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## INTRODUCTION

The cerebral cortex represents information in widely distributed, highly overlapping neural networks. Whereas entire networks are engaged in the representation or temporary retention of the information that they encode, dedicated subcomponents of those networks may preferentially mediate specific cognitive operations. In the case of visual working memory (WM), the degree of functional specialization for processing spatial information in the lateral prefrontal cortex (LPFC) remains unclear. Because of methodological differences between different investigations (the animal studies that suggest such local specialization have been electrophysiological while the conflicting human studies have used imaging) questions remain pertaining to the hypothesis of “domain-specific differentiation” in the LPFC, where dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) are proposed to selectively process spatial and non-spatial visual information, respectively. The present study aims to test that hypothesis by simultaneously examining BOLD activations in posterior parietal cortex (PPC) and LPFC. Specifically, the following hypotheses are tested:

1) During the performance of a spatial visual WM task, DLPFC exhibits a higher degree of covariance with PPC than does VLPFC.

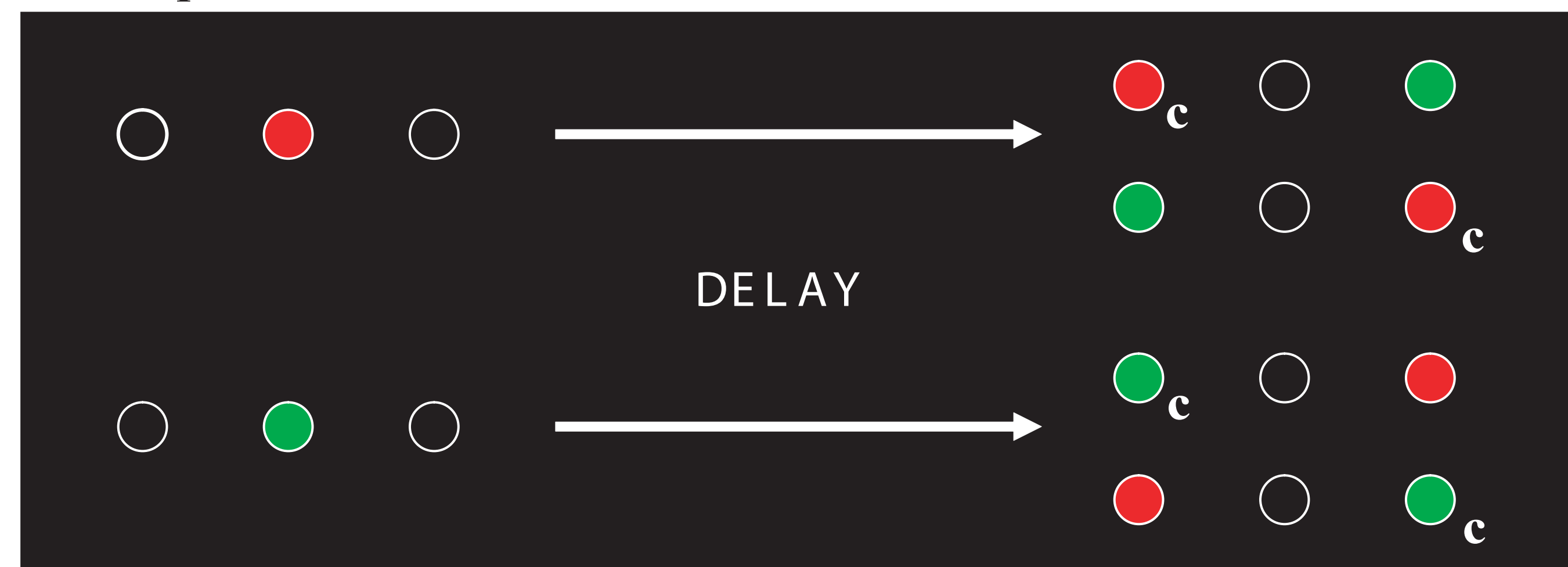
2) Within DLPFC, the degree of covariance with PPC is greater during the performance of a spatial WM task than during a non-spatial WM task.

