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研究課題名（和文）Differential dopamine dynamics of DMS and DLS projecting SNc neurons during reversal learning

研究課題名（英文）Differential dopamine dynamics of DMS and DLS projecting SNc neurons during reversal learning

研究代表者
ＲＩＯＳ・ＤＡＶＩＬＡ　ＡＬＡＩＮ・ＡＮＴＯＮＩＯ（RIOS DAVILA, ALAIN ANTONIO）

東京医科歯科大学・大学院医歯学総合研究科・助教

研究者番号：９０８９７９９３

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研究成果の概要（和文）：この研究は、脳が過去の報酬情報をどのように統合して将来の行動に影響を与えるかを理解することを目的とし、ニグロストリアタル経路に焦点を当てました。この経路は、報酬処理に重要なSNcと背側線条体を含みます。ラットに基づいて報酬を得る可能性が高い行動を選ぶタスクを訓練し、SNcと背側線条体の活動をモニタリングしました。その結果、報酬の期待が運動に関与するニューロンの活動を大幅に高めることを発見しました。この発見は、脳が過去の報酬を処理して将来の行動を効果的に導くことを示し、行動が報酬を得るために最適化されていることを示唆しています。これは、運動および意思決定障害の治療法の開発に重要な意味を持ちます。

研究成果の学術的意義や社会的意義
この研究は、脳が過去の報酬情報をどのように統合して将来の行動を導くかを探求しました。結果、報酬の期待が運動に関与するニューロンの活動を大幅に高めることを発見しました。これは、パーキンソン病や依存症など、意思決定や運動に影響を与える疾患の治療法開発において重要です。

脳がどのようにして報酬情報を処理し、行動を最適化するかの基本的なメカニズムについての洞察を提供します。社会的には、これらの知見は神経疾患の治療法改善につながり、影響を受けた人々の生活の質を向上させる可能性があります。報酬の期待が脳活動に与える影響を明らかにすることで、脳機能に関する知識を広げ、医学

研究成果の概要（英文）：We aimed to understand how the brain integrates past reward information to influence future actions, focusing on the nigrostriatal pathway. This pathway involves the SNc and the dorsal striatum, crucial for reward processing. We trained rats to perform a task where they chose one action which is more likely to result in a reward based on recent outcomes. Monitoring the neuronal activity in the SNc and dorsal striatum, we found that reward expectation significantly enhances the activity of neurons involved in movement. Our findings showed that the brain processes past rewards to guide future actions effectively, suggesting behaviors are optimized for obtaining rewards. This has important implications for developing treatments for movement and decision-making disorders. Demonstrating that reward expectations modulate the activity of neurons involved in movement and decision-making, contributing to the understanding of how the brain integrates reward information to influence behavior.

研究分野：Neuroscience

キーワード：Basal ganglia　Striatum　Dopamine　Decision making

研究課題名: Differential dopamine dynamics of DMS and DLS projecting SNc neurons during reversal learning

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所属研究機関名: 東京医科歯科大学

部局名・職名: 大学院医歯学総合研究科　助教

研究者番号: 90897993

研究代表者名: RIOS DAVILA ALAIN ANTONIO

１．研究開始当初の背景

At the beginning of our research, we aimed to address the fundamental question of how the brain integrates information about past rewards to influence future actions. The nigrostriatal pathway, involving the substantia nigra pars compacta (SNc) and the dorsal striatum, plays a crucial role in movement and reward processing. Despite extensive studies, the specific mechanisms by which reward expectations modulate neuronal activity in these regions remained unclear.

Understanding these mechanisms is critical, not only for advancing our basic knowledge of brain function but also for developing effective treatments for neurological disorders such as Parkinson's disease and addiction. These conditions involve impaired decision-making and motor control, making it essential to explore how the brain uses reward information to guide actions. Our research was designed to fill this knowledge gap by investigating the neuronal activity in the SNc and dorsal striatum in response to reward expectations during a decision-making task in rats.

２．研究の目的

The primary objective of our research was to investigate how the brain integrates information about past rewards to influence future actions, specifically focusing on the nigrostriatal pathway. This pathway includes the substantia nigra pars compacta (SNc) and the dorsal striatum, which are essential for movement and reward processing.

We aimed to:

1. Examine how reward expectation affects the movement-related activity of dopaminergic neurons in the SNc and the direct and indirect pathway projection neurons in the dorsal striatum.

2. Understand how these neuronal activities are modulated by recent outcomes in a reward-based decision-making task.

3. Explore the differences in neuronal activity between the medial and lateral regions of the nigrostriatal pathway to uncover any functional segregation.

By achieving these objectives, we sought to provide deeper insights into the fundamental mechanisms of how the brain processes reward information to guide behavior, which could inform the development of treatments for disorders involving impaired motor control and decision-making.

