ADAPTIVE CHANGES IN MEMORY-RELATED BRAIN REGIONS UPON CHRONIC CIRCADIAN MANIPULATION

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Background: The impact of circadian disruption on cognition has been highlighted by the consequences of shift-work and the experimental manipulation of sleep-wake cycles in humans and rats (Marquié et al, Occup. Environ. Med. 2015; Fekete et al, Physiol. Behav. 1985) and reinforced by a link between circadian rest-activity pattern changes in aging and preclinical Alzheimer's Disease (Musiek et al, Jama Neurology. 2018). Despite these observations, the functional connections between Suprachiasmatic Nucleus (SCN) and memory-related regions, such as the Hippocampus (HIPP), have never been defined, and little is known of how circadian timing modulates hippocampal-based learning and memory.

Aims: We proposed to elucidate the mechanisms by which circadian pathways may impact in hippocampal-related function and memory output.

Methods: Whole-brain functional connectivity was modelled by combining ^{14}C-2-deoxyglucose functional brain imaging and Partial Least Squares Regression (as in Dawson et al, Neuropsychopharmacol. 2014) on male Sprague-Dawley rats (13 week-old); either under a normal circadian cycle or after a chronic circadian alteration of 4 cycles of repeated phase shifts and recovery sessions (Craig et al, Brain Res. Bull. 2008). A battery of behavioral tests was used to assess different components of memory performance. The anatomical connectivity between SCN and memory-related regions was traced by injecting transsynaptic anterograde [rVSV-(VSV-G)-Venus] and retrograde [rVSV-(RABV-G)-eGFP] viral tracers in the rat SC N and HIPP, using our optimized surgical procedure (Marcelo, Marques-Morgado et al, eNeuro.2021)

Preliminary results: We analysed 67 brain regions (n = 10/group) and found alterations in the metabolic activity of SCN and the HIPP, Medial Entorhinal Cortex, Perirhinal Cortex and Dorsal Raphé. We then modeled the relationship between the activity of these seed regions and all the other regions measured. A total of 127 functional interactions were impacted by the circadian shift, suggesting a disruption of HIPP-cortical communication. There was a strong remodelling of the connections between cognitive regions, indicating theta oscillations as a mechanism involved in the interaction between circadian rhythms and cognition. Moreover, trans-synaptic antero- and retrograde tracing using viral vectors also suggested a role of theta rhythm in the interaction between circadian rhythms and cognition: we found anatomical projections between the SCN and the HIPP with a relay in the Septum, that may act as a hub of circadian information onto the hippocampal system. Shifted animals displayed reduced performance in the Novel Object Recognition Test, whereas the performances in the Morris Water Maze and the Y-maze were preserved.

Conclusions: We describe a functional network between circadian clock components and memory-encoding regions, pointing new targets to explore the physiological role of circadian rhythms in memory. Furthermore, these connectivity signatures suggest that circadian disturbance induces pronounced changes in dominant functional circuits as an adaptive mechanism to preserve cognitive performance upon circadian insult.

Keywords: circadian rhythms, suprachiasmatic nucleus, hippocampus, functional connectivity, anatomical tracing

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