The Mesocortical System Encodes the Strength of Subsequent Force Generation

Neuroscience Insights
Volume 19: 1–3
© The Author(s) 2024
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/26331055241256948

Sho K Sugawara and Yukio Nishimura

Neural Prosthetics Project, Tokyo Metropolitan Institute of Medical Science, Setagaya, Tokyo, Japan.

ABSTRACT: Our minds impact motor outputs. Such mind–motor interactions are critical for understanding motor control mechanisms and optimizing motor performance. In particular, incentive motivation strongly enhances motor performance. Dopaminergic neurons located in the ventral midbrain (VM) are believed to be the center of incentive motivation. Direct projections from the VM to the primary motor cortex constitute a mesocortical pathway. However, the functional role of this pathway in humans remains unclear. Recently, we demonstrated the functional role of the mesocortical pathway in human motor control in the context of incentive motivation by using functional magnetic resonance imaging (fMRI). Incentive motivation remarkably improved not only reaction times but also the peak grip force in subsequent grip responses. Although the reaction time has been used as a proxy for incentive motivation mediated by dopaminergic midbrain activity, the premovement activity of the mesocortical pathway is involved in controlling the force strength rather than the initiation of subsequent force generation. In this commentary, we review our recent findings and discuss remaining questions regarding the functional role of the mesocortical pathway in mind–motor interactions.

KEYWORDS: Ventral midbrain, motor cortex, reaction time, force, reward

RECEIVED: March 26, 2024. **ACCEPTED:** May 8, 2024.

TYPE: Commentary

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by research grants from JSPS KAKENHI (grant numbers 18 K13378, 18H05145, and 21H00967 to S.K.S.; 18H05287, 18H04038, and 18 K19767 to Y.N.) and JST [Moonshot R&D] (grant number JPMJMS2023 to Y.N.). This work was also partly supported by the National Institute for Physiological Sciences (the "Cooperative Study by Functional Imaging" Program, grant to S.K.S).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Sho K. Sugawara, Neural Prosthetics Project, Tokyo Metropolitan Institute of Medical Science, Kamikitazawa 2-1-6, Setagaya 156-8506, Tokyo, Japan. Email: sugawara-sh@igakuken.or.jp.

COMMENT ON: Sho K Sugawara, Tetsuya Yamamoto, Yoshihisa Nakayama, Yuki H Hamano, Masaki Fukunaga, Norihiro Sadato, Yukio Nishimura, Premovement activity in the mesocortical system links peak force but not initiation of force generation under incentive motivation, Cerebral Cortex, 2023; bhad376, https://doi.org/10.1093/cercor/bhad376

Ryoko Tani-Tamura, a five-time Olympic medalist in judo, said *"At best a gold, at least a gold"* before the Sydney Olympic Games in 2000 and then won a gold medal as she promised. Thus, athletes are motivated to achieve their goals. Psychological studies have demonstrated that incentive motivation facilitates motor performance. Specifically, in a simple reaction time paradigm, reward-predicting stimuli have been shown to reduce reaction times.[1-4] The improvement in the reaction time depends on the anticipated reward, indicating that an improved reaction time reflects incentive motivation. Based on this background, many studies have used faster reaction times as a proxy for incentive motivation. Thus, motivation and motor systems in the central nervous system are closely related. However, the neural mechanisms by which motivational states modulate subsequent motor performance remain largely unknown.

Using functional magnetic resonance imaging (fMRI), we recently reported that the mesocortical system from the ventral midbrain to the primary motor cortex links subsequent motor performance with incentive motivation in humans. This commentary aims to summarize our recent findings and the remaining questions that should be investigated in future studies.

Motivational effects are observed in the primary motor cortex (M1), which sends motor commands to spinal motoneurons. Reward anticipation facilitates cortical excitability in M1, as measured by transcranial magnetic stimulation.[5-8] Thus, incentive motivation modulates M1 activity, resulting in improved motor performance. This evidence raises another question: where does the motivational effect in M1 originate? The dopaminergic midbrain is believed to be the center of motivation.[9,10] Dopaminergic neurons respond to stimuli associated with subsequent rewards.[11-14] In humans, previous neuroimaging studies have demonstrated that the ventral midbrain (VM), where dopaminergic neurons are located, is activated by monetary reward anticipation.[15-19] VM neurons directly innervate M1 in monkeys and rodents,[20-23] constituting the mesocortical dopaminergic system. In humans, diffusion tractography has shown the anatomical connection from the VM to the M1.[24] According to these findings, the mesocortical system is the most plausible candidate for motivation-dependent improvement in motor performance. However, no study has demonstrated that the premovement activity of the mesocortical system is associated with future reaction times.

