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研究課題名（和文）Neural mechanisms underlying behavioral flexibility

研究課題名（英文）Neural mechanisms underlying behavioral flexibility

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研究成果の概要（和文）：日常生活では、新しい状況や環境の変化に柔軟に適応することが求められます。いくつかの研究では、線条体が逆転学習などの柔軟な行動をサポートしていることが示唆されています。本研究の目的は、強化条件の変化に対するアセチルコリン（ACh）の活動性に焦点を当て、行動の柔軟性を支配する線条体のメカニズムを明らかにすることです。このためにVR行動タスクと線条体のACh動態の2光子イメージングを使用した結果、強化条件が反転した後に否定的な結果の符号化がAChの一過性増加と関連していることが明らかになりました。この結果は、AChの基本機能と、持続的・反復的行動を特徴とする神経精神障害の理解を修正するものです

研究成果の学術的意義や社会的意義
By enhancing our understanding of cognitive processes underlying adaptive behavior, the results of this study also holds potential implications for fields such as psychology, neurology, and artificial intelligence, contributing to the broader conversation about adaptability in complex systems.

研究成果の概要（英文）：Daily living often requires individuals to flexibly adapt to new changes in the environment. Several studies have suggested that the striatum is part of the neural network that supports flexible behaviors such as reversal learning. The goal of this study was to clarify the striatal mechanisms governing reversal, focusing on nature of the activity of acetylcholine (ACh) in response to changes in reinforcement contingencies. To this end, I employed a virtual reality behavioral task combined with in vivo 2-photon imaging of ACh dynamics. Following the reversal, it was uncovered that the encoding of negative outcomes was associated with increases in ACh transients with distinct spatiotemporal dynamics, suggesting that violations of previously learned contingencies triggered ACh release in the striatum. Overall, results of this study will revise the current understanding of the fundamental roles of ACh and the pathology of neuropsychiatric disorders characterized by perseverative behaviors.

研究分野：Neuroscience (Motivation and decision-making)

キーワード：Acetylcholine　Striatum　Reversal learning

１．研究開始当初の背景

A hallmark of flexible and intelligent behavior is the ability to select appropriate actions in a dynamic environment when conditions demand a shift in response. Several studies have suggested that the striatum is part of a larger neural network that supports flexible adaptations. In particular, findings in humans and experimental animals have highlighted the dorsomedial striatum (DMS) as a nodal part of the brain network for certain forms of behavioral flexibility such as reversal learning (Okada et al., 2014). Studies from our lab and others have established that lesioning of striatal cholinergic interneurons, and pharmacological manipulation of acetylcholine (ACh) release impair flexible behaviors (Bradfield et al., 2013; Aoki et al., 2015). However, the cholinergic mechanisms for detecting an unexpected outcome and altering the responses associated with that outcome have not been clarified. To address this, I developed a rule-switching mouse behavioral task by employing a virtual reality (VR) behavioral system in combination with *in vivo* 2-photon imaging of ACh dynamics.

２．研究の目的

This study aimed to clarify the striatal mechanisms governing behavioral flexibility, focusing on the nature of the activity of acetylcholine in response to changes in reinforcement contingencies. For this purpose, I focused on two main goals:
(1) To design and establish a virtual reality response learning task (VR-RL) for mice
(2) To image ACh spatiotemporal activity via two-photon imaging as mice were engaged in a virtual reality response learning (VR-RL) task.

３．研究の方法

The first goal was to confirm the efficiency of the virtual reality (VR) system for response learning in awake, head-fixed mice on an air-supported styrofoam ball. The VR-RL task comprised acquisition and reversal phases lasting 12-15 days. Mice of both sexes were trained on a self-initiated adaptive decision-making task to navigate a two-dimensional linear corridor in a VR environment (320 cm long x 10 cm wide), and their performance was monitored as they learned to navigate in a Y-maze requiring choice of the left or right arm for reward. After sufficient learning, the rules of the task were switched and mice were required to enter the side of the maze opposite to the previously reinforced arm, similar to previous protocols used in our lab (Aoki et al, *J. Neurosci*, 2015). To image the dynamics of ACh profiles in relation to behavioral flexibility, I used ultrafast biosensors measuring ACh dynamics at subcellular resolution. Offering ultrafast temporal resolution, this recently developed fluorescent indicator (iAChSnFR) was expressed specifically in the dorsal striatum by the injection of a viral vector. A gradient index (GRIN) lens probe was implanted directly above the injection site, and the changes in fluorescence intensity was then measured (3-4 weeks later) with a 2-photon microscope.

