Robust bilateral hippocampal activation with a visual encoding paradigm using Canonical Correlation Analysis

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Introduction

The detection of functional activation in the hippocampus has always been a challenging problem due to its small size and location near regions that show susceptibility artifacts. It is often necessary to optimize the hardware to make it sensitive enough for the robust detection of hippocampal activation. Constable et. al. has demonstrated that an fMRI Z-shimming pulse sequence can aid in detecting robust hippocampal activation using a conventional block design visual encoding paradigm and event related designs [1]. We will use the same block design encoding paradigm without the Z-shimming pulse sequence and demonstrate that it is possible to obtain robust bilateral hippocampal activation by instead implementing a multivariate fMRI tool known as canonical correlation analysis (CCA) [2,3,4]. In other words, analyzing the data with CCA has the effect of increasing the detectibility of weak fMRI activations. Results will also be compared with SPM2.

Methods

Paradigm – The block design visual encoding paradigm has been used several times in the past, where blocks of novel complex outdoor scenes are alternated with blocks of fixation. In our study, each activation block is 30 sec long where 10 novel complex scenes were presented at 3 sec intervals and the subject was asked to memorize the presented images. The control block was also 30 sec long when we presented a random sequence of 10 letters from the pair "A" and "B" at 3 sec intervals. The subject was instructed to press a button whenever the letter "A" changed to "B" and vice versa to distract the subject from performing any encoding during the block. There were 5 periods in the paradigm and an initial 10 sec rest period and was not used in the data analysis. At the end of the scanning session, the subject was presented a series of novel and previously encoded scenes and tested for the percentage of correctly remembered scenes.

Scanner protocol - The pulse sequence parameters for EPI were: FOV 24 cm x 24 cm, BW +/- 62.5 KHz, TR 1 sec, Flip 70 deg, 310 volumes, slice thickness 4 mm/skip 0.5 mm, 64x64 resolution, coronal acquisition with 10 slices covering the hippocampal formation. A resting-state dataset with identical scanner protocol is also collected, where the subject is asked to refrain from any active task and close her eyes. The resting-state data was used to obtain empirical null distribution for a fair comparison of CCA and SPM2.

Data Analysis – We analyzed the datasets with SPM2 using a high-pass filter of length 120 and a spatial filter of FWHM=6mm. The canonical HRF was used as the reference function. We have also used CCA, a multivariate extension of ordinary correlation, where instead of looking at the single voxel timecourse, we investigate the joint timecourses of a group of neighboring voxels. A detailed description of CCA is beyond the scope of this abstract, but there are several available references [2,3,4]. It has been established that CCA is more sensitive than conventional univariate analysis when the CNR is low [3,4]. We have used 3×3 voxel neighborhoods within the same slice for CCA. The Wilks' Lambda statistic [2,3] is used as a measure of activation. For CCA, we used the same high-pass filter, but did not use any spatial filtering since CCA automatically determines the optimal linear combination of the voxels in the neighborhood.

Choosing the right threshold for comparison - It is important to choose the right thresholds for the activation maps for a fair comparison of CCA and SPM2 once the data are analyzed using the two methods. A natural choice for such a comparison is to use the same *p*-value threshold for both maps. However, it is well known in the fMRI research community that the parametric *p*-values are not very accurate primarily due to the inherent temporal autocorrelation in fMRI data. Hence, the activation maps using two different methods may not be comparable even if the parametric *p*-value threshold is the same. Instead, we used thresholds based on the False Positive Fraction (FPF) that is defined to be the fraction of voxels incorrectly detected to be active at a given threshold. To estimate FPF for different thresholds, we used the resting-state data that can be considered to be null relative to the activation paradigm since the subject does not have any knowledge of the task timing to be performed later. Thus, any voxel detected to be active in resting-state data is a False Positive and FPF can be estimated.

Results

Figure 1 (top) shows the activation map using CCA at a FPF=0.001. Hippocampal activation is evident in several slices (see arrows). Furthermore, there is strong activation at the fusiform gyrus. For a fair comparison, we have performed a univariate analysis in SPM2 on the smoothed echoplanar images and plotted the activation maps at the same FPF threshold (Figure 1 middle). The univariate method failed to detect hippocampal activation at this threshold. Overall, there is far less activation than with CCA. Increasing the number of false positives using an FPF=0.01 does show some hippocampal activation in SPM2 (Figure 1 bottom). But there are still significant differences between CCA and this noisy SPM2 map. For example, CCA shows bilateral activation of the hippocampus in slice 1, whereas SPM2 only gives left hippocampal activation.

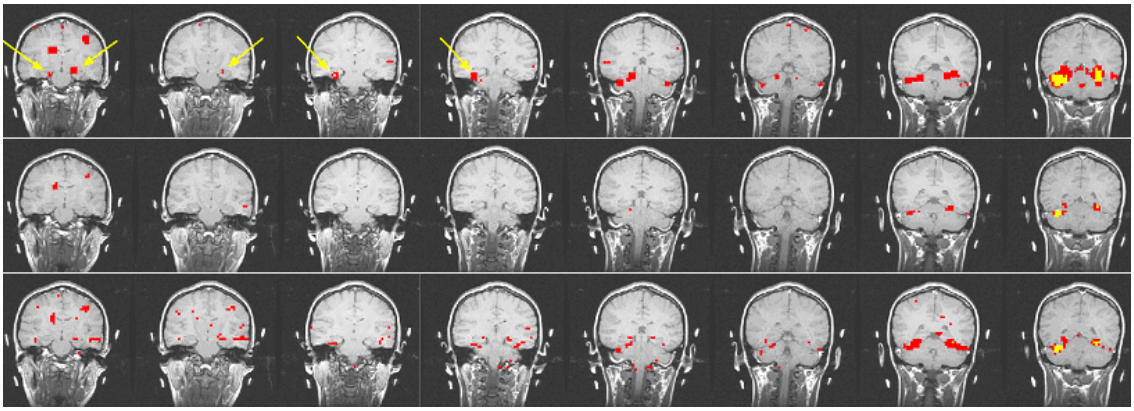

Figure 1. Activation maps for visual memory encoding using complex outdoor scenes with CCA **(top)** and SPM2 **(middle)** using the same HRF at FPF threshold 0.001 (images are in radiological convention). Note hippocampal activation (see arrows) is detected by CCA but not by SPM2 at this FPF threshold. **(Bottom)** The false positive fraction was increased to 0.01 for the SPM2 analysis. Note that this map looks far noisier than before and shows activations at several single voxels, which are suspicious of being noise. At this threshold, SPM2 does show hippocampal activation.

References

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