acquires a signal with the special SL preparation at preselected frequencies (here, f=120, 240 Hz) as well as a reference signal (Sref) without SL preparation. In order to calculate the essential NCI effects, Sref was deconvolved from SSL(f) for all frequencies. Median filtering and contrast-limited adaptive histogram equalization were applied to reduce noise and to avoid amplifying any noise respectively. Main B0 field distortion corrections were applied using the approach proposed by Holland Co-registration of the NCI results to the structural 3D-T1 dataset was performed with SPM 12. In order to identify the grey and white matter contributions on the resulting NCI maps, the latter were masked with the segmented T1 maps using the SPM12 segmentation module. Difference maps (SL minus non-SL

acquisition) were normalized to a range of 0-1000 and the cluster with the maximum z score was used for localization. No SIRS effects were detected in healthy controls.

3. To investigate, if highly intense stimuli generate a response in SIRS experiments in control subjects, we performed stimulation experiments in 19 patients with flickering visual stimulations at a pre-defined frequency of 8 Hz to screen for synchronous activations. In 12 of the patients a weak response to visual stimulation could be generated in the experiments. Experiments with Fingertapping were negative in all tested subjects. From this pilot results we conclude that only very strong and synchronized stimuli (as IEDs) generate sufficient SL effects in the B1 magnetic field

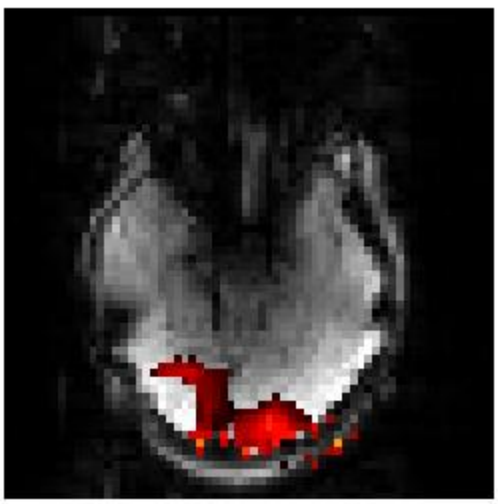

Figure 3: SL effects related to flickering stimulation at 8 Hz in healthy volunteers. No effects were detectable w/o stimulation (SL off) or and higher frequencies (120 Hz/240 Hz) relevant for epilepsy. The effect was present in 12/19 pts.

4. A total of 13 patients with different focal and generalized epilepsies were prospectively studied at the Excellence Center for Magnetic Resonance (ECMR) of the Medical University of Vienna. The examiners were blinded to any clinical or EEG information. The classification was performed by the ECMR (Prof. Wiest) at the end of the study period and compared to the diagnostic workup of the Epilepsy Center at the Department of Neurology (Prof. Beisteiner). In the SL experiments, patients showed constant activation at preselected frequencies of 120 and 240 Hz. We have shown that SL effects can be detected at the hemispheric level in patients with focal epilepsy whereas the effects were distributed more widespread in generalized epilepsies. Using this technique, an identification of the underlying class of epilepsy (focal vs. general) was feasible in 11/13 cases. The pilot study complements the ongoing data collection of epilepsy surgery patients at the Inselspital and was

essential for the ongoing prospective cohort study (SINERGIA project SWISS FIRST, PI Prof. R. Wiest) in first seizure patients that opened in 2019 in 7 epilepsy centers in Switzerland.

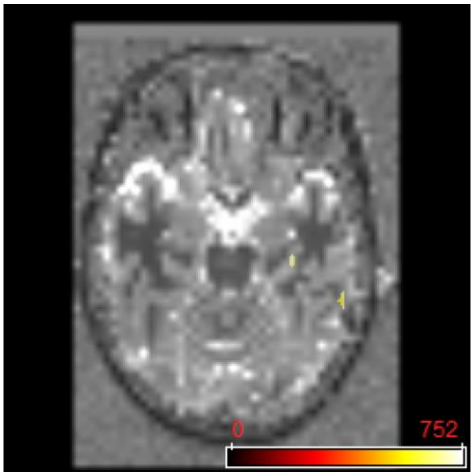

Figure 4a: f, 30 y (Vienna 2)

MRI negative TLE

SL effects left posterior HC
(concordant with focal epilepsy)

