Dopamine stimulation of the septum enhances exercise efficiency during complicated treadmill running in mice

Tetsuya Shiuchi1 · Takuya Masuda1,2 · Noriyuki Shimizu1 · Sachiko Chikahisa1 · Hiroyoshi Séi1

Received: 29 April 2019 / Accepted: 18 October 2019 / Published online: 29 October 2019
© The Physiological Society of Japan and Springer Japan KK, part of Springer Nature 2019

Abstract
We aimed to identify the neurotransmitters and brain regions involved in exercise efficiency in mice during continuous complicated exercises. Male C57BL/6J mice practiced treadmill running with intermittent obstacles on a treadmill for 8 days. Oxygen uptake (VO2) during treadmill running was measured as exercise efficiency. After obstacle exercise training, the VO2 measured during treadmill running with obstacles decreased significantly. Obstacle exercise-induced c-Fos expressions and dopamine turnover (DOPAC/dopamine) in the septum after obstacle exercise training were significantly higher than that before training. The dopamine turnover was correlated with exercise efficiency on the 3rd day after exercise training. Furthermore, the training effect on exercise efficiency was significantly decreased by injection of dopamine receptor antagonists into the septum and was associated with decreased c-Fos expressions in the septum and hippocampus of the mice. These results suggest that dopaminergic function in the septum is involved in exercise efficiency during continuous complicated exercises.

Keywords Exercise efficiency · Septum · Dopamine turnover · Exercise training · Oxygen uptake

Introduction
Exercise efficiency is defined as high performance with low energy expenditure [1–3] and is enhanced by relevant exercise training. Higher exercise efficiency during certain intensity movements increases enjoyment during exercise and promotes motivation for further spontaneous exercise, which is needed to prevent the development of locomotive syndrome or sarcopenia. Exercise efficiency involves adaptations of the skeletal muscle metabolism, respiratory–cardiovascular system, hemodynamics and motor skills [4–16].

Motor learning is involved in improvements in exercise techniques, which are possible after training for a certain period of time. Motor skills contribute to the ability to perform complicated exercises and are adapted earlier than other parameters [17], such as hypertrophy, hormonal sensitivity, and gene expression. Procedural memory also contributes to improvements in exercise techniques. The basal ganglia, cerebellum, and motor cortex have central roles in procedural memory [18]. Moreover, disorders of the basal ganglia in patients with Parkinson’s disease and Huntington’s disease hamper the ability to learn motor techniques [19]. Biomechanical mechanisms in motor skills, including somatosensory recognition both in “closed skills” and “open skills”, were systematically reviewed in previous literature [20–22]. However, biochemical mechanisms in the brain for improvement of combined (closed and open skills) continuous exercises have not been understood. Biochemical neuromodulators such as dopamine and serotonin have physiological roles in physical behavior, arousal, movement, and motivation. Clarifying the brain mechanisms involved in complicated continuous exercises will provide valuable information for sports performance, rehabilitation, and movement therapy.

Although several studies have demonstrated that some exercises activated various neurons in the brains of rodents
[23–25], no reports have indicated biochemical and physiological associations between motor skills and exercise efficiency. Therefore, the aim of the present study was to identify responsive biochemical alterations and brain regions involved in exercise efficiency during continuous complicated exercises in mice. In this study, we creatively developed a continuous complicated exercise model for mice, using a treadmill with obstacles. Moreover, we regarded oxygen consumption during continuous complicated exercise as a marker of exercise efficiency in our model.

**Methods**

**Animals**

All experiments were performed using 8-week-old male C57BL/6J mice (Slc Inc., Shizuoka, Japan). They were housed individually in plastic cages at 24 ± 1 °C with a 12-hour light/12-hour dark cycle (lights on from 0800 to 2000) and were freely fed a laboratory diet (Oriental Yeast, Tokyo, Japan) and water. This study was performed with approval from the Animal Study Committee of Tokushima University, and all regulations of our institution involving proper animal care and handling were followed during our experiments.

