Simultaneous FDG-PET and 3D Tomographic EEG in Resting Brain

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Abstract

Introduction: This work compares 3D tomographic estimates of the intracerebral source location(s) that underlie observed EEG recordings with corresponding measurements of brain metabolism obtained from FDG-PET. Brain activity in a resting state was measured nearly simultaneously with FDG-PET and EEG for 29 human subjects. Although the actual measurements were not simultaneous, they both reflect the brain's physiological state during the FDG uptake period. The PET data show overall regional brain metabolism, whereas each EEG frequency band shows different patterns of electrical activity in specific regions. Tomographic 3D reconstructions of metabolic activity (FDG) and electrical source localization (EEG) were compared on a voxelwise basis for each of 6 different EEG frequency bands.

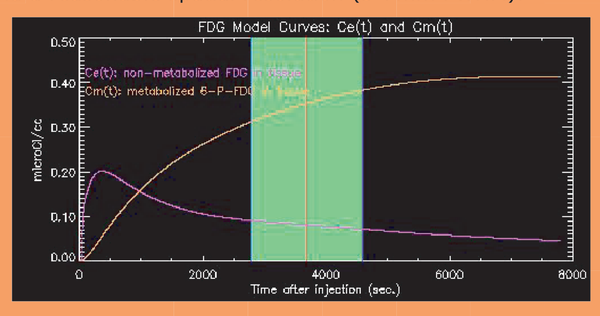
Methods: Seventeen depressed subjects who underwent subsequent treatment and 12 controls were studied [1, 2]. Measurements from a 28-channel EEG cap were recorded for 30 minutes following injection of FDG (10x3 minute segments), corresponding to the uptake period of the majority of the FDG tracer. Verbal instructions to open or close eyes were given prior to the start of each 3-minute trial. Arterialized venous blood samples were collected. Low Resolution Electromagnetic Tomography (LORETA, [3,4]), a 3D source localization algorithm for EEG data, estimated the locations of the source(s) giving rise to the observed surface EEG recordings for 6 different frequency bands (6.5-30 Hz). The quantified PET data (mg/min/100g) were smoothed with a 6mm Gaussian kernal and resampled to match the size and location of each of the LORETA voxels (7x7x7mm). For each of the EEG bands, a Spearman's rank order correlation was computed between the PET and EEG/LORETA data at each voxel location across all 29 subjects and for control and depressed subjects separately. These correlations were converted to 3D parametric maps for visual inspection. Additionally, correlations for specific ROIs were computed between the PET and LORETA data.

Results: There are strong positive as well as negative correlations between EEG/LORETA and FDG-PET data at various locations within each frequency band; the specific locations and and strength of correlations vary from one band to the next. Regions which are thought to give rise to electrical activity in a particular band were examined; two examples follow. The longstanding assumption of inverse relationship between alpha activity (especially for lower alpha sub-bands) and brain activation is supported by negative correlation in large brain areas between PET and the LORETA alpha1 activity (8.5-10 Hz) in the whole-brain correlational maps. We had previously found [1] that rostral ACC theta activity predicted treatment response in depression; ROI analysis showed a significant positive correlation between modalities, with the following Pearson's correlation coefficients for the theta band (6.5-8.0 Hz): all subjects: n=29, r=0.60, p<0.001; depressed: n=17, r=0.60, p<0.01; and controls: n=12, r=0.65, p<0.05.

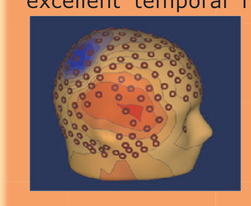
Conclusions: To our knowledge, this work is the first to demonstrate a method for comparing EEG and other more traditionally tomographic functional imaging data on a 3-dimensional voxelwise basis.This method will likely yield powerful new information when it is applied to functional imaging methods with faster time resolution, such as short-halflife PET blood flow tracers and functional MRI.

