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Appendix E1

Materials and Methods

Pulse Sequences

Figure 1 illustrates the fMRI and DTI sequences used in this study. The T2prep BOLD fMRI sequence consists of a double refocusing T2 preparation module for generating the BOLD contrast, followed by a 3D fast GRE readout similar to MPRAGE (6). One entire 3D image volume is acquired in a single repetition time (TR) period. Double refocusing T2 preparation is adopted as it is more robust against phase variations and inflow effects compared with single refocusing T2 preparation (27). The diffusion-prepared DTI sequence has a similar structure as T2prep BOLD, which includes a diffusion preparation module for generating the desired diffusion contrast, followed by a similar 3D fast GRE readout. The diffusion preparation module uses the same RF pulse series as T2 preparation (double refocusing), with additional diffusion weighting gradients inserted between the RF pulses (10,11,28,29). To minimize eddy current related artifacts and reduce T1 effects during the readout, a stimulated echo scheme (12,16) is adopted: a dephasing gradient before the last 90° pulse in the diffusion preparation module, and a set of rephasing gradients in the 3D fast GRE readout (each of which has the same area as the dephasing gradient) are added to generate the stimulated echoes. Although the signal intensity is halved and the point spread function may be widened (due to a longer echo train to incorporate the dephasing and rephasing gradients) with the stimulated echo scheme, it has been shown that the stimulated echo approach can effectively reduce eddy current induced artifacts and T1 contaminations that are commonly seen in DTI (12,16), which is of utmost importance for accurate measurement of diffusion parameters. The dephasing and rephasing gradients are applied in the slice-encoding direction, and the areas of these gradients are carefully chosen to be 1.5 times the area of the maximum slice-encoding gradient to avoid overlapping of the primary and stimulated echoes (12,16).

Dental Brace

To compare image artifacts induced by dental braces, the same subject should be scanned using identical methods with and without braces. However, the procedure of installing and removing braces is not trivial. Therefore, a pair of bonding trays that can be easily mounted on and removed from the subject's teeth was used for each subject. The braces were custom-made for the participants (Fig 2) from alginate impression. Stainless steel brackets (Master Series; American Orthodontics, Sheboygan, WI, USA) were bonded to trays made of hard plastic. A Beta-Titanium archwire was seated and secured in the bracket slots.

MRI

All scans were performed on an Ingenia 3.0 Tesla (3T) Philips MRI scanner (Philips Healthcare, Best, the Netherlands). A 32-channel phased-array head coil was used for signal reception and a body coil for transmit. A respiratory belt was placed around the subject's chest during the MRI scans. Foam pads were used to restrain head motions and scanner noise was attenuated by earplugs. The following scans were acquired for each subject:

1) 3D T1-weighted MPRAGE, repetition time (TR)/inversion time (TI)/echo time (TE) = 3000/812/3.8 ms, voxel = 1 × 1 × 1 mm^3, matrix = 224 × 224, 150 slices, acquisition time per 3D volume = total acquisition time = 4 minutes and 18 seconds;

2) GRE EPI BOLD fMRI: TR/TE = 2000/30 ms, flip angle (FA) = 90°, voxel = 3.75 × 3.75 × 4 mm^3, matrix = 64 × 64, 40 slices, single-shot GRE-EPI readout, parallel imaging (SENSE) factor = 3, fat suppression, acquisition time per 3D volume (TR) = 2s, total acquisition time (determined by the duration of the functional paradigm used, see next paragraph) = 4 minutes and 20 seconds;

3) T2prep BOLD fMRI: TR/TE (T2prep effective) = 2000/50 ms, FA = 20°, voxel = 3.75 × 3.75 × 4 mm^3, matrix = 64 × 64, 40 slices, 3D fast GRE, SENSE factor = 2 × 1.5, partial-Fourier = 0.6 × 0.8, centric phase encoding profile starting from the center of k-space, TR_{GRE}/TE_{GRE} = 3.2/1.4 ms, acquisition time per 3D volume (TR) = 2s (ie, one entire 3D image volume acquired per TR), total acquisition time (determined by the duration of the functional paradigm used, see next paragraph) = 4 minutes and 20 seconds;

