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

令和　６ 年　 ６ 月　 ６ 日現在

機関番号：８２４０１
研究種目：基盤研究(S)
研究期間：2019～2023
課題番号：１９Ｈ０５６４６

研究課題名（和文）Elucidating the Dynamics of Memory

研究課題名（英文）Elucidating the Dynamics of Memory

研究代表者
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交付決定額（研究期間全体）：（直接経費）　 102,500,000円

研究成果の概要（和文）：4年間の資金提供期間に、プロジェクトの目標に関連する9本の研究論文と2本の総説論文を執筆しました。Neuron誌に掲載された影響力のある招待論文「Perspectives」や、ストレスが記憶符号化ニューロンに与える影響に関する論文（Tomar et al, 2021a,b）などがあります。また、環境操作と遺伝子操作が記憶回路に与える影響についても研究しています。第3目標では、2019年の牧野らの研究が記憶想起の生理学的特徴を確立し、遠隔記憶の多段階モデルに実験的裏付けを与えました。第4目標では、2021年のHeらのNeuron誌の研究と国際共同研究（Robert,2021）を発表しました。

研究成果の学術的意義や社会的意義
Our work has advanced the understanding of how brains organize and store information in a distributed network. Further, we have identified mechanisms for the selection and prioritization of specific memory traces, both during consolidation and recall.

研究成果の概要（英文）：Over the 4 years of funding provided we produced 9 research papers and 2 review articles directly related to the aims of the project. For the first 2 aims these include of an influential invited Perspectives commentary published in Neuron, a research manuscript on how memory encoding neurons are impacted by stress, and papers detailing the impact of both environmental manipulations (stress; Tomar et al, 2021a, 2021b) and genetic manipulations (He et al, 2021; Guan et al 2021, He et al 2022, Adaikkan et al 2024) on local and global memory circuit function. Related to the third aim our 2019 Makino et al study was the first study to establish a physiological signature of behaviorally relevant memory recall based on memory age, as well as the first to lend experimental support to a multistage model of remote memory recall. Under the scope of aim 4 we have published one international collaborative study (Robert et al 2021) in addition to our 2021 He et al Neuron study addressing this topic

研究分野：Systems neuroscience

キーワード：hippocampus　memory　engram　cortex　oscillations

様　式　Ｃ－１９、Ｆ－１９－１（共通）

１．研究開始当初の背景

The hippocampus plays a key role in the formation, consolidation and recall of memory and has been best characterized in the rodent as a center for spatial learning. *In vivo* recordings in freely behaving genetically modified mice have been central in understanding how individual neurons in this structure encode spatial memory (‘**place cells’)** and how oscillations in the local field potential (LFP) impact communication and information transfer both within and outside the circuit. The HPC has two distinct and well-characterized oscillatory states, a robust ~8 Hz theta oscillation, accompanied by underlying gamma oscillations (slow gamma ~40 Hz and fast gamma ~80Hz) observed during exploration/encoding and a second state, defined by the appearance of sharp-wave ripples (SWRs), short ~140Hz oscillations seen during rest. Disrupting theta or SWRs impairs spatial learning and the stability of neuronal activity. *However, previous experiments have lacked the tools to selectively disrupt information content without also disrupting the oscillatory activity itself, making it impossible to disambiguate their contributions to the mechanisms and dynamics of memory.*

Recent technological and conceptual advances allow us to now conduct experiments that will disambiguate information (spiking) and oscillations in the encoding, consolidation and recall of a specific memory. First, we have recently combined our expertise in physiology with the emerging technology of memory engram labeling, based on the combination of immediate early gene expression and optogenetics, to functionally tag, identify & manipulate neurons involved in the encoding of a specific memory (Tanaka et al, *Science*, 2018). In that project we found that while the cFos+ ‘engram’ neurons, cells necessary and sufficient for a specific memory, are place cells, they only make up ~25% of the active ensemble. Further, they could be distinguished by firing repetitive bursts paced at the theta frequency and an increase in the responsiveness to fast gamma oscillations- *suggesting a neural signature of a cell participating in memory based on its temporal dynamics* Crucially, our data demonstrates that we can now physiologically identify and manipulate a small subset of neurons necessary and sufficient for memory- effectively manipulating the ‘information’ content of a specific memory- with a precision that will leave the overall population activity oscillations intact- a breakthrough in the field. Finally, my laboratory is a world leader in collecting and analyzing high-density recording of hippocampal neuronal activity, allowing us to decode information content during SWR ‘replay’ events (Middleton et al, *Nature Neuro*, 2018) and during theta and gamma oscillations (Middleton & McHugh, *Nature Neuro*, 2016). These advances leave us in a unique position to investigate the mechanisms of integration of information and oscillations and reveal their individual roles in memory, as well as yield insight to treatments of disorders involving aberrant neural dynamics.