Introduction

A resting FDG-PET study measures the basal metabolism of the brain during the FDG tracer uptake period. Approximately half of the tracer uptake into the brain occurrs during the first 30 minutes after tracer injection, with the remainder being taken up over the subsequent ~90 minutes. These PET data thus integrate the brain's metabolism over a relatively long time period. The PET data have excellent chemical sensitivity and a reasonable spatial resolution (5-7mm FWHM).



EEG data reflects the brain's electrical activity with an excellent temporal resolution (~milliseconds). The spatial resolution is typically poor and confined to the scalp surface, where the measurement electrodes are located. EEG examines a range of frequency bands; various functional brain states are associated with each particular band.

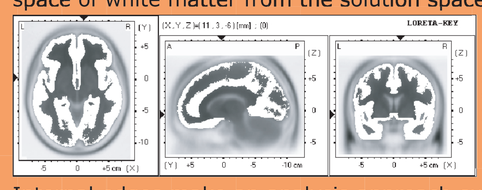


Since the EEG data were acquired during the first 30 minutes of the FDG uptake into the brain, the two modalities measure the brain state during the same period, even though the actual PET scan occurs after the EEG measurement.

The major methodological challenge in comparing EEG and PET data is to find a common space where three-dimensional tomographic images of the underlying metabolism for both modalities can be compared. The 3D tomographic reconstructions of the EEG data were performed using Low Resolution Electromagnetic Tomography (LORETA; [3,4]). From scalp-recorded electrical potential distribution, LORETA computes the 3D intracerebral distributions of current density for specified EEG frequency bands. A recent study [5] provided direct cross modality validation by showing that LORETA generators of ictal discharge were remarkably close to the locations of MRI-identified epileptic foci.

The PET data show the overall regional brain metabolism, whereas each frequency band from the EEG/LORETA data tend to show a different pattern of electrical activity in specific regions. Thus, the PET data are a sort of composite or integral of the activity for all of the activity bands, but it is not clear how much each band contributes to the overall metabolism at a particular location. A methodological challenge lies in comparing the two modalities when a voxelwise 1-1 correspondence is not expected.

LORETA makes two major assumptions in estimating the source location of electrical activity: (i) that the activation field is smoothly varying , and (ii) that the signal measured at the brain's surface does not emanate from white matter or from some subcortical structures deep within the brain. The latter assumption is used to limit the solution space, and white-matter voxels are excluded from consideration. The resulting solution space has abrupt edges separating the null space of white matter from the solution space of gray matter.



Orthogonal slices showing the regions considered by LORETA (in white) and excluded from consideration (shades of gray). The solution space (white) has many abrupt edges. Most of the finer detail shown here is lost when the actual voxel dimensions (7x7x7mm) is considered

Internal edges make an analysis approach such as SPM99 [6] problematic. Since there are hard edges within the volume, operations such as smoothing are ill-defined. Without this operation, however, the assumption by SPM of a random Gaussian field cannot be assured, so the statistical results of the analysis are difficult to interpret.

How the data are normalized has a large influence on the intermodality correlation. Since PET is quantitative and EEG is sensitive to absolute electrical signal, non-normalized data will emphasize subject-to-subject differences. Normalizing the data to a grand mean tends to emphasize regional or voxel-wise variations within each subject.

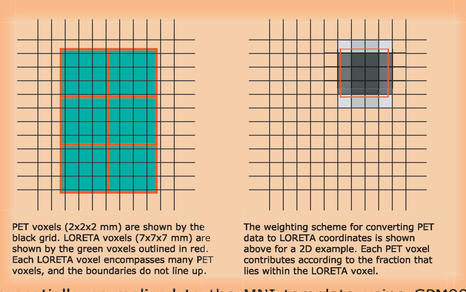
Methods

Subjects: A total of 29 subjects were studied. Twelve of the subjects were normal control, and the remaining 17 were depressed. Of the depressed subjects, nine (9) were melancholic and the remainder (8) were non-melancholic.