## METHODS

### Visual working-memory tasks

A rhesus macaque was trained to perform two visual WM tasks, one spatial and the other non-spatial. Non-spatial trials begin with a 2s presentation of either a red or green light. After a delay period of 20s the animal is presented with two lights – one green and the other red – from which he must select the color of the trial-initiating stimulus. Spatial trials begin with the white illumination in either the right or left position, and after 20s the monkey must choose between two white lights to indicate the position of the initial stimulus. Trials are randomized and separated by 30s-50s.

### Non-Spatial Task

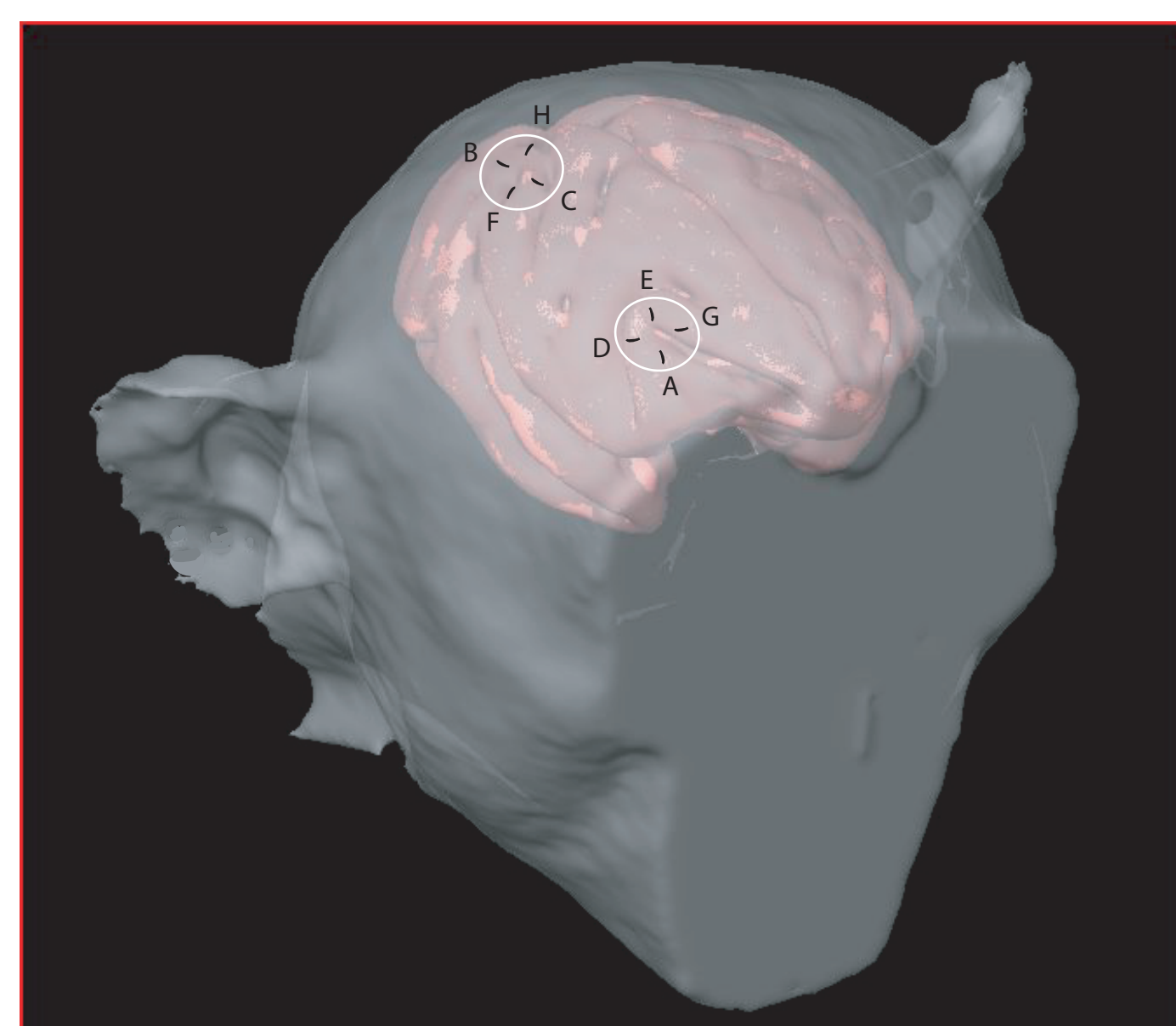


### Spatial Task



### NIRS Recording

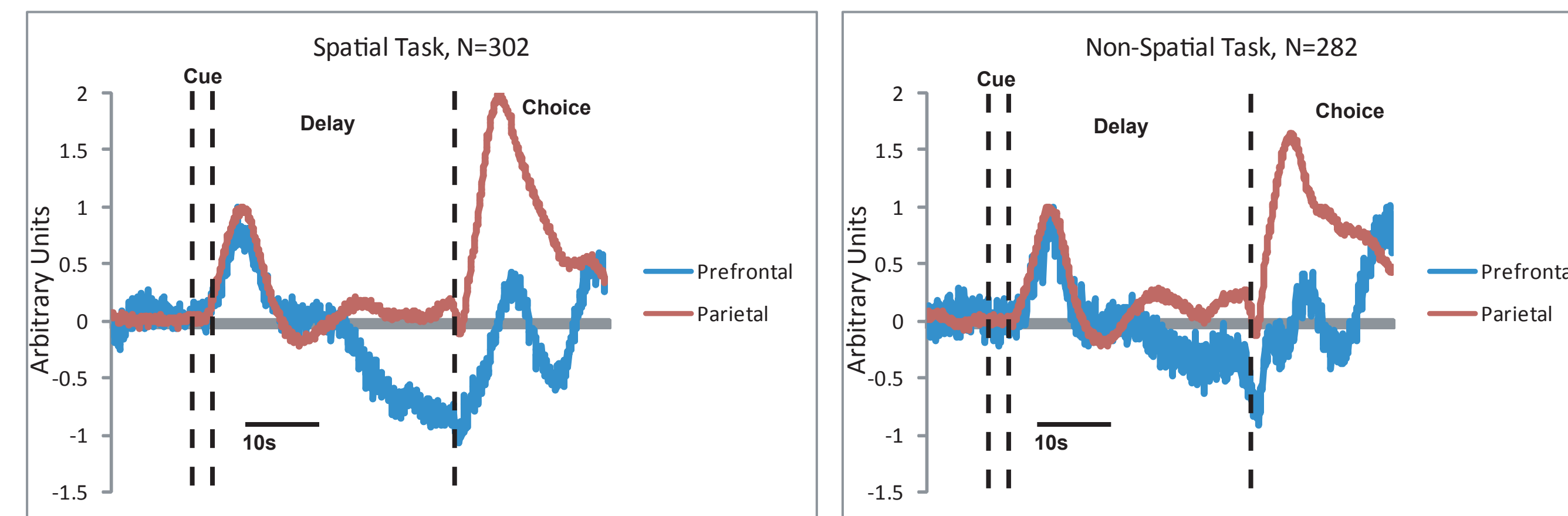
BOLD activation trends were recorded directly above the dura using Near-Infrared Spectroscopy (NIRS). Optical probes housing a central light emitter and four surrounding detectors were placed above the two cortical regions of interest in this study, LPFC and PPC. The optical path determined by the geometry of the optode placement defined four discrete channels per region. In LPFC, the probe was positioned over the sulcus principalis to simultaneously sample both DLPFC and VLPFC. Optical signal acquisitions were taken every 20ms and underwent regression analysis using a modified Beer-Lambert law to produce oxygenated hemoglobin (Hb<sub>02</sub>) concentration profiles. Letters A-H denote NIRS channels. *Image courtesy of Belma Dogdas, USC Signal and Image Processing Institute.*



