Sodium fMRI detects grey and white matter activations: neuronal firing or blood volume change?

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Target Audience: Scientists and clinicians interested in novel fMRI methods.

Purpose: To demonstrate that sodium functional magnetic resonance imaging (23Na-fMRI) is sensitive to functional activation, resulting in an alternative method to blood oxygenation level dependent (BOLD) fMRI, potentially directly associated to neuronal firing.

Introduction: BOLD-fMRI and electroencephalography (EEG) based methods have provided great insight into brain function, despite known limitations: fMRI utilises an indirect effect based on blood oxygenation and blood volume changes, while EEG is limited to detect electrical activity from the surface area of the brain. During neuronal activity, sodium channels open and currents flow through the plasma membrane causing approximately a 2000-fold increase in permeability in favour of sodium ions entering the cells. The ionic imbalance created by intracellular sodium accumulation establishes an action potential across the cell's membrane, resulting in electrical signalling[1]. 23Na is MRI visible and can be quantified in vivo. 23Na-MRI techniques at 3T are sensitive to total sodium content, observed macroscopically as the weighted average between intra- and extra-cellular sodium[2]. Here we used 23Na-MRI to perform a motor-task sodium functional MRI (23Na-fMRI) study to assess whether sodium signal changes during brain activity.

Methods: *23Na-fMRI protocol:* Data was acquired on a 3T Philips Achieva system (Philips, Netherlands) with a single-tuned volume head-coil (Rapid, Germany) using a 4-times undersampled 3D-Cones ultra-short echo time sequence[3], 4mm isotropic resolution, 240mm field-of-view, 90° flip-angle, TR=50ms, TE=0.22ms, 6 NEX, total scan time per volume = 1min. *Subjects:* 8 healthy volunteers (mean age 33yrs, range 27-45, 5 males, right-handed) gave written consent to this study approved by our local ethics committee. *fMRI design:* 23Na-fMRI was performed back-to-back 6-times during which the subject was asked to alternatively rest or perform a right-hand finger-tapping task (frequency = 1Hz). *Analysis:* Images were reconstructed to 2mm isotropic resolution using SNR-enhancing sub-Nyquist k-space sample weighting[4]. All analysis were performed with SPM8. Images were rigidly registered, smoothed with a 8x8x8mm^3 Gaussian-kernel and normalised to the proton density (PD) template. Statistical analysis was performed using the PET group analysis toolbox. Statistical maps were calculated with p=0.001 and family-wise error correction.

Results and discussion: Figure 1 shows transverse slices from one 23Na-fMRI volume. Figure 2 shows 23Na-fMRI statistical activation maps from the group analysis overlaid on the PD template. 23Na-fMRI correctly shows classical activations in contralateral primary motor and premotor cortices and ipsilateral cerebellum (VIIIA). Ipsilateral secondary somatosensory cortex and superior parietal lobule indicate functional activity related to tactile attention and processing of sensory inputs. A cluster at the insula level can be related to its known role in motor control. The ipsilateral Crus I, II of the cerebellum are in line with their contribution to executive functions and known connections to the premotor cortex. Beyond motor and motor-related areas, activations in grey and white matter relative to visual and auditory functions were also found. Activations located in grey matter regions cannot be attributed solely to 23Na intracellular accumulation during neuronal firing. In fact, with the current data it is not possible to exclude that 23Na-fMRI changes are also due to a change in blood volume in grey matter. Nevertheless, it is very significant that most of the activated regions are at the border between grey and white matter; here one would expect the greatest accumulation of intracellular sodium, due to the high concentration of sodium channels in the axon initial segment where it connects to the soma. Also, we have been able to detect clear patches of activity in white matter regions, including: the corticospinal tract, the superior longitudinal fasciculus, which connects parietal to prefrontal cortices and is known to be part of associative fibers that integrate information of body awareness and perception, and the inferior cerebellar peduncle which is the gateway for fibers connecting the spinal cord and the cerebellum, forming a key pathway for integrating proprioceptive sensory inputs. These tracts are myelinated and enriched in sodium channels in the Ranvier nodes.

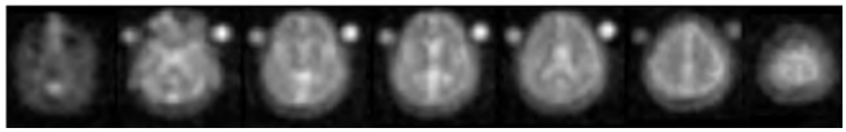

Figure 1: Example of transverse slices from one 23Na-fMRI volume of one volunteer after smoothing. The circles either side of the brain are known concentration phantoms.

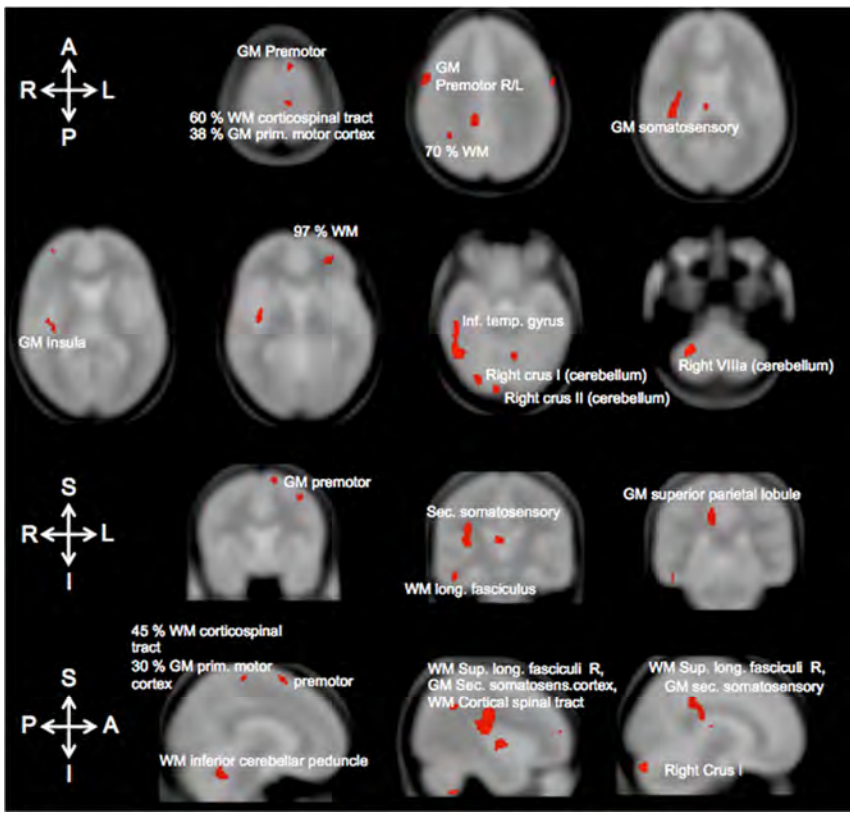

Figure 2: Examples of activation clusters (FWE corrected, p< 0.001, 20 voxels) overlaid on the PD template indicating also anatomical regions.

Conclusions: 23Na-fMRI is an exciting and promising method for assessing functional activity of the brain. The current results, especially relative to white matter activations warrants further investigations to determine the neurophysiological underpinning of these signal changes.

References: 1. Hodgkin and Katz, 1949. J Physiol (London), 108:37 2. Maudsley and Hilal, 1984. Br Med Bull 40:165 3. Gurney et al, 2006. MRM 55:575 4. Pipe, 2000. MRM 43:867

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