Independent sources of spontaneous BOLD fluctuation along the visual pathway

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Introduction

BOLD fMRI experiments of spontaneous brain activity in humans have generally found inter-hemispheric correlation between homologous regions. Reduction of this correlation with compromised or absent callosal fibers suggests contribution of a direct neural connection to this activity [1,2]. We studied spontaneous activity in the Lateral Geniculate Nuclei (LGN) of the human visual system, which have no direct commissural connections. Functional MRI at 7 T was performed during visual stimulation and rest. Correlation analysis was performed in a cluster of regions, including left (L) and right (R) LGN, and L and R visual cortex (VC).

Materials and Methods

All measurements were conducted on a GE (Milwaukee, WI) Signa 7 T scanner using a 32-channel receive-coil array (Nova Medical, Wilmington, MA). Gradient-echo EPI images were acquired: 2.5×2.5×2.0 mm^3 voxels; 30 ms TE; 2 s TR; twenty 2-mm axial slices (1 mm gap); rate-2 SENSE. The 720-volume experiments on 13 volunteers, consented under an IRB-approved protocol, lasted 12 min and consisted of a 5-min localizer block paradigm, followed by 2 min eyes-open rest and 5-min eyes-closed (EC) rest. Only localizer (task) and EC-rest were analyzed. The 30/30-s on/off, 7.5-Hz full-field checkerboard task was used to identify L and R LGN as well as VC. LGNs were manually selected in activation maps (e.g. Fig. 1) using GRE data (0.23×0.23×1.00 mm^3) as anatomical reference. VC was split along brain midline (a 3-voxel strip encompassing it was discarded). Data processing consisted of image registration and physiological noise reduction (RETROICOR; cardiac & respiratory rate), after which cross-correlation (CC) of ROI-averaged time series signal was performed.

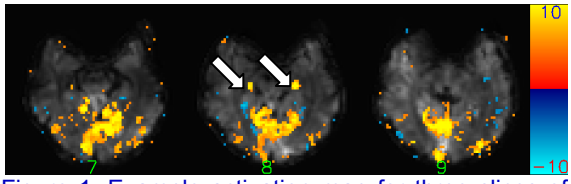

Figure 1: Example activation map for three slices of one volunteer. Arrows highlight bilateral LGN activation. Significance threshold: t=4.96 (p<0.05).

Results and Discussion

Figure 1 shows an example activation map for 3 slices of one volunteer. Bilateral LGN activation, marked by arrows, is apparent. Five volunteers were excluded due to lack of significant bilateral LGN activation. CC analysis on the remaining 8 datasets showed that: **1)** During rest, significant CC exists not only between L and R VC (0.95), but also between L and R LGN (0.39) (Table 1), even though no known direct connection exists between LGNs. **2)** Regression-based exclusion of VC signal from LGN does not remove this correlation (Table 1). Monte-Carlo simulations indicate that this finding can be explained by the presence of a bilateral LGN signal independent from VC (possibly originating from the retina or brain stem), and/or an additional source of signal fluctuation in VC that is not present in LGN. **3)** The opposite, exclusion of LGN signal from VC, yields similar results, indicating that VC resting state fluctuations do not simply result from LGN fluctuations or vice-versa. **4)** Similar analysis on the task-phase of the data (Table 1) shows that independent signals are present in that brain state as well. **5)** CC between L and R LGN does not result from systemic fluctuations (see below).

To investigate specificity of the observed phenomena, other thalamic and cortical areas with no known role in vision where chosen (respectively labeled 'thalamus' and 'insula', Table 2). Global signal regression was also performed, in which the mean signal time course from all brain voxels not in any of the ROIs used was regressed out. Although some bilateral 'thalamus' and 'insula' correlation was found, as well as correlation of those areas with LGN and VC, this correlation was mostly suppressed when global signal regression was applied. On the other hand, correlations for LGN and VC suffered only minor reduction in case of global signal regression, with strong bilateral correlation remaining (CC is 0.39 for LGN, 0.87 for VC, Table 2), demonstrating the specificity of the observed signal coherences. Fluctuation level in the various areas was comparable and substantially exceeded image noise level (data not shown). No consistent negative CC between thalamic regions and VIS was found (results not shown), as was suggested previously [3].

Conclusion

Correlated spontaneous activity exists between all visual system nodes studied, including those without monosynaptic connections. Bilateral LGN correlation did not entirely arise from synchrony with VC activity or vice versa, suggesting that other pathways contribute to these. Potential contributors are other nodes of the visual pathway, either upstream or downstream from the areas studied. These results also demonstrate that observation of strong cross correlation in resting state fMRI may not reflect a direct neuronal connection.

References

[1] JM Johnston et al., J Neurosci 2008, 28:6453-6458
[2] M Quigley et al., AJNR Am J Neuroradiol. 2003, 24:208-212
[3] Q Zou et al., Hum Brain Mapp 2009, 30:3066-3078

state	regressed out	cross correlation (standard error)		
		CC(LGN_L,LGN_R)	CC(LGN,VIS)	CC(VIS_L,VIS_R)
EC rest	-	0.39 (0.07)	0.29 (0.07)	0.95 (0.01)
	VIS (from LGN)	0.35 (0.06)	0.00 (0.00)	-
	LGN (from VIS)	-	0.00 (0.00)	0.85 (0.03)
task	-	0.67 (0.07)	0.72 (0.04)	0.98 (0.00)
	VIS (from LGN)	0.36 (0.08)	0.00 (0.00)	-
	LGN (from VIS)	-	0.00 (0.00)	0.65 (0.03)
	task paradigm	0.50 (0.07)	0.50 (0.05)	0.96 (0.00)

Table 1: Inter-regional cross correlation values and standard error over volunteers (n=8). The value for CC(LGN,VIS) is the mean of CC(LGN_L,VIS_L) and CC(LGN_R,VIS_R).

global signal regression	SIG	cross correlation (standard error over volunteers)		
		CC(**SIG**$_L$,**SIG**$_R$)	CC(**SIG**,LGN)	CC(**SIG**,VIS)
no	LGN	0.39 (0.07)	-	0.29 (0.07)
	visual cortex	0.95 (0.01)	0.29 (0.07)	-
	thalamus	0.22 (0.06)	0.14 (0.08)	0.27 (0.04)
	insula	0.94 (0.02)	0.11 (0.09)	0.50 (0.06)
yes	LGN	0.39 (0.06)	-	0.20 (0.06)
	visual cortex	0.87 (0.03)	0.20 (0.06)	-
	thalamus	0.11 (0.07)	-0.08 (0.07)	-0.01 (0.04)
	insula	0.86 (0.04)	-0.07 (0.07)	-0.09 (0.05)

Table 2: Inter-regional cross correlation values, comparing a reference cortical (insula) and thalamic region to LGN and visual cortex. Results are shown with and without global signal regression.