

Research Award Brief

Daily Changes in the Excitation/Inhibition Balance and its Impact on Synaptic Plasticity (2014 - 2016)

PI: Alfredo Kirkwood, Ph.D.
Professor
Department of Neuroscience
School of Medicine

Co-Investigator: Samer Hattar, Ph.D.
Associate Professor
Department of Biology
Krieger School of Arts and Sciences

Research Question: How does the sleep/wake cycle (circadian rhythm) regulate the neural plasticity mechanisms that impact learning?

Interdisciplinary Approach: This project integrates methodological and conceptual expertise on neural plasticity and circadian rhythms to understand the cellular mechanisms underlying daily fluctuations in learning.

Potential Implications of Research: Besides providing a cellular understanding for circadian variations in learning, findings of this research may have significant implications for understanding learning deficits in schizophrenia and autism.

The 24-hour sleep/wake cycle shapes and regulates multiple brain functions, including brain plasticity and learning. While evidence suggests changes in the sleep/wake cycle, also known as the circadian rhythm, profoundly impairs neural plasticity, much less clear is how such changes affect the neural mechanisms of learning. Learning likely results from the strengthening and weakening of distinct excitatory synaptic connections within brain networks. A crucial variable that controls this synaptic plasticity is the relative balance of synaptic excitation and synaptic inhibition ('E/I balance'), and it has been largely assumed that the E/I balance needs to be maintained within some narrow permissive range. Indeed learning deficits in models of schizophrenia and autism are attributed to modest alterations (~50%) in the E/I balance. However, our preliminary results revealed a much larger fluctuation of the E/I balance within a circadian cycle (~300%), suggesting that the E/I balance is better characterized by its dynamic range rather than by a particular value. In addition, since high and low values of E/I respectively promote weakening and strengthening of excitatory connections, the circadian fluctuations in E/I suggest that plasticity and learning might also fluctuate during the circadian cycle. To test these ideas we plan to study the modulation of E/I and synaptic plasticity induced in vitro in slices and in vivo in mice at defined moments of the circadian cycle. Specifically, we will determine:

1. Whether the daily modulation of the E/I balance simply reflects the circadian cycle or whether sleep plays an active role in this phenomenon.
2. How the modulation of the E/I balance impacts the mechanisms that modify synaptic connections learning. We expect that synaptic weakening will be more prominent at the beginning of the cycle, while strengthening will prevail at the end of the waking cycle.
3. Whether forms of learning that rely preferentially on synaptic weakening are better induced at the beginning of the waking cycle, while those forms that rely on synaptic strengthening are better induced at the end of the cycle.