**Measurement of oxygen uptake and treadmill running with intermittent obstacles**

We used the Mousebelt-2000 (Arco System Inc., Chiba, Japan) as the belt-type treadmill chamber for mice. Oxygen uptake (VO₂) during treadmill running (15 m/min) was measured with the ARCO-2000 mass spectrometer (Arco System Inc., Chiba, Japan) to determine exercise efficiency, which defined the same exercise performance with lower oxygen cost as an efficient movement. Before and after obstacle exercising training, VO₂ during treadmill running (15 m/min) was measured to determine exercise efficiency; the same exercise performance with lower oxygen cost was defined as an efficient movement.

One trial took a total of 14 min (0 m/min for the first 2 min, 10 m/min for the next 2 min, 15 m/min for the next 10 min), and the stimulation electrode was constant at 0.7 mA. All treadmill running experiments were performed between 1300 and 1730, and we measured VO₂ on the first and last trial day. During the 1st day, mice ran on the treadmill without intermittent obstacles; the next day, they ran with intermittent obstacles. Three sponges were shaped into a regular triangular prism (length, 10 mm; height, 50 mm), and they were arranged at random intervals on the belt chamber as the intermittent obstacles (Fig. 1a). For the next 10 days, mice performed treadmill running with intermittent obstacles as motor training once per day; however, they had 2 rest days during the middle of the 10 days. During the last trial day, they performed treadmill running with intermittent obstacles. Some mice did not undergo exercise training and were part of the control group.

**Immunohistochemistry**

We examined the brain region where the neural activity changed before and after exercise training. Immunostaining was performed to assess the differences in c-Fos expressions in several brain regions of the mice before and after obstacle exercise training. Ninety minutes after the last trial, the mice were anesthetized with a cocktail of ketamine (100 mg/kg; Daiichi-Sankyo, Tokyo, Japan) and xylazine (25 mg/kg; Sigma, St. Louis, MO, USA) and transcardially perfused with isotonic phosphate-buffered saline (PBS). This was followed by fixation with 4% paraformaldehyde in 0.1 M phosphate buffer before brain excision. The whole brain was removed and post-fixed for 24 h. For the following 4 days, the brains were soaked in a 20% sucrose solution. The tissue was embedded in the OCT compound (Sakura Fine-Technical, Tokyo, Japan), immediately frozen, and stored at −80 °C until further analysis. Then, serial 30-μm cryosections were prepared using a cryostat (Leica CM1850, Wetzlar, Germany).

Sections received a 1-h quenching treatment at 3% H₂O₂ in methanol. For diaminobenzidine (DAB) antibody staining of c-Fos, sections were exposed for 2 h at 25 °C to 3% normal donkey serum and incubated for 3 days at 4 °C with rabbit antibodies to c-Fos (1:1000 dilution; Cell Signaling Technology, MA, USA). After washing the sections with PBS, immune complexes were detected using the Vectastain ABC HRP kit (peroxidase, rabbit IgG; Vector Laboratories, Burlingame, CA, USA). Sections were colored using a peroxidase stain DAB kit (Nacalaitesque, Kyoto, Japan) and metal enhancer for DAB staining (Nacalaitesque). Sections were finally examined with a microscope (Leica DM4000B Wetzlar, Germany or KEYENCE BZ-X700, Osaka, Japan). The c-Fos expression on one side of each brain region was manually counted in 700×350-pixel areas for inconsecutive three sections.

**Monoamine concentration in the brain**

The whole brain was removed, and 1-mm-thick coronal sections of the fresh brain were dissected from six regions (striatum, motor cortex, hypothalamus, hippocampus, septum, and cerebellum), frozen rapidly in liquid nitrogen, and stored at −80 °C. Monoamine levels (dopamine [DA], 3,4-dihydroxyphenyl acetic acid [DOPAC], serotonin [5-HT], and 5-hydroxy indoleacetic acid [5-HIAA]) were quantified by high-performance liquid chromatography (HPLC) according...
to previously published methods with slight modifications [26]. DOPAC/DA and 5-HIAA/5-HT ratios were used to estimate the metabolic ratio.

