Measurement of distinctive features of Cortical Spreading Depolarizations with different MRI contrasts

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INTRODUCTION: Growing clinical evidence suggests critical involvement of spreading depolarizations (SD) in the pathophysiology of several neurological disorders such as migraine, ischemic stroke, subarachnoid hemorrhage.[1] Thus, identifying their causes and effects is important. MRI is a powerful tool to assess the co-occurring cerebral hemodynamic and cellular changes during SD.[2] In this study we report the feasibility and advantages of two MRI scans heretofore unexplored for SD monitoring. A pass-band, 3d balanced-steady-state-free-precession (SSFP) scan and a diffusion-weighted 2d adiabatic multi-spin-echo EPI scan (denoted as DT2) were compared with a conventional 3d gradient-echo EPI scan (GE) for their advantages in monitoring SD-induced changes in rat brain. Known for high SNR, and T_2- and T_1-based contrast, SSFP was hypothesized to provide better spatiotemporal specificity compared with the T_2^*-based GE scan. The DT2 scan was designed to provide simultaneous T_2 and ADC map updates at 10s temporal resolution, thus enabling combined quantitative assessment of hemodynamic and cellular changes during SD.

METHODS: In 15 adult male Wistar rats, a unilateral 2x2mm cranial window was made 7mm posterior and 2mm lateral to bregma. The dura was removed and the exposed cortex was covered with a saline-soaked cotton wad. A tube was placed to drop 1M KCl solution on the wad to induce SD inside the scanner. Rats were ventilated with 2-2.5% isoflurane in 70:30 air/O_2 mixture and scanned at 4.7T using a surface coil Tx/Rx setup. DT2 (echo spacing: 25ms, TR: 1.67s, interleaves: 2, echoes: 6, FOV: 32x32x12mm, matrix: 64x64x10, diffusion-weighting: 0, 300 and 500s/mm^2 in lateral direction) was the first scan in all sessions, followed by SSFP (TE: 2ms, TR: 4ms, PExPE2: 64x24, FOV: 32x32x12mm, matrix: 64x64x24, flip angle: 25^o) and GE (TE: 20ms, TR: 40ms, interleaves: 1, PE2: 28, averages: 2, FOV: 32x32x14mm, matrix: 64x64x28) in mixed order. All scans were optimized for highest SNR (by adjusting flip angle) and lasted 40min. SD were first induced by dropping 50µl KCl at10min during DT2 scan. 10µl KCl was used to refresh the wad between subsequent scans. SSFP and GE data were temporally filtered using robust smoothing.[3] DT2 data underwent anisotropic spatial filtering (weighting based on correlation of ADC and T_2 values among neighbors) and were re-analyzed using moving-window (width: 80s) nonlinear fit. All datasets were programmatically analyzed voxelwise for SD-induced temporal contrast changes (peak finding). The total scans of various contrasts (some were repeated in a few animals) and the significant peak waveforms (Z≥3) obtained are summarized in Table 1. Peak waveforms were used to estimate the full-width-at-half-maximum (fwhm) and maximum signal changes. These were statistically compared across scans. Cluster analysis was used to elucidate distinct temporal patterns in each scan. Movies were created to visualize SD evolution.

RESULTS: The frequency of SD events estimated from histogram analysis of peak time points of SSFP and GE data is summarized in Table 2, and shows typical recurrence of SD in 10-14 minutes. Fig.1 shows representative Z-scores of contrast changes in various scans overlaid on axial brain images. In DT2, only ADC showed large responses. Fig.2 compares GE, SSFP and ADC peak signal changes and fwhm. SD-related contrast changes were largest for ADC, followed by SSFP and GE signals (all significantly different in pairwise t-Tests, $p<0.05$). SSFP signals had narrower fwhm compared with GE (t-Test, $p<0.05$). Further, the spatial extent of SD patterns detected with SSFP was restricted to about 60% of the volume detected with GE scanning. Increasing Z-threshold during peak-detection (from 3 to 6 in 7 steps) revealed a greater drop-out rate for GE waveforms than SSFP, perhaps indicating higher false positive rates in GE scanning. Fig.3 shows k-Means clustering results (200 trials) from scaled peak waveforms. The first 3 major clusters contained more than 75% of the data in each scan type. Apart from the expected contrast changes in response to SD, i.e., increase in GE and SSFP signals due to hyperemia (Figs. 3a,b), and decrease in ADC due to cell swelling (Fig. 3c), cluster analysis revealed several other temporal patterns, such as an initial dip in GE scans (Fig.3a) and temporally shifted T_2 and proton density changes in DT2 data (Figs.3d,e).