Scanning protocol: A modified lycra electrode cap (Electro-Cap International, Inc.) with tin electrodes was used to record EEG from 28 scalp sites, as detailed in [1]. PET data were acquired using a GE/Advance PET scanner with a 15 cm field of view, as in [2]. Subjects fasted for 5 hours prior to injection of FDG. EEG data collection began at the time of the FDG injection and involved 10 contiguous 3-minute trials to cover the 30 minute period corresponding to the majority of FDG uptake. Verbal instructions to open or close eyes were given prior to the start of each trial, with an alternating order counterbalanced across participants. Arteriolized blood samples were drawn for 30 minutes. After a 10 minute break to void, the subject was positioned on the PET scanner bed. The PET scan started approximately 50 minutes after injection, and consisted of a 30 minute 2D (septa in) emission scan, followed by a 10 minute 3D (septaless) emission scan, followed by a 10 minute transmission scan.

EEG Analysis: All EEG epochs were analyzed with LORETA [3], as in [1], with the image volumes spatially normalized to the same MNI template as the PET data. The voxel dimension of the 3D tomographic reconstruction is 7x7x7mm. The epochs with eyes open were collapsed with the eyes-closed epochs within LORETA. Most white-matter voxels and some deep grey-matter voxels are excluded from consideration by LORETA, resulting in some empty voxels within the reconstructed brain volume. The resulting tomographic volumes thus are not completely spatially connected, as many voxels have a "null" voxel as a neighbor. There are 2394 voxels for each measured frequency band in a LORETA data set.

PET analysis: 2D PET data were reconstructed to 1.75x1.75x4.25 mm voxels, then converted to parametric images of an influx constant (Ki, 1/sec) using a variation of the Sokoloff method [7]. They were



PET voxels (2x2x2 mm) are shown by the black grid. LORETA voxels (7x7x7 mm) are shown by the green voxels outlined in red. Each LORETA voxel encompasses many PET voxels, and the boundaries do not line up.

The weighting scheme for converting PET data to LORETA coordinates is shown above for a 2D example. Each PET voxel contributes according to the fraction that lies within the LORETA voxel.

then spatially normalized to the MNI template using SPM99 [6] and converted to 2x2x2mm voxels upon reslicing. These data were further smoothed with a 6x6x6mm Gaussian kernal (SPM99) to approximately match the lower resolution of the LORETA data. The PET data were resampled to yield voxels with the same size and center location as the LORETA voxels. The fractional volume of a PET voxel which was completely or partially within a particular LORETA voxel was used as a weighting factor. Only voxel locations considered by LORETA were resampled, yielding image volumes with the same pattern of missing voxels as the LORETA data.

Normalization: The data were normalized in several ways. First, the EEG data were processed by LORETA to include both the eyes-open and eyes-closed states, which is most comparable to the PET data. The PET data were converted to LORETA coordinates (see above) and all subsequent steps were performed using the converted PET data.

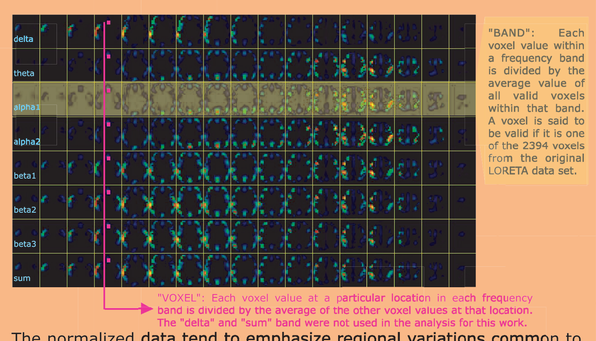
Three diffferent types of normalization were considered:

1. No normalization
2. Normalize LORETA and PET
3. Normalize LORETA but not PET

The PET data were normalized by first computing the average value for each image volume for voxels above a threshold of 12.5% of the range of the entire volume, and then scaling each image volume so its mean was the the same as the mean of all of the individual means. This is similar the "Grand Mean" normalization performed by SPM99.