Pharmacological treatments and injection procedure

Mice were anesthetized by intraperitoneal (ip) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg), and a double-walled stainless steel cannula (Plastics One, Roanoke, VA, USA) was stereotaxically implanted into the septum bilaterally (AP + 0.5 mm, L ± 0.5 mm, and H + 3 mm from the bregma) according to an atlas [27] (Supplemental Fig. 1). We used SCH 23,390 hydrochloride (Abcam PLC, Cambridge, UK) as a dopamine D1 receptor antagonist (D1 antagonist) and (S)-(-)-Sulpiride (Abcam PLC) as a dopamine D2 receptor antagonist (D2 antagonist). We handled mice for 10 min per day during the recovery period (10 days)
after cannula implantation. After recovery, exercise training with obstacles was performed using the same process as described above, and pharmacological administration was performed only once before the last trial on the final day. Each drug was dissolved in 10% DMSO in Ringer’s solution and adjusted to 100 mM. One to two minutes before the last trial, mice were administered a 0.2-μL bilateral LS injection of vehicle (10% DMSO in Ringer’s solution), SCH 23,390 hydrochloride, or (S)-(-)-Sulpiride.

Statistical analyses

The results were expressed as mean ± standard error of the mean (SE). Data from the two groups were analyzed using the Student’s paired or unpaired t test. Data from more than two groups were analyzed using the one-way analysis of variance, followed by the Bonferroni test. p values <0.05 were considered statistically significant.

Results

Exercise efficiency before and after treadmill training with intermittent obstacles

Before and after obstacles exercising training, VO2 during treadmill running (15 m/min) was measured as exercise efficiency, wherein the same exercise performance with lower oxygen cost was defined as an efficient movement. First, we examined whether the treadmill with intermittent obstacles was difficult for the mice. As a result, VO2 during obstacle treadmill running was significantly higher than that without obstacles (Fig. 1b). After the training period, VO2 during obstacle treadmill running decreased (Fig. 1b, c), while treadmill running training without obstacle did not lead to decrease in VO2 during obstacle treadmill running (Fig. 1d). VO2 at rest before and after training did not change (Fig. 1e). These results demonstrated that obstacle treadmill running created difficulty for the mice, and those 8 days of training improved exercise efficiency.

Changes in c-Fos expression of each brain region before and after training

The immunostaining for c-Fos expressions in septum, striatum and motor cortex of the mice before and after obstacle exercise training is shown in Fig. 2a, c, e, respectively. In the septum and striatum, the c-Fos expression of mice that underwent training was significantly higher than that of mice that did not undergo training (Fig. 2f). There were no differences in other brain regions (data not shown).

Dopamine and serotonin turnover in each brain region before and after training

To identify which monoamine was involved in changes in neural activity, we next quantified monoamine and its metabolites in the brain regions that had significant differences and the other regions, including the hypothalamus, hippocampus, and cerebellum, immediately after treadmill running using HPLC. Mice that underwent training [training (+)] showed significantly higher dopamine turnover (DOPAC/DA) in the septum than training (−) mice, but there were no significant differences in the motor cortex or striatum (Fig. 3a–f). There were no significant differences involved in serotonin turnover (5-HIAA/5-HT) for any regions (Fig. 3a–f). These results indicated that dopamine action in the septum increased after obstacle treadmill running training in mice.

Relationship of dopamine turnover in brain and exercise efficiency on the 3rd day of training

Alteration of dopamine turnover in the septum and VO2 during obstacle treadmill running was completed at 8 days of training. In contrast, these training effects had not been completed but we observed individual difference on the 3rd day of training. Therefore, we examined whether dopamine turnover in the septum was related to exercise efficiency on the 3rd day of training by checking exercise efficiency (VO2 during complicated treadmill running). We measured dopamine turnover in the septum of the mice immediately after complicated treadmill running on the 3rd day of the training period in blocking groups. We observed that there was a significant inverse correlation between VO2 during obstacle treadmill running and dopamine turnover in the septum but not in the motor cortex, hippocampus or striatum (Fig. 4a–d).

