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Review

Deconstructing Circadian Rhythmicity with Models and Manipulations

Scott D. Pauls,[1] Ken-Ichi Honma,[2] Sato Honma,[2] and Rae Silver[3,4,5,*]

A master brain clock, localized to the hypothalamic suprachiasmatic nucleus (SCN), coordinates daily rhythms of physiology and behavior. Within the SCN, interconnected individual neurons are oscillators that, as an ensemble, function to send a coherent timing signal to the brain and body. However, individually, these neurons display different amplitudes, periods, and phases of oscillation. The dynamic properties of the SCN have been characterized over several spatial levels of analysis, from proteins to cells to tissues, and over several temporal ranges, from milliseconds to weeks. Modeling tools guide empirical research in this complex and multiscale spatiotemporal environment. Given that the SCN is a prototypical example of oscillating neural systems, principles of its organization hold promise as general prototypes of rhythms in other frequencies.

Extracting Principles from Studying Networks Underlying Circadian Rhythmicity

Rhythmicity is a General Property of Brain Tissue

Rhythms in the brain are ubiquitous, and oscillation is a fundamental feature of neuronal organization [1]. Oscillatory activity can be generated in many ways, and can be the product of mechanisms within individual neurons, interactions among neurons, or both. While oscillations of numerous and varied frequencies, including delta (0.1–3 Hz), theta (4–7 Hz), beta (16–31 Hz), and gamma waves (32–100 Hz), are among those detected in the brain, the best-understood rhythms are **circadian** (~24 h; *circa* = about, *die* = day; see Glossary): those that enable our bodies to anticipate regularly recurring events on a daily basis.

Amazingly, in mammals, the neurons controlling the phase of **daily rhythms** in the brain and throughout the entire body are coordinated by an internal 'clock', localized in the **SCN**, a nucleus that appears to have this single function. The SCN is a bilateral nucleus, with approximately 10 000 neurons, lying above the optic chiasm, on each side of the third ventricle. The SCN clock is itself synchronized to local time by phase-setting signals, the most salient of which is the daily light–dark cycle, and sustains rhythmicity in the complete absence of external synchronizing cues. Findings pointing to the SCN as the locus of a master brain 'clock' have survived decades of scrutiny [2,3]. As proof of its independent 'clock' function, the SCN retains rhythmicity when isolated from the rest of the body *in vivo* and *ex vivo*. It can be transplanted from the brain of one animal to another, and the period of the donor is expressed by the host recipient [4].

The SCN is a valuable system for understanding internally organized rhythmicity in the brain and body. In addition to being the only rhythm that has been both isolated and localized, circadian rhythms can be probed using the entire scientific toolkit, from molecular to electrophysiological

Trends

The SCN generates a master circadian rhythm via the coordination of a heterogeneous group of oscillatory neurons.

Researchers have studied dynamics over several spatial and temporal scales, informed by, and informing, mathematical models of components of the function of the SCN.

Emerging techniques enable the observation of multiple systems within the SCN simultaneously, showing directly how different subprocesses in the formation and maintenance of the circadian rhythm interact.

Multiplex network models of interacting processes, informed by these new observations, will provide new insights into circadian organization and guide new experimentation.

Given that the SCN serves as a canonical example of an oscillating neural system, these models will likely form prototypes for general models applicable to other oscillatory systems.

[1]Mathematics Department, Dartmouth College, Hanover, NH, USA
[2]Department of Chronomedicine, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan
[3]Neuroscience Program, Barnard College, New York, NY, USA
[4]Department of Psychology, Columbia University, New York, NY, USA
[5]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA

*Correspondence:
Rae.Silver@columbia.edu (R. Silver).

to behavioral mechanisms, and can be tracked at multiple temporal and spatial levels, including the individual cell, specific brain nuclei, tissues, and organs, and the behavior and physiology of the organism as a whole (Figure 1). Furthermore, the consequences of perturbing circadian oscillations by numerous genetic, environmental, and hormonal perturbations can be monitored experimentally. While localization to a discrete nucleus may be unique to the circadian domain, we suggest that analyzing rhythmicity in the SCN can yield general models and principles of dynamic neural network organization.

Trajectory of Biological Studies of SCN Networks Underlying Rhythmicity

The empirical and modeling studies on SCN organization that have provided an overview of the trajectory of discoveries in the biology of circadian rhythmicity are listed in Box 1, and the parallel development of models that attempt to capture the general principles that explain these observations is shown in Box 2 [5]. Here, we describe these developments and show how new empirical findings on the nature of the SCN network and its constituent elements are associated with updated metaphors and models with more empirically derived elements substituting for the abstractions over time.