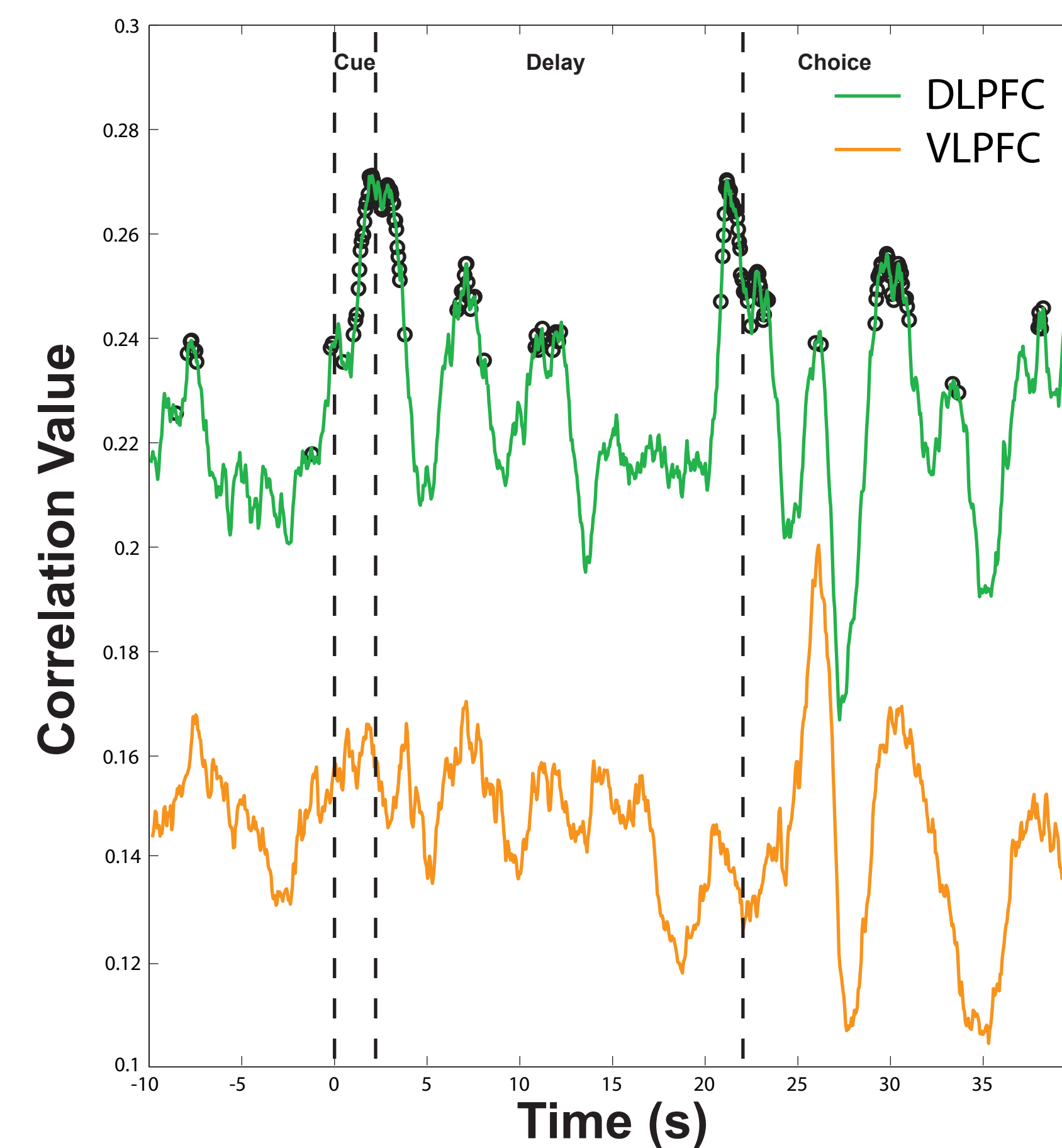
### Data Analysis

Hb<sub>02</sub> trends were submitted to a covariance analysis that calculated the correlation in oxygenation between pairs of channels recorded simultaneously in LPFC and PPC. A 2.6s sliding window was used to calculate the time-varying correlation between individual trials, assuming zero lag between signals from the two regions. Random permutations of the data were used to determine covariance significance ( $p < 0.01$ ). In order to assess directional Granger causal influences between channels, a multivariate autoregressive (MVAR) model was used. The MVAR spectral analysis quantifies the degree to which inclusion of a channel enhances the predictive power of the model for another channel, thereby yielding a measure of causality between the two.