Change in exercise efficiency after administration of a dopamine receptor antagonist to the septum

Finally, we investigated whether increased dopamine turnover in the septum was involved in improving exercise efficiency. A dopamine receptor antagonist was administered to the septum bilaterally before the final trial. The D1 antagonist and D2 antagonist groups showed significantly higher VO2 than the vehicle group (F_{2,21} = 6.421, p = 0.0067; Fig. 5a). This effect was not observed in no obstacle treadmill running even after training (F_{2,21} = 0.093, p = 0.9118; Fig. 5a). Additionally, c-Fos expression in the septum (F_{2,12} = 16.751, p = 0.0003; Fig. 5b, c) and in the hippocampus-CA3 in
the D1 antagonist group ($F_{2,12} = 8.319, p = 0.0054$; Fig. 5d, e) significantly decreased compared to that in the vehicle group. There were no significant differences between the D2 antagonist group and vehicle group in the septum or hippocampus-CA3. No differences were observed in the c-Fos expression in other hippocampal regions (CA1, CA2, and dentate gyrus) with or without the administration of dopamine receptor antagonist (Supplemental Fig. 2).

**Discussion**

We hypothesized that dynamic biochemical stimulation at critical brain sites was required for continuous complicated exercises. Our results indicated that the dopaminergic function in the septum is involved in exercise efficiency during continuous complicated exercises. In this study, we used VO$_2$ as an indicator of exercise efficiency. VO$_2$ during exercise is generally used as an indicator of energy expenditure,
and is dependent on energy demand, nutritional status, and motor skills [28, 29]. Since VO$_2$ before and after training were measured at the same exercise intensity (15 m/min) and obstacle frequency, energy demand for the work load during treadmill running would be identical. Motor skill proficiency leads to efficient exercise performance without excess energy expenditure. We observed significantly lower VO$_2$ during the obstacle treadmill exercise after obstacle treadmill training, suggesting that exercise efficiency was increased with improved motor skills to avoid obstacles on the treadmill. VO$_2$ of the mice at rest did not differ by training, although we did not determine the metabolic adaptation in the contracting skeletal muscle, which was responsible for energy expenditure during exercise. In addition, a previous report demonstrated that neural factors accounted for the larger proportion of the initial strength increments with resistance training [17]. Since exercise training was performed for a short period (8 days) in this experiment, it is reasonable that motor skills, but not metabolic or respiratory–cardiovascular functions, were necessary for alterations in exercise efficiency.

The results of this study suggested that the dopaminergic function in the septum is involved in exercise efficiency. Injection of dopamine receptor antagonists into the septum did not change VO$_2$ during treadmill running without obstacle (Fig. 5a), suggesting that dopamine activity in the septum might not affect energy cost during running exercise. The septum is located inside the lateral ventricle in front of the anterior commissure and it communicates with the hippocampus and hypothalamus. The lateral septum is thought to be critical for processing emotional information and for modulating behavioral responses to stress [30, 31]; however, there are few reports describing the association between exercise and the septum. Regarding the relationship between the septum and dopamine, it has been reported that early social stress affects the dopamine D3 receptor of...
the lateral septum and is a risk factor for social dysfunction [32]. In addition, it has been reported that activation of glutamate and the gamma-aminobutyric acid (GABA) system in the septum during treadmill running and wheel running increases brain wave θ power in the hippocampus [33, 34]. However, the effect of the dopamine system on motor function in the septum has not yet been clarified. When we injected a dopamine receptor antagonist into the bilateral septum, VO2 did not change during simple treadmill running (without obstacles) even after training (Fig. 5a), suggesting that dopamine stimulation in the septum was not involved in energy expenditure during exercise.

