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TITLE

Increased cerebral blood volume in cortical and subcortical brain regions in Glioblastoma patients after EPI distortion correction

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SYNOPSIS

We studied the changes in rCBV introduced by echo-planar imaging (EPI) distortion correction methods when applied to EPI dynamic susceptibility contrast (DSC)-MRI. The results obtained using FSL TOPUP and EPIC distortion correction methods indicate that both subcortical and cortical regions are affected and returning an overall increase in rCBV. In the context of longitudinal EPI-based analysis in glioblastoma patients, EPI distortions and subsequent corrections are important determiners for assessing robust responses of rCBV change.

INTRODUCTION

Dynamic Susceptibility Contrast (DSC)-based cerebral blood volume (CBV) is a useful imaging biomarker in glioblastoma patients and it has proven valuable in both predicting overall survival and treatment response^{1,2}. CBV is typically derived from multiple Echo-planar Images (EPIs) during injection of an intravascular tracer³. EPI-based acquisition methods are inherently limited by geometric distortions^{4,5} that can be corrected using different distortion correction algorithms. To investigate the impact on CBV change from EPI distortion correction, we evaluated two correction methods, FSL TOPUP⁴ and EPIC⁵, on pre-treatment DSC-data from 45 patients with glioblastoma. We here present brain regions where rCBV is prone to change from EPI corrections. To relate the regions to tumor location, we count the number of patients with enhancing, necrotic and edema tumor overlapping those regions.

METHODS

First, using TOPUP and EPIC, we obtained uncorrected and corrected rCBV maps from 45 spin-echo and gradient-echo EPIs in nordicICE (NordicNeuroLab, Bergen, Norway)⁶. The rCBV maps were normalized to normal-appearing reference tissue, as well as corrected for contrast agent leakage using the Weisskoff method⁷. Second, the rCBV maps were resliced to MNI space in SPM12 using 3D T2-FLAIR images from the same MRI exam as basis. Third, total rCBV before and

after EPI correction were assessed in 66 brain regions in NMI space⁸. Tumors, ventricles and cerebrospinal fluid were excluded from the analysis and symmetric left and right brain regions were merged for simplicity. Fourth, apparent changes in total rCBV were determined using two-sided paired Wilcoxon signed rank tests with Bonferroni correction for multiple comparisons. Finally, we summarized the number of patients to have at least 4cm³ of enhancing, necrotic and edema tumor overlapping with brain regions depicting a significant change in rCBV following EPI correction.

RESULTS

Of the regions with significant ($P < 0.001$) change in rCBV following distortion correction, all but one region depicted an increase in CBV (Figure 1 and 2). Regions with CBV increase included the pallidum, putamen, occipital pole and caudate nucleus. EPIC corrected spin-echo EPIs had the highest mean increase in rCBV (~13%), whereas TOPUP corrected spin-echo EPIs had a higher number of regions with high rCBV increase (4 of 16 regions above mean increase) (Figures 1-3). Moreover, correction of spin-echo EPIs led to a higher number of regions with significant rCBV change compared to gradient-echo EPIs. Of note, 56% of the patients had at least 4cm³ of enhancing tumor overlapping with significantly increasing rCBV from TOPUP corrected spin-echo EPIs (Table 1).

DISCUSSION

The EPI corrections returned a shift towards higher rCBV values in subcortical and cortical areas. Consequentially, our results indicate that if EPI distortions are not corrected, the rCBV values in these regions could be underestimated. Because the apparent magnetic susceptibility as observed in the tissue may also change with the natural history of the disease and treatment, subsequent uncorrected estimates of parameters like rCBV may also reflect unwanted EPI distortions.

CONCLUSION

Our results indicate that EPI distortion correction tends to increase total rCBV in subcortical and cortical areas when analyzed in MNI space. Moreover, because various degrees of EPI distortions may occur during treatment of brain cancer, the estimation of CBV values will likely be affected if not corrected for.

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Table 1: Number of patients with tumor in at least 4 cm³ of significantly increased CBV caused by EPI distortion correction (n=45).

		GE TOPUP	GE EPIC	SE TOPUP	SE EPIC
	Number of significant regions (L, R)	6	6	16	13
> 4 cm ³ signif. rCBV increase (P < 0.001)	Enhancing ⁹	5 (11 %)	3 (7 %)	25 (56 %)	13 (29 %)
	Necrotic ⁹	6 (13 %)	1 (2 %)	15 (33 %)	6 (13 %)
	Edema ⁹	19 (42 %)	12 (27 %)	32 (71 %)	21 (47 %)