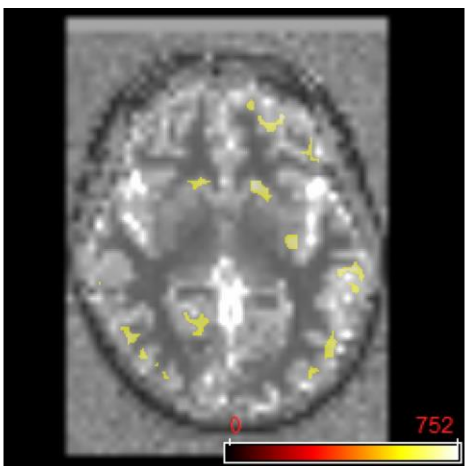

Figure 4b: f, 23 yrs (Vienna 6)

MRI negative GGE

SL effects bifrontal, biparietal, lt. insula, ventrostriatal cortex

(concordant with generalized epilepsy)

5. In the above mentioned SWISS FIRST project we now observe patients who are assessed for a possible first epileptic seizure and collect their EEG and MRI. In the Bernese epilepsy protocol, besides the routinely acquired sequences, we acquire the Neuronal Current Imaging (SIRS). Up to now, we have enrolled 32 patients with epileptic seizures and 4 patients with seizure mimics. Our interim findings demonstrate a two-fold higher sensitivity for SIRS than for postictal EEG (Table 1, 40.6% vs. 81.3%). Interictal epileptiform discharges, that can truly confirm an epileptic seizure, are rarely visible after first seizure. However, the SIRS technique yielded a lower specificity in comparison to pathologic EEG findings (Table 1, 75% vs. 50%).

A) EEG in comparison to clinical appraisal

	Epileptic seizure	Seizure mimic	
EEG +	13*	1	14
EEG -	19	3	22
	32	4	36

Sensitivity$_{EEG}$ = 40.6% **Specificity**$_{EEG}$ = 75%

Sensitivity$_{IED}$ = 6.3% **Specificity**$_{IED}$ = 100%

Sensitivity$_{NCI}$ = 81.3% **Specificity**$_{NCI}$ = 50%

B) NCI in comparison to clinical appraisal

	Epileptic seizure	Seizure mimic	
NCI +	26	2	28
NCI -	6	2	8
	32	4	36

PPV$_{EEG}$= 92.9% **NPV**$_{EEG}$ = 13.6%

PPV$_{IED}$ = 100% **NPV**$_{IED}$ N/A

PPV$_{NCI}$ = 92.9% **NPV**$_{NCI}$ = 25%

C) EEG in comparison to NCI in epilepsy patients

	NCI +	NCI -	
EEG +	9**	4	13
EEG -	17	2	19
	26	6	32

Overall Accuracy$_{EEG}$ = 44.4%

Overall Accuracy$_{IED}$ = 5.6%

Overall Accuracy$_{NCI}$ = 77.8%

Table 1: Diagnostic accuracy of SIRS vs. EEG (ongoing study)

Key findings of the pilot study

1. Magnetic field effects related to focal vs. generalized epilepsy can be depicted with the SL-technique (NCI). Related patterns were focal (unilateral) in 7 patients, generalized in 4 (bilateral) and misinterpreted (unilateral instead of focal) in 2 patients.

2. No SL effects were observed in healthy volunteers with SL preparations at 120 or 240 Hz.

3. SL effects were detectable in healthy volunteers during 8-Hz visual stimulations with SL preparations of 8 Hz. No effects were detected during a control condition (SL off).

4. Phantom experiments reveal a bandwith of ± 3 Hz for detectable signal decay.

5. The work of this pilot study is continued with in a prospective observational, swiss-wide SNSF study (SWISS FIRST).

References:

Kiefer C., Abela E, Schindler K, Wiest R. Focal Epilepsy: MR Imaging of Nonhemodynamic Field Effects by Using a Phase-cycled Stimulus-induced Rotary Saturation Approach with Spin-Lock Preparation. Radiology 2016; 280:237–243

Papers related to the project:

1. Wiest R, Beisteiner R. Recent Developments in Imaging of Epilepsy. Curr Opin Neurol. 2019 32(4):530-538.

2. Rebsamen, M; Rummel, C; Reyes, M; Wiest, R; McKinley, R. Direct cortical thickness estimation using deep learning-based anatomy segmentation and cortex parcellation. Hum Brain Mapp 2020 41(17):4804-4814

3. Unger D., Wiest R., Kiefer C et al. Neuronal current imaging – an experimental imaging method to investigate electric currents in canine idiopathic epilepsy (under review).