４．研究成果

In brief, I have successfully developed a closed-loop virtual reality-response learning task with rule switches to examine flexible responding, when reward contingencies are reversed. To assess the effects of learning across days, training sessions were divided into two stages: ‘‘early’’ and ‘‘late’’ sessions per animal. Trained mice adapted their choice behavior across sessions. Selection of the rewarded arm of the maze increased with learning, during which the proportion of correct choices increased across training days. Thus, consistent with expectations, mice showed a higher tendency to select the maze arm associated with reward (Fig. 1, Acquisition). When mice reached an acquisition criterion of 80% correct performance, behavioral switching was evaluated through a reversal learning procedure where the positions of the correct and incorrect arms were switched. As expected, mice gradually adapted their choice behavior and motivation in response to the reversed contingency (Fig. 1, Reversal).

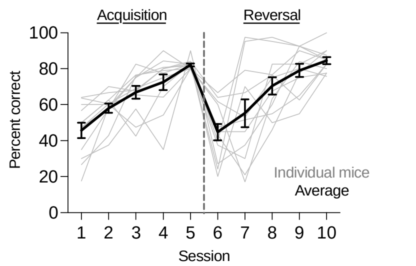

Fig. 1 Data showing mice choice performance in the VR-RL task, n = 12, *unpublished*

To characterize ACh activity, I have successfully combined the VR-RL task with 2-photon imaging of ACh release. The results show that ACh transients during task acquisition convey information about upcoming decision-related variables including reward expectation and trial outcomes. Following reversal of reinforcement contingencies, it was uncovered that ACh responses increased in response to no-reward outcomes and closely tracked reversal learning trajectories. These results suggest that distinct spatiotemporal transients of DS ACh in the encoding of choice-outcome associations mediate behavioral adaptations when previously learned contingencies are violated (manuscript in preparation).

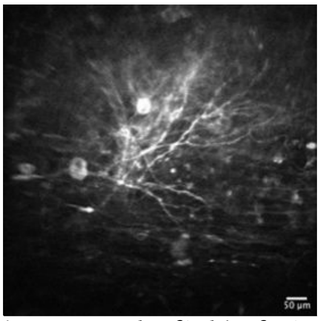

Fig. 2 Example field of view showing iAChSnFR expression in the DMS, *unpublished*

References

(1) Okada, K. et al. Enhanced flexibility of place discrimination learning by targeting striatal cholinergic interneurons. Nat. Commun. 5, 3778 (2014).

(2) Aoki S, Liu AW, Akamine Y, Zucca A, Zucca S, Wickens JR. Cholinergic interneurons in the rat striatum modulate substitution of habits. (2018), Eur J Neurosci 47:1194-1205. doi:10.1111/ejn.13820 pmid:29359362

(3) Brown HD, Baker PM, Ragozzino ME. The parafascicular thalamic nucleus concomitantly influences behavioral flexibility and dorsomedial striatal acetylcholine output in rats. (2010), J Neurosci 30:14390-14398. doi:10.1523/JNEUROSCI.2167-10.2010 pmid:20980596

(4) Bradfield LA, Bertran-Gonzalez J, Chieng B, Balleine BW. The thalamostriatal pathway and cholinergic control of goal-directed action: interlacing new with existing learning in the striatum. (2013), Neuron 79:153-166. doi:10.1016/j.neuron.2013.04.039

5．主な発表論文等

〔雑誌論文〕　計0件

〔学会発表〕　計3件（うち招待講演　1件／うち国際学会　2件）

1．発表者名 Gideon Anokye Sarpong, Rachel Pass, Kavinda Liyanagama, Kiyoto Kurima, Jeffery Wickens	
2．発表標題 Acetylcholine signaling in the dorsomedial striatum is associated with behavioral flexibility in mice learning a virtual reality response task	
3．学会等名 Annual meeting of the Society for Neuroscience (SfN)（国際学会）	
4．発表年 2023年	

1．発表者名 Gideon Anokye Sarpong, Kavinda Liyanagama, Kiyoto Kurima, Jeffery Wickens	
2．発表標題 Acetylcholine activity in the dorsomedial striatum mediates reversal learning in mice learning a virtual reality response task	
3．学会等名 Junior Scientist Workshop on Mechanistic Cognitive Neuroscience, HHMI Janelia Research Campus, USA（国際学会）	
4．発表年 2023年	

1．発表者名 Gideon Anokye Sarpong	
2．発表標題 Dopamine and acetylcholine signaling in reinforcement learning and adaptive behaviors	
3．学会等名 Invited talk, Tokyo Medical and Dental University（招待講演）	
4．発表年 2023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