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September 5, 2019

To the editors of *Nature Neuroscience*:

We have enclosed our manuscript entitled *High-level cognition during story listening is reflected in high-order dynamic correlations in neural activity patterns*, which we wish to submit for publication as a Brief Communication in *Nature Neuroscience*.

Our manuscript reports on a series of analyses carried out on neuroimaging data collected by Uri Hasson's group (Simony et al, 2016) as participants listened to either an auditory story or a temporally scrambled version of the story. We applied to this dataset a new computational framework for estimating high-order dynamic correlations that reflect ongoing cognitive processing.

Prior work has indicated that dynamic functional (first-order) correlations—i.e., pairwise correlations between brain structures that change from moment to moment—change according to ongoing cognitive processes. Our computational framework also enabled us to examine higher-order dynamic correlations. For example, second-order correlations reflect *homologous* patterns of correlation. In other words, if the changing patterns of correlations between two regions, *A* and *B*, are similar to those between two other regions, *C* and *D*, this would be reflected in the second-order correlations between (*A*–*B*) and (*C*–*D*). In this way, second-order correlations identify similarities and differences between subgraphs of the brain's connectome. Analogously, third-order correlations reflect homologies between second-order correlations– i.e., homologous patterns of homologous interactions between brain regions. More generally, higher-order correlations reflect homologies between patterns of lower-order correlations. We can then ask: which "orders" of interaction are most reflective of high-level cognitive processes?

When participants listened to an intact recording of the story, they exhibited similar (across-participants) high-order brain network dynamics. These across-participant similarities are a reflection of the extent to which neural patterns are stimulus-driven, since the shared experimental stimulus was the only constant shared across participants. By contrast, when participants instead listened to temporally scrambled recordings of the story, only lower-order brain network dynamics were similar across participants. Further, the brain areas that mediate high-order correlations are associated with higher-level cognitive processes (cross-modality sensory integration, cognitive control, etc.), whereas low-order correlations and non-correlational activity dynamics most involve brain areas associated with lower-level cognitive processing (auditory processing, speech processing areas). Our results indicate that higher orders of network interactions support higher-level aspects of cognitive processing

In addition to the theoretical advances we report, identifying higher-order network dynamics associated with high-level cognition also required several important methods advances. First, we used kernel-based dynamic correlations to extended the notion of (static) inter-subject functional connectivity (Simony et al., 2016) to a dynamic measure of inter-subject functional connectivity that does not rely on temporal sliding windows, and that may be computed at individual timepoints. This allowed us to precisely characterize stimulus-evoked network dynamics that were similar across individuals. Second, we developed a computational framework for efficiently and scalably estimating high-order dynamic correlations. Our approach uses dimensionality reduction algorithms and graph measures to obtain low-dimensional embeddings of patterns of network dynamics. Third, we developed an analysis framework for identifying robust decoding results by carrying out our analyses using a range of parameter values and then identifying which results were robust to specific parameter choices.

We have published and documented all of the data and analysis code used to generate the figures in our manuscript (link: github.com/ContextLab/timecorr-paper), along with a concurrent release of a Python toolbox for carrying out analogous analyses on new datasets (link: timecorr.readthedocs.io).

We have suggested the following scientists as expert reviewers: Richard Betzel (EMAIL), Danielle Bassett (EMAIL), Emily Finn (EMAIL), Olaf Sporns (EMAIL), and Christopher Honey (EMAIL).

We note that we have included the complete methods section in the main text to facilitate peer review. If deemed potentially suitable for publication, we will update our manuscript by moving the current methods section into our supporting document, and by adding a methods summary conforming to the Brief Communications format. Thank you for considering our manuscript for publication in Nature Neuroscience.

Sincerely,

Jeremy R. Manning, Ph.D.