What is the ultimate sensitivity of fMRI: Does the whole brain activate?

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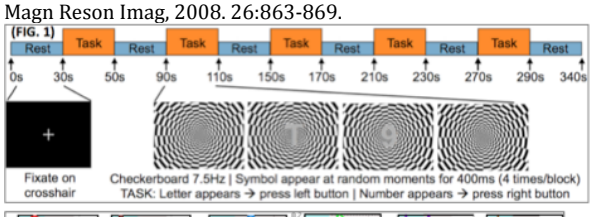
INTRODUCTION: Despite converging evidence suggesting that the whole brain is continuously working & adapting to anticipate & actuate in response to the environment, over the last 20 years fMRI have emphasized a localizationist view of brain function by showing only a handful of regions responding to task/stimulation. Here, we challenge that view with evidence that under optimal TSNR conditions, fMRI activations extent beyond areas of primary relationship to the task; and that task-correlated signal changes appear in over 90% of the brain for a visual stimulation + attention control task. Moreover, we show that responses vary greatly across regions; and that whole-brain parcellations based on response shape differences produce functionally meaningful clusters that are symmetrical across hemispheres; and reproducible across subjects and clustering algorithms. To do this, we acquired and combined 100 EPI scans (e.g., approx. 9 hours of data) in each of 3 subjects. This way we increased white matter TSNR by approx. a factor of 6 from $TSNR_{1run}$=339 to $TSNR_{100runs}$= 2218.

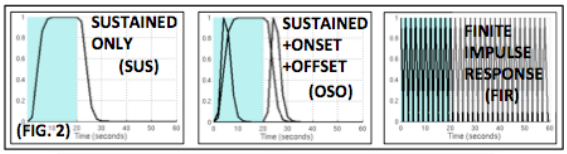
METHODS: *Task:* Fig. 1 *Data Acquisition:* 100 functional scans (EPI, TR=2s, 32Slices, 3.8x3.8x3.8mm) were acquired in each of 3 subjects on a 3T scanner over the span of 10 visits. *Data Pre-processing:* physiological noise removal, slice timing correction; head motion correction, inter-run registration, discard first 5 volumes, remove fluctuations correlated with motion and its 1st derivative, intensity normalization. *Statistical Analysis*: to evaluate the effect of TSNR & versatility of response models on activation extent, statistical analysis with 3 different predictive response models (see Fig. 2) was conducted using only 5 runs (to simulate the amount of data on a regular study) or all 100 runs (to maximize TSNR). Percentage of signicantly active voxels was computed for each case. *Clustering*: averaged trial responses (computed using all 500 trials) for each subject were input to both k-means (d=Pearson Correlation) and hierarchical clustering (link=Ward; d=Euclidean) algorithms to evaluate if observed responses clustered spatially in a meaningful manner. We generated clusters for k levels ranging from 2 to 70.

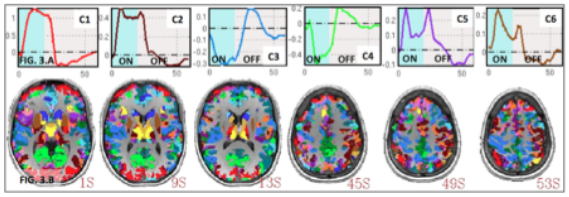
RESULTS: The percent of active voxels increased markedly between 5 & 100 scans (Table 1) going from 16% (SUS Model; 5 Runs) to 95% (FIR Model; 100 Runs). Figure 2 shows the results of the k-means clustering for one representative subject and k=20. Figure 2.A shows a subset of responses associated with these clusters, which include: positive sustained (red & brown), negative sustained (light blue, green), and stimulus onset/offset responses (magenta and light brown). Within each of these 3 categories there are regional differences in magnitude, timing and actual shape. For example, responses C1 & C2 are both positively sustained; still C1 is smooth and has a descending ramp during the ON period. C2 is flat during the ON period and it has positive deflections at stimulus onset and offset. Differences in the post-stimulus undershoot also exists between C1 & C2. Similar arguments apply to the other responses. Figure 2.B shows the spatial distribution of clusters for K=20 (color coded in agreement with the time-series in 2.A). Clusters are not random, symmetrical across hemispheres and anatomically and functionally meaningful. For example, visual (red) and left motor cortices (brown) are part of different clusters (although both show positively sustained responses). Left (positively sustained, brown) and right (negatively sustained, blue) motor cortices are segregated into different clusters too. This agrees with the fact that subjects were responding using only their right hand. Left primary and supplementary motor cortices are part of the same cluster (brown). Finally, occipital cortex shows 3 different clusters in the anterior/posterior direction (red, magenta and green). Figure 4 shows clustering results for k=5 when the analysis is restricted to the subcortical grey matter (GM). Subcortical GM clusters agree to a great extent with anatomically based parcellations of these regions. When hierarchical clustering is attempted, results are very similar (not shown here) and the average cophenetic distance is 0.8.

DISCUSSION & CONCLUSSIONS: The substantial increase in activation extent with number of scans and model versatility (Table 1) suggests that the sparseness of fMRI activation maps is not the result of truly isolated foci of activation, but a consequence of insufficient TSNR and overly strict predictive response models. Detected responses time-locked with task-timing go beyond those commonly used as markers of neuronal activity in fMRI; i.e., positively sustained. Our results show that consideration of additional response shapes, and paying attention to subtle interregional differences in response shape, not only leads to increased volumes of activation, but has the potential to provide additional information about the functional organization of the brain in response to an external perturbation (task/stimulus). This is in agreement with previous studies [1,2,3]. Clustering permitted segregation of activated areas into groups of regions with similar response profiles. In other words, it permitted classification of voxels in a manner more informative than the common active/inactive dichotomy that results from the application of a given statistical threshold. Overall, these findings highlight the exquisite detail lying in fMRI signals beyond what it is normally tested for. They also emphasize the pervasiveness of false negatives in fMRI, and open interesting questions on how to analyze and interpret fMRI results in the near future when better hardware and software will allow attaining TSNR levels equivalent to the ones shown here with 100 scans using a practical number of scans.

REFERENCES: [1] Harms et al. Hum. Brain Mapp., 2003. 20:168-183. [2] Fox et al. Neuroimage, 2005 28:956-966. [3] Uludag K. Magn Reson Imag, 2008. 26:863-869.







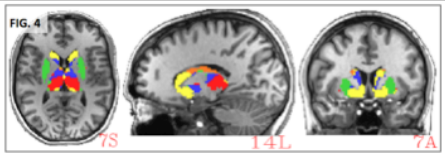


Table 1

Nscans	pFDR<0.05 SUS	OSO	FIR
5	46 ± 6%	47 ± 6%	32 ± 2%
100	85 ± 2%	93 ± 1%	95 ± 1%