Observation of two distinct spatial-temporal BOLD clusters during sensory stimulation in rats

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Introduction CBF and CBV processes during neuronal activity are temporally different but little is known on their spatial differences. Comparison of CBV and CBF measurements is difficult due to their different experimental parameters and low spatial resolution. In order to test if the BOLD signal contains distinct spatial-temporal information on changes in CBF and CBV, a non-linear analysis in both space and time, is needed. We show that the *R*adial *C*orrelation *C*ontrast (*RCC*) method (1) that is a non-linear analysis in both the temporal and spatial dimensions, can be used to identify two distinct spatial-temporal BOLD responses to sensory stimulation. We argue that these distinct responses correspond to the CBF and the CBV processes and show their spatial relationships.

The *RCC* method groups neighboring voxels in terms of their degree of temporal cross-correlation. In this respect it is a model-free cluster type analysis. The method averages the correlation coefficients of each voxel with its neighbor's voxels that lie at a distance that we term its "scale". It is grounded on the assumption that significant spatial correlations that exist during one time segment (e.g. task 1) are different from spatial correlations existing during another time segment (e.g., task 2); therefore, the method compares these correlations. In this way, nonlinear temporal responses that are limited to a predefined time segment can be identified. The *RCC* enables observation of temporal responses with higher degrees of freedom compared with the conventional linear approach. This freedom is reflected in two ways. One is the locality of the assumption, allowing voxels at different locations to be correlated to different temporal patterns, and second is that the correlation is over a time segment smaller than the acquisition length. In this work we test whether the spatial-temporal BOLD response to sensory stimulation onset (the transition between stimulation-OFF and stimulation-ON) is different than the spatial-temporal response to stimulation decline (the transition between stimulation-ON and stimulation-OFF) using the *amplitude-RCC* analysis. To test whether these transitions reflect different physiological processes, analysis was carried out on data with the highest available BOLD contrast using an 11.7T magnetic field with ultra high spatial and temporal resolutions: $0.1\times0.1\times1\ mm^3$ spatial and 750msec temporal.

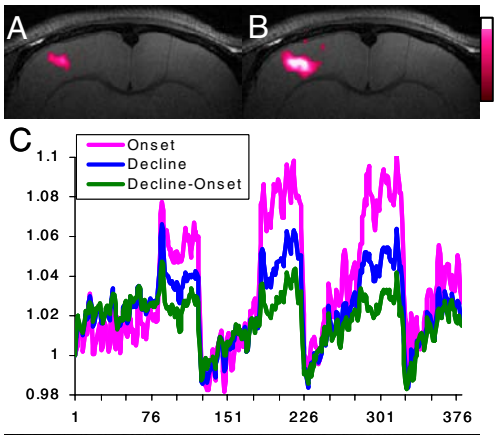

Figure 1 Typical amplitude-*RCC* maps showing differences between stimulation onset (A) and stimulation decline (B) clusters. C shows the average temporal signal from the clusters. The green trace shows the average signal from the volume difference between stimulation decline and stimulation onset clusters.

Method Ten male Sprague-Dawley rats (~200 g) were used with the common electric forepaw stimulation. Amplitude-*RCC* maps of the different time-segments (stimulation onset and stimulation decline) were generated by subtracting each of these time-segment amplitude-*RCC* values from the amplitude-*RCC* values calculated during the first OFF period with segment-size of 40 images each (30sec). Cluster size statistics was used for the cutoff.

Results Figure 1 show a typical example of the difference in amplitude-*RCC* clusters obtained for stimulation onset and stimulation decline time segments. Stimulation onset clusters are smaller, lower in value and usually are contained within the stimulation decline clusters. The clusters are characterized by different temporal patterns with a higher positive BOLD signal for stimulation onset and a deeper post stimulus undershoot for the stimulation decline clusters. To identify the average location of stimulation onset and stimulation decline clusters, amplitude-*RCC* values from different rats were registered and averaged together (figure 2). As seen, clusters characterized by stimulation onset are smaller and embedded in the stimulation decline clusters with the later centered in deeper cortical layers.

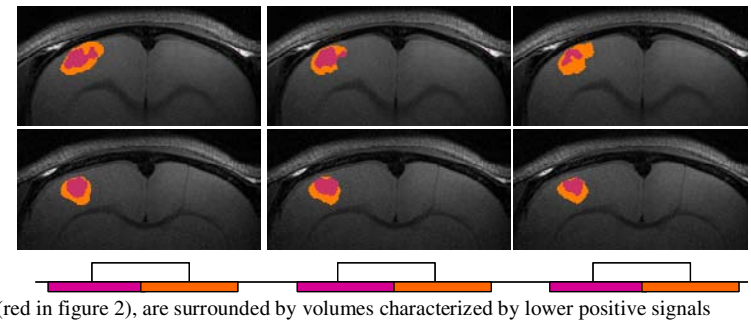

Figure 2 Average amplitude *RCC* maps for stimulation onset (red) and stimulation decline (orange) for the three sequential stimulations and two adjacent slices. Clusters are overlaid on each other and both on an anatomical image. The stimulus temporal pattern is shown below with color rectangles illustrating the time segments during which the analysis was performed.

Discussion The strongest positive BOLD signals, seen in the stimulus onset clusters (red in figure 2), are surrounded by volumes characterized by lower positive signals and stronger post stimulus undershoots (orange in the figure). A strong positive BOLD signal is thought to present high CBF, whereas according to the balloon model, a strong post stimulus undershoot corresponds to high CBV. Whereas many studies concentrated on the transient relationships between CBF and CBV during neuronal activity, only few dealt with their spatial relationship. We have demonstrated a method to differentiate between the two using conventional fMRI data. We have shown that these two processes are spatially and temporally distinct and propose a unique relationship between them.

1. Goelman, G. (2004). Neuroimage 23(4): 1432-9.