In addition to the septum, significant differences in c-Fos expression were confirmed in the striatum and motor cortex after training. The motor cortex comprises a “motion loop” that is involved in motor control with strong consciousness during exercise [35]. We considered that the decrease in c-Fos expression in the motor cortex after training compared with before training was due to motor control stabilization attributable to training. On the other hand, it was clinically reported that exercise has a beneficial effect on reactivity and movement behavior in Parkinson’s disease following administration of levodopa, a dopamine precursor, indicating that augmented synthesis and release of endogenous dopamine occurred in some brain regions [36]. The striatum is involved in motor learning and the formation of habitual movement patterns, i.e., procedural memory. Moreover, motor skills are mediated by the dopaminergic system in the striatum; the deletion is involved in the development of the Parkinson’s disease. However, this was not a concern in this study because dopamine turnover in the striatum was not altered.

In this experiment, administration of the dopamine D1 receptor antagonist to the bilateral septum decreased c-Fos expression in the CA3 area of the hippocampus with increased VO2, suggesting that dopamine stimulation in the septum is involved in exercise efficiency through the CA3 area of the hippocampus. Exercise increased brain-derived neurotrophic factors in CA3 neurons in the hippocampus [37–40]. Dopaminergic input to the septum has been implicated in modulating the pathway from the septum to the hippocampus and involved in learning spatial recognition ability. This pathway might be required to hurdle continuing obstacles in complicated running. Dopaminergic neuron is in the ventral tegmental area (VTA) and substantia nigra. The lateral septum receives dopaminergic projections primarily from the VTA [41]. This dopaminergic input has been implicated in modulating the pathway from the septum to the hippocampus [42–44]. However, in this study, we were
unable to identify the dopaminergic neurons from the VTA or substantia nigra involved in exercise efficiency or verify which molecule stimulated the dopaminergic neurons projecting into the septum.

This study has some limitations. First, we could not clarify the significance of increase in c-Fos expression in the striatum after training. Dopaminergic system in the striatum is involved in motor skill and reward similar with septum although dopamine turnover was not altered in striatum. Second, we also could not uncover the role of dopamine D2 receptor in septum during obstacle treadmill exercise though the injection of D2 receptor antagonist into the septum significantly decreased exercise efficiency. Further investigation is needed.

These results provide valuable information for sports performance, rehabilitation, and movement therapy. However, our findings apply only to improving exercise efficiency during forced complicated exercise and cannot be applied
to spontaneous complicated exercise. Therefore, it will be necessary to investigate whether the dopaminergic system in the septum is involved in improvement in exercise efficiency during spontaneous complicated exercise.

Acknowledgements This work was supported by grants from the JST Precursory Research for Embryonic Science and Technology (JPMJPR13MG to T.S.), JSPS Grants-in-Aid for Scientific Research (26560398, 18H03152 to T.S.). We thank Editage for English language editing.

Author contributions TS and TM contributed to experimental design, data collection, analysis, and manuscript preparation. NS and SC contributed to data collection and analysis. HS contributed to experimental design and manuscript preparation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement on the welfare of animals All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of which at the studies were conducted.

