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研究課題名（和文）Neural mechanisms underlying the motivation to overcome disappointment

研究課題名（英文）Neural mechanisms underlying the motivation to overcome disappointment

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交付決定額（研究期間全体）：（直接経費）　　3,200,000円

研究成果の概要（和文）：自然環境において採餌や求愛は生存に不可欠であるが、すぐに成功せず、失望につながることも多い。この失望を乗り越えるための動機づけの神経機構は不明である。本研究では、従来、失望を受動的に受け入れるのに重要であると考えられていた報酬系の要素である中脳ドーパミン神経細胞の活動を明らかにすることを目的とした。この動機づけを強く誘導するラット行動モデルにおいて、腹側被蓋野に存在するドーパミン細胞の一部の集団が、予期せぬ報酬の省略に反応して活動を増加させることを発見した。また、カルシウムイメージング技術を用いることで、多くのドーパミンニューロンのカルシウム活性を同時に測定できた。

研究成果の学術的意義や社会的意義
We developed a behavioral task that enabled us to quantitatively measure the ability to adaptively switch toward the next opportunity to obtain a probabilistic reward after the lack of reward. The study provides a better understanding of neuropsychiatric disorders such as depression or “hikikomori”.

研究成果の概要（英文）：In the natural environment, adapting to variations in foraging and courtship, which are highly dynamic and often not immediately successful, are critical for survival. However, the neural mechanisms underlying the motivation to overcome disappointment are unknown. This study aimed to reveal a new type of activity of midbrain dopamine neurons (DN), the most important element of the brain reward system that was traditionally thought to be critical for passive acceptance of disappointment. In a novel rat behavioral model that strongly induces such motivation, we found that a subpopulation of DN in the ventral tegmental area increased activity in response to unexpected omission of reward. By employing calcium imaging technique at single-cell resolution, it was possible to measure the calcium activity of many dopamine neurons simultaneously. Overall, this study clarified the central neural mechanisms responsible for overcoming the omission of reward.

研究分野：Neuroscience

キーワード：Dopamine　Motivation　Imaging

１．研究開始当初の背景

Humans naturally set high goals in their work and study. Even in the event of “disappointment” when those goals are not achieved, increasing motivation to overcome it, rather than accepting and “giving up”, will lead to future success. If one lacks this ability, he/she will be socially unsuccessful, and will lead to problems such as depression or “hikikomori” after experiencing a setback. In animal behavior, overcoming disappointments in foraging and courtship, which are often not immediately successful, are critical for survival. Despite these universal and important functions, the neural mechanisms underlying such motivation has not been addressed. This is because, traditionally, an animal behavior model that mimics such motivation has not been linked to a technique for monitoring neural activity in millisecond-order.

For this purpose, we introduced a novel rat behavioral paradigm in combination with *in vivo* calcium imaging of dopamine neurons (DN) at single-cell resolution, in order to address a specific question “what is the central neural mechanism responsible for the motivation to overcome disappointment?”

２．研究の目的

The goal of this study was to clarify the central neural mechanisms responsible for overcoming the omission of reward, focusing on the nature of the activity of the new type of DN which show increased activity in response to reward omission.

(1) How are these two types of DN generated through the learning process?

(2) To what attributes associated with the unexpected reward omission do the DN exhibit their activity

３．研究の方法

To address these questions, we developed a behavioral task that strongly induces the motivation to overcome unexpected reward omission, in head-fixed rats (Figure 1). In this task, a rat receives an odor stimulus after pushing a lever integrated with a reward presentation port, and then pulls the lever to obtain a probabilistic reward. After conditioning of each of three different odors with reward probabilities 100%, 50%, and 0% [Fig. 1, order of actions (1) to (2)], the latency to pull the lever after stimulus presentation [Fig. 1, (3)] was relatively longer when expecting a 50% reward probability than a 100% reward (the longest when 0% was expected). This behavior is explained by the assumption that rats were motivated when disappointments were induced (Esber & Haselgrove, 2011).

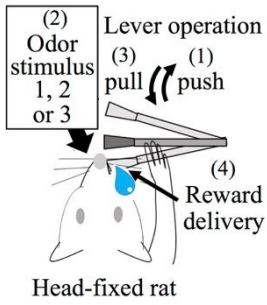

Fig.1 Behavioral task used in this study

Regarding *in vivo* imaging, a genetically-encoded Ca^{2+} indicator, GCaMP6f was expressed specifically in DN by the injection of a viral vector into the VTA of DAT-iCre rats. A gradient index (GRIN) lens was implanted directly above the VTA, and the changes in fluorescence intensity as a result of changes in the intracellular Ca^{2+} concentration

was measured with a miniature fluorescence microscope (Inscopix, USA).