The LORETA data were normalized in one of three ways:

a. "ALL": across all voxels and all frequency bands for all subjects;
b. "VOXEL": across all bands for each voxel across all subjects;
c. "BAND": across all voxels within each band across subjects.



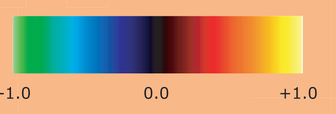
"BAND": Each voxel value within a frequency band is divided by the average value of all valid voxels within that band. A voxel is said to be valid if it is one of the 2394 voxels from the original LORETA data set.

The normalized data tend to emphasize regional variations common to all subjects, while the non-normalized data include this aspect but also examine subject-to-subject variations of the absolute values of the quantitative (or nearly quantitative) data. Since the PET data are considered quantitative and the LORETA data "nearly so", we also performed comparison #3 in the above list, which acknowledges the difference in absolute quantitation between these two modalities.

Each of the three main types of normalization (#1-3) may be valid, depending on the accuracy and repeatability of the quantification obtained for each modality. The correlation maps and subsequent interpretation of results can vary considerably for each normalization.

Correlation analysis: A Spearman's rank correlation coefficient between PET and LORETA data was calculated for every valid LORETA voxel across all subjects. These coefficients were converted to a 3D parametric map for visual inspection. Since the Spearman's test ranks the values from each group and compares the ranks, not the actual values, the type of normalization has a bearing on the results. We selected the Spearman's rank test because the distribution of values was likely to be quite different between the two modalities as well as between EEG frequency bands.

All correlation maps in the Results section have values ranging between -1.0 and +1.0, and use the following color scale, so all of the maps are directly comparable:



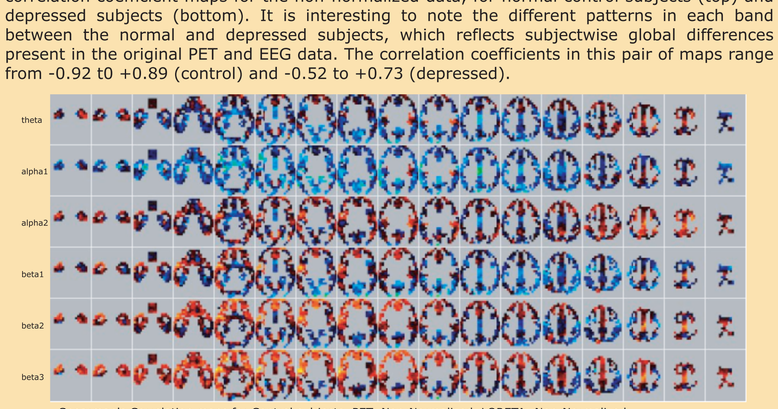
Voxels which are not part of the original LORETA solution space are shown in grey.

ROI Analysis: ROI data for specific regions or anatomic structures were extracted from the 7x7x7mm PET and LORETA data. The ROIs were defined either anatomically (using the MNI probability atlas results supplied with LORETA) or statistically, based on previous functional findings [1]. Each voxel on the list was extracted from the converted PET data and the native LORETA data, and the average was computed to yield a ROI value for each modality.

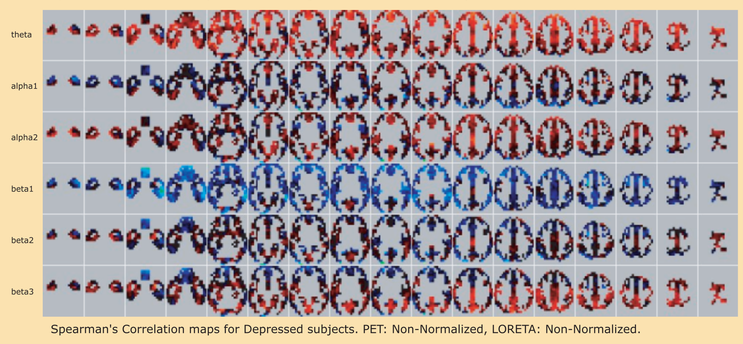
Results and Discussion

Correlational Maps: Perhaps the most immediately apparent result is the large regional variation between the various bands of the correlation coefficients, evident in any of the maps shown here. There are generally large positive and negative Spearman's correlation coefficients within each band regardless of the type of normalization.