３．研究の方法

To investigate the neuronal mechanisms underlying reward expectation and action selection, we employed a combination of behavioral, optogenetic, and electrophysiological techniques in rats. Here are the key methods used:

1. *Behavioral Task*. We trained rats to perform a reward-based decision-making task under head-fixed conditions. The task involved choosing between two actions, push or pull, with varying probabilities of receiving a reward based on recent outcomes. This

setup allowed us to examine how past rewards influenced future action choices.

2. *Optogenetic Identification*. We used optogenetics to selectively stimulate and identify specific neuron types. By injecting viral vectors expressing light-sensitive proteins into the substantia nigra pars compacta (SNc) and dorsal striatum, we were able to control and monitor the activity of dopaminergic neurons and striatal projection neurons (direct and indirect pathways).

3. *Electrophysiological Recording*. We performed in vivo electrophysiological recordings to measure neuronal activity during the task. Silicon probes were inserted into the SNc and dorsal striatum to record the action potentials of individual neurons. This allowed us to capture the precise timing and patterns of neuronal firing in response to reward expectation and action execution.

4. *Fiber photometry*. We performed in vivo photometry recordings to measure the local release of dopamine in the medial and lateral part of the dorsal striatum, and contrast that local signal with the phasic activity of the dopaminergic neurons.

5. *Data Analysis*. We analyzed the recorded neuronal activity to determine how it correlated with reward expectation and recent outcomes. We used statistical methods to compare the firing rates of neurons during different task phases (e.g., cue presentation, movement execution, reward delivery) and to assess the influence of reward history on neuronal activity.

5. *Histological Verification*. At the end of the experiments, we performed histological analyses to verify the locations of the viral vector injections and electrode placements. Brain tissues were processed and stained to confirm the expression of optogenetic proteins and the accurate targeting of brain regions.

By combining these methods, we were able to investigate the dynamic interactions between reward expectation and neuronal activity in the nigrostriatal pathway, providing insights into the neural mechanisms underlying reward-based action selection.

４．研究成果

Our research yielded several significant findings regarding the role of the nigrostriatal pathway in integrating reward information to influence future actions. Here are the key achievements:

1. *Enhancement of Neuronal Activity by Reward Expectation*. We discovered that the expectation of a reward significantly enhances the movement-related activity of neurons in both the substantia nigra pars compacta (SNc) and the dorsal striatum. This enhancement was observed in dopaminergic neurons as well as in the direct and indirect pathway projection neurons, indicating a widespread effect of reward expectation across the nigrostriatal system.

2. *Modulation of Outcome-Related Activity*. Our findings showed that outcome-related neuronal activity, which reflects whether an action resulted in a reward or not, is modulated by recent reward history. This modulation aligns with classical models of basal ganglia function and reinforcement learning theories, suggesting that the brain uses past reward information to adjust future actions appropriately.

3. *Functional Segregation in the Nigrostriatal Pathway.* We observed differences in neuronal activity between the medial and lateral regions of the nigrostriatal pathway. The medial SNc and dorsal striatum neurons were more involved in encoding motivational value, while the lateral regions were more associated with encoding motivational salience. This functional segregation provides insights into how different parts of the nigrostriatal pathway contribute to goal-directed and habitual behaviors.

4. *Correlation Between Dopamine Release and Reward Rate*. Using fiber photometry to monitor dopamine release in the dorsal striatum, we found that dopamine levels were correlated with the reward rate. Higher dopamine release was associated with higher reward expectation, supporting the role of dopamine in encoding reward prediction errors

and guiding behavior based on recent outcomes.

5. *Implications for Neurological Disorders*. Our research has important implications for understanding and treating neurological disorders such as Parkinson's disease and addiction. By revealing how reward expectation influences neuronal activity, we provide a foundation for developing therapies that target these mechanisms to improve decision-making and motor control in affected individuals.

Overall, our study advances the understanding of how the brain integrates reward information to influence behavior, highlighting the critical role of the nigrostriatal pathway in this process. These findings contribute to the broader field of neuroscience and have potential applications in medical research and treatment development.

５．主な発表論文等

〔雑誌論文〕　計1件（うち査読付論文　1件／うち国際共著　1件／うちオープンアクセス　1件）

１．著者名 Rios Alain、Nonomura Satoshi、Kato Shigeki、Yoshida Junichi、Matsushita Natsuki、Nambu Atsushi、Takada Masahiko、Hira Riichiro、Kobayashi Kazuto、Sakai Yutaka、Kimura Minoru、Isomura Yoshikazu	４．巻 6
２．論文標題 Reward expectation enhances action-related activity of nigral dopaminergic and two striatal output pathways	５．発行年 2023年
３．雑誌名 Communications Biology	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/s42003-023-05288-x	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

〔学会発表〕　計1件（うち招待講演　0件／うち国際学会　1件）

１．発表者名 Rios Alain
２．発表標題 Dynamic and pathway-specific signaling in the dorsomedial striatum and dopamine neurons during behavioral adaptation
３．学会等名 The 45th Annual Meeting of the Japan Neuroscience Society（国際学会）
４．発表年 2022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 （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