２．研究の目的

Information in the brain is conveyed by the spiking of neurons and the computations underlying memory require these spikes are organized, both spatially and temporally. This organization is

achieved through rhythmic oscillations, a fundamental mechanism of communication and organization throughout the brain. In this project we build on our recent technological and conceptual advances in the control and decoding of the physiology of memory to investigate how oscillations in hippocampal/cortical circuits organize the information required for memory and how temporally organized information is altered by dysfunction and disease. Combining novel genetic techniques with *in vivo* physiology and computational and analytical approaches we will address several fundamental aims:

- **A01: How general is the physiological signature of a neuron encoding a memory?**
- **A02: Are neurons encoding a memory interconnected between brain regions and how is their communication coordinated?**
- **A03: How does the dynamics of memory recall evolve with time and experience?**
- **A04: Can memory loss due to disease and aging be improved by controlling synchrony?**

３．研究の方法

Overall, the research methods employed in our experiments are based on our genetic access to specific neuronal subtypes using transgenic mice and viral approaches, including neurons active in the encoding of specific memories, and on our expertise in *in vivo* physiology in the freely behaving mouse. *In vivo* recordings in genetically modified mice have been central in understanding how individual neurons in this structure encode spatial memory (‘place cells’; McHugh et al, Cell 1996) and how oscillations in the local field potential (LFP) impact communication and information transfer both within and outside the circuit (Middleton & McHugh, Nature Neuro. 2016, Middleton et al, Nature Neuro 2018). To achieve the aims of this project we have added several important features to our experimental approaches over the last year, including the incorporation of custom hardware and software which allows real-time detection of physiological events on-line (such as ripples; 120-180Hz oscillation in the CA1 LFP) and subsequent milli-second lag triggering of lasers for time-locked optogenetic intervention with high temporal precision, as well as the further development of transgenic and viral-based methods for activity-dependent cell labeling using both the cFos and Npas4 promoter systems. As described in the research results below, these advances, in combination with our established expertise in specific neuronal and circuit manipulations and high-density activity monitoring, have allowed us to identify populations of neurons involved in the encoding or modulation of memories or behaviors and analyze their circuit connectivity and function.

We have also incorporated emerging high-density recording techniques, specifically the neuropixel 2.0 probes (Jun et al 2017) for data collection in addition to the use of our established tetrode recording approaches. With these approaches we have examined the information represented by population activity of neurons both with and without manipulations of activity in the hippocampal circuit. pattern will be affected by photoinhibition of the CA1 engram cells during SWRs.

４．研究成果

Over the four years of funding provided we have produced 9 research papers and 2 review articles directly related to the aims of the project. Of the four aims, the first [A01: How general is the physiological signature of a neuron encoding a memory?] was the most challenging, as the hardware and personnel required were the most impacted by the COVID-19 pandemic (see section 4-2 above). However, the preliminary data and goals of this project formed the backbone of an influential invited Perspectives commentary that we published in Neuron. In this top-rated journal, Perspectives cover new, emerging ideas, with the goal of informing the readership and to provide insights and ideas that will help push the field forward. In addition, we published a research manuscript on how memory encoding neurons are impacted by stress, directly related to this aim.

Under the scope of Aim 2 [A02: Are neurons encoding a memory interconnected between brain regions and how is their communication coordinated?], we have been very successful in publishing important findings, detailing the impact of both environmental manipulations (stress; Tomar et al, 2021a, 2021b) and genetic manipulations (He et al, 2021; Guan et al 2021, He et al 2022, Adaikkan et al 2024) on local and global memory circuit function.

Related to the third aim [A03: How does the dynamics of memory recall evolve with time and experience?] our 2019 Makino et al study was the first study to establish a physiological signature of behaviorally relevant memory recall based on memory age, as well as the first to lend experimental support to a multistage model of remote memory recall. Moreover, using machine learning based classification approaches we demonstrated in the work the first across subject application of unbiased memory-age determination based on physiology alone; a highly novel and impactful discovery. This work serves as the basis for ongoing experiments focused on the identification and manipulation of engram neurons in this memory task, as well as work soon to be submitted using more sophisticated machine learning approaches to classify memory age based on physiology. In addition, we touched on this theme in our 2021 Tomar et al paper looking at the impact of stress on memory consolidation over time.

Finally, under the scope of aim 4 [A04: Can memory loss due to disease and aging be improved by controlling synchrony?] we have published one international collaborative study (Robert et al 2021) in addition to our 2021 He et al Neuron study addressing this topic.