4) SE EPI DTI: b = 0 and 800s/mm^2, 15 diffusion gradient directions (x, y, z plus 12 oblique directions, standard clinical protocol optimized and provided by the vendor), TR/TE = 5000/90 ms, FA = 90°, voxel = 2.5 × 2.5 × 2.5 mm^3, matrix = 96 × 96, single-shot SE EPI readout, SENSE factor = 3, fat suppression, acquisition time per 3D volume (TR) = 5s, total acquisition time = 1 minute and 20 seconds;

5) diffusion-prepared DTI: b = 0 and 800s/mm^2, 15 diffusion gradient directions (same as the SE EPI DTI scan), TR/TE (effective) = 5000/90 ms, FA = 11°, voxel = 2.5 × 2.5 × 2.5 mm^3, matrix = 96 × 96, 3D fast GRE, SENSE factor = 2 × 1.5, partial-Fourier = 0.6 × 0.8, centric phase encoding profile, TR_{GRE}/TE_{GRE} = 4.1/2.0 ms; dephasing gradient = 2mT/m and 5 ms, rephasing gradient has the same area as the dephasing gradient, acquisition time per 3D volume (TR) = 5s (ie, one entire 3D image volume acquired per TR), total acquisition time = 1 minute and 20 seconds.

The order of the scans was chosen to be unique for each participant to avoid potential systemic biases. Note that all EPI images were acquired with optimized field homogeneity achieved by higher order shims using the toolbox described in (17) and image distortions corrected using the optimized procedure provided by the vendor. On the other hand, only first-order volume shim was applied in T2prep BOLD fMRI and diffusion-prepared DTI scans. To assess BOLD signal changes in the entire brain, a breath-hold task was performed during the GRE EPI and T2prep BOLD fMRI scans. The breath-hold task consists of 4 blocks of 40-second normal breathing, 4-second inhalation (4), and 16-second breath-holding, with an additional 20-second normal breathing period after the last block. The total task duration is 4 minutes and 20 seconds.

Point Spread Function (PSF)

A uniform semisolid phantom made of cross-linked 18% bovine serum albumin (BSA) was used for the measurement of PSF for the T2prep-BOLD, GRE-EPI-BOLD, diffusion-prepared-DTI, and SE-EPI-DTI sequences. The T1 and T2 values of this phantom were measured to be 1301 msec and 61 ms, respectively, which were similar to those of human gray matter (GM) at 3T. An optimized method published previously by others (18) was employed to measure the PSF for each sequence.

Data Analysis

BOLD fMRI data analysis was performed using the statistical parametric mapping (SPM) software package (Version 12, Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/) and other in-house code programmed in Matlab (MathWorks, Natick, MA, USA). Preprocessing steps include motion correction using the realignment routine in SPM, slice timing correction (for 2D multislice EPI BOLD scans only, not needed for 3D T2prep BOLD scans), coregistration between *fMRI* and anatomic images, segmentation, and normalization to the Montreal Neurologic Institute (MNI) space. A general linear model was employed to detect functional activation (adjusted $P < .05$, cluster size ≥ 3). Motion parameters estimated from the realignment routine and time courses recorded from the respiratory belt were regressed out. Functional results between the EPI and T2prep fMRI methods were compared using a region-of-interest (ROI) based analysis. Two ROIs were manually delineated in each subject: an ROI covering the signal dropout region in EPI images (strong susceptibility artifacts) caused by the metallic braces, and an ROI covering bilateral motor cortex with minimal susceptibility artifacts in EPI. The same ROIs were used in both fMRI methods in each subject. Signals over the GM voxels in the ROIs were averaged. To calculate the relative signal change ($\Delta S/S$) between breath-hold and normal breathing, the BOLD time course from each scan was first averaged across the 4 blocks, and the peak-to-trough difference described in the literature with similar breath-hold paradigms was taken as the signal change (30). Temporal signal-to-noise ratio (tSNR) was calculated as the signal divided by standard deviation along the time course in each voxel. Contrast-to-noise ratio (CNR) was defined as the product of tSNR and $\Delta S/S$.

The DTI data were processed using MRI Studio (www.mristudio.org). The DTI images from different b values and orientations were first coregistered using the automated image registration (AIR, http://air.bmap.ucla.edu/AIR5/) tool. Apparent diffusion coefficient (ADC) maps and fractional anisotropy (FA) maps color coded by v1 orientation (using standard RGB convention) were then calculated for each DTI method. To compare the two DTI approaches quantitatively, the SNR, ADC and FA values were calculated in two manually drawn ROIs: bilateral inferior fronto-occipital fasciculus (IFOF) with strong susceptibility artifacts in EPI, and bilateral posterior limb of internal capsule (PLIC) with minimal susceptibility artifacts in EPI.

