様　式　C－19、F－19－1、Z－19　（共通）

科研費
KAKENHI

科学研究費助成事業　　研究成果報告書

令和　５ 年　６ 月 ２９ 日現在

機関番号：３８００５
研究種目：若手研究
研究期間：2019～2022
課題番号：１９Ｋ２０３４８

研究課題名（和文）Experimental and theoretical investigation of Bayesian inference across multiple layers in somatosensory cortex

研究課題名（英文）Experimental and theoretical investigation of Bayesian inference across multiple layers in somatosensory cortex

研究代表者

ＬＩ　Ｙｕｚｈｅ（Li, Yuzhe）

沖縄科学技術大学院大学・神経計算ユニット・スタッフサイエンティスト

研究者番号：３０８１５４３６

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）：このプロジェクトでは、不確実な環境下での動物の意思決定と異なる皮質層の神経活動の関係を調査します。そのために、マウスを対象にレバー操作タスクを設計し、プリズムレンズを皮質に埋め込んで同時に複数の層のカルシウムイメージングデータを取得しました。ノイズの多いデータを解析するため、次元削減にデュアルARD手法を開発し、デコーディングとエンコーディングにも活用しました。さらに、異なる層のニューロン間の時間的・空間的な接続パターンを探索しました。現在はベイズモデルを用いて神経活動を分析中です。開発した手法を統合し、異なる皮質層間での意思決定プロセスについて貴重な洞察を得ることを期待しています。

研究成果の学術的意義や社会的意義
The exploration of neural activity patterns across cortical layers provides insights into how different layers of the brain communicate and organize information. Understanding how decision-making occurs at the neural level will deepen our understanding of human behavior, cognition, and perception.

研究成果の概要（英文）：This project aims to investigate how animals make decisions in uncertain environments and how neural activity across different cortical layers contributes to the decision-making process. To achieve this, we designed a lever push/pull task for mice and implanted a prism lens in the cortex to simultaneously capture calcium imaging data from multiple layers. To analyze the noisy calcium imaging data, we developed a dual ARD (Automatic Relevance Determination) method for dimensionality reduction, which also was used for decoding and encoding in subsequent analyses. Furthermore, we have explored the temporal and spatial connectivity patterns among neurons from different layers. We are currently utilizing Bayesian models to analyze the neural activities. By integrating the various approaches we have developed throughout this project and continuing our ongoing efforts, we anticipate uncovering valuable insights into decision-making process that takes place among different cortical layers.

研究分野：Computational neuroscience

キーワード：Bayesian inference　Decision making　Uncertainty　Cortical layers　Calcium imaging　functional connectivity　dimensionality reduction　metastate

様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

The concept of the “Bayesian brain” has attracted enormous attention in neuroscience and has become increasingly popular in recent years. We expect to find neural activities related to Bayesian inference in the cerebral cortex. It is also worth noticing the multi-layer structure of the cortex. Theoretical studies have proposed some possible mathematical models of hierarchy calculations of Bayesian inference held in the cortex. However, the specific roles of different cortical layers in a Bayesian inference model are not clearly defined in these models due to the lack of experiment evidence.

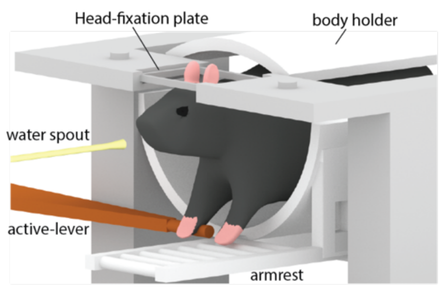
２．研究の目的

This project aims to investigate how animals make decisions in uncertain environments and how neural activity across different cortical layers contributes to the decision-making process. To achieve this, we designed a lever push/pull task for mice and implanted a prism lens in the cortex to simultaneously capture calcium imaging data from multiple layers. To analyze the noisy calcium imaging data, we developed a dual ARD (Automatic Relevance Determination) method for dimensionality reduction, which also was used for decoding and encoding in subsequent analyses. Furthermore, we have explored the temporal and spatial connectivity patterns among neurons from different layers. We are currently utilizing Bayesian models to analyze the neural activities. By integrating the various approaches we have developed throughout this project and continuing our ongoing efforts, we anticipate uncovering valuable insights into decision-making process that takes place among different cortical layers.