DISCUSSION: Comparison of SSFP and GE data shows that signal responses to SD events in SSFP scans are larger and spatiotemporally more specific. These factors, and the fact that SSFP was the only scan to provide SD visualization without post-processing, encourage its adoption for SD monitoring. But, SSFP data quality strongly depends on shim conditions. The suitability of DT2 scanning to detect SD was shown in this work. Unlike commonly used diffusion-weighted scans, DT2 concurrently provides two quantitative parameters, ADC and T_2. ADC was the most sensitive to SD-induced changes, with 20% drop in value during SD. T_2 and proton density showed time-shifted responses which may point to regions with differing hemodynamics during SD. Although their physiological underpinnings are yet to be ascertained, the capacity of DT2 scanning to simultaneously provide information on cellular and hemodynamic changes may lead to a better understanding of the inter-relationship between these processes, and could improve SD monitoring in (pre)clinical settings.

REFERENCES:[1] Nature Medicine 17, 439-447, 2011;[2] Biological Reviews 81, 457-481, 2006;[3] Comp.Stat and Data Anal., 54, 1167-1178, 2010

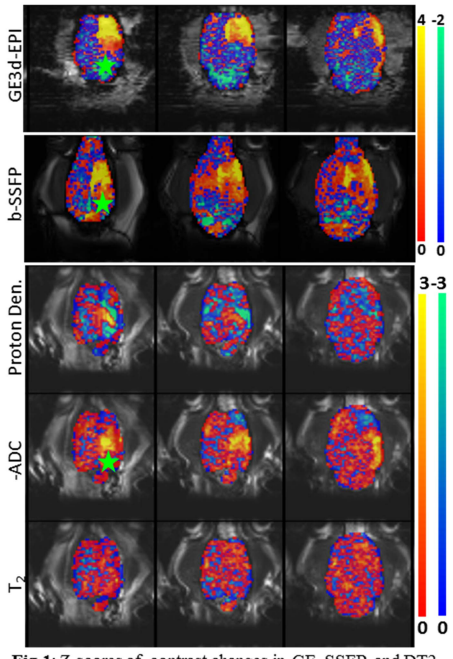

Fig.1: Z-scores of contrast changes in GE, SSFP and DT2 scans during SD events. ★: Site of KCl application.

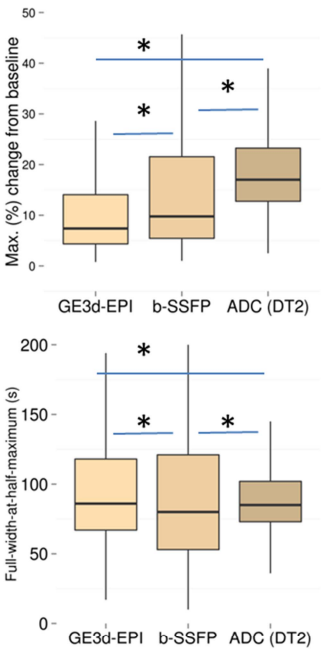

Fig.2: Max contrast changes and FWHM of SD waveforms. *: $p < 0.05$

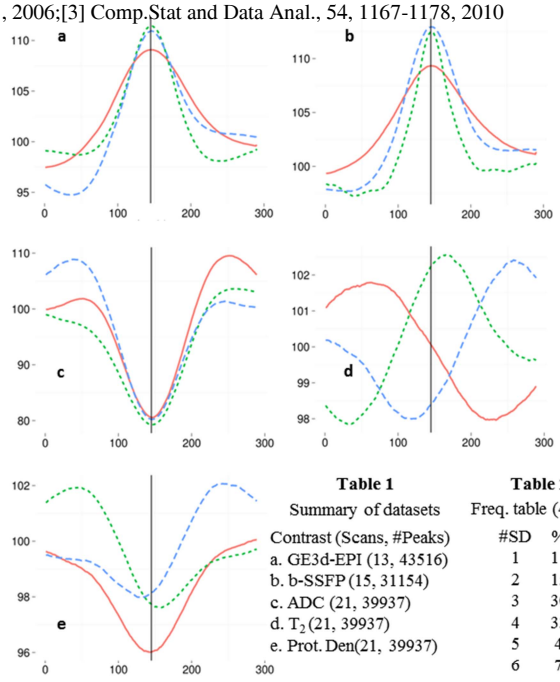

Table 1 Summary of datasets

Contrast (Scans, #Peaks)
a. GE3d-EPI (13, 43516)
b. b-SSFP (15, 31154)
c. ADC (21, 39937)
d. T_2 (21, 39937)
e. Prot. Den(21, 39937)

Table 2 Freq. table (40min)

#SD	%
1	11
2	15
3	30
4	33
5	4
6	7

Fig.3: k-Means results from scaled peak-waveforms (centroids of 3 major clusters). x: time(s), y: % of baseline. Waveforms were aligned at the vertical line.