RESEARCH HIGHLIGHT

Network-level time computations in the suprachiasmatic nucleus

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Deciphering neuronal circuit dynamics is critical for understanding how the brain encodes information. In a recent study in *Cell Research*, Wang et al. shed light on how neuronal ensemble activity encodes time in the suprachiasmatic nucleus, and demonstrate the transformative potential of machine learning to decode complex neural processes.

In recent years, advances in imaging and computational techniques have enabled unprecedented insights into the spatiotemporal dynamics of neuronal circuit activity across the brain, and enabled linking them to behavior and cognitive function.[1] The neuronal signatures of memory and temporal processing in the hippocampus and cortex, for example, often involve sequential activation of neuronal assemblies,[2] and a modular structure in which specific subgroups of neurons represent different aspects of the task or memory.[3] Here, focusing on the suprachiasmatic nucleus (SCN), which orchestrates daily rhythms of physiology and behavior in mammals, Wang et al.[4] explore the network-level calcium dynamics that encode circadian time, showing that some general principles of information encoding are maintained across brain regions, such as sequential activation of neurons encoding temporal information,[2] while also bringing to light novel signatures of time encoding in the SCN.

Using a new approach for high-speed dual-view two-photon microscopy for volumetric calcium imaging in explants of the adult SCN, the authors recorded thousands of GABAergic neurons simultaneously across more than a day. This enabled the characterization of neuronal calcium dynamics at multiple scales, including individual calcium bursts (lasting seconds to minutes), calcium states (lasting minutes), and calcium activity across hours. Calcium bursts showed large variability across neurons, differing in frequency, amplitude, duration and waveform. The authors classified calcium bursts using a clustering algorithm, and showed that neurons change their bursting activity frequently, often to bursts of shorter duration. Over longer intervals of 5 min, six distinct calcium dynamic states were identified and a graph convolutional network was trained to detect their frequency across the network. The most frequent state featured fast, irregular fluctuations, while the rarest involved consistently elevated calcium levels with brief dips. Most neurons changed their calcium dynamics state over time, and had prolonged segments of generally higher or lower activity across the 24-h day. In addition, there was a coordinated wave of activity, which propagated from the dorsomedial to the ventrolateral aspect of the SCN over a few hours, which the authors termed 'phase wave of hyperactivity'. This is consistent with phase waves previously observed in neuronal calcium levels and clock gene expression ex vivo and in vivo,[5] implicated in encoding day length and accurately timed engagement of downstream targets.[6]

Such variability in calcium dynamics across the SCN may reflect the integrative nature of calcium signaling, relaying information from synaptic and paracrine connectivity, to a wide array of downstream processes, including transcription and metabolic regulation.[7] Calcium concentration may therefore dynamically capture network inputs to generate a complex multiscale signal tuned to engage with several different downstream processes.[8]

But how do these network dynamics support information encoding in the SCN? A key demonstration of the power of using machine learning to analyze large-scale imaging data is their approach to decoding circadian time from neuronal activity. A simple principal component analysis of 5-min calcium traces is sufficient to delineate their temporal trajectory across circadian time (see Fig. 3a in [4]). Moreover, a convolutional neural network enabled them to predict time even from a single neuron at above chance level, with accuracy increasing with the number of neurons sampled, thus showing that time is encoded via group decision-making. Interestingly, the contribution of each neuron to overall time encoding varies across the day but is relatively uniform across neurons, such that across a circadian day, all SCN neurons contribute equally to time computation.

Are there spatial differences in time-encoding signatures across the network? The authors used self-supervised contrastive learning, a learning algorithm that trains a model such that augmented or transformed versions of the same sample are mapped closer together in the feature space, while different samples are pushed further apart, thereby yielding meaningful representations of the data. A 2D spatial representation of the resulting clusters shows a symmetrical continuous ripple-like pattern from the medial to the ventral SCN (see Fig. 4b in [4]). Interestingly, this does not resemble the phase wave of hyperactivity, therefore representing another independent level of spatiotemporal organization of network activity (Fig. 1). This organization of neurons into 'modules' of activity resembles an organization of neuronal activity also seen in neural traces of memory and temporal information in other brain areas[1] and may confer the SCN increased tuning ability via combinatorial computation of time from different neuronal modules.

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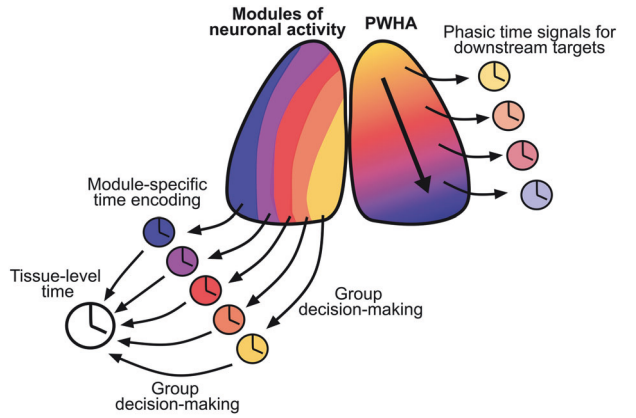

Fig. 1 System-level time encoding in the SCN. Schematic diagram showing how modules of neuronal activity (left) and the phase wave of hyperactivity (PWHA) (right) encode time at the tissue-level in the SCN.

Do these modules of activity differ in their time computation properties? Using only cells from one module severely degraded the accuracy of time prediction compared to random polling, yet when the model was trained on module-specific data, it reached a high accuracy on same-module calcium data but performed badly on cross-module data. This suggests that the detected modules of activity can fully represent time features, yet do so in a unique manner to other modules (Fig. 1), potentially enabling each subregion to tune its circadian output to effectively communicate with downstream targets.

Further work is needed to decipher the underlying mechanisms that shape neuronal ensemble activity. Calcium dynamics likely integrate signals from multiple origins,[8] which in the SCN includes synaptic input, neuromodulator signaling, paracrine signals from other neuronal and non-neuronal cells, particularly astrocytes, as well as intracellular signaling pathways, including the cell-autonomous circadian clock and energy homeostasis. By using the methodologies presented here together with specific manipulations and physiological challenges, it may be possible to gain insight into how diverse network signals are integrated to represent complex features in the SCN network, and generate a coherent circadian output.

Future work should leverage these insights and methodology to further understand how time computation is maintained in response to physiological changes, such as seasonal adaptations. Synchronization across SCN neurons is known to encode photoperiod, with longer days associated with increased circadian phase distance between neurons (i.e., less synchronized rhythms).[9] Furthermore, the network-level dynamics underlying more intricate physiological network features, such as time-of-day-dependent response gating in the SCN, could be investigated. For example, light induces a phase delay when perceived early during the night, but a phase advance when perceived late during the night.[10] How does the neuronal ensemble of the SCN adapt its signaling and coupling at different timescales across the network to retain accurate timekeeping in the face of such changes?

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ADDITIONAL INFORMATION

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