Towards an integrated understanding of the biology of timing

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As time passes by, our own understanding of time is close to the truth. The brain is an efficient machine in orchestrating temporal information across a wide range of time scales. Remarkably, circadian and interval timing processes are shared phenomena across many species and behaviours. Moreover, timing is a pivotal biological function that supports fundamental cognitive (e.g. memory, attention, decision-making) and physiological (e.g. daily variations of hormones and sleep–wake cycles) processes. Behavioural, neurobiological and computational investigation of timing has formed a rich literature on this theme. However, the study of timing now deserves to enter an era of genetic and epigenetic exploration in order to reveal how evolution has shaped the biology of timing. Within the brain, we have now identified specific brain regions, circuits and neuromodulators that are central to the physical realization of our perception and storage of timing information [1–4]. Nevertheless, with only the exception of the circadian clock [5], the genetic and molecular machinery that regulates biological clocks is far from being fully revealed.

Although many neuroscience investigations seriously take into account temporal properties, the exact mechanisms by which neural activity in the brain codes for duration and temporal order are still unknown. In humans, mice and many other species, conditioned behaviours are subjected to temporal determinants and a brief (seconds to minutes) duration of a light or tone may itself embody the critical information to be learned from the signal. The other most studied example of timing is around the daily 24-h oscillations. Single-cell organisms have adapted, during evolution, their internal metabolic processes to the environment by entraining with external stimuli (caused by the Earth’s rotation around the Sun). Multi-cellular organisms built upon the temporal regularity of this rest-activity cycle by incorporating it into the circadian clock that controls sleep–wake rhythms [6].

The success in discovering molecular loops that set and reset the circadian clock has favoured the diffusion of clock-like research models across many time scales and, classically, the neural mechanisms underlying timing and time perception have been theorized to rely on pacemakers. By contrast, different computational models suggest that timing is an intrinsic property of oscillating neural networks, which are modulated by the same circadian rhythms described above.

Recent advances in molecular and cellular biology, genomics and other ‘–omics’ promote the investigation of new dynamics in the brain. Genetic polymorphic variations at different genomic regions are not only responsible for stable trait changes across organisms, but also have the potential to affect gene expression over time [7] and, hypothetically, to modulate the neuronal coding of timing. The understanding of how genetic sequences translate into complex phenotypes is a major challenge in current functional genomics. This difficulty may be due to the fact that modules of genes and gene variations that co-express [8] must respond to precise temporal dynamics in order to encode a particular phenotype. In addition, a number of epigenetic regulators are set in time to modulate gene expression and cell cycle and are intimately associated with the functioning of neural processes. Indeed, the temporal relationship between, for
example, chromatin mechanisms and transcription is pivotal in many circadian processes and sleep [9].

The investigation of the interplay between genetic elements and neuronal functioning requires a multidisciplinary effort across molecular genetics and behavioural and computational neuroscience. Although many mechanisms within the organism rely on well-defined timed processes, there is limited cross-talk among disciplines that investigate timing at different levels and on different time scales. For this reason, we provide in this Theme Issue a series of overviews and original research papers that aim to broaden the understanding of the biological clock and to develop a common dialect across scientists with different expertise but with a common goal: the study of timing [6,10].

World-renowned experts in the fields of genetics/genomics, neurobiology and psychology address the dynamics among these distinct chronobiological dimensions within the Theme Issue. In particular, we would like to emphasize in this issue that the investigation of timing mechanisms can go further and target specific mechanisms at sub-cellular level, which we envisage will represent a new perspective in the field of timing.

References


