Detecting Brain Activity Using Direct Water Saturation

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Background and Objective. Functional magnetic resonance imaging (fMRI) using the blood-oxygenation-level-dependent (BOLD) technique [1] has emerged as the leading research tool for detecting brain activity, largely due to its robust signal, non-invasiveness and ease of implementation for whole brain coverage [2,3]. However, since BOLD contrast is derived primarily from T_2* changes induced by a decrease in magnetic susceptibility, gradient echo sequences with long echo time (TE) are required to achieve maximal contrast. Such long TE sequences are not optimal in many brain regions, such as the frontal cortex where susceptibility effects caused by nasal cavities are high. This shortcoming clearly limits the extent of BOLD fMRI for measuring global cerebral hemodynamics. Here, we attempt to address this limitation by investigating a new, short TE, spin echo fMRI technique for measuring brain activity based on direct saturation (DS) of the water pool. It has recently been shown that an off-resonance saturation pulse generates a susceptibility-influenced signal reduction around superparamagnetic iron nanoparticles [4]. During increased brain activity, it is well known that magnetic susceptibility changes in parenchyma as well [1-3]. This susceptibility change will lead to increases in parenchymal T_2, which will yield a more narrow saturation line shape [4,5] and in turn will increase MR signal when a DS pulse is applied. The hypothesis to be investigated is that when a DS pulse of short duration and low power (to avoid magnetization transfer effects) is applied at the correct offset frequency, a detectable signal increase will result during elevated brain activity, which will be due to a narrowing in the saturation line shape of parenchyma consequential to neuronal activation.

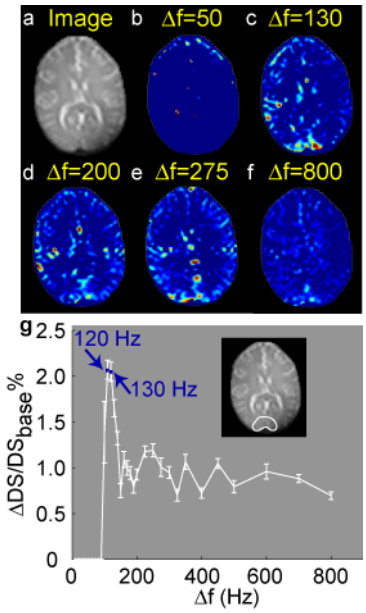

Fig. 1. Raw Δf=130 Hz image (a) along with $\Delta DS/DS_{base}$ maps for varying Δf. In (g), occipital (white ROI) $\Delta DS/DS_{base}$ is shown for different Δf.

Methods. *Experiment.* All volunteers participating in this study provided informed, written consent in accordance with the local IRB and HIPAA guidelines. Gray matter- and intravascular blood-T_2 increases by approximately 0.6 ms and 8 ms, respectively, during increased neuronal activity, depending on the ratio of arteries/veins in a given voxel [6]. We first studied the possibility of detecting DS effects by acquiring images during both baseline activity (cross-hair fixation) and visual stimulation (8 Hz black/white flashing checkerboard) for a range of DS frequency offsets (Δf=0-800 Hz), pulse powers (P=0.6-1.5 μT), pulse shapes (block or sinc-gauss) and pulse lengths (δ=150-250 ms). It was determined that when using a sinc-gauss pulse with Δf =125 Hz, P=0.8 μT and δ=200 ms, a statistically significant change ($p<0.05$) could be seen in high SNR (SNR>20) voxels in the visual cortex. Based on these preliminary data, five healthy volunteers (age: 34±9) were scanned at 3.0T under (1) an identical *DS* protocol as above, (2) a *Pulse Off* protocol where the DS pulse was removed, and (3) a conventional *BOLD* protocol. All scans contained the common parameters TR=5000 ms, 3.75x3.75x5 mm^3 spatial resolution, single-shot EPI, SENSE=2.5, 84 image acquisitions, 11 slices centered at the calcarine fissure. Other scan parameters: *DS:* three-lobed sinc-gauss pulse (Δf=125 Hz, P=0.8 μT and δ=200 ms), spin echo, TE=12 ms; *Pulse Off*: identical to *DS* except with sinc-gauss pulse removed; *BOLD*: gradient echo, TE=45 ms. *fMRI Paradigm*: Volunteers were instructed to perform a visual task consisting of 30/45s flashing checkerboard/cross-hair fixation, repeated five times. 45s of initial resting was added before the first task in each scan; data from this period were discarded. Activation criteria: z-score≥6 ($p<0.05$), SNR≥20, cluster size≥4.