By the early 1950s, it was known that there were daily rhythms in a plethora of physiological and behavioral responses, and it was established that these were internally organized and not driven by salient (e.g., the light–dark cycle) or subtle (e.g., geophysical) cues in the environment. However, it was not known whether the function was localized to a specific brain region or was the product of interactions among cells or organs. With the discovery of the SCN in 1972, much

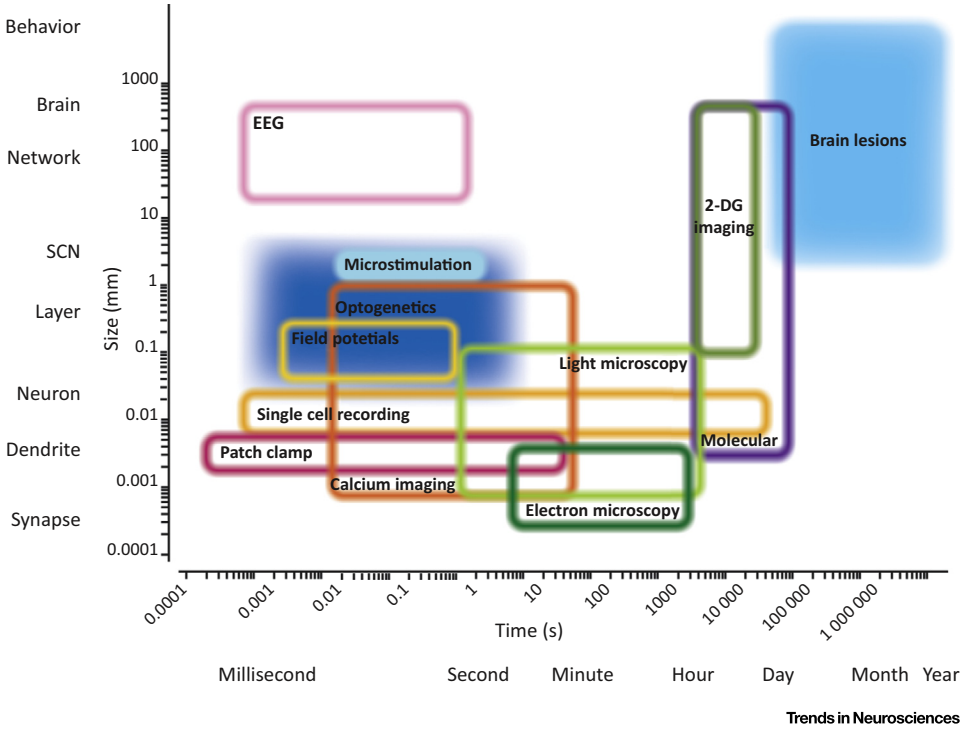

Figure 1. Methods Used to Study of the Spatial and Temporal Domains of Suprachiasmatic Nucleus (SCN) Rhythmicity. Each color-toned area indicates a domain of spatial and temporal resolution for one of the methods that have been applied to the study of the SCN and circadian timing. Open regions represent measurement methods and filled regions indicate perturbation techniques. Note that almost all of the methods available to study the brain as a whole have also been applied to the study of circadian rhythmicity. In addition, uniquely for the SCN, the molecular basis of circadian rhythmicity is understood, and can be assessed at several levels (purple). Modified from [73].

Glossary

Arginine vasopressin (AVP): highly expressed in the shell SCN, and has a circadian pattern of release.
Circadian (intrinsic of endogenous) rhythm: rhythm with a periodicity of about 24 h that persists in constant conditions.
Core and shell SCN: the SCN is often divided into two functional regions: the core and shell regions. Core neurons receive retinal input via a direct retinohypothalamic tract and from other thalamic and midbrain structures. The amplitude of rhythms of gene expression is high in the shell and low in the core.
Daily (extrinsic or exogenous) rhythms: rhythm with a periodicity of about 24 hours, that does not persist in constant conditions, but requires a daily resetting signal. It is important to distinguish these from intrinsic of endogenous (circadian) rhythms.
Entrainment: synchronization of circadian oscillation to an environmental stimulus that occurs at regular intervals (usually approximately 24 h.
Free-running period: the period of an oscillation in the absence of any entraining signals reflecting the intrinsic period of the oscillator.
Gastrin-releasing peptide (GRP): highly expressed in neurons of the core SCN. Administration of GRP produces phase shifts in the SCN and in behavioral rhythms.
Neuromedin S (NMS): contained within VIP and AVP, but not in GRP cells and NMS-containing cells are thought to be critical for the maintenance of intercellular synchrony within the SCN.
Rhythm amplitude: a measure of the level of expression, from peak to trough.
Suprachiasmatic nucleus (SCN): The SCN is the locus of the master circadian pacemaker in mammals; entails a bilateral nucleus lying above the optic chiasm and on either side of the third ventricle and comprised of about 10,000 neurons on each side in mice and rat.
Vasoactive intestinal polypeptide (VIP): highly expressed in neurons of the core SCN reviewed. The VIP receptor VPAC2 (encoded by Vipr2) is expressed both within the VIPergic neurons and in the cells of the shell SCN.