

Fine-scale functional connectivity network revealed at high field (9.4T) within somatosensory cortices of anesthetized new world monkeys

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Introduction: Correlations between low frequency fluctuations of BOLD signals in widely distributed brain regions in a resting state have been proposed as indicating functional connectivity and as a key signature of consciously driven mental activity in humans [1]. However, a recent demonstration of the presence of similar phenomena in oculomotor, somatomotor, and visual systems in anesthetized monkeys has led to an alternative hypothesis [2. Vincert et al Nature 2007], i.e., the spontaneous BOLD fluctuation may actually reflect the intrinsic anatomical architectural connections of brain regions rather than a feature of mental conscious activity [2]. To test this hypothesis, we attempted to address two questions: 1) whether a fine scale (millimeter) functional connectivity can be detected within the anatomically well defined primary somatosensory cortex (SI) at high field and 2) if the functional connectivity reflects anatomical hierarchical relationships. Specifically, by addressing these questions in anesthetized monkeys, we aim to establish that functional connectivity exists among anatomically interconnected cortical subregions (areas 3a, 3b, 1 and 2) within SI without the involvement of consciousness (or alertness), and the strengths of the correlation among these subregions reflect the strength of their underlying anatomical connections. In this study, we adopted two approaches: 1) we identified functionally (versus anatomically) seed regions according to a stimulus driven BOLD activation map, and a detailed map determined by intracortical signal/multi unit electrophysiology, 2) we chose single submillimeter sized (0.625x0.625mmx2) voxels as seed regions.

Method: Animal: Squirrel monkeys were anesthetized with isoflurane. Animals were artificially ventilated while vital signals were monitored. **MRI:** All scans were performed on a 9.4T 21-cm bore Varian INOVA magnetic, using a 3cm surface transmit-receive coil positioned over the somatosensory cortices. GE images (512x512 matrix) and GE-EPI (64x64 matrix) were used to acquire anatomical and functional images (35x35 mm² FOV) respectively. The animal head was physically stabilized to minimize motion related artifacts. A 0.3mm vertical indentation of a 2mm dia. at 8Hz (provided by a piezoelectric device) was presented on the monkey's distal fingerpad with alternating 30s stimulus on and 30s stimulus off. TR: 1.5s. Stimulus driven EPI images were drift corrected and low-pass filtered at 0.25Hz. Voxel-wise correlations of the BOLD signal time-course were performed with a reference waveform to generate stimulus driven activation maps. For resting state data, a GLM analysis, with movement-related and global signals as regressors was performed followed by a low pass filter (Chebyshev type II, 3dB pass band and 60db stop band) on the resting state EPI data. **Intracortical Electrophysiology:** In a separate session, a craniotomy and durotomy were performed to expose the SI cortex. A single microelectrode electrophysiological mapping procedure was used to locate the distal fingerpad regions in cortical areas of 3a, 3b, 1 and 2 by evaluating neuronal receptive field locations, sizes and their preferred stimulus (details r.f. [3]). Electrophysiologically determined digit locations (color coded dots) were mapped on the vessel map of the brain surface (F1B). Visible vessel landmarks on both MRI and vessel maps (white arrows in F1) were used for aligning electrophysiological and activation maps (F1 A&B). The detailed electrophysiology map (F1B) was used to refine single voxel seed regions (green boxes in F1 A&B) in four targeted cortical areas (areas 3a, 3b, 1 and 2) and two control regions (Fig1B, color dots indicate the responsive sites to individual digit stimulation). The spatial relationship between stimulus-driven (D3 stimulation) BOLD responses and seed regions was illustrated in F1A. The activation map was thresholded at $p < 1e-10$ and overlaid on a high-resolution structural image for display.

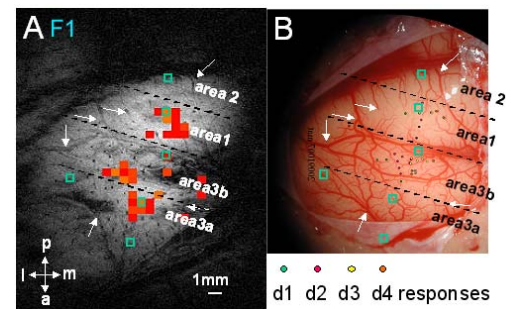
Results: Data from three animals (7 sessions) were analyzed. In one sample animal, significant correlations ($r > 0.5$) are identified among areas of 3b, area 1(ar1) and area2 (ar2) (table). We observe a similar correlation pattern across runs acquired within the same imaging session (runs 1&2). Importantly, the correlation strength differs between area 3b-area 1 and area 3b- area2 or area1-area2. Group data from 7 cases are illustrated in Figure 2 (F2, below). F2A illustrates a scatter plot (each symbol indicates one sample) while F2B shows the average correlation value (+/- SE) from all cases (n=7). Overall, targeted ROIs show much higher correlations than control regions. Correlations between area 3b-area1 and area3a-area1 are the highest among ROIs. This finding is consistent with the known strong anatomical connections between these areas.

Discussion: In conclusion, we observed robustly correlated low frequency BOLD signal fluctuations among somatosensory areas of 3a, 3b, 1 and 2, which are located a few millimeters apart. The strengths of inter-areal (between cortical areas) correlations are consistent with their anatomical hierarchical

connections. This study not only provided further evidence supporting the intrinsic anatomical architectural connectivity hypothesis, but also for the first time demonstrated that spontaneous BOLD signal fluctuations are present among sub-regions of the primary somatosensory cortex, and those are spatially very close to each other. The excellent signal to noise ratio and high resolution data acquisition at high field allowed us to probe these fine scale functional networks. In particular, these networks were not distinguishable in previous studies [2] as they were considered a single entity in the broader somatomotor network. This study provides a reference for comparable studies in humans at high field. In addition, this experimental model in combination with single neuron electrophysiology provides a unique test bed for understanding the neural basis of the resting state fluctuation of BOLD signals.

References: 1. Morcom AM & Fletcher, PC. 2007 *NeuroImage*. 37:1073-1082. 2. Vincent et al. 2007 *Nature* 447:83-86. 3. Chen et al. *J. Neurosci.* 2007;27(34):9181-9191.

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	cont1	cont2	ar2	3b	ar1	
Run1	0	0.092	0.295	0.437	0.300	cont1
	0	0	0.452	0.365	0.392	cont2
	0	0	0	0.516	0.578	ar2
	0	0	0	0	0.722	3b
Run2	0	-0.059	0.182	0.426	0.310	cont1
	0	0	0.448	0.140	0.205	cont2
	0	0	0	0.506	0.591	ar2
	0	0	0	0	0.808	3b