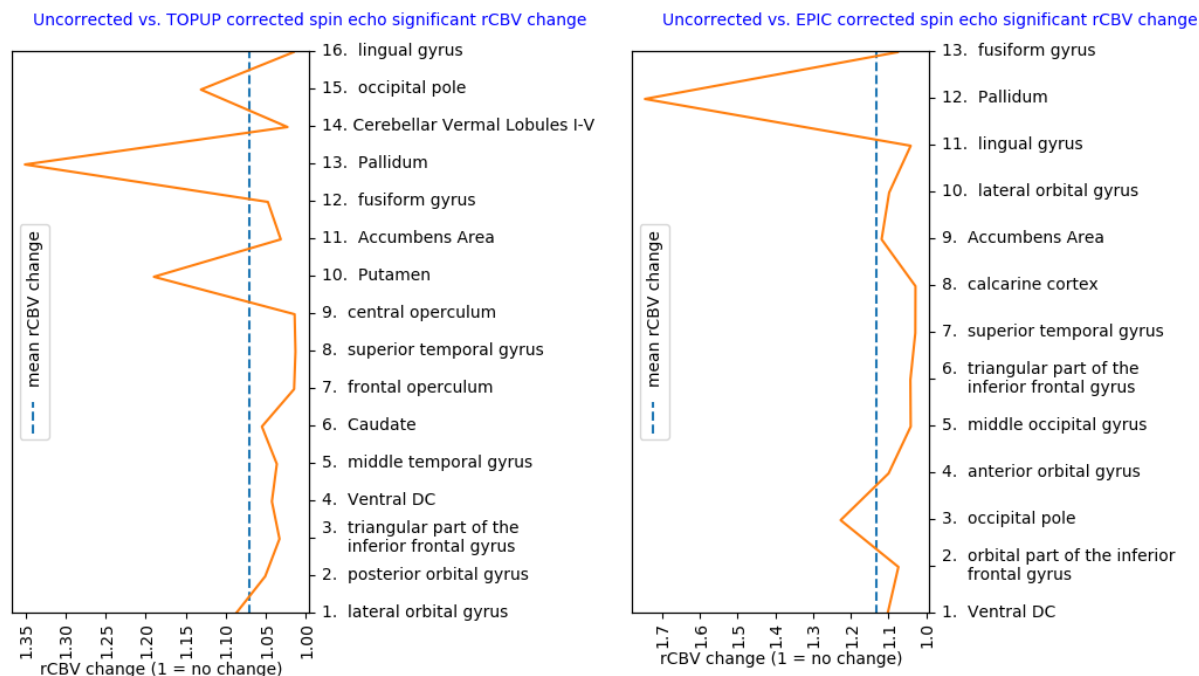


Figure 1: Regions with significant increase in CBV (1. most significant) by TOPUP (left) and EPIC (right) correction of **spin echo** DSC ($P < 0.001$, $n = [14, 34]$).

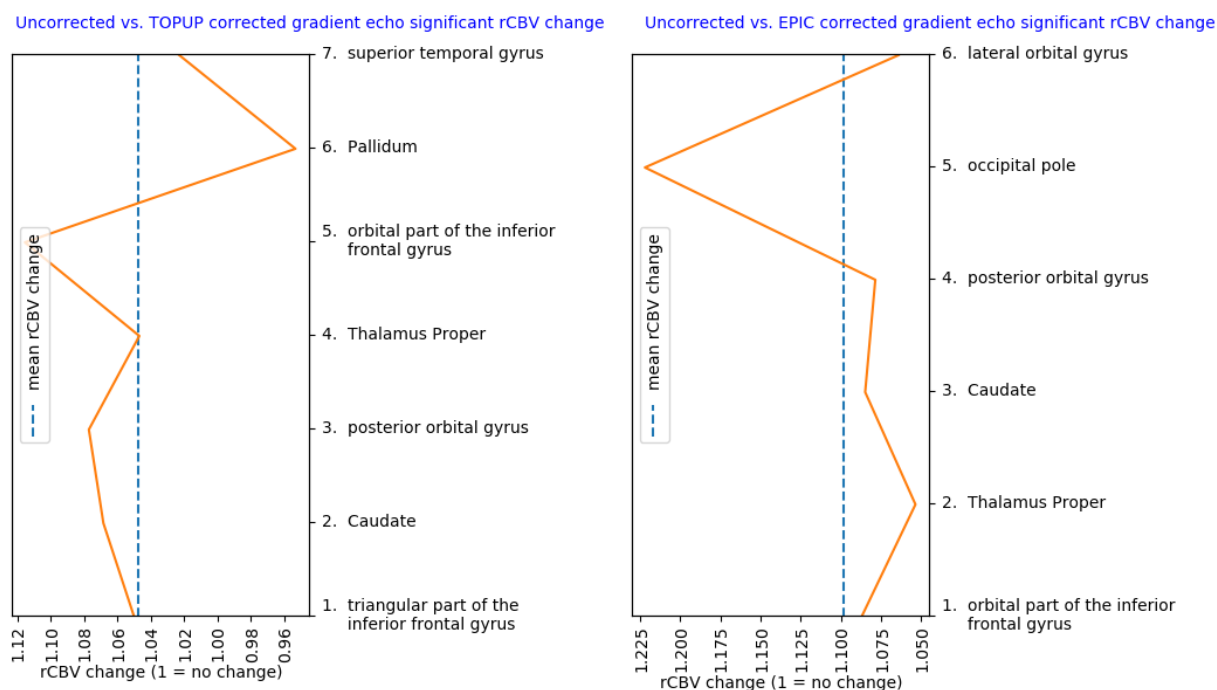


Figure 2: Regions with significant increase in CBV (1. most significant) by TOPUP (left) and EPIC (right) correction of **gradient echo** DSC ($P < 0.001$, $n = [22, 32]$).