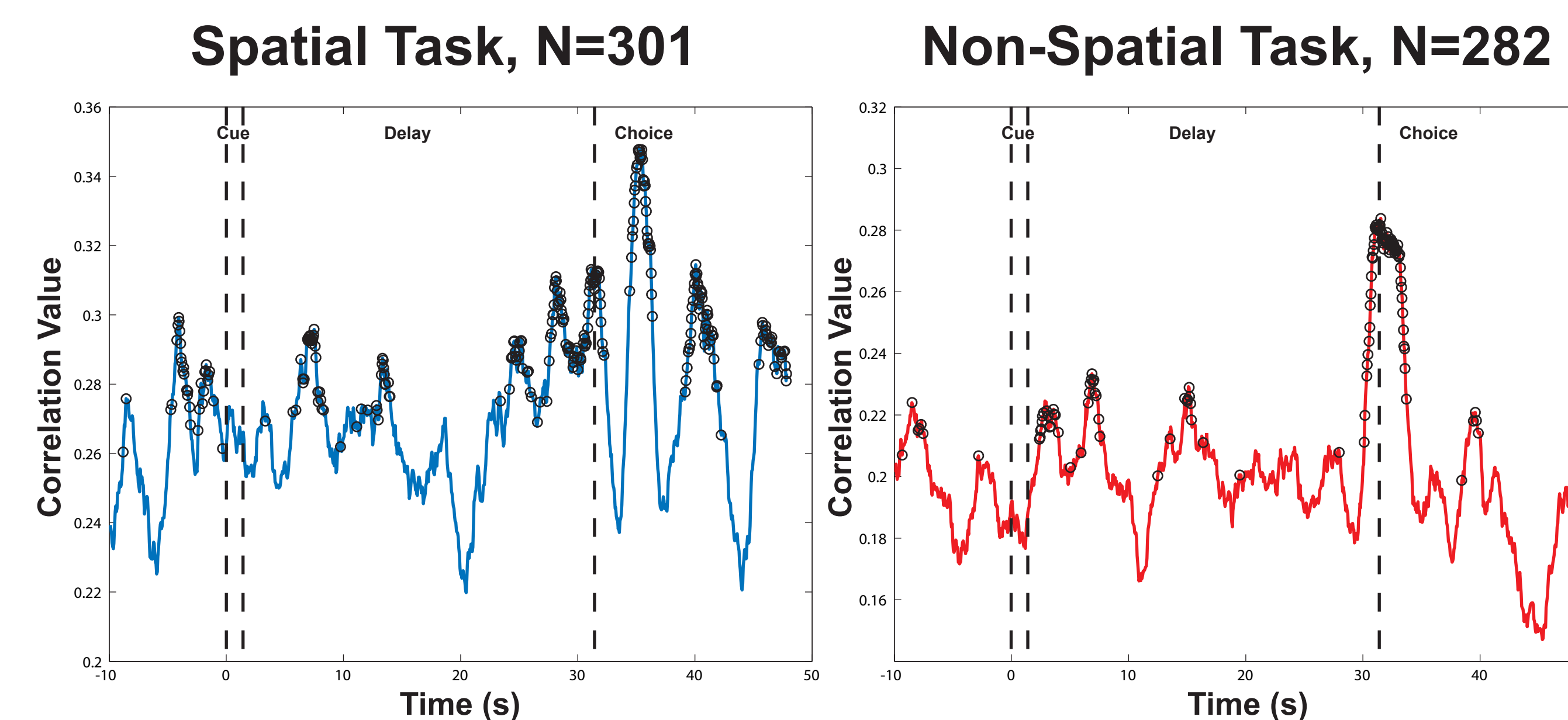
## RESULTS



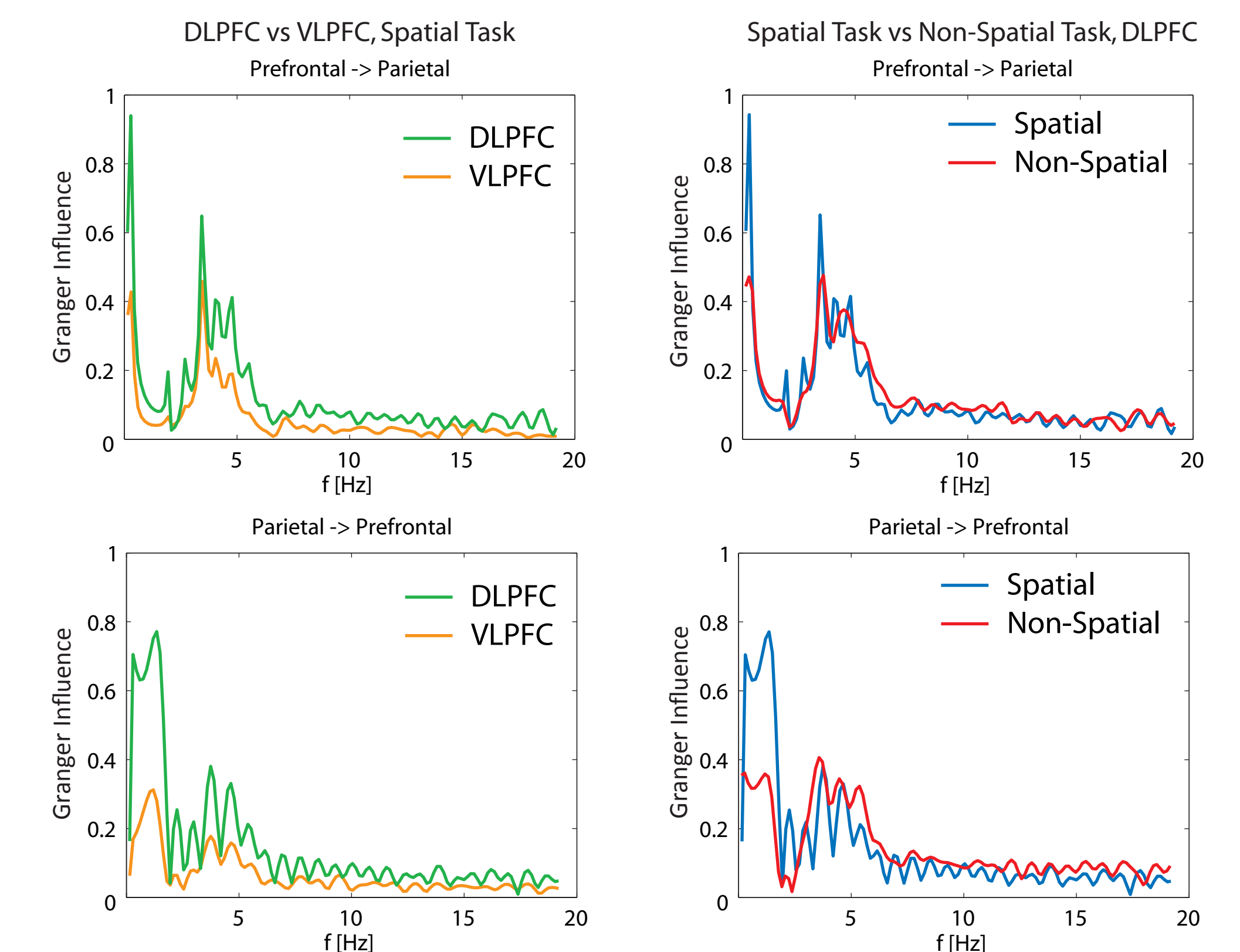
**Normalized average HbO<sub>2</sub> trends for the two tasks.** Slightly varying optical parameters between the cortical regions of interest in this primate prevent direct comparisons of NIRS signal magnitude between them. Data are thus normalized to illustrate trial-related changes relative to baseline. LPFC activations generally exhibit decay throughout the delay, while PPC trends are more sustained and slightly above baseline. In all channels and tasks, PPC shows higher relative activation during the delay and subsequent choice periods than does LPFC.



