Study reveals role of retrosplenial cortex in regulating sub-stage transition during rapid eye movement sleep

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In a study published in *Nature Neuroscience*, researchers from Dr. Liu Danqian's Lab at the Institute of Neuroscience, Center for Excellence in

Brain Science and Intelligence Technology of the Chinese Academy of Sciences demonstrated that selective retrosplenial cortex activation encodes and regulates rapid eye movement (REM) sleep, revealed the cortical activity patterns and a selectively activated cortical region during REM sleep—the retrosplenial cortex (RSC)—discovered and characterized two distinct substages of REM sleep, and confirmed that RSC neuronal activity encodes and regulates the two substage transition.

REM sleep was discovered and defined in 1951 by America scientist Eugene Aserinsky, who recorded the Electroencephalogram (EEG) and electro-oculogram (EOG) on his 8-year-old son during sleep, and discovered a special sleep state with bursts of eye movements and high brain activation. In the following studies, he confirmed that this state is different from normal sleep states with enriched dream, and named it REM sleep, or Dream sleep.

The mechanism underlying REM sleep regulation, including how the brain can gate external sensory stimulation during REM sleep with such a high brain activation level, and the biological meaning of its existence and the role of this state in brain development remains elusive. From the point of view of evolution, REM sleep appears nearly at the same time with the evolution of the cortex. To this end, studying the brain activity pattern and regulatory mechanism of REM sleep could advance the understanding of the evolution of central nervous system.

In order to investigate whether cortex participates in REM sleep regulation, researchers implanted a chronic window on Thy1-GCaMP6s mice covering the entire dorsal cortex.

They used a two-channel wide-field imaging system to capture the calcium and hemodynamic signals, with EEG, electromyogram (EMG) and video recording concurrently. After spatial independent component analysis, eleven function modules named each by their corresponding

anatomical structure were separated. Among those modules, RSC exhibited the highest activation than others.

Using Granger causality and convolutional non-negative matrix factorization analysis, researchers found that cortical waves mostly originated from RSC and such waves are specifically happened in REM sleep but not in other brain states. Furthermore, they discovered that RSC neuronal activation is layer-specific, with selective activation of layer 2/3 instead of layer 5.

Interestingly, by inspection of video recording, researchers found that during REM sleep, mice showed enriched facial movements besides of bursts of rapid eye movement. By analyzing the facial movements using unsupervised method to extract the features and cluster, they discovered two substages of REM sleep: with (aREM) or without (qREM) enriched facial movement. These two substages have distinct autonomic activity and differential EEG spectrum, and REM sleep always transit from qREM to aREM.

Strikingly, researchers found that RSC L2/3 neuron exhibited two distinct temporal patterns, which highly matched with the two REM substages. Using closed-loop optogenetics, researchers finally found that RSC inactivation during REM sleep largely abolished qREM to aREM transition, suggesting that RSC is essential for substage transition.

This study for the first time showed the role of cortex in REM sleep regulation and paves the way for understanding the complex role of cortical activation during REM sleep. The discovery of two substages provides a new direction for studying the complex function of REM sleep.

More information: Yufan Dong et al, Cortical regulation of two-stage rapid eye movement sleep, *Nature Neuroscience* (2022). DOI:

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