Our results showed that a subpopulation of DN increased their activity in response to unexpected reward omission (ie. disappointment). Specifically, their activity increased at the timing of several hundred milliseconds in response to 50% no-reward, following the presentation of odor 2. In contrast, there was another type of DN (type 1 "conventional" type) which decreased their activity in the case of reward omission, in agreement with the reward prediction error hypothesis (Schultz et al., 1997).

4. 研究成果

In brief, we developed a behavioural paradigm that enabled us to quantitatively measure the ability to actively and adaptively switch toward the next opportunity to obtain a probabilistic reward after the lack of reward. Results of imaging DN in the anterior part of lateral VTA revealed that about half of Type 2 neurons showed increased responses to unexpected reward omission and decreased responses to unexpected reward. The responses of type 2 neurons were consistently slower than the RPE-type DA responses. Measurements of the DA levels showed that the trial-by-trial correlation between the type 2 dopamine response in dorsal part of anterior nucleus accumbens and behavioral switch toward the next reward became evident upon extinction and reintroduction of 50% reward that required new learning to adjust behavior to cope with unexpected no-reward actively and efficiently. Type 2 DN primarily signal error to actively cope with reward omission and provide a mechanism to switch toward future reward.

Through this study, we have clarified the nature of the activity of new DN based on the degree of learning and their relationship with behavior. In addition, novel dopamine cells may work in complement to the conventional dopamine neurons, and investigating the relationship between these two types of DN is an important key to clarifying their fundamental. Also, this study will create new possibilities including the development of new therapies targeting the new DN, for a better understanding and diagnosis of neuropsychiatric disorders such as depression or "hikikomori" and addictions such as gambling in which dopamine function is deeply involved. The work has been published in Science Advances (Ishino et al., 2023).

References

(1) Esber GR, Haselgrove M. Reconciling the influence of predictiveness and uncertainty on stimulus salience: A model of attention in associative learning. (2011) Proc. Biol. Sci., 278: 2553-2561

(2) Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. (1997) Science, 275: 1593-1599

(3) Ishino S, Kamada T, Sarpong GA, Kitano J, Tsukasa R, Mukohira H, Sun F, Li Y, Kobayashi K, Naoki H, Oishi N, Ogawa M. Dopamine error signal to actively cope with lack of expected reward. (2023) Science Advances, 9 (10), eade5420. DOI: 10.1126/sciadv.ade5420

５．主な発表論文等

〔雑誌論文〕　計1件（うち査読付論文　0件／うち国際共著　0件／うちオープンアクセス　1件）

１．著者名 Ishino S, Kamada T, Sarpong GA, Kitano J, Tsukasa R, Mukohira H, Sun F, Li Y, Kobayashi K, Naoki H, Oishi N, Ogawa M	４．巻 9
２．論文標題 Dopamine error signal to actively cope with lack of expected reward	５．発行年 2023年
３．雑誌名 Science Advances	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） 10.1126/sciadv.ade5420	査読の有無 無
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 －

〔学会発表〕　計4件（うち招待講演　0件／うち国際学会　4件）

１．発表者名 Seiya Ishino, Taisuke Kamada, Sarpong Gideon, Reo Tsukasa, Hisa Mukohira, Kenta Kobayashi, Naoki Honda, Naoya Oishi, Masaaki Ogawa
２．発表標題 Midbrain dopamine neurons signal opposing reward prediction errors to continue reward pursuit
３．学会等名 The 45th Annual Meeting of the Japan Neuroscience Society（国際学会）
４．発表年 2022年

１．発表者名 S. Ishino, T. Kamada, G. A. Sarpong, J. Kitano, R. Tsukasa, H. Mukohira, F. Sun, Y. Li, K. Kobayashi, N. Honda, N. Oishi, M. Ogawa
２．発表標題 A dopamine circuit for active switching toward the pursuit of future reward
３．学会等名 Annual Meeting of the Society for Neuroscience (SfN), USA（国際学会）
４．発表年 2022年

１．発表者名 Seiya Ishino, Gideon Sarpong, Taisuke Kamada, Hisa Mukohira, Reo Tsukasa, Yulong Li, Naoki Honda, Kenta Kobayashi, Naoki Oishi & Masaaki Ogawa
２．発表標題 A potential role of mesolimbic dopamine system in overcoming omission of expected reward
３．学会等名 The 44th Annual Meeting of the Japan Neuroscience Society（国際学会）
４．発表年 2021年

１．発表者名 Seiya Ishino, Gideon Sarpong, Taisuke Kamada, Hisa Mukohira, Reo Tsukasa, Masaaki Ogawa
２．発表標題 A potential role of dopamine neurons in reinforcing behavior for uncertain reward
３．学会等名 The 43rd annual meeting of the Japan Neurosience Society（国際学会）
４．発表年 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 （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