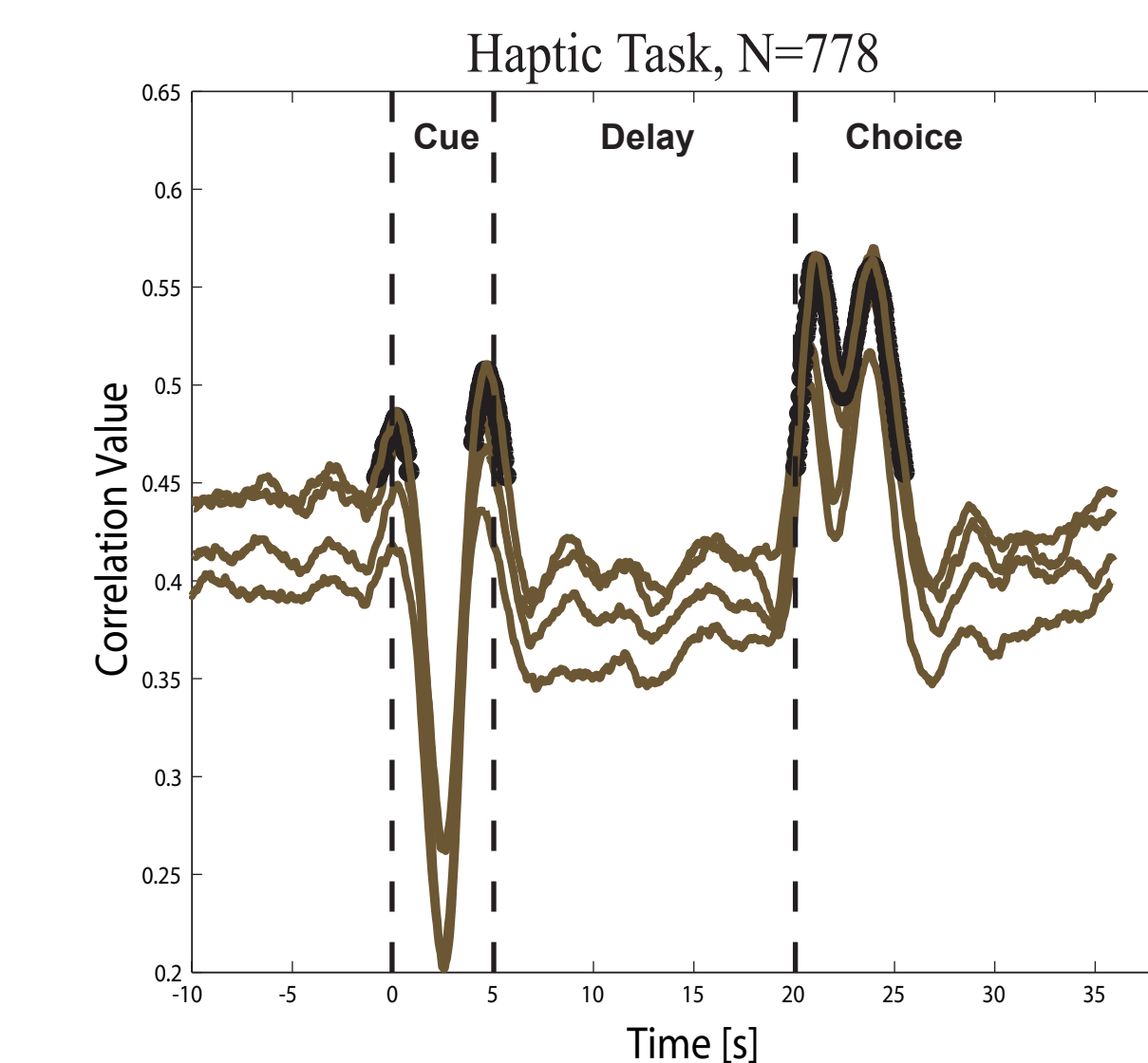
**Differences in covariance between DLPFC-PPC and VLPFC-PPC in the spatial WM task.** Even though the oxygenation time courses differ significantly between channels, the covariance between them reveals coherent cross-cortical activations. When compared to each sampled position in PPC, DLPFC channels exhibit more covariance than do VLPFC regions during performance of the spatial WM task. In the covariance trends with PPC channel H, DLPFC channel E (green) exhibits significant correlation ( $p < 0.01$ , denoted by black circles) that decreases throughout the delay period and then subsequently resumes at the choice. No significant correlations are seen in the VLPFC-PPC pair (channels D-H, orange).



