様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

# 科学研究費助成事業　　研究成果報告書

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研究課題名（和文）Role of sleep in creativity and problem solving

研究課題名（英文）Role of sleep in creativity and problem solving

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　3,300,000円

研究成果の概要（和文）：重複する記憶に関する以前の知識に基づいて、これまで学習されていなかった新しい情報を推論する能力を評価する、マウスにおける推移的推論パラダイムを開発しました。睡眠不足が推論をブロックしました．ノンレム睡眠 とレム睡眠中の前帯状皮質（ACC）の活動を操作しました。 ノンレム睡眠またはレム睡眠中の光遺伝学的阻害は、推論を混乱させました．レム睡眠中のみのACCにおける内側嗅内皮質ニューロン終末の人工的活性化は正しい推論行動をもたらした

研究成果の学術的意義や社会的意義
Our study demonstrate a novel mechanism for creating novel ideas during sleep, which may open new horizon in the sleep research.
Our findings may help in the development of novel approaches to boost cognitive performance of normal and diseased subjects.

研究成果の概要（英文）：We developed a transitive inference paradigm in mice that assesses the ability to infer new information that was not learned before, based on previous knowledge of overlapping memories. Sleep deprivation (SD) blocked the inference.
We manipulated the activity of anterior cingulate cortex (ACC), during non-rapid eye movement (NREM) and rapid eye movement (REM)sleep. Optogenetic inhibition of the ACC during wakefulness did not affect inference evolution, as mice achieved high correct performance during inference tests. Conversely, mice that received optogenetic inhibition of the ACC during either NREM or REM sleep failed to infer correctly. Artificial activation of the medial entorhinal cortex neuronal terminals in ACC during REM, but not NREM, sleep resulted in correct inferential behavior.

研究分野：Cognitive Neuroscience

キーワード：Inference　Sleep

**１．研究開始当初の背景**

My previous studies focused on the storage of multiple memories that constitute our knowledge, which is the source of creativity. We demonstrated the mechanism of memory storage and showed that multiple associated memories are stored and interacted in the same neurons, while they are differentiated in specific synapses (Abdou et al., Science, 2018, Shehata and Abdou* et al., Journal of Neuroscience, 2018). In our lab, we found that contextual memory is replayed during sleep by offline reactivation of engram cells that store the memory. Since our knowledge is formed from the association of several memories, and the creativity emerges from the interaction of our past experiences and memories. Therefore, I aim to examine how our memories interact and replayed during sleep to generate new unlearned information. I have successfully established the transitive inference paradigm in mice and I learned the required techniques to conduct this research.

**２．研究の目的**

Creative problem-solving is critical for all aspects of innovation and pioneering thought. Therefore, it is critical to investigate how our memories are interacted and reorganized during sleep to solve a problem or create ideas.

**３．研究の方法**

a) Establish the sleep-dependent transitive inference behavior paradigm as a model for creative problem solving.
b) Determine the brain regions that are necessary for the emergence of inference by optogenetic inhibition and determine which sleep stage is crucial for this inference, by combining the optogenetic inhibition with simultaneous sleep stage detection system.
c) Investigate the neuronal activity dynamics during the emergence of the inferred information by using head mounted miniature microscope (nVista).

**４．研究成果**

a) We developed a transitive inference paradigm in mice that assesses the ability to infer new information that was not learned before, based on previous knowledge of overlapping memories. Sleep deprivation (SD) blocked the inference; the performance of mice remained at the chance level and their decision making was delayed (Figure 1).

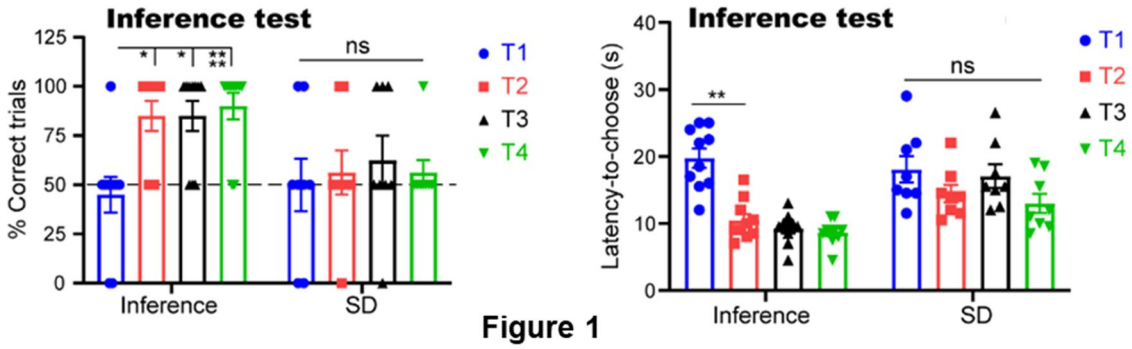


Figure 1

b) We manipulated the activity of anterior cingulate cortex (ACC), during non-rapid eye movement (NREM) and rapid eye movement (REM)sleep. Optogenetic inhibition of the ACC during wakefulness did not affect inference evolution, as mice achieved high correct performance during inference tests. Conversely, mice that received optogenetic inhibition of the ACC during either NREM or REM sleep failed to infer correctly (Figure 2). These data indicate that offline ACC activity is crucial for inference evolution.