３．研究の方法

【Design and construct Setup】

I have designed and constructed the active-lever based operant conditioning system, which includes a 3D-printed plastic body holder and head fixation, a lever for the animal to grasp with its forepaw, a water-reward delivery system, and a control system for the lever and reward delivery (Fig. 1).　The animal is required to pull or push the lever to receive a reward, which is delivered through a waterspout in the form of a water drop. The lever is controlled by an actuator. To introduce uncertainty into the task, we can adjust the settings of the lever. In order to address motor adaptation, the lever movement can include fluctuation for variability. This allows the animal to adapt and adjust its movements accordingly. Additionally, for decision-making purposes, we can set the required direction of the lever (either pull or push) to be probabilistic, meaning the animal has to make probabilistic choices when deciding which action to take.



Active-lever based operant conditioning system

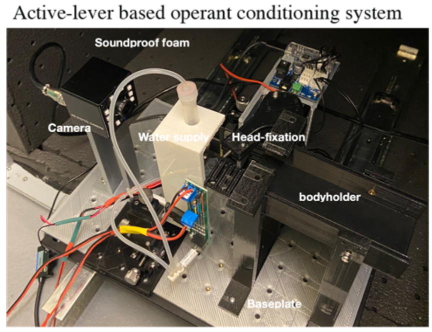


Fig. 1　Setup of the active-lever pull/push task

【Virus injection and prism lens implantation】

We targeted the upper-limb region in the primary cortex (SSp-ul) for imaging. To infect neurons spanning from superficial to deep layers, we injected the virus at multiple locations within the cortex at varying depths (as shown in the figure). Subsequently, we implanted a prism lens (1mm × 1mm) perpendicular to the cortical layers, facing the area of virus injection (Fig. 2). We then attached a microendoscope for imaging the calcium dynamics of neurons. The resulting calcium imaging data clearly exhibits a distinct layer structure, indicating that the prism lens effectively captures neural activity from superficial (layer 2/3), middle layer (layer 4) and deep layers (Layer 5/6) of the cortex (Fig. 3).

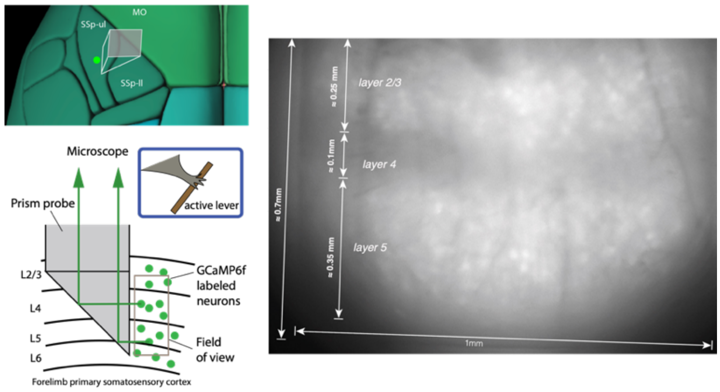


Fig. 2 Virus injection and field of view via a prism lens

The acquisition of imaging data from multiple cortical layers is indeed a challenging task. After persistent efforts and testing, we have successfully achieved this significant milestone, which marks a major breakthrough in our research. This accomplishment opens up new avenues for exploring the intricacies of neural activity across different cortical layers.

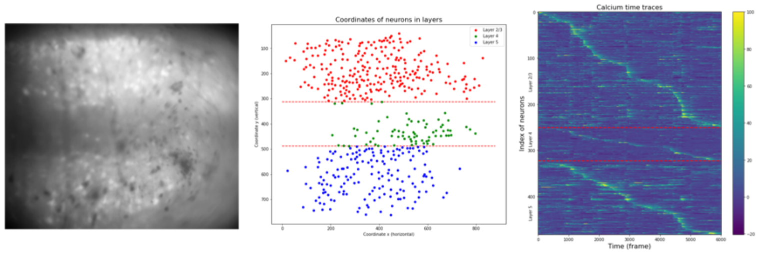


Fig. 3 Calcium imaging dynamics in different cortical layers

4. 研究成果

【Dual ARD for automatic dimensionality reduction】

1. **Y Li**, K Doya. (2023) “Dual automatic relevance determination in latent variable models and its application to calcium imaging data”, in submission.