Non-Normalized PET and LORETA: The pair of images below shows the Spearman's correlation coefficient maps for the non-normalized data, for normal control subjects (top) and depressed subjects (bottom). It is interesting to note the different patterns in each band between the normal and depressed subjects, which reflects subjectwise global differences present in the original PET and EEG data. The correlation coefficients in this pair of maps range from -0.92 t0 +0.89 (control) and -0.52 to +0.73 (depressed).

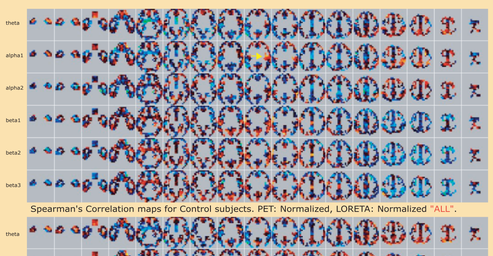


Spearman's Correlation maps for Control subjects. PET: Non-Normalized, LORETA: Non-Normalized.

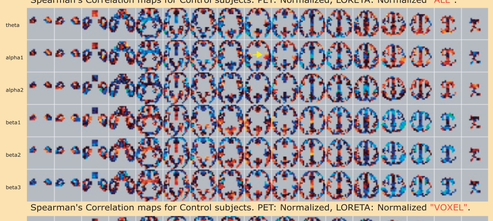


Spearman's Correlation maps for Depressed subjects. PET: Non-Normalized, LORETA: Non-Normalized.

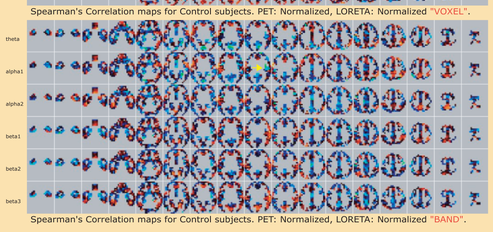
Since these data are non-normalized, there is a large dependence on the subject-to-subject variation in global metabolism. These data show larger correlation coefficients than normalized data (shown e.g. for control subjects in the three images to the upper right), indicating that the absolute global metabolism is an important factor in both of these modalities. There are extended regions in the non-normalized data which show large positive and negative correlations, as well as large areas with little or no correlation. Generally, the non-normalized data show larger areas with homogenous correlation coefficients, whereas the normalized maps show a greater regional variation in correlation coefficients.



Spearman's Correlation maps for Control subjects. PET: Normalized, LORETA: Normalized "ALL".



Spearman's Correlation maps for Control subjects. PET: Normalized, LORETA: Normalized "VOXEL".

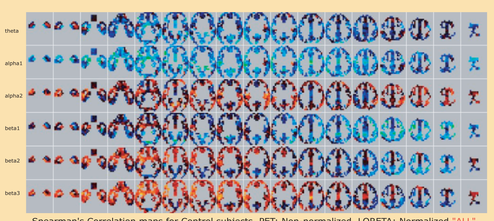


Spearman's Correlation maps for Control subjects. PET: Normalized, LORETA: Normalized "BAND".

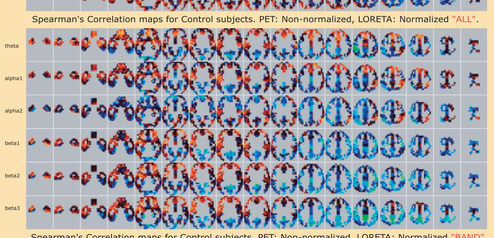
Normalized PET and LORETA: There are three (3) types of normalized data. For all types, the PET data were normalized to the grand mean value across all subjects within each group. The LORETA data were normalized in three ways, "ALL", "VOXEL", and "BAND", as explained in the Methods section above.

