ウェブサイト公開用

（様式 10）
（海外特別研究員事業）
令和　3 年　10 月　26 日

海 外 特 別 研 究 員 最 終 報 告 書

独立行政法人日本学術振興会 理事長　殿

採 用 年 度　2019 年度
受 付 番 号　201960607
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海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：　ボストン　　（国名：　アメリカ合衆国　　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
記憶と感覚の統合に基づく意思決定の神経基盤の解明

3. 派遣期間：平成　31　年　4　月　1　日　～　令和　3　年　9　月　30　日（　914　日間）

4. 受入機関名及び部局名
受入機関名：　ハーバード医科大学
部局名：　神経生物学部

5. 所期の目的の遂行状況及び成果…書式任意　**書式任意（A4 判相当 3 ページ以上、英語で記入も可）**

【記載事項】
- 研究・調査実施状況及びその成果の発表・関係学会への参加状況等
- 新型コロナウイルス感染症の影響にかかる特例措置のうち、国内採用開始・採用期間延長・翌年度渡航のいずれかの適用を受けた場合は、当該措置の適用による影響等

（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

5. 所期の目的の遂行状況及び成果

記憶と感覚の統合に基づく意思決定の神経基盤の解明

5-1. Scope of my research project

My long-term research goal is to understand the neurobiology of decision-making that generalizes to the complexity in the real world, and to restore the ability to make rational decisions in novel situations for patients who incurred cognitive impairment. During my medical training, I found that the field faces a lack of mechanistic understanding of cognition and effective treatments for most cognitive dysfunctions. I have therefore focused my research career on a fundamentally important mental operation for cognitive recovery: decision-making, the process through which we produce rational behavioral outputs based on sensory and internal signals. Whereas most previous studies focused on specific decisions that only require the perception of sensory input and a fixed association from the sensory input to stereotyped motor output, I have endeavored to expand the framework to more elaborate and flexible decisions that are essential in the real world. The goal of the funded project was to understand a neural mechanism for flexible decision-making during navigation. During this process, the brain combines the memory of recent experiences and sensory signals to choose an appropriate navigation path. Here, I define flexibility as the ability to associate the same sensory signal to different actions depending on recent experiences stored in the memory. Such memory-dependent flexible decision-making is severely disrupted in many cognitive disorders, including Alzheimer's disease, schizophrenia, autism, and obsessive-compulsive disorders (OCD). The finding in this project suggests that retrosplenial cortex is a candidate area that mediates such flexibility of decision-making, and it is a potential therapeutic target for the recovery of cognitive flexibility.

5-2. Research goals, methodology, and results:

The survival of many animals requires the flexibility of decision-making, which often manifests as distinct navigation actions for a specific sensory cue depending on the context. However, most studies of decision-making required animals to take only one action for a given sensory cue, precluding the investigation into the flexibility. Other studies on the flexibility of decision-making were conducted without systematic screening across multiple brain areas to test their causal involvement, obscuring their behavioral relevance. Here we aimed to identify brain areas and neural activity patterns that are critical for flexible navigation decisions by systematic screening.

We developed a delayed match-to-sample (DMTS) task for mice, based on navigation in a virtual reality T-maze (Fig. 1). A head-fixed mouse navigated through the maze by running on a spherical treadmill. A sample cue (black or white wall pattern)

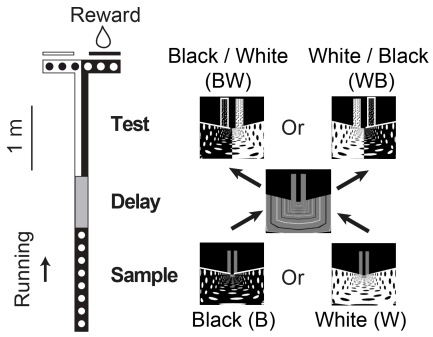

Figure 1. Delayed Match to Sample Task

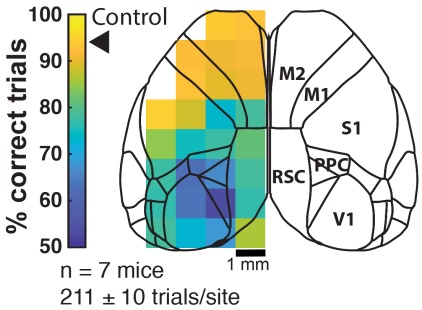

Figure 2. Effect of optogenetic bilateral inhibition throughout a trial during the DMTS task. For each inhibition area, the fraction of correct trials is indicated in color.