When dealing with high-dimensional data, extracting meaningful information directly from the data can be challenging, which necessitates the use of dimensionality reduction techniques. Moreover, identifying the appropriate reduced dimensionality remains an additional challenge.

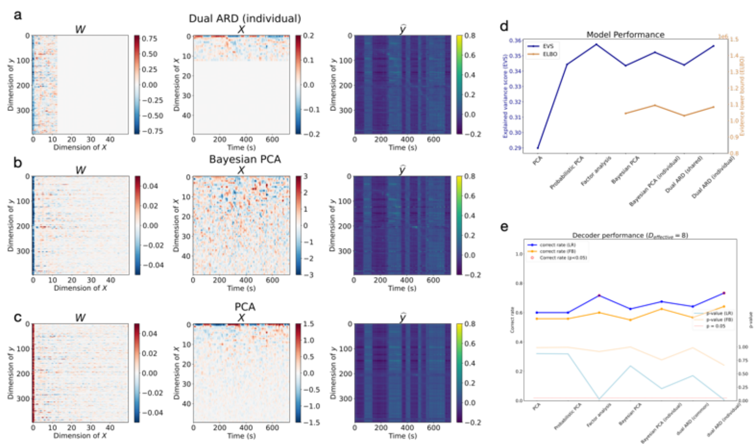


Fig. 4 Model comparisons on two-photon calcium imaging data

In this paper, to encourage sparsity in the latent variables, I proposed a dual ARD formulation that integrates ARD priors for both loading weights and latent variables. This approach automatically and effectively reduces dimensionality while identifying the most relevant features for analysis. We discussed the sparsity properties mathematically and evaluated its performance against existing models using both simulated datasets and real-world calcium imaging data recordings (**Fig.4**). The dual ARD outperformed the previous models, demonstrating its efficiency in reducing dimensionality (**Fig.4a-c**), and the remaining low-dimensional latent variables were sufficient to capture enough information for both decoding and encoding tasks (**Fig.4d-e**).

【Explore the spatial and temporal patterns of neural activities among layers】

1. **Y Li,** K Doya. (2023) "Temporal and spatial activity patterns of neurons across multiple cortical layers in metastates", in preparation.