The "ALL" and "VOXEL" methods are fairly similar, while the "BAND" map shows some regional differences from the other two. For example, there are several regions that show strong positive correlations for "ALL" and "VOXEL", but show strong negative correlations for "BAND". (See the yellow arrows in each of the maps to the left.)

The similarity of the "ALL" and "VOXEL" maps is an indication that for normalization, the band-to-band differences are more important than the variation of voxels within a particular frequency band.



Spearman's Correlation maps for Control subjects. PET: Non-normalized, LORETA: Normalized "ALL".

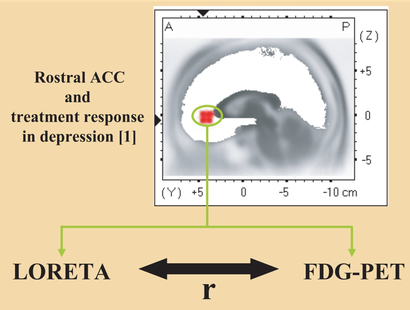


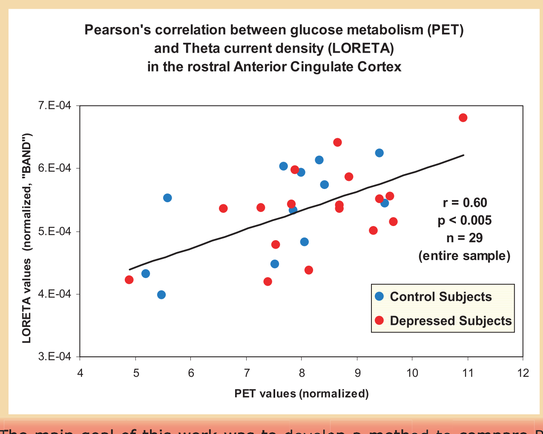
Spearman's Correlation maps for Control subjects. PET: Non-normalized, LORETA: Normalized "BAND".

Non-Normalized PET and Normalized LORETA: The two maps to the left show results for correlating non-normalized PET data with LORETA data normalized using the "ALL" and "BAND" methods. (The "VOXEL" map is quite similar to the "ALL" map and is not shown.)

Surprisingly, these analyses yield the largest contiguous regions with high positive and negative correlations of any of the normalization combinations presented here (see "ALL", alpha1 and beta3, respectively). Although the interpretaion of these results is unclear, they suggest that a different approach to normalization for these two modalities may yield a more powerful comparison.

ROI Analysis: In agreement with prior PET studies [e.g. 8,9], we recently reported that theta activity in the rostral anterior cingulate cortex (ACC) was associated with later treatment response in major depression [1]. In light of evidence suggesting that the ACC may be a possible neural generator of theta activity in the human brain [10,11], we found that the relationship between treatment response and ACC activity emerged for the theta band only. To directly test the relationship between glucose metabolism and theta current density, we extracted ROI values for both the PET and LORETA data from the region of the ACC found to be associated with treatment response (see region highlighted in red in the figure below). For both the control (r=0.65, n=12, p<0.05) and depressed (r=0.60, n=17, p<0.01) subjects as well as for the entire sample (r=0.60, n=29, p<0.005), a robust positive correlation between glucose metabolism and theta current density emerged (see below).





Conclusions: The main goal of this work was to develop a method to compare PET and EEG data on a voxelwise, three-dimensional basis. This is challenging because the data are fundamentally different, and the relative contribution of the electrical signal in each frequency band to the local metabolism is currently unknown. The correlational approach presented here demonstrates a method for comparing these two modalities in a three-dimensional tomographic coordinate system.

Although certain results are consistent with a current understanding of EEG signal generation, the results depend strongly on the type of normalization. Various combinations of normalization types may be appropriate, depending on the accuracy of the quantification of each modality as well as on whether it is believed that regional or subject-to-subject differences are more important.

This method will likely yield powerful new information when it is applied to functional imaging methods with faster time resolution, such as short-halflife PET blood flow tracers and functional MRI.

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Acknowledgements

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