References

1. Poole DC, Jones AM (2017) Measurement of the maximum oxygen uptake \( \dot{V}O_{2\text{max}} \): \( \dot{V}O_{2\text{peak}} \) is no longer acceptable. J Appl Physiol 122:997–1002
2. Ferretti G, Fagoni N, Taboni A, Bruseghini P, Vionetti G (2017) The physiology of submaximal exercise: the steady state concept. Respir Physiol Neurobiol 246:76–85
3. Westerterp KR (2018) Exercise, energy expenditure and energy balance, as measured with doubly labelled water. Proc Nutr Soc 77:4–10
4. Chiu CN, Chen CY, Muggleton NG (2017) Sport, time pressure, and cognitive performance. Prog Brain Res 234:85–99
5. Seifert L, Kolmar J, Barbosa T, Toussaint H, Milet G, Davids K (2014) Coordination pattern variability provides functional adaptations to constraints in swimming performance. Sports Med 44:1333–1345
6. Millet GP, Vleck VE, Bentley DJ (2009) Physiological differences between cycling and running: lessons from triathletes. Sports Med 39:179–206
7. Holloway GP (2017) Nutrition and training influences on the exercise. J Endocrinol Invest 26:851–854
8. Sarma S, Levine BD (2015) Soothing the sleeping giant: improving skeletal muscle oxygen kinetics and exercise intolerance in HFpEF. J Appl Physiol 119:734–738
9. Hopker J, Passfield L, Coleman D, Jobson S, Edwards L, Carter H (2009) The effects of training on gross efficiency in cycling: a review. Int J Sports Med 30:845–850
10. De Feo P, Di Loreto C, Lucidi P, Murdolo G, Parlanti N, De Cicco A, Piccioni F, Santusiano F (2003) Metabolic response to exercise. J Endocrinol Invest 26:851–854
11. Ulrich S, Schneider SR, Bloch KE (2017) Effect of hypoxia and hyperoxia on exercise performance in healthy individuals and in patients with pulmonary hypertension: a systematic review. J Appl Physiol 2017(123):1657–1670
12. Sandbakk Ø, Solli GS, Holmberg HC (2018) Sex differences in world-record performance: the influence of sport discipline and competition duration. Int J Sports Perform 13:2–8
13. Conley KE (2016) Mitochondria to motion: optimizing oxidative phosphorylation to improve exercise performance. J Exp Biol 219:243–249
14. Tamura K, Sugita S, Tokunaga T, Minegishi Y, Ota N (2019) TRPM8-mediated cutaneous stimulation modulates motor neuron activity during treadmill stepping in mice. J Physiol Sci. https://doi.org/10.1007/s12576-019-00707-3
15. Li FH, Li T, Su YM, Ai JY, Duan R, Liu TC (2018) Cardiac basal autophagic activity and increased exercise capacity. J Physiol Sci 68:729–742
16. Moritani T, DeVries HA (1979) Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med 58:115–130
17. Squire LR, Zola SM (1996) Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci 93:13515–13522
18. Pascual-Leone A, Grafman J, Clark K, Stewart M, Massaquoi S, Lou J-S, Hallett M (1993) Procedural learning in Parkinson’s disease and cerebellar degeneration. Ann Neurol 34:594–602
19. Dobkin BH (2013) Wearable motion sensors to continuously measure real-world physical activities. Curr Opin Neurol 26:602–608
20. Luczko J, Latash ML (2016) Progress in motor control. Springer International, Cham, Switzerland
21. Brueckner D, Kiss R, Muehlbauer T (2018) Associations between practice-related changes in motor performance and muscle activity in healthy individuals: a systematic review. Sport Med Open. https://doi.org/10.1186/s40798-018-0123-6
22. Yangaida S, Motomura K, Ohashi A, Hiraoka K, Miura T, Kanba S (2016) Effect of acute imipramine administration on the pattern of forced swim-induced c-Fos expression in the mouse brain. Neurosci Lett 629:119–124
23. Foley TE, Brooks LR, Gilligan LJ, Burghardt PR, Koch LG, Britton SL, Fleshner M (2012) Brain activation patterns at exhaustion in rats that differ in inherent exercise capacity. PLoS ONE. https://doi.org/10.1371/journal.pone.0045415
24. Soya H, Mukai A, Deocaris CC, Ohiwa N, Chang H, Nishijima T, Fujikawa T, Togashi K, Saito T (2007) Threshold-like pattern of neuronal activation in the hypothalamus during treadmill running: establishment of a minimum running stress (MRS) rat model. Neurosci Res 58:341–348
25. Paxinos G, Flanklin K (2012) Paxinos and flanklin’s the mouse brain in stereotoxic coordinates, 4th edn. Academic Press, Cambridge, MA
26. Kitaoaka K, Hattori A, Chikahisa S, Miyamoto K, Nakaya Y, Sei H (2007) Vitamin A deficiency induces a decrease in EEG delta power during sleep in mice. Brain Res 1150:121–130
27. Sahlin K, Sorensen JB, Gladden LB, Rossiter HB, Pedersen PK (2005) Prior heavy exercise eliminates \( \dot{V}O_{2\text{slow}} \) component and reduces efficiency during submaximal exercise in humans. J Physiol 564:765–773
28. Schefer V, Talan MI (1996) Oxygen consumption in adult and AGED C57BL/6J mice during acute treadmill exercise of different intensity. Exp Gerontol 31:387–392
29. Guzmán YF, Tronson NC, Jovasevic V, Sato K, Guedea AL, Mizuno S, Lou J-S, Hallett M, Miller (2003) Prior heavy exercise eliminates \( \dot{V}O_{2\text{slow}} \) component and reduces efficiency during submaximal exercise in humans. J Physiol 564:765–773
30. Schefer V, Talan MI (1996) Oxygen consumption in adult and AGED C57BL/6J mice during acute treadmill exercise of different intensity. Exp Gerontol 31:387–392
31. Singewald GM, Rjabokon A, Singewald N, Ebner K (2011) The modulatory role of the lateral septum on neuroendocrine