Overall, the published and ongoing research funded with this project has advanced the cellular and millisecond resolution quantification of how our brains organize and store information distributed across the neural circuits of memory. Further, our ability to combine specific circuit manipulations with high-density observation of neuronal dynamics has identified hitherto unknown mechanisms for the selection and prioritization of specific memory traces, both during periods of consolidation, such as sleep, as well as during active recall. In total, the published research studies and reviews, as well as the ongoing

research related to the project position our laboratory as a leader in the field of hippocampal neuronal dynamics and memory.

Additionally, the Chen et al study, published in Nature in late 2020, began outside of the scope of the original plan, but due to technology development spurred by the project, has proven highly synergistic to the ongoing work. The main finding in that study is the identification of parallel hypothalamic circuits that can signal novelty to the dorsal hippocampus. This identification of a hitherto unidentified novelty circuit in the mammalian brain has motivated us to understand the impact of these circuits on hippocampal physiology and memory dynamics in our future experiments and has already been featured in high profile commentaries (Oliva, 2020 Trends in Neuroscience) and reviews (Walsh et al, Current Opinion in Neurobiology 2021; Watarai et al Current Opinion in Neurobiology 2021; Lee et al, Cell 2021, Goode et al, Neuron 2020), receiving 122 citations since being published and being accessed over 31,000 times on the Nature website. As stated above, although this study began prior to the adoption of the project, the technology developed as part of this project was instrumental in completing this work and has opened new synergistic avenues of investigation concerning how novelty and novelty signaling impacts the dynamics of memory representations.

５．主な発表論文等

〔雑誌論文〕　計12件（うち査読付論文　10件／うち国際共著　10件／うちオープンアクセス　3件）

１．著者名 He Hongshen、Wang Yi、McHugh Thomas J.	４．巻 33
２．論文標題 Behavioral status modulates <scp>CA2</scp> influence on hippocampal network dynamics	５．発行年 2023年
３．雑誌名 Hippocampus	６．最初と最後の頁 252～265
掲載論文のDOI（デジタルオブジェクト識別子） 10.1002/hipo.23498	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 He Hongshen、Guan Hefei、McHugh Thomas J.	４．巻 189
２．論文標題 The expanded circuitry of hippocampal ripples and replay	５．発行年 2023年
３．雑誌名 Neuroscience Research	６．最初と最後の頁 13～19
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.neures.2022.12.010	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Tomar Anupratap、Polygalov Denis、Chattarji Sumantra、McHugh Thomas J.	４．巻 14
２．論文標題 Stress enhances hippocampal neuronal synchrony and alters ripple-spike interaction	５．発行年 2021年
３．雑誌名 Neurobiology of Stress	６．最初と最後の頁 100327～100327
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.ynstr.2021.100327	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Tomar Anupratap、Polygalov Denis、McHugh Thomas J.	４．巻 15
２．論文標題 Differential Impact of Acute and Chronic Stress on CA1 Spatial Coding and Gamma Oscillations	５．発行年 2021年
３．雑誌名 Frontiers in Behavioral Neuroscience	６．最初と最後の頁 "-"
掲載論文のDOI（デジタルオブジェクト識別子） 10.3389/fnbeh.2021.710725	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 He Hongshen、Boehringer Roman、Huang Arthur J.Y.、Overton Eric T.N.、Polygalov Denis、Okanoya Kazuo、McHugh Thomas J.	4．巻 109
2．論文標題 CA2 inhibition reduces the precision of hippocampal assembly reactivation	5．発行年 2021年
3．雑誌名 Neuron	6．最初と最後の頁 3674～3687.e7
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.neuron.2021.08.034	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Robert Vincent、Therreau Ludivine、Chevaleyre Vivien、Lepicard Eude、Viollet Cecile、Cognet Julie、Huang Arthur JY、Boehringer Roman、Polygalov Denis、McHugh Thomas J、Piskorowski Rebecca Ann	4．巻 10
2．論文標題 Local circuit allowing hypothalamic control of hippocampal area CA2 activity and consequences for CA1	5．発行年 2021年
3．雑誌名 eLife	6．最初と最後の頁 "-"
掲載論文のDOI（デジタルオブジェクト識別子） 10.7554/eLife.63352	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

1．著者名 Guan Hefei、Middleton Steven J.、Inoue Takafumi、McHugh Thomas J.	4．巻 12
2．論文標題 Lateralization of CA1 assemblies in the absence of CA3 input	5．発行年 2021年
3．雑誌名 Nature Communications	6．最初と最後の頁 "-"
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/s41467-021-26389-3	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