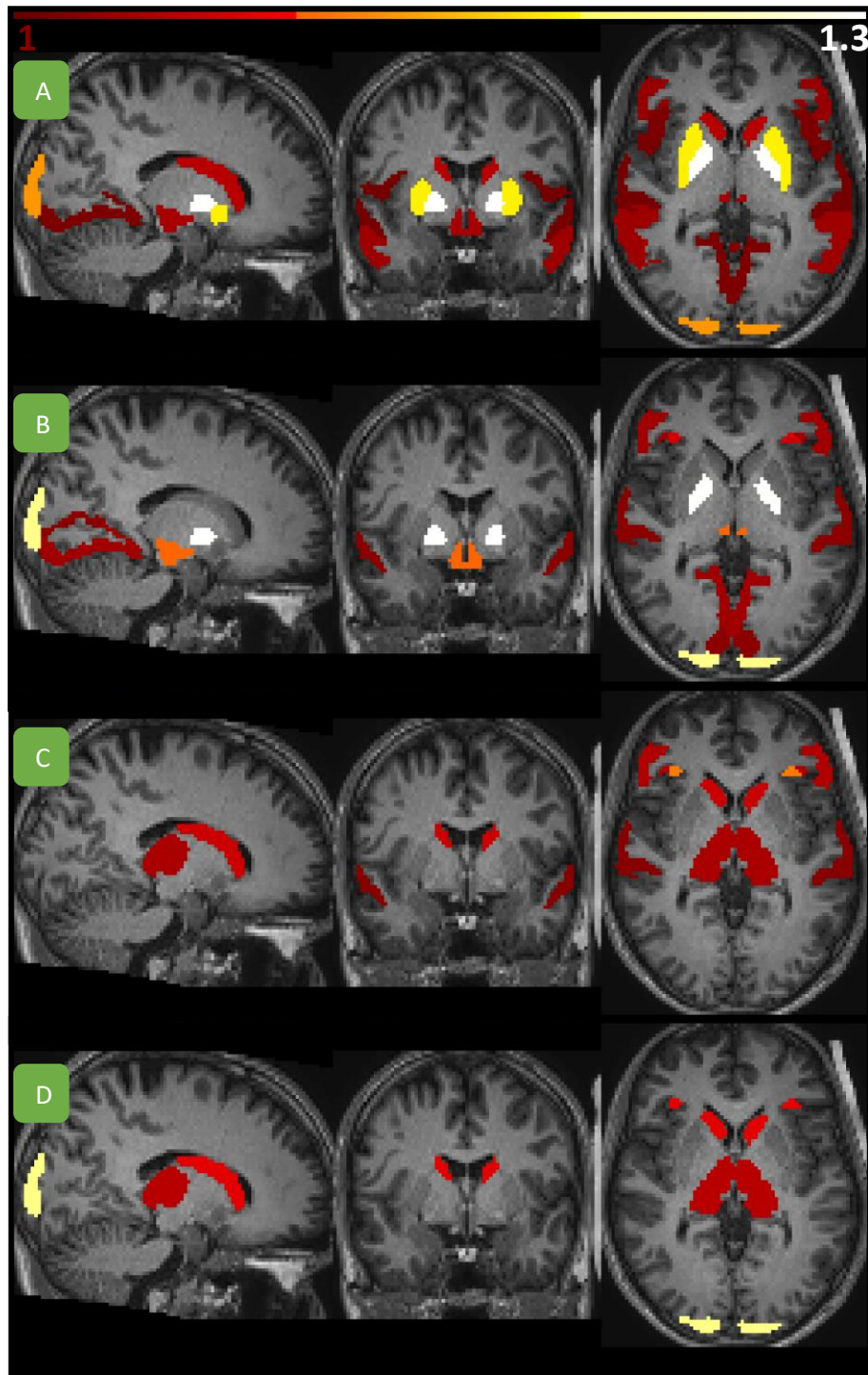


Figure 3. Regions with significant increase in CBV from EPI distortion correction ($rCBV$ change > 1). The heat maps are medians of $rCBV$ change for A, B: TOPUP and EPIC spin echo correction (as in Figure 1); and C, D: TOPUP and EPIC gradient echo correction (as in Figure 2). Pallidum is

shown in white in A and B, while yellow regions in A depict putamen. The outermost posterior regions in A, B and D depict occipital pole.