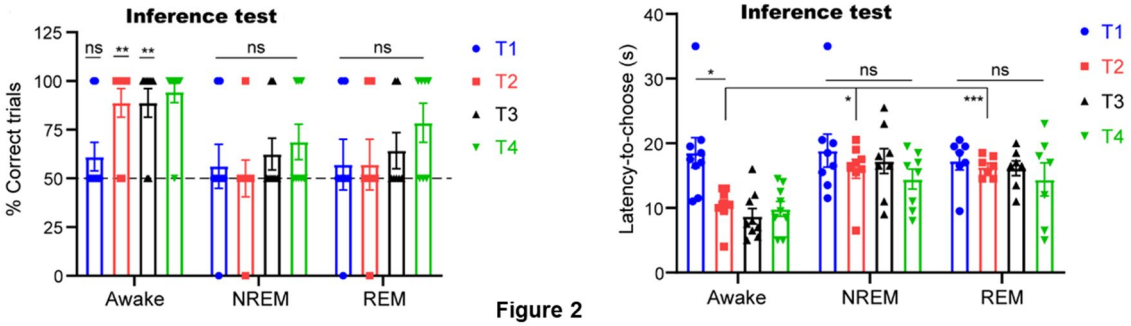


Figure 2

c) Artificial activation of the medial entorhinal cortex neuronal terminals in ACC during REM, but not NREM, sleep resulted in correct inferential behavior (Figure 3).

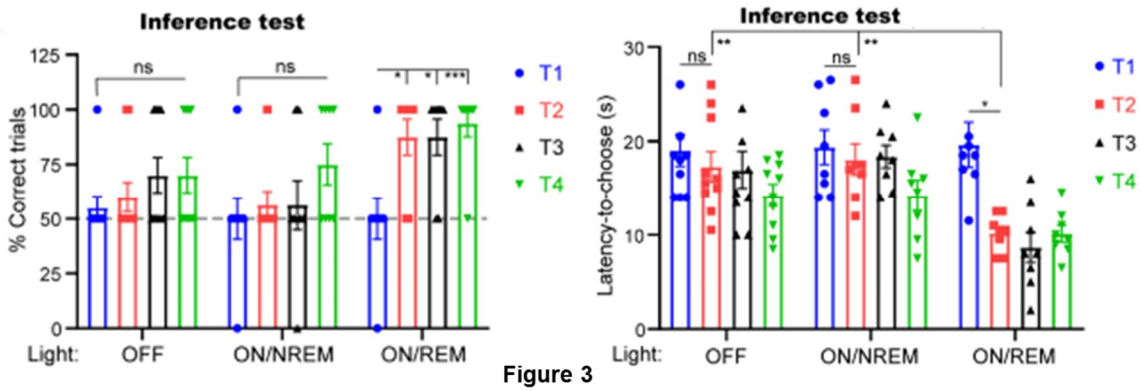


Figure 3

d) In vivo calcium imaging showed that inferential behavior was represented by two distinct neuronal populations in ACC. The first population developed gradually during randomized training and both sleep stages, while the other population started to emerge during REM sleep. Post-training NREM sleep showed high reactivation of original memory to build up the hierarchy. While, REM sleep showed an important role for using this hierarchy to weave inference-related ensembles.

**＜引用文献＞**

Kareem Abdou, Kiriko Choko, Mohamed H. Aly, Reiko Okubo-Suzuki,Shin-ichi Muramatsu, Kaoru Inokuchi. *BioRxiv* (2021).
https://doi.org/10.1101/2021.04.08.439095

５．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計2件（うち招待講演　0件／うち国際学会　1件）

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| １．発表者名<br>Kareem Abdou, Kiriko Choko, Mohamed H.Aly, Reiko Okubo Suzuki, Kaoru Inokuchi |
| ２．発表標題<br>Dissociable roles of sleep stages in the emergence and consolidation of transitive inference |
| ３．学会等名<br>The 43rd Annual Meeting of the Japan Neuroscience Society |
| ４．発表年<br>2020年 |

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| １．発表者名<br>Kareem Abdou, Kiriko Choko, Mohamed H.Aly, Reiko Okubo Suzuki, Kaoru Inokuchi |
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| ４．発表年<br>2020年 |

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

| | 氏名<br>（ローマ字氏名）<br>（研究者番号） | 所属研究機関・部局・職<br>（機関番号） | 備考 |
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７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

| 共同研究相手国 | 相手方研究機関 |
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