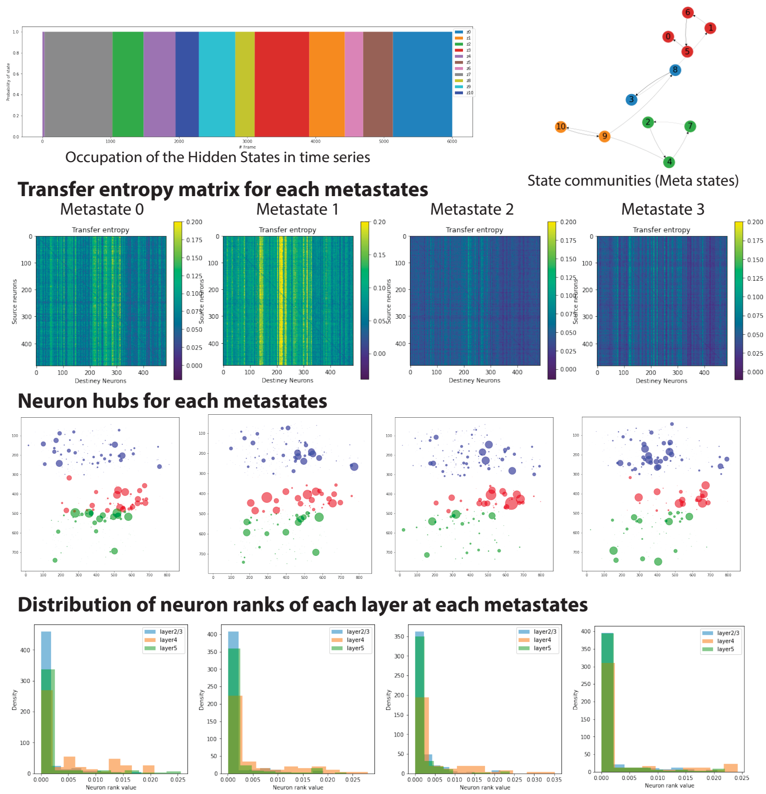


Fig. 5 Metastate-based functional connectivity analysis

We then evaluated the functional connectivity and distribution of neural hubs across different layers. Interestingly, we observed that neural hubs in the middle layer (layer 4) played a prominent role throughout the metastates. This finding suggests that neurons in layer 4 have a crucial function in integrating and transmitting information within the network, contributing significantly to the overall dynamics and functionality of the metastates. We aimed to investigate the spatial and temporal activity patterns among neurons from different layers. We first applied a hidden Markov model (HMM) to the population neural activities to define the temporal structure. In our HMM, we assume that the activities of the population neurons are driven by discrete hidden brain states. Each state is represented by a multivariate Gaussian-mixture model, resulting in a total of 11 states for the 5-minute recording period. Subsequently, we analyzed the transition probability matrix in the HMM model, and we discovered the presence of 4 metastates that exhibited a higher probability of transitioning within the metastate compared to transitioning out of it.

Next, we explored the spatial connections between neurons within each metastate. To measure functional connectivity, we used transfer entropy, which accounts for the non-linear dependency of neurons by calculating the conditional mutual information of their time series. Additionally, we employed the Pagerank algorithm to quantify the neural hubs within each metastate. PageRank assigns scores to neurons based on their connectivity and the importance of their connections.

５．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計8件（うち招待講演　1件／うち国際学会　7件）

１．発表者名 Yuzhe Li
２．発表標題 Investigation of information flow and temporal-spatial organization of neurons across cortical layers from multi-depth two-photon imaging data.
３．学会等名 The 44th Annual Meeting of the Japan Neuroscience Society / The 1st CJK International Meeting.（国際学会）
４．発表年 2021年

１．発表者名 Yuzhe Li
２．発表標題 Investigation of temporal and spatial origination of neural network in sensory cortex
３．学会等名 The 30th Annual Conference of Japanese Neural Network Society（国際学会）
４．発表年 2020年

１．発表者名 Yuzhe Li
２．発表標題 Neuron hubs distributed differently in deep layers and superficial layers in different brain states. The 1st Asia-Pacific Computational and Cognitive Neuroscience Conference
３．学会等名 The 1st Asia-Pacific Computational and Cognitive Neuroscience Conference（国際学会）
４．発表年 2020年

１．発表者名 Yuzhe Li
２．発表標題 Extracting information flow across cortical layers from multi-depth two-photon imaging data
３．学会等名 第63回自動制御連合講演会-講演論文集（国際学会）
４．発表年 2020年

１．発表者名 Yuzhe Li
２．発表標題 Investigation of information flow and temporal-spatial organization of neurons across cortical layers from multi-depth two-photon imaging data
３．学会等名 データ駆動生物学ワークショップ（招待講演）
４．発表年 2020年

１．発表者名 Yuzhe Li
２．発表標題 Investigation of temporal and spatial origination of neural network in sensory cortex
３．学会等名 第43回日本神経科学大会（国際学会）
４．発表年 2020年

１．発表者名 Yuzhe Li
２．発表標題 Dual Bayesian PCA for Factor Analysis on Calcium imaging data
３．学会等名 The 45th Annual Meeting of the Japan Neuroscience Society (Neuron2022)（国際学会）
４．発表年 2022年

１．発表者名 Yuzhe Li
２．発表標題 Neural connectivity among different layers changes at different brain states
３．学会等名 Workshop on Mechanism of Brain and Mind（国際学会）
４．発表年 2023年

〔図書〕　計0件

〔産業財産権〕

〔その他〕

－

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