1．著者名 Tomar Anupratap、McHugh Thomas J.	4．巻 45
2．論文標題 The impact of stress on the hippocampal spatial code	5．発行年 2022年
3．雑誌名 Trends in Neurosciences	6．最初と最後の頁 120～132
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.tins.2021.11.005	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Chen Shuo、He Linmeng、Huang Arthur J. Y.、Boehringer Roman、Robert Vincent、Wintzer Marie E.、Polygalov Denis、Weitemier Adam Z.、Tao Yanqiu、Gu Mingxiao、Middleton Steven J.、Namiki Kana、Hama Hiroshi、Therreau Ludivine、Chevaleyre Vivien、Hioki Hiroyuki、Miyawaki Atsushi、Piskorowski Rebecca A.、McHugh Thomas J.	4．巻 586
2．論文標題 A hypothalamic novelty signal modulates hippocampal memory	5．発行年 2020年
3．雑誌名 Nature	6．最初と最後の頁 270～274
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/S41586-020-2771-1	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Goode Travis D.、Tanaka Kazumasa Z.、Sahay Amar、McHugh Thomas J.	4．巻 107
2．論文標題 An Integrated Index: Engrams, Place Cells, and Hippocampal Memory	5．発行年 2020年
3．雑誌名 Neuron	6．最初と最後の頁 805～820
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.neuron.2020.07.011	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Chen Shuo、He Linmeng、Huang Arthur J. Y.、Boehringer Roman、Robert Vincent、Wintzer Marie E.、Polygalov Denis、Weitemier Adam Z.、Tao Yanqiu、Gu Mingxiao、Middleton Steven J.、Namiki Kana、Hama Hiroshi、Therreau Ludivine、Chevaleyre Vivien、Hioki Hiroyuki、Miyawaki Atsushi、Piskorowski Rebecca A.、McHugh Thomas J.	4．巻 586
2．論文標題 A hypothalamic novelty signal modulates hippocampal memory	5．発行年 2020年
3．雑誌名 Nature	6．最初と最後の頁 270～274
掲載論文のDOI（デジタルオブジェクト識別子） 10.1038/S41586-020-2771-1	査読の有無 無
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

1．著者名 Goode Travis D.、Tanaka Kazumasa Z.、Sahay Amar、McHugh Thomas J.	4．巻 107
2．論文標題 An Integrated Index: Engrams, Place Cells, and Hippocampal Memory	5．発行年 2020年
3．雑誌名 Neuron	6．最初と最後の頁 805～820
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.neuron.2020.07.011	査読の有無 無
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 －

〔学会発表〕　計17件（うち招待講演　15件／うち国際学会　5件）

1．発表者名
Thomas McHugh

2．発表標題
CA2 circuit mediating hippocampal modulation of cholinergic tone

3．学会等名
Australia Neuroscience Society Annual Meeting（招待講演）（国際学会）

4．発表年
2022年

1．発表者名
Thomas McHugh

2．発表標題
engrams, inhibition and oscillaitons

3．学会等名
Neuronal Representations Meeting, univ of Freiburg（招待講演）

4．発表年
2022年

1．発表者名
Thomas McHugh

2．発表標題
memory modulation by noncanonical hippocampal circuits

3．学会等名
KIST BSI, Seoul, Korea（招待講演）

4．発表年
2022年

1．発表者名
Thomas McHugh

2．発表標題
hippocampal memory dynamics

3．学会等名
KSBNS Annual Meeting（招待講演）（国際学会）

4．発表年
2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal circuits

３．学会等名
Weizmann Institute Neurobiology Seminar（招待講演）

４．発表年
2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal circuits

３．学会等名
Brain States and Beyond（招待講演）

４．発表年
2021年

１．発表者名
Thomas McHugh

２．発表標題
Hypothalamic novelty signaling

３．学会等名
Society for Neuroscience Annual Meeting（国際学会）

４．発表年
2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal-subcortical circuits

３．学会等名
Dandrite/Aarhus University（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal-subcortical circuits

３．学会等名
PKU-JNC Neurotechnology & Discovery Series（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
physiological signatures of memory

３．学会等名
Duke University, CMB Seminar Series（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
physiological signatures of memory

３．学会等名
UTSW Seminar Series（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
Subcortical Modulation of Hippocampal Memory

３．学会等名
FENS Meeting（招待講演）（国際学会）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal-subcortical circuits

３．学会等名
Dandrite/Aarhus University（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
memory modulation by noncanonical hippocampal-subcortical circuits

３．学会等名
PKU-JNC Neurotechnology & Discovery Series（招待講演）

４．発表年
2020年～2021年

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Thomas McHugh

２．発表標題
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Duke University, CMB Seminar Series（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
physiological signatures of memory

３．学会等名
UTSW Seminar Series（招待講演）

４．発表年
2020年～2021年

１．発表者名
Thomas McHugh

２．発表標題
Subcortical Modulation of Hippocampal Memory

３．学会等名
FENS Meeting（国際学会）

４．発表年
2020年～2021年

〔図書〕　計0件

〔産業財産権〕

〔その他〕
小さな海馬CA2領域が記憶の固定に果たす大きな役割
www.riken.jp/en/news_pubs/research_news/rr/20211227_1/index.html

６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

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