was presented at the start of the maze. The mouse then entered a delay period in which the wall patterns were identical between trial types, and the identity of the sample cue had to be stored in memory. After the delay segment, a test cue appeared in one of two configurations: black walls on the left and white walls on the right (BW) or vice versa (WB). To receive a reward, the mouse was required to turn at the T-intersection toward the T-arm that contained the same wall color that matched the sample cue. Importantly, in the test segment, the mouse therefore needed to combine its memory of the sample cue with the sensory information of the test cue to produce an appropriate choice (left or right turn).

An optogenetics screen identified the posterior parts of the cortex were necessary for flexible navigation decisions in the DMTS task. In mice expressing ChR2 in inhibitory interneurons, we targeted laser to a different bilateral pair of cortical sites on each trial. When inhibition was applied throughout the trial, behavioral performance was impaired during inhibition of V1, retrosplenial cortex (RSC), or posterior parietal cortex (PPC) (Fig. 2). When inhibition was restricted to a specific maze segment, the performance decrease was largest when the inhibition was applied during the decision-making phase in the test segment. Thus, the results suggest that these areas may play a central role in combining memory and visual information to generate navigation choices.

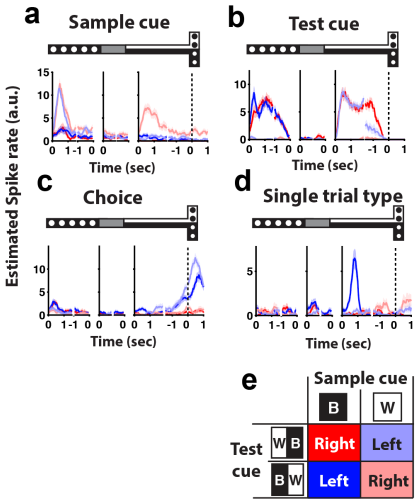

Figure 3. Example cells that showed selective activity for (a) sample cue, (b) test cue, (c) choice, and (d) single trial type. (e) Activity for four trial types is plotted in different colors as in the contingency table.

Calcium imaging in V1, RSC, and PPC revealed that cells in each area showed activity with selectivity to key task variables. We observed neural activity selective for the sample cue, test cue, and choice (Fig. 3a-c). Strikingly, a large fraction of cells were preferentially active on a single trial type and were thus active during trials with a specific combination of sample cue and test cue (Fig. 3d). These cells appeared as candidates for mixing sample cue and test cue information as is needed to make appropriate choices in the DMTS task, which requires a logical exclusive OR (XOR) operation[1] (Fig. 3e).

To test this quantitatively, we measured information about the key task variables encoded in individual cells. Because previous studies have shown that locomotion variables, such as running speed, can modulate cortical activity, we evaluated the selectivity of individual cells using generalized linear models (GLMs) that include both task and locomotor variables as predictors of a neuron's activity. Then we quantified the information encoded in each cell about each task variable by inverting the GLM in a Bayes decoder[2,3].

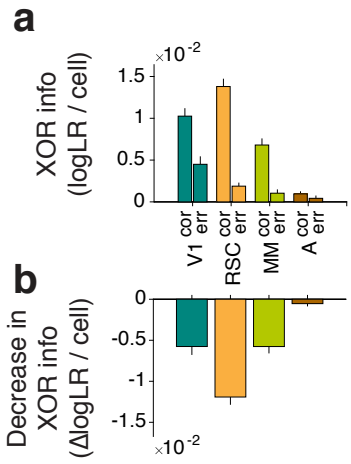

Figure 4. (a) Average information about the reward direction (XOR info) per cell in a decision epoch for correct and error trials. Error bars indicate s.e.m. (b) Difference in XOR information between correct and error trials, calculated per cell and averaged across cells. Error bars indicate mean ± s.e.m.

This analysis revealed that navigation goals were encoded by single-trial-type selective neurons that mixed specific combinations of memory and visual information (Fig. 3d). These neurons formed efficient, easy-to-decode population codes that appeared to govern accurate decision-making because they were informative before correct choices but degenerated during errors (Fig. 4). These cells were distributed across posterior cortex, even V1, and surprisingly were densest in RSC and sparsest in PPC. Therefore, we propose the flexibility of navigation decisions arises from distributed neurons that mix memory and visual information within a visual-parietal-retrosplenial network, centered in RSC.