Results and Discussion. Fig. 1a shows spin echo data for a DS sinc-gauss saturation pulse with P=0.8 μT, δ=200 ms and Δf=130 Hz. The colored maps represent the DS image acquired during visual stimulation minus the DS image acquired during baseline, normalized by the DS baseline signal ($\Delta DS/DS_{base}$) for Δf=50 (b), 130 (c), 200 (d), 275 (e) and 800 (f) Hz; only voxels with SNR≥20 are shown. For small Δf <100 Hz, the DS pulse is too close to the water line to detect any possible physiological changes. A sharp peak in occipital $\Delta DS/DS_{base}$ can be seen for Δf=120-130 Hz, which decays for large Δf (g). These preliminary results were the basis for our choice of DS parameters. Fig. 2 shows a representative z-score map for a single subject for the *DS* (a), *Pulse Off* (b) and *BOLD* (c) experiments. Note that z-scores are highest in *DS* and *BOLD* experiments, yet persist to a lesser degree in the *Pulse Off* experiment as well. Fig. 2d shows the corresponding time courses (z≥6); *BOLD* signal changes (ΔS/S) are largest (ΔS/S=3.8±0.2 %), followed by *DS* (ΔS/S=1.3±0.2 %); for *Pulse Off*, ΔS/S=0.9±0.1 %. The white line shows the *DS* time course divided by the *Pulse Off* time course. When only time courses from voxels meeting activation criteria in the *DS* experiment are analyzed, *Pulse Off* ΔS/S remains nearly unchanged (ΔS/S=0.8%±0.2%), whereas *BOLD* ΔS/S increases (ΔS/S=8.3%±3.2%), an effect attributed to this subset of voxels containing high cerebral blood volume (CBV). Finally, *DS* SNR was a factor of 3.2 higher than the *BOLD* SNR, which is due to the comparatively short TE in *DS* experiments; this led to a *DS* CNR that was a factor of 1.1 higher than *BOLD* CNR. Several promising conclusions can be taken from this preliminary study. First, similar to as was previously demonstrated in iron-oxide particles and in human gray matter, DS effects appear to provide contrast in the human brain consequential to changes in the oxygenation state of blood. These effects were most obvious at DS Δf =120-130 Hz, and became smaller at larger Δf. Due to the small power used, we believe these effects are due to DS and not magnetization transfer. The advantage of such a technique is the ability to use spin echo and short TE, thereby reducing-susceptibility-related artifacts in conventional BOLD fMRI. Also, while ΔS/S is smaller in DS fMRI compared with BOLD fMRI, the SNR is much higher in DS fMRI, thereby potentially allowing for smaller ΔS/S to be reliably detected. Several important limitations of the current study should also be considered. First, the long DS pulse limits the number of slices that can be acquired in a TR due to specific absorption ratio constraints. Therefore, for whole brain coverage, longer TRs must be used (here, TR=5000 ms; 55 mm thick imaging volume). Second, without the DS pulse, a residual ΔS/S=0.9% persists in the short TE, spin echo sequence. We tentatively attribute this to blood inflow associated with the limited volume coverage (11 slices) as well as residual BOLD spin echo effects, which could cause a ΔS/S=0.2-0.3% at this TE ($\Delta T_{2,tissue}$=0.6 ms, $\Delta T_{2,blood}$=8 ms, ΔCBV=30%), but may increase further in voxels with higher CBV. However, *DS* experiments provided additional contrast compared with the *Pulse Off* experiment, indicative of a DS effect contributing in addition to possible blood inflow and BOLD effects. Importantly, since the majority of the T_2 change occurs in intravascular blood, DS fMRI may be useful for measuring CBV changes.

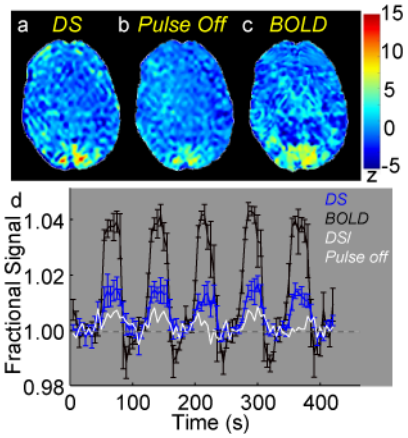

Fig. 2. Z-score maps for *DS* (a), *Pulse Off* (b) and *BOLD* (c). Corresponding time courses (z≥6; SNR>20) are shown in (d).

Conclusions. We present for the first time the possibility of detecting brain activity in humans based on DS fMRI. While additional methodological improvement is necessary, the current approach shows promise for complementing BOLD fMRI as well as for measuring CBV changes.

References. [1] Ogawa S, et al. *PNAS*;87:9868-72. [2] Jezzard P, et al. Functional *MRI: An Introduction to Methods*; Oxford University Press. [3] Logothetis NK, et al. *MRI*;22:1517-31. [4] Zurkiya O, et al. *MRM*;56:726-732. [5] Henkelman RM. *MRM*;29:759-66. [6] Donahue MJ, et al. *MRM*;56:1261-73.. **Funding:** NIH/NCRR: P41 RR015241.