**Differences in DLPFC-PPC covariance between the two tasks.** In all pairs of channels between DLPFC and PPC, the spatial WM task elicits more correlated activation than does the non-spatial task. In the example above, the channel G-B pair shows longer periods of significant correlation during spatial WM (blue), especially during the late-delay period, than during the non-spatial WM task (red).



**Directional influences between regions exhibiting covariance.** MVAR analysis shows that in the low (<2Hz) and ~4.5Hz frequencies, DLPFC has more pronounced reciprocal connections with all channels of PPC than does VLPFC. Additionally, during the spatial WM task, the Granger causal influences from PPC are much stronger to DLPFC than they are to VLPFC. That increased parietal influence on DLPFC is less apparent during performance of the non-spatial task, but this task-dependent difference in causality is not apparent in VLPFC.



**Absence of differential regional covariance in a network subserving a haptic WM task.** Comparisons between LPFC and SI during the performance of a haptic WM task, show fairly uniform patterns of correlation between pairs of channels, unlike that which is apparent when comparing LPFC and PPC. For clarity, significance (black circles,  $p < 0.01$ ) is denoted in only one trace, but is evident in all investigated pairs.

## DISCUSSION

The present data show changes in the local oxygenation of prefrontal and posterior parietal areas temporally related to the performance of WM tasks. Relatively higher Hb<sub>02</sub> levels were detected in parietal than prefrontal cortex during spatial WM. However, significant temporal coherence was found in Hb<sub>02</sub> levels between prefrontal and parietal areas, especially in spatial working memory. That coherence was particularly prominent between dorsolateral and parietal cortices. The changes in oxygenation, as well as BOLD coherence, were relative and preferential – “weighted” – in terms of both task and area. These findings suggest that working memory recruits a widely distributed network of neuronal assemblies. That network appears to represent all the associated features of the WM task, though some of its component assemblies are preferentially and jointly attuned to the information in WM. This inference is in accord with the concept of distributed and associative working memory. The application of Granger-causality algorithms reveals bidirectional causal linkages between the oxygenation fluctuations of the two cortices, prefrontal and parietal. This finding is consistent with the concept of reentrant cortical reverberation in WM. The results indicate that cortical networks, at different levels of organization and distribution, cooperate in an integrative fashion in the execution of goal-oriented behavior.

## CONCLUSIONS

- NIRS signals in working-memory tasks show that the dorsolateral prefrontal cortex is more engaged in the processing of spatial memory than is the ventrolateral prefrontal cortex.

- Granger-causality analysis suggests that working memory is maintained by dynamic interactions between prefrontal and posterior cortices.

## REFERENCES

- Brovelli A, Ding M, Ledberg A, Chen Y, Nakamura R, Bressler SL. 2004. Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. *Proc Natl Acad Sci USA.* 101(26):9849-54.
- Fuster JM, Bauer RH, Jervey JP. 1982. Cellular discharge in the dorsolateral prefrontal cortex of the monkey in cognitive tasks. *Exp Neurol.* 77(3):679-94.
- Goldman-Rakic PS. 1996. The prefrontal landscape, implications of functional architecture for Understanding human mentation and the central executive. *Philos. Trans. R. Soc. Lond. B.* 351, 1445-1453.
- Kojima T, Onoe H, Hikosaka K, Tsutsui K, Tsukada H, Watanabe M. 2007. Domain-related differentiation of working memory in the Japanese macaque (*Macaca fuscata*) frontal cortex: a positron emission tomography study. *Eur J Neurosci.* 25(8):2523-35.
- Zhou YD, Ardestani A, Fuster JM. 2007. Distributed and associative working memory. *Cereb Cort.* 17: i77-i87.