References

1 Rigotti, M. *et al. Nature* **497**, 585-590, (2013).
2 Park, I. M., Meister, M. L., Huk, A. C. & Pillow, J. W. *Nat Neurosci* **17**, 1395-1403, (2014).
3 Runyan, C. A., Piasini, E., Panzeri, S. & Harvey, C. D. *Nature* **548**, 92-96, (2017).

5-3. Significance of research on the development of treatments or prevention

The long-term goal of my research is to develop treatments for cognitive disorders based on the understanding of neural computation. For this goal, it is essential (1) to understand the neural computation underlying a regular cognitive function, (2) to identify components of the neural computation that causes a failure of the cognitive function in animal models, and (3) to correct or compensate the neural computation with physiological and/or pharmacological interventions. My current research project provides important results and insights for the first two levels. I demonstrated that the activity of RSC neurons generated mixed representation of memories and sensory signals, in a way useful for guiding action in a flexible manner. Moreover, this mixed representation degenerated when the animals failed to make correct decisions. Such failure could underlie the impairment of flexible decision-making in a wide range of cognitive disorders. Based on these findings, my future research aims to aid the recovery of cognitive flexibility for patients who incurred cognitive impairments. In particular, I will use the methods used in this funded project to investigate the neural basis of cognitive recovery after permanent brain lesions in a mouse model. Furthermore, I plan to develop bioengineering interventions by artificial stimulations of neurons and implantation of embryonic neurons. This research direction is likely to provide therapeutic methods for a large number of patients who suffer from behavioral and cognitive impairments due to brain lesions from stroke and trauma.

5-4. Benefits from the extended fellowship period

Due to the pandemic, all labs at Harvard Medical School were closed for a prolonged time in 2020. I was required to work remotely for eight months, during which the progress of my research has been severely slowed down due to the lack of childcare and access to essential resources in the lab. I am deeply grateful for the JSPS's arrangement to extend the fellowship period, which allowed me to complete this project and submit the manuscript to a journal. Based on the significance of the funded project, I was also invited to give online oral presentations at highly competitive seminars, as detailed below.

5-5. Relevant presentations and publications

Invited seminars

2021 Winner for *Emerging Neuroscientists Seminar Series (ENSS)*
Sainsbury Wellcome Centre, University College London, online, October 2021.
A distributed and efficient population code of mixed selectivity neurons for flexible navigation decisions.

2021 Winner for *NeuroLaunchpad*, online, March 2021.
Mixed representations in a visual-parietal-retrosplenial network for flexible navigation decisions.

Park City Winter Conference, online, January 2021.
Mixed representations in a visual-parietal-retrosplenial network for flexible navigation decisions.

Conference presentations

Kira S., Safaai H., Morcos A.S., Panzeri S., Harvey C.D.
Society for Neuroscience Annual Meeting, Online & Chicago, IL, November, 2021.
Mixed representations of memory and visual information for flexible navigation decisions.

Kira S., Safaai H., Morcos A.S., Pica G., Panzeri S., Harvey C.D.
COSYNE, Online, February, 2021.
Mixed representations in a visual-parietal-retrosplenial network for flexible navigation decisions.

Kira S., Safaai H., Morcos A.S., Pica G., Panzeri S., Harvey C.D.
Society for Neuroscience Global Connectome, Online, January, 2021.
Mixed representations in a visual-parietal-retrosplenial network for flexible navigation decisions.

Kira S., Safaai H., Morcos A.S., Pica G., Panzeri S., Harvey C.D.
COSYNE, Denver, CO, February, 2020.
Mixed representations in retrosplenial cortex for flexible navigation decisions in mice.

Kira S., Pica G., Panzeri S., Harvey C.D.
Society for Neuroscience Annual Meeting, Chicago, IL, October, 2019.
Neural mechanisms for flexible navigation-based decisions in mice.

Publications

Kira S., Safaai H., Morcos A.S., Panzeri S., Harvey C.D.
A distributed and efficient population code of mixed selectivity neurons for flexible navigation decisions. (Under Review)