The degree of geometric distortion in SE EPI and diffusion-prepared DTI images was compared using the following procedures. First, the Slicer tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Miscvis) was adopted to visualize the geometric distortion by overlaying the contours of brain structures obtained from coregistered MPRAGE images from the same subject onto the raw DTI images from the two approaches. Second, the Jaccard index (JI), which is commonly used to quantify the degree of distortion, was calculated for each slice in the DTI images:

$$JI = \frac{\sum_i D_i \cap S_i}{\sum_i D_i \cup S_i}, \quad [1],$$

where D and S are the binary masks (generated from the previous step) of the brain from the DTI image and the structural image, respectively, and i is the voxel index in each volume. Thus, the Jaccard index ranges from zero to one, indicating no overlap to complete agreement, respectively, between the geometric shapes of the structural and DTI images.

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Table E1. Comparison of group-averaged quantitative results from all subjects (*n* = 6) with and without wearing metallic braces in each fMRI approach.†

	tSNR†	ΔS/S (%)	CNR
T2prep BOLD			
Dropout region††			
With brace	37.8 ± 2.38†††	2.30 ± 0.66	0.83 ± 0.16
Without brace	37.0 ± 2.45	2.93 ± 0.54	1.14 ± 0.12
P value	0.38	0.18	0.14
Motor cortex			
With brace	41.6 ± 5.92	2.93 ± 0.73	1.08 ± 0.52
Without brace	44.4 ± 2.23	2.81 ± 0.59	1.27 ± 0.58
P value	0.22	0.47	0.17
GRE EPI			
Dropout region			
With brace	15.5 ± 5.29	1.81 ± 0.23	0.29 ± 0.10
Without brace	45.3 ± 6.31	2.83 ± 0.43	1.29 ± 0.16
P value	0.02*	0.01*	0.01*
Motor cortex			
With brace	48.9 ± 7.61	2.58 ± 0.44	1.38 ± 0.40
Without brace	52.8 ± 5.77	2.84 ± 0.42	1.48 ± 0.10
P value	0.20	0.27	0.19

GRE EPI: gradient-echo echo-planar-imaging; T2prep: T2-prepared.

* $P < .05$.

† ΔS/S, tSNR and CNR values are the same as Table 1 but are reorganized for the comparison between results with and without braces.

†† The “dropout region” refers to the area showing large signal wipeout in EPI scans in subjects wearing metallic dental braces, which mainly includes the orbitofrontal and ventromedial prefrontal cortex.

††† mean ± SD.

Table E2. Comparison of group-averaged quantitative results from all subjects (*n* = 6) with and without wearing metallic braces in each DTI approach.†

	SNR†	ADC ($10^{-3}mm^2/s$)	FA
Diffusion-prepared			
Inferior fronto-occipital fasciculus (IFOF)			
With brace	5.83 ± 1.47††	0.75 ± 0.08	0.45 ± 0.07
Without brace	5.78 ± 1.11	0.79 ± 0.23	0.49 ± 0.02
P value	0.43	0.37	0.35
Posterior limb of the internal capsule (PLIC)			
With brace	5.73 ± 1.09	0.73 ± 0.04	0.61 ± 0.03
Without brace	6.18 ± 1.64	0.68 ± 0.27	0.60 ± 0.01
P value	0.28	0.17	0.33
SE EPI			
Inferior fronto-occipital fasciculus (IFOF)			
With brace	3.77 ± 0.70	0.16 ± 0.16	0.10 ± 0.12
Without brace	6.18 ± 0.48	0.80 ± 0.18	0.45 ± 0.01
P value	0.01*	<0.001*	<0.001*
Posterior limb of the internal capsule (PLIC)			
With brace	6.97 ± 1.29	0.72 ± 0.03	0.59 ± 0.05
Without brace	7.03 ± 1.48	0.69 ± 0.20	0.58 ± 0.01
P value	0.31	0.21	0.23

SE EPI: spin-echo echo-planar-imaging.

* $P < .05$.

† SNR, ADC and FA values are the same as Table 2 but are reorganized for the comparison between results with and without braces.

†† mean ± SD.