\( \dot{V}O_{2\text{max}} \)
and behavioral stress responses. Neuropsychopharmacology 36:793–804
32. Shin S, Pribiag H, Lilascharoen V KD, Wang XY, Lim BK (2018) Drd3 signaling in the lateral septum mediates early life stress-induced social dysfunction. Neuron 97:195–208.e6
33. Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E (2015) Theta sequences are essential for internally generated hippocampal firing fields. Nat Neurosci 18:282–288
34. Fuhrmann F, Justus D, Sosulina L, Kaneko H, Beutel T, Friedrichs D, Schoch S, Schwarz MK, Fuhrmann M, Remy S (2015) Locomotion, theta oscillations, and the speed-correlated firing of hippocampal neurons are controlled by a medial septal glutamatergic circuit. Neuron 86:1253–1264
35. Takakusaki K, Okumura T (2008) Neurobiological basis of controlling posture and locomotion. Adv Robot 22:1629–1663
36. Müller T, Muhlack S (2010) Effect of exercise on reactivity and motor behaviour in patients with Parkinson’s disease. J Neurol Neurosurg Psychiatry 81:747–753
37. Noble EE, Mavanji V, Little MR, Billington CJ, Kotz CM, Wang CF (2014) Exercise reduces diet-induced cognitive decline and increases hippocampal brain-derived neurotrophic factor in CA3 neurons. Neurobiol Learn Mem 114:40–50
38. Nishijima T, Kawakami M, Kita I (2013) Long-term exercise is a potent trigger for ΔFosB induction in the hippocampus along the dorso-ventral axis. PLoS ONE. https://doi.org/10.1371/journal.pone.0081245
39. Baj G, D’Alessandro V, Musazzi L, Mallei A, Sartori CR, Sciancalepore M, Tardito D, Langone F, Popoli M, Tongiorgi E (2012) Physical exercise and antidepressants enhance BDNF targeting in hippocampal CA3 dendrites: further evidence of a spatial code for BDNF splice variants. Neuropsychopharmacology 37:1600–1611
40. Nam SM, Yi SS, Yoo K-Y, Park OK, Yan B, Song W, Won M-H, Yoon YS, Seong JK (2011) Differential effects of treadmill exercise on cyclooxygenase-2 in the rat hippocampus at early and chronic stages of diabetes. Lab Anim Res 27:189–195
41. Adams BW, Moghaddam B (2000) Tactile stimulation activates dopamine release in the lateral septum. Brain Res 858:177–180
42. Robinson SE, Malthe-Sørenssen D, Wood PL, Commissiong J (1979) Dopaminergic control of the septal-hippocampal cholinergic pathway. J Pharmacol Exp Ther 208:476–479
43. Yamamuro Y, Hori K, Tanaka J, Iwano H, Nomura M (1995) Septo-hippocampal cholinergic system under the discrimination learning task in the rat: a microdialysis study with the dual-probe approach. Brain Res 684:1–7
44. Sotomayor R, Forray MI, Gyssling K (2005) Acute morphine administration increases extracellular DA levels in the rat lateral septum by decreasing the GABAergic inhibitory tone in the ventral tegmental area. J Neurosci Res 81:132–139

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.