To investigate this hypothetical relationship between the mesocortical system and motor performance, we recently reported an fMRI study in humans.[25] In this study, we asked participants to prepare during the Ready period and to grip a force device as quickly as possible during the Go period. To manipulate motivational levels, three different ready cues associated with different expected monetary rewards were used for the high-, low-, and no-reward conditions. Consistent with previous neuroimaging studies, reward anticipation activated the VM. As expected, the reaction time was faster with increasing motivational level. Moreover, although the strength of the grip force was independent of reward, the peak grip force was greater with increasing motivational level. These behavioral

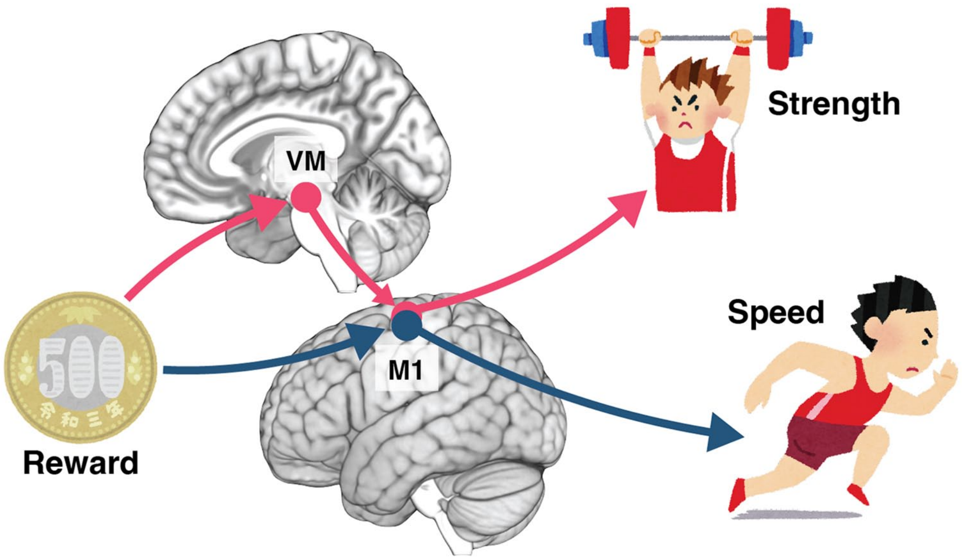

Figure 1. Two distinct neural pathways control subsequent force generation under incentive motivation. Anticipating rewards increases premovement activity in both the ventral midbrain (VM) and primary motor cortex (M1). VM activity increases M1 premovement activity through direct mesocortical projections (red lines), enhancing the strength of the subsequently generated force. M1 premovement activity is increased through another neural pathway that might be mediated by the basal ganglia, leading to faster response times (blue lines).

results suggest that the strength of the grip force is involuntarily modulated by incentive motivation for fast responses. Additionally, the trial-by-trial correlation between reaction time and peak grip force was weak, suggesting that the initiation and strength of the force generation are independently controlled by different neural pathways. Thus, the important question was whether the activities of VM and M1 were associated with subsequent reaction times. Surprisingly, we found that VM premovement activity was correlated with only the subsequent peak grip force, whereas M1 activity was related to both the reaction time and peak grip force. Our findings suggest that incentive motivation modulates M1 activity through different neural pathways that decrease the initiation of the force generation and increase the strength of the force generation (Figure 1). The mesocortical pathway from the VM to the M1 is associated with the strength (red lines in Figure 1) but not the initiation of the generated force. A recent study in monkeys showed that VM neurons have multiple synaptic projections to the spinal cord and that electrical stimulation of the VM generates muscle activity in accordance with the current intensity.[26]

Our recent findings elucidated the pivotal role of the mesocortical system in controlling motor performance in situations involving incentive motivation (Figure 1). In parallel, these findings raise several questions. First, what neural pathways mediate the improvement in reaction time with incentive motivation? Although VM activity was not correlated with trial-by-trial reaction times, premovement activity in the corticostriatal network, including the M1, the premotor cortex, the supplementary motor area, and the putamen, was associated with subsequent reaction times. In addition to the M1 activity, premovement activities in the putamen and premotor cortex are modulated by reward-predicting stimuli.[1,2,27] Furthermore, the premovement activities in M1, the premotor cortex, and the putamen are closely linked with movement initiation.[28-30] In addition, anticipatory activity in the nucleus accumbens (NAc), which has multisynaptic projections to the M1,[31] is associated with subