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Effect of MRI Acoustic Noise on Cerebral FDG Uptake in Simultaneous MR-PET Imaging

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Abstract

Integrated scanners capable of simultaneous PET and MRI data acquisition are now available for human use. Although the scanners' manufacturers have made substantial efforts to understand and minimize the mutual electromagnetic interference between the two modalities, the potential physiological inference has not been evaluated. In this work, we have studied the influence of the acoustic noise produced by the MR gradients on brain FDG uptake in the Siemens MR-BrainPET prototype. While particular attention was paid to the primary auditory cortex (PAC), a brain-wide analysis was also performed.

Methods—The effects of the MR on the PET count rate and image quantification were first investigated in phantoms. Next, ten healthy volunteers underwent two simultaneous FDG-PET/MR scans in the supine position with the FDG injection occurring inside the MR-BrainPET, alternating between a “quiet” (control) environment in which no MR sequences were run during the FDG uptake phase (the first 40 minutes after radiotracer administration) and a “noisy” (test) case in which MR sequences were run for the entire time. Cortical and subcortical regions of interest (ROIs) were derived from the high-resolution morphological MR data using FreeSurfer. The changes in FDG uptake in the FreeSurfer-derived ROIs between the two conditions were analyzed from parametric and static PET images, and on a voxel-by-voxel basis using SPM8 and FreeSurfer.

Results—Only minimal to no electromagnetic interference was observed for most of the MR sequences tested, with a maximum drop in count rate of 1.5% and a maximum change in the measured activity of 1.1% in the corresponding images. The ROI-based analysis showed statistically significant increases in the right PAC in both the parametric ($9.13 \pm 4.73\%$) and static ($4.18 \pm 2.87\%$) images. SPM8 analysis showed no statistically significant clusters in any images when a $p < 0.05$ (corrected) was used; however, a $p < 0.001$ (uncorrected) resolved bilateral statistically significant clusters of increased FDG uptake in the area of the PAC for the parametric image (left: $8.37 \pm 1.55\%$, right: $8.20 \pm 1.17\%$), but only unilateral increase in the static image (left: $8.68 \pm 3.89\%$).

Conclusion—Although the operation of the BrainPET prototype is virtually unaffected by the MR scanner, the acoustic noise produced by the MR gradients causes a focal increase in FDG

uptake in the PAC, which could affect the interpretation of pathological (or brain-activation related) changes in FDG uptake in this region, if the expected effects are of comparable amplitude.

Keywords

PET; MRI; multimodality imaging; physiological interference; auditory cortex

INTRODUCTION

Integrated systems that simultaneously acquire MRI and PET data have recently become a reality for human imaging [1, 2]. The quantitative nature of PET, which provides the absolute radiotracer concentration in a specific voxel, can provide complementary information to structural MR imaging and could be combined with simultaneously collected functional MRI (fMRI) data. Similarly, the MR information can be used for PET motion [3], attenuation [4–6], partial volume effects correction [7], and image-based arterial input function estimation [8], to give just a few examples. In addition to these methodological opportunities, simultaneous MR-PET systems will directly benefit patients that need both examinations as they will observe shorter scan times.

Simultaneous MR-PET systems are a result of considerable advances in both technologies. While significant work has been done to address the hardware integration and to minimize the electromagnetic interference, there are other aspects that have to be considered in an integrated scanner. For example, the potential “physiologic interference” in a combined system – the influence of one modality on the biological process measured by the other – has not been thoroughly investigated. While the effects of static and varying magnetic fields on the resting brain’s metabolic activity have been studied [9, 10], others sources remain and must be understood for the validation of simultaneous MR-PET as a clinical tool. One potential source, for example, is the MR gradient-induced acoustic noise stimulating the auditory pathways of the brain.

The MR-PET environment is significantly different from the traditional PET environment; for routine clinical brain FDG-PET studies, it is common practice to isolate the patient in a quiet environment for the initial uptake phase [11]. Because acquiring MR data during this phase would shorten the total MR-PET scan duration, and could directly benefit PET (e.g. motion correction, etc.), it is desirable to administer the radiotracer on the table and perform MR immediately after radiotracer administration. However, the repetitive acoustic noise characteristic to the MR environment can reach as high as 131 dB [12], which causes neuronal stimulation of the primary auditory cortex (PAC), leading to focal increase in blood flow and glucose consumption [13]. Using fMRI techniques, MR acoustic noise has been shown to directly stimulate the PAC, requiring the development of specialized paradigms to minimize signal artifacts when studying the PAC [14–16]. Unlike fMRI, whose timecourse is on the order of seconds for the measurement of a stimulus, and thus allows for special data collection paradigms, FDG has an uptake on the order of tens of minutes and is influenced by any changes experienced over this timeframe. As FDG-PET non-specifically images glucose uptake, the acoustic noise could potentially lead to artifacts in the form of focal uptake of FDG. These artifacts could, in turn, significantly impact the FDG-PET metabolic patterns observed in PET studies.

This pilot study sought to characterize any regional changes in FDG uptake resulting from MR acoustic noise and set an upper limit on its effect. As a first step, phantom experiments were performed to assess the hardware-related effects (i.e. electromagnetic interference and MR eddy-current induced heating) on the PET data acquisition using our standard MR protocol. Next, advanced data analysis tools were used to compare the FDG-PET data

acquired with and without running MR sequences during the FDG uptake phase in healthy volunteers that underwent two MR-PET imaging sessions. While particular attention was paid to the primary auditory cortex and associated areas, an explorative analysis of the entire brain was also performed.

MATERIAL AND METHODS

Integrated MR-PET Scanner

The imaging studies were performed on a 3T TIM MAGNETOM Trio MR scanner (Siemens Healthcare Inc.) modified to support the BrainPET (Siemens), an MR-compatible brain-dedicated PET scanner prototype. The BrainPET, which uses magnetic-field insensitive avalanche photodiodes in combination with Lutetium Oxyorthosilicate (LSO) crystals as photodetectors, has a transaxial/axial field of view of 32/19.125 cm. 3D coincidence event data are collected with a maximum ring difference of 67 and stored in list mode format. For reconstruction, the list mode files are sorted into line-of-response space and further compressed into sinogram space (span=9). The PET data are reconstructed with a standard 3D ordinary Poisson ordered-subset expectation maximization (OP-OSEM) algorithm using both prompt and variance-reduced random coincidence events [17] as well as normalization, scatter [18], and attenuation sinograms. The attenuation sinograms are derived from dual-echo ultra-short echo time (DUTE) MR images [4]. The data are reconstructed with a voxel size of 1.25 mm isotropic into a volume consisting of 153 transverse slices of 256×256 pixels. The volumes are smoothed using a 3D filter with a 3 mm isotropic Gaussian kernel.

MR imaging was performed using two concentric head coils – an outer circularly-polarized transmit-receive coil and an inner 8-channel receive-only coil – specially designed for the BrainPET with considerations for their 511 keV photon attenuation properties. In this study, we focused on the MR sequences that are part of our standard brain tumor imaging protocol. In addition to the localizer, these included: T2 prepared variable flip angle turbo spin echo [**T2-SPACE**] (0.9 mm isotropic, TR/TE=3200/487 ms, TA=4:43 min); flow attenuated inversion recovery with turbo spin echo readout [**FLAIR**] (1.1×0.9×5 mm³, TR/TE/TI=10000/70/2500 ms, FA=150°, TA=3:02 min); **DUTE** (1.67 mm isotropic, TR/TE1/TE2=200/0.07/2.24 ms, flip angle=10°, TA=3:20 min); blood oxygen level dependent [**BOLD**] T2* weighted echo planar imaging (3.4×3.4×8 mm³, TR/TE=2000/19, FA=90°, TA=14:06 min); Time-of-Flight [**TOF**] MR angiography (0.7×0.5×0.7 mm³, TR/TE=24/3.68 ms, FA=18°, TA=6:16 min); multi-echo spoiled gradient echo sequence [**MEFLASH**] (2 mm isotropic, TR/TE1/TE2/TE3/TE4=2.46/4.92/7.38/9.84 ms, TA=2:28 min); mapping T1 relaxation effects with multiple inversion recovery [**T1 Mapping**] (1.8 mm isotropic, TR/TE=7.3/4.41 ms, FA=15°, TA=00:13 min); dynamic contrast enhancement [**DCE**] imaging with T1 weighted gradient echo imaging (2.6×1.8×2.1 mm³, TR/TE1/TE2=6.8/2.6/3.89 ms, FA=10°, TA=5:59 min); diffusion tensor imaging [**DTI**] with diffusion weighted spin echo echo-planar imaging (1.9 mm isotropic, TR/TE=7990/84 ms, TA=6:57); and multiple echo magnetization prepared gradient echo imaging [**ME-MPRAGE**] (1 mm isotropic, TR/TI/TE=2530/1200/1.64 ms, flip angle=7°, TA=4:56 min).

Phantom Studies

Phantom experiments were first performed to evaluate the effect of running MR sequences on the PET data acquisition. Particular attention was given to temperature effects as it is known that the performance of the avalanche photodiodes is a strong function of temperature. The BrainPET manages temperature changes using two mechanisms. The first method is a hardware based temperature controller which activates a closed-loop chiller. When sensors in the cassettes measure temperatures outside the optimal operating range, the

chiller is activated, providing a heat sink for the forced air that directly cools the cassettes. The second method is a software-based photopeak tracking algorithm which adjusts the crystals' 511 keV photopeak position based on the cassette's temperature. For these measurements, a uniform cylindrical Ga-68/Ge-68 phantom (Siemens Healthcare Inc.) (~5 MBq, 25 cm length, 20 cm inner diameter) was placed inside the head coil and simultaneous MR-PET imaging was performed using the MR protocol described above. PET data were acquired in list mode format for one hour and 30-second frames were subsequently generated. From the prompt and delayed events, total true coincident events were determined for each frame. The measurements were repeated five times. To determine the reproducibility, each frame was normalized to the average number of counts per 30 seconds for that trial. Relative change from the count averaged baseline was determined as well as the difference between the minimum and maximum values. To evaluate changes in the reconstructed images, 300 second frames were reconstructed and the maximum relative change from the average was determined over the imaging session. For comparison, the same experiment was also performed with the software photopeak tracking feature disabled.

Human Volunteer Studies

Subject Selection—Ten healthy volunteers (10 males, mean age 38.6 ± 11.2 years) were enrolled in this study. The mean height and weight among subjects was 181.4 ± 5.1 cm and 88.9 ± 22.1 kg. All subjects gave written informed consent and were studied in accordance with a protocol approved by the affiliated Institutional Review Board. Subjects were asked to follow a similar routine for the 24 hours prior to each scan to minimize metabolic changes prior to imaging which included fasting for at least 6 hours prior to the injection. Immediately prior to imaging, subjects' blood glucose levels were measured. The mean blood glucose levels for the control and stimulation environment were 103.9 ± 6.57 g/dl and 103.9 ± 9.29 g/dl, respectively; mean difference between visits one and two was 0.00 ± 5.79 g/dl.

Data Acquisition Protocol—Due to the relatively long half-life of FDG (110 minutes), to minimize residual uptake, subjects underwent simultaneous FDG-PET/MR imaging on two consecutive days, alternating between an MR “quiet” (control) and “noisy” (stimulation) environment. The subjects were divided equally into two groups, one group undergoing the control environment on day one and the noisy environment on day two, while the other group had the order reversed. Prior to PET data collection in either environment, an MR localizer was run to assess the subject's position in the field of view. Next, after PET data collection was initiated, ~185 MBq of FDG was administered intravenously allowing for dynamic PET imaging. In the control condition (i.e. no MR acoustic noise during the FDG uptake phase), no MR sequences were run for the first 40 minutes of the PET data acquisition. Subsequently, the ME-MPRAGE and DUTE sequences were run for deriving regions of interest (ROIs) and the attenuation correction map, respectively. For the “noisy”/auditory stimulation environment, the MR sequences that make up our standard brain tumor imaging protocol were run immediately after FDG injection (i.e. MR acoustic noise was present during the FDG uptake phase). As per required protocol, standard earplugs with a noise reduction rating of 29 dB were used in both environments; however, the acoustic noise of the MR scanner remained clearly audible to the subjects.

Data Analysis—Voxel-wise and ROI-based analyses were performed to identify potential effects of the MR on the FDG uptake in the brain by evaluating:

- time activity curves derived from dynamic (4-D) PET data with a framing of 8×60 sec, 2×150 sec, 2×180 sec, and 8×300 sec;

- local cerebral metabolic rate of glucose (LCMRGlu) parametric images derived from the first 40 minutes of dynamic data using the method presented by Wu [19] [20];
- static images reconstructed from the data acquired 40–60 minutes post-injection (similar to a static FDG-PET scan). Standardized uptake values (SUVs) corrected for lean body mass (SUV_{lbm}) were calculated in each case.

In addition to voxel-wise statistical analysis using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) [21], FreeSurfer [22] was used for both voxel-wise analysis and to automatically segment subject specific ROIs corresponding to cortical and subcortical structures. These ROIs were used for the PET data analysis as described in the following subsections. Global whole brain, grey and white matter mean values were also computed. A diagram of the experimental design, processing, and subsequent analysis can be found in Figure 1.

Time Activity Curves Analysis: For analysis of the dynamic PET data, time activity curves were defined as the mean within a ROI at each time point with the standard deviation defined as the inter-subject standard deviation. To determine the effect of gradient acoustic noise on the PAC (labeled in FreeSurfer as the superior transverse temporal gyrus) the left and right PACs were combined to yield a single ROI. For each time point across subjects, the brain regions of interest were normalized to whole brain and then averaged over the subject population. The mean uptake for the control and stimulation environment for each time point were then compared to one another using a paired, two-sample Student's t-test.

SPM-based Analysis: As SPM8 does not provide subject specific definition of cortical and subcortical structures, group analysis requires that the subjects be first registered to a common space using non-rigid transformations. For the SPM8 analysis, the common space to which the images were normalized to was the Montreal Neurological Institute (MNI) PET contrast template (subsequently referred to MNI-normalized). To derive the transformation fields to MNI space, a smoothed (3 mm isotropic Gaussian kernel) version of the individual PET images was fit using an 12-parameter affine transformation followed by a non-linear deformation using SPM8 and the normalized image was cropped to a volume of 79×95×68 voxels measuring 2 mm isotropic. Prior to statistical analysis, the MNI-normalized PET images were smoothed (8 mm isotropic Gaussian kernel) using SPM8. A paired t-test was performed on the data with a cluster size requirement of greater than 20 voxels and both an uncorrected $p < 0.001$ and a familywise-error (FWE) of 0.05 for significance. Anatomic correlation of the PAC, defined as Herschel's gyrus for SPM8 based analyses, and more general cluster location was determined using the Talairach Daemon and the Automated Anatomical Labeling atlas with the xjView toolbox for SPM8 (<http://www.alivelearn.net/xjview8/>) and is described in detail elsewhere [23, 24].

FreeSurfer ROI-based Analysis: In the FreeSurfer anatomic segmented output, each voxel is given an integer label corresponding to the segmented region [25]. For all FreeSurfer-based analyses, the PAC was determined as the transverse temporal gyrus from the cortical parcellation. Binary masks were generated for each segmented region using Matlab and the voxel addresses of the ROIs were determined and used to create a lookup table which was then applied to the PET image. To account for the differences in spatial resolution and the spatial mismatch between the two scanners, a downsampling operation and an affine transformation were applied to the segmentation maps using nearest-neighbor interpolation, and the subsequent analysis was performed in the PET space. To account for interscan motion, the skull-stripped MPRAGE image was coregistered to the PET image using a

mutual information algorithm to derive any additional affine transformations, which in turn were applied to the segmentation map prior to downsampling and interpolation.

For analysis of the parametric and static images, paired two-sample Student's t-test between the control and stimulation environments were performed across subjects for each cortical and subcortical brain region segmented in FreeSurfer. To normalize the static images across subjects, the regions were divided by the whole brain activity (WB-normalized). As the goal of this work is to identify any potential regions of significant change, to be conservative, no Bonferroni corrections were included in determining statistical significance ($p < 0.05$) across the brain regions.

FreeSurfer GLM-based Analysis: For group analysis, FreeSurfer uses a space obtained from “inflating” the ME-MPRAGE-derived brain of the individual subject into a sphere and registering it to a reference sphere. From this registration, FreeSurfer can map a subject's data onto a reference inflated brain representing the cortical surface. The same transformations were applied to the PET data and a surface was derived where each vertex value was the mean value along the normal path through the cortical ribbon. The subject specific changes were determined by subtracting the stimulation and control PET images and a study averaged image was derived by taking the mean change across subjects. The resulting image was smoothed (10 mm isotropic Gaussian kernel) on the surface of the brain and a generalized linear model (GLM) analysis was performed. For conservative evaluation, data were visualized with a $p < 0.01$ which is equivalent to the default threshold of $-\log(p) = 2$ used in FreeSurfer and FSL.

RESULTS

Phantom Studies

The normalized count rate versus time and the corresponding temperature time-courses for five representative trials with and without photopeak tracking can be found in Figure 2 and 3, respectively, demonstrating very high reproducibility when photopeak tracking was either enabled or disabled. With photopeak tracking enabled, the maximum change in count rate was less than 1.5%. Reconstructing this data into 300 second frames yielded a maximum drop of $1.08 \pm 0.39\%$ in a large ellipsoidal ROI. This drop in counts occurred during simultaneous DCE imaging, and shortly after DCE imaging was concluded the count rate returned to baseline. When photopeak tracking was disabled the normalized count rate decreased linearly with time with a maximum change from baseline the order of 25%. Comparatively, DCE imaging didn't seem to have as proportionally strong of an influence on the count rate when photopeak tracking was disabled.

Human Volunteer Studies

Time Activity Curves—105 cortical and subcortical regions of the brain were automatically segmented from the ME-MPRAGE image using FreeSurfer and were subsequently used for ROI-based analyses. A representative subject's segmentation, along with the ME-MPRAGE image, can be found in Figure 4. The combined left and right PAC ROI had a mean volumetric change of 0.157 ± 0.196 ml between the two visits ($p = 0.21$). A representative subject's time activity curves for the PAC, motor cortex (M1), and white matter for the control and stimulation environments can be found in Figure 5. As previously mentioned, for time activity curve analysis the PAC and white matter time points were normalized to whole brain and averaged across patients to create a group time activity curve, which can be found in Figure 5. A paired t-tests for each cross-subject time point yielded no significant points ($p < 0.05$) for either whole brain, white matter, or the PAC for the nonWB-

normalized images; however, a paired t-test of the WB-normalized PAC showed significant differences at all time points after 270 seconds.

Parametric Images—The mean uptake in the whole brain for the stimulation and control cases was 22.993 ± 0.005 $\mu\text{mol}/\text{min}/100\text{g}$ and 22.997 ± 0.005 $\mu\text{mol}/\text{min}/100\text{g}$ respectively with a mean change of -0.004 ± 0.006 $\mu\text{mol}/\text{min}/100\text{g}$ ($p=0.0643$). The mean uptake in the gray matter for the stimulation and control cases was 26.577 ± 0.492 $\mu\text{mol}/\text{min}/100\text{g}$ and 26.515 ± 0.425 $\mu\text{mol}/\text{min}/100\text{g}$, respectively, with a mean change of 0.0625 ± 0.4182 $\mu\text{mol}/\text{min}/100\text{g}$ ($p=0.648$). The mean uptake in the white matter for the stimulation and control cases was 20.896 ± 0.766 $\mu\text{mol}/\text{min}/100\text{g}$ and 20.877 ± 0.615 $\mu\text{mol}/\text{min}/100\text{g}$, respectively, with a mean change of 0.019 ± 0.500 $\mu\text{mol}/\text{min}/100\text{g}$ ($p=0.907$). When tested with a paired t-test, none of these regions were found to have $p\text{-values} < 0.05$.

SPM-based Analysis: SPM8 analysis using a FWE of 0.05 and minimum cluster size of 20 voxels yielded no significant activation clusters between the stimulation and control environments. SPM analysis using a $p < 0.001$ (uncorrected) resolved focal bilateral activation clusters which extended into Herschel's gyrus and can be found in Figure 5. Both regions were found to have increased metabolism of glucose in the stimulation environment as compared to the control environment. No regions with significantly decreased metabolism were detected. The left and right cluster sizes were 45 and 41 voxels with a change between stimulation and control of 2.46 ± 0.51 $\mu\text{mol}/\text{min}/100\text{g}$ ($8.37 \pm 1.55\%$) and 2.66 ± 0.55 $\mu\text{mol}/\text{min}/100\text{g}$ ($8.70 \pm 1.17\%$), respectively.

FreeSurfer ROI-based Analysis: The parametric images showed a bilateral increase in PAC LCMRGlu in six subjects with opposing changes in the left and right PAC uptake in the remaining four. The mean LCMRGlu of the control environment for the left and right PAC glucose metabolism was found to be 31.631 ± 1.895 $\mu\text{mol}/\text{min}/100\text{g}$ and 31.734 ± 1.263 $\mu\text{mol}/\text{min}/100\text{g}$, respectively, and 32.952 ± 2.642 $\mu\text{mol}/\text{min}/100\text{g}$ and 34.615 ± 1.683 $\mu\text{mol}/\text{min}/100\text{g}$ for the stimulation environment. No statistically significant change was found in the left PAC (1.321 ± 2.927 $\mu\text{mol}/\text{min}/100\text{g}$, $4.42 \pm 9.27\%$; $p=0.1872$), however a significant increase in the right PAC was noted (2.88 ± 1.46 $\mu\text{mol}/\text{min}/100\text{g}$, $9.13 \pm 4.73\%$; $p=0.0002$). When the left and right PAC were treated as a single ROI the mean change was found to be 2.10 ± 1.52 $\mu\text{mol}/\text{min}/100\text{g}$ ($6.67 \pm 4.91\%$; $p=0.0018$).

Statistically significant increases in LCMRGlu were found in five other regions: the long gyrus of the left insula (0.79 ± 0.89 $\mu\text{mol}/\text{min}/100\text{g}$, $3.48 \pm 4.08\%$; $p=0.0204$), the left superior temporal plane (1.19 ± 1.16 $\mu\text{mol}/\text{min}/100\text{g}$, $4.52 \pm 4.33\%$; $p=0.0097$), the left middle temporal gyrus (0.70 ± 0.94 $\mu\text{mol}/\text{min}/100\text{g}$, $3.14 \pm 4.10\%$; $p=0.0429$), the right superior temporal plane (1.38 ± 1.66 $\mu\text{mol}/\text{min}/100\text{g}$, $4.94 \pm 5.73\%$; $p=0.0279$), and the right transverse temporal sulci (2.92 ± 3.52 $\mu\text{mol}/\text{min}/100\text{g}$, $10.03 \pm 12.32\%$; $p=0.0277$). A statistically significant decrease in the LCMRGlu was found in the right chroid plexus (-1.01 ± 1.27 $\mu\text{mol}/\text{min}/100\text{g}$, $-6.66 \pm 8.09\%$; $p=0.0336$).

FreeSurfer GLM-based Analysis: The results of the FreeSurfer GLM-based analysis can be found in Figure 6. Surface-based analysis using FreeSurfer displayed increased metabolism in the left hemisphere's frontal inferior triangular gyrus, superior temporal lateral gyrus extending into the temporal superior plane, and inferior circular sulci of the insula extending into the superior transverse temporal gyrus. Additionally, in the left hemisphere small foci of decreased activation were observed in the postcentral sulci, occipital middle gyrus, inferior angular parietal gyrus. The right hemisphere showed increased uptake in the superior transverse temporal gyrus, superior transverse temporal sulci, the temporal superior plane, opercular part of the inferior frontal gyrus, as well as the

H-shaped orbital sulcus and orbital gyrus. The right hemisphere showed a small focus of decreased uptake in the inferior angular parietal gyrus.

Static Image—The mean uptake in the whole brain for the stimulation and control cases was 4.127 ± 0.823 SUV_{lbm} and 4.149 ± 0.624 SUV_{lbm} respectively with a mean change of -0.022 ± 0.856 SUV_{lbm} ($p=0.937$). The mean uptake in the gray matter for the stimulation and control environments was 4.870 ± 0.954 SUV_{lbm} and 4.90 ± 0.758 SUV_{lbm} respectively with a mean change of -0.0357 ± 0.980 SUV_{lbm} ($p=0.911$). The mean uptake in the white matter for the stimulation and control cases was 3.617 ± 0.650 SUV_{lbm} and 3.636 ± 0.548 SUV_{lbm} respectively with a mean change of -0.019 ± 0.700 SUV_{lbm} ($p=0.933$). The WB-normalized mean uptake in the gray matter for the stimulation and control cases was 1.180 ± 0.023 and 1.18 ± 0.021 respectively with a mean change of -0.001 ± 0.011 ($p=0.780$). The WB-normalized mean uptake in the white matter for the stimulation and control cases was 0.880 ± 0.037 and 0.877 ± 0.004 respectively with a mean change of 0.004 ± 0.017 ($p=0.476$).

SPM-based Analysis: SPM8 analysis using a FWE of 0.05 and minimum cluster size of 20 voxels yielded no significant activation clusters between the stimulation and control environments. SPM analysis using a $p < 0.001$, which can be found in Figure 7, resolved four distinct clusters: one within the left Heschel's gyrus, one in the right superior temporal gyrus on the border of Broadman's 22 and 42, and two in the frontal white matter. The volume of the clusters in Heschel's gyrus and the right superior temporal gyrus were 74 and 36 voxels, respectively. The mean change in the left Heschel's gyrus was 0.100 ± 0.041 ($8.68 \pm 3.89\%$) and 0.082 ± 0.024 ($6.75 \pm 1.94\%$) in the superior temporal gyrus

FreeSurfer ROI-based Analysis: The analysis of the static frames revealed a bilateral increase in PAC SUV_{lbm} in four subjects, bilateral decrease in one, and opposing changes in the left and right PAC in five subjects. The mean FDG uptake for the left and right PAC glucose uptake was found to be 5.660 ± 0.953 SUV_{lbm} and 5.723 ± 0.837 SUV_{lbm} , respectively for the control environment, and 5.766 ± 1.048 SUV_{lbm} 5.931 ± 1.187 SUV_{lbm} for the stimulation environment. After normalizing the subjects to their whole-brain activity, seven subjects showed bilateral increases in FDG uptake while the remaining three showed a decrease in the left PAC. The WB-normalized mean uptake or the left and right PAC glucose uptake was found to be 1.363 ± 0.084 and 1.381 ± 0.063 , respectively for the control environment, and 1.40 ± 0.083 1.438 ± 0.065 for the stimulation environment. The change between the stimulation and control environments for the left and right PACs was found to a 0.0398 ± 0.969 ($3.17\% \pm 7.28\%$; $p=0.202$) and 0.0572 ± 0.0397 ($4.18 \pm 2.87\%$; $p=0.001$), respectively. When the left and right PAC were treated as a single ROI the mean change was found to be 0.0485 ± 0.0437 ($3.61 \pm 3.34\%$; $p=0.007$).

The remaining 103 cortical and subcortical regions of the brain were evaluated across subjects using a paired, two-sample Student's t-test between the control and stimulation environments. Statistically significant regional changes in the normalized brains were found in the midposterior of the corpus callosum (-0.020 ± 0.027 , $-4.00 \pm 5.23\%$; $p=0.0422$), the left long gyrus and central sulcus of the insula (0.019 ± 0.021 , $1.94 \pm 2.10\%$; $p=0.0186$), the left temporal superior plane (0.032 ± 0.036 , $2.80 \pm 3.00\%$; $p=0.0188$), left H-shaped orbital sulcus and orbital gyrus (0.028 ± 0.034 , $2.11 \pm 2.53\%$; $p=0.027$), right choroid plexus (-0.033 ± 0.038 , $-5.21 \pm 5.78\%$; $p=0.022$), right opercular part of the inferior frontal gyrus (0.024 ± 0.019 , $1.97 \pm 1.69\%$ $p=0.003$), and the right superior transverse temporal gyrus (0.057 ± 0.040 , $4.18 \pm 2.87\%$; $p=0.001$).

FreeSurfer GLM-based Analysis: The results of the FreeSurfer GLM-based analysis can be found in Figure 8. Surface-based analysis using FreeSurfer demonstrated increased

metabolism in the left hemisphere's front inferior triangular gyrus, superior temporal lateral gyrus extending into the temporal superior plane, and inferior circular sulci of the insula extending into the superior transverse temporal gyrus. Additionally in the left hemisphere small foci of decreased activation were observed in the occipital middle gyrus. The right hemisphere showed activation in the superior transverse temporal gyrus, superior transverse temporal sulci, the temporal superior plane, opercular part of the inferior frontal gyrus, as well as the inferior angular parietal gyrus. Foci of decreased uptake were noted in the middle occipital gyrus and the superior parietal gyrus.

DISCUSSION

Phantom studies were first performed to characterize the hardware-related effects of the MR on the PET data quantification. While count rate changes were found to correlate with temperature changes, total count rate changes were found to be relatively insignificant. The robust operation of the BrainPET is likely due to its ability to address temperature changes induced in the PET cassettes as a result of eddy currents. With both the photopeak tracking software- and the hardware-based temperature controllers activated, a drop in counts on the order of 1.5% was observed which was determined to have little impact on the PET data quantification; however, when photopeak tracking was disabled there was a drop in true counts on the order of 45%. This severe change suggests that, in addition to hardware-based temperature control, software-based photopeak tracking is essential for simultaneous imaging using the BrainPET and even for sequential imaging as heat is not immediately dissipated.

The primary purpose of this study was to explore MR physiologic interference on FDG uptake. Although likely not an issue for most applications, the observed MR-induced increase in FDG uptake in the PAC could have implications for certain studies. For example, care should be taken when evaluating progression in lesions that lie near the auditory cortex if MR sequences are run during the uptake phase of the FDG. It is worth noting that both the static and parametric images showed a statically significant decrease in the right choroid plexus uptake. While the change in FDG uptake of the choroid plexus is likely an artifact due to its small size, which makes it susceptible to artifacts arising from motion, studies in rats have reported that intense noise can lead to cell damage [26]; however, given the limited body of existing work concerning this potential phenomena, a more extensive study is necessary before a correlation should be suggested.

The unintended physiological effects of combining other medical devices with PET have been previously explored. For instance, transcranial magnetic stimulation has been combined with PET to explore *in vivo* brain connectivity [27–29]. Siebner et al. found that repetitive transcranial magnetic stimulation of the sensorimotor hand area lead to increased FDG uptake in the PAC as a result of acoustic noise produced by the transcranial magnetic stimulation hardware [30]. Stimulating the left sensorimotor hand area, they noted a change in the left and right PAC of 7.2% and 6.6%, respectively using an ROI-based analysis. While the changes reported here of $8.37 \pm 1.55\%$ and $8.70 \pm 1.17\%$ are slightly larger, they are consistent with those presented by Siebner especially considering the higher resolution of the BrainPET compared to the Siemens 951 R/31 PET scanner and the smaller smoothing kernel used in this study. Furthermore, Siebner used 2 cm circular ROIs centered on the peak activation in regions using registered T1-weighted MR images for anatomic landmarks [31].

Direct analysis of the time activity curves, the parametric 0–40 minute image, and the static 40–60 minute image illustrate three different situations which are of importance for evaluating potential physiological interference.

First, by distinguishing significant changes in uptake on a frame-by-frame basis, the time activity curve analysis is sensitive to specific MR sequences. The dynamics of FDG uptake in unstimulated brain tissue has a predictable time course; any deflections from its smooth projected trajectory would suggest prior stimulation and spikes would suggest possible RF interference. The absence of spikes in the whole brain activity time activity curve (Figure 4A) and WB-normalized white matter (Figure 4B), as determined by serial t-tests, suggests lack of RF interference (at least for the framing and reconstruction used in our study). This in turn suggests that any changes in FDG uptake are linked to physiologic changes induced from sources other than hardware interference. This result is further confirmed by the ROI analysis of PAC time activity curve where a statistically significant change between the control and stimulation environment is maintained across subsequent time points.

Second, the parametric images, in addition to being sensitive to the integral of the activity and accounting for the FDG transport and trapping components, allow for the detection of the cumulative effects of noise in the uptake phase. In this study we used a blood-free approach to estimate LCMRGlu using the method presented by Wu [19]. An appealing aspect of this method is that the whole brain value of each patient is normalized to a constant, which has been used in other group studies on the effects of MR on LCMRGlu [9, 10]. Similarly, we only use the first 40 minutes rather than 60. Monden et al. demonstrated that using a shorter duration could lead to an increase in K_i on the order of 3–5% [20]; however, in this study we are interested in the relative change between the control and stimulation environments so the error derived from this reduced duration should be present in both control and stimulation datasets.

The SPM8/MNI-normalized parametric images showed a bilateral statistically significant increase in LCMRGlu within PAC suggesting that this region was being activated over the first 40 minutes in the stimulation case relative to the control. Activation of the PAC is also supported by the FreeSurfer ROI-based analysis of the LCMRGlu image, where a statistically significant increase was observed in an ROI spanning both the left and right PACs. When taken separately, the left PAC did not show significance; however, upon closer observation of the FreeSurfer GLM image, this could be due to the small size of the region with significant uptake with respect to the ROI. In addition to a statistically significant increase in LCMRGlu in the right PAC, the ROI analysis showed statistically significant activation in other regions known to have involvement in auditory stimulation: the left and right superior temporal planes, right transverse temporal sulci, and left middle temporal gyrus [32].

Third, the semi-quantitative static analysis is most likely to be used clinically with the early adopters of simultaneous MR-PET, and thus any interference as a result of adopting our protocol (i.e. administer the FDG in the scanner while running MR sequences) should be determined. In this study the simultaneously acquired MR sequences during the static frame (i.e. 40–60 minutes post injection) were the same in both the control and stimulation environments; as a result, differences between the static images of the stimulation and control environments should only reflect changes in uptake that occurred between injection and minute 40. The static images showed a glucose uptake pattern which had some similarities to the parametric images – increased uptake in the PAC using all three analytic methods (SPM8, FreeSurfer ROI-, FreeSurfer GLM-based). An ROI spanning the combined left and right PAC showed a significant increase in FDG uptake, however only the right PAC was found to be significantly different between the control and stimulation environments. The GLM-based analysis explains this difference – a region of increased uptake is apparent just anterior to the PAC. While this activation may be physiologic, it could also be a result of stochastic errors.

The two FreeSurfer-based methods used for analyzing the PET data in this work provided complementary information concerning activation. The minimum requirement for significance in the ROI-based analysis is that there must be either a small focal change (or a number of smaller foci) of rather significant intensity (when compared to the ROI size), or a less intense change distributed over a large portion of the ROI. The ROI-based method places no requirements on the connectedness of the regions of increased or decreased activation within an ROI, rather it is sensitive to the average change in the region likely detecting whether or not the PAC has been activated. The FreeSurfer GLM-based analysis, on the other hand, focuses on clusters of activation allowing them to traverse multiple brain regions. This method may be preferred to detect focal changes within a brain region, for example tonotopic activation [33, 34].

Aside from evaluating the effects of MR acoustic noise on cerebral FDG uptake, we have shown that FreeSurfer, in comparison to SPM8, can provide statistical descriptions of cerebral FDG uptake. In the case of non-simultaneous acquisition, where spatial registration of the two modalities may be inaccurate, the more conservative analytic technique is to transform the PET data directly to a conformed space. Accurate transformation to this conformed space usually requires that the subject data be significantly smoothed as it must have a smoothness similar to that of the template. Smoothing the data can obscure small and/or less intense clusters of uptake. In an integrated system, where the spatial transformation between the MR and PET images is known, the MR data can provide all the necessary transformations to a conformed space reducing the need for additional smoothing of the PET data. In FreeSurfer, where this conformed space is derived directly from the subject specific brain, there is a better inter-subject alignment of cortical regions which can improve the localization or contrast of statistically significant changes in the brain [35]. Similarly, and perhaps equally if not more importantly, SPM uses volumetric smoothing where in cortical voxels that are nearby but may be on different cortical folds will have an significant influence on each other after in computing the smoothed values. However, FreeSurfer computes its smoothing on the inflated cortical surface so there distance between points on different cortical folds are increased. If the assumption is that function follows the cortical surface rather than absolute distance between neurons, then FreeSurfer has a more logical smoothing algorithm. One example of these improvements in contrast is the conservation of the uptake patterns between the parametric and static images. As the static image occurs over a time period where the glucose uptake is small relative to earlier time points it should have a metabolic pattern which resembles the parametric image which is sensitive to the 0–40 minute uptake phase. Comparing the similarities of the metabolic patterns between the static and parametric frames provides a metric for evaluating SPM- and FreeSurfer-based analyses. The PAC cluster in the right hemisphere is not conserved between the parametric and static images using SPM8; however, they, in addition to the clusters in the temporal superior plane are conserved in the FreeSurfer-based analysis. Another example is the conservation of activation of the left opercular part of the inferior frontal gyrus which is associated with Broca's Area.

FreeSurfer does not entirely replace the need for SPM-based analyses. A drawback to FreeSurfer is the processing time required to segment and inflate the brain. While the transformation to the MNI space with SPM8 can be computed in minutes, processing of the MR data can take on the order of 20 hours with FreeSurfer making SPM appealing for realtime clinical targeted applications [36]. For studies where the activation area is expected to be larger or where ROIs can be determined prior to analysis, SPM8 can provide faster results. Additionally, FreeSurfer does not segment some of the brainstem structures, like the inferior colliculus, a region which has been shown to play a role in auditory processing [37, 38].

One aspect which was not controlled in this experiment was patient motion. Spurious patient motion can lead to a virtual loss of resolution and contrast in the PET images, can introduce artifacts from mismatch between the data and the attenuation map, and can lead to misregistration between the MR-derived ROIs and PET data. Although we have previously implemented an MR-assisted PET motion correction for the BrainPET [3], motion estimates were not available for all the sequences used in this study. To reduce the effects of misregistration due to motion on the static image, the MPRAGE used to derive the ROIs was collected near the middle of the 40–60 minute window. Additionally, each of the dynamic frames were coregistered to a 5-minute frame reconstructed from the data acquired 38–43 minutes post injection. Had there been more accurate motion tracking and correction, it is possible that smaller foci of increased or decreased uptake could have been detected and the uptake better localized.

Finally, the placement of the earplugs was not standardized, subjects were given the option to place the ear plugs in themselves or have a technologist place them for them, which is our center's standard protocol for hearing protection in the MR environment. Subjects were asked for confirmation that the earplugs were adequately placed and whether or not they were equal bilaterally prior to initiating MR scanning. To ensure maximum efficacy from the earplugs, we could have tested the subjects' hearing, however this would bias our results as this is not done routinely for MR subjects and it is not likely to occur in a clinical setting.

CONCLUSION

This study sought to determine the effects of MR on brain FDG uptake when MR sequences are run during the FDG uptake phase in a integrated MR-PET system. Group analyses of parametric images derived from the uptake phase, along with static images reconstructed from the data acquired 40–60 minutes post radiotracer administration showed foci of uptake in cortical areas associated with auditory processing likely a result of acoustic noise produced by the MR gradients. The relative increase in the PAC glucose uptake ranged from 3–9% depending on the image type and method. Using SPM8 and distorting the data to the MNI normalized space showed clusters of statistical significance only with an uncorrected $p < 0.001$, however no clusters were observed with a FWE of 0.05. ROI analysis showed similar results of increased uptake in the PAC with some ROIs significant and some trending towards significance, however they were insensitive to focal activations in large ROIs and activations which spanned the border of multiple ROIs. Statistical maps of the parametric and static images derived from FreeSurfer were qualitatively more similar than those derived from SPM8 with many of the clusters conserved, suggesting that in a simultaneous system where software coregistration is unnecessary an improvement in group analysis can be attained using FreeSurfer and the simultaneously acquired MR data. This suggests that while the MR-PET environment is considerably different than the traditional PET environment, its impact on patient physiology is minimal and can thus still produce comparable results. Our results also demonstrate that the performance of the PET scanner is virtually unaffected by the MR data acquisition and highly reproducible PET data can be obtained. Still, for certain experiments specific knowledge on effects of integrated multimodal imaging is required.

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FIGURE 1.

Design of paradigm, data processing and analysis. Subjects were scanned on two separate days in either a quiet control environment or a stimulation environment with MR acoustic noise present during the FDG uptake phase. The data processing steps were identical in both cases and are only shown for the control environment for simplicity. Similarly, the analysis of the static and parametric PET image was identical. Ovals represent raw list-mode PET data. Squares represent images, where green are PET and purple are MR. Triangles represent processes (e.g. image reconstruction) and green, purple, and black denote that only PET, MR, or combined MR-PET data, respectively, were used as inputs. Only ROI-based analysis was performed on the time activity curves.

FIGURE 2.

PET count rate fluctuation over the course of the protocol (top) with corresponding temperature fluctuation (bottom) for five independent runs. The highly reproducible drop occurred during simultaneous MR-DCE imaging. The maximum drop in count rate was less than 1.5% over the duration of the protocol.

FIGURE 3.

The PET count rate fluctuation for the same protocol as performed in Figure 2, but without photopeak tracking, shows a steady decline in counts over the duration of the protocol. The maximum deviation from the average count rate is found to be on the order of 25%, while a total change on the order of 45% is observed over the duration of the protocol.

FIGURE 4.

Generation of high-resolution ROIs for PET analysis. The high-resolution ME-MPRAGE (A) is used to generate a labeled mask volume (B) with FreeSurfer, both of which were subsequently resampled to the PET geometry. The labeled mask volume was then used for automated ROI PET analysis of the 4-D PET images to derive the time activity curves as well as for analysis of both parametric [0–40 minute] images (C) and static [40–60 minute] images (D). Unlike the static images, where MPRAGE and UTE were acquired during PET acquisition in a similar manner in both the stimulation and control environments, no MR sequences were run in the control environment during the timeframe used to generate the parametric images.

FIGURE 5.

(A) Representative subject's time activity curves for both the control (solid line) and stimulation (hashed line) environments. In addition to the PAC (blue), the M1 (green) and white matter (red) are shown for reference. Solid line represents the control environment (no MR performed during first 40 minutes post injection) while the dashed lines represent stimulation environment. (B) Whole Brain time activity curves; (C) White Matter normalized to WB; (D) PAC time activity curves normalized to white matter. Each point represents the average of the four subjects with error bars representing one standard deviation (* represents $p < 0.05$).

FIGURE 6.

SPM8 Glass Brain of parametric image. Cluster analysis performed with $p < 0.001$ (uncorrected) and minimum cluster size of 20 voxels (left). Activation is also plotted on three orthogonal slices of single subject's MRI from MNI database (right). Statistically significant increases in CMRGlu are localized to the left and right PAC when a paired T-test is performed on the "noisy" MR-environment (continuous MR imaging immediately after FDG injection) versus the "quite" control environment where no MR sequences were run for the first 40 minutes.

FIGURE 7.

Cortical FreeSurfer analysis of parametric image generated from dynamic 4-D PET data. Segmented cortical regions are shown in color. Activation clusters are shown in a hot and cold color scheme corresponding to Z score reflecting statistical increase or decrease of FDG compared to no change in uptake, respectively. P-values<0.01 are shown. Clusters of increased uptake are localized proximal in and around the PAC.

FIGURE 8.

SPM8 Glass Brain of static image encompassing the PET signal from minutes 40–60. Cluster analysis performed with $p < 0.001$ (uncorrected) and minimum cluster size of 20 voxels (left). Activation plotted on three orthogonal slices of single subject's MRI from MNI database (right). A Statistically significant increase in FDG accumulation is localized to the left PAC and right superior temporal gyrus when a paired T-test is performed on the stimulation versus control environments.

FIGURE 9.

Cortical FreeSurfer analysis of static image. Segmented cortical regions are shown in color. Activation clusters are shown in a hot and cold color scheme corresponding to Z score reflecting statistical increase or decrease of FDG compared to no change in uptake, respectively. P-values < 0.01 are shown. Similar to the FreeSurfer image in Figure 7, increased FDG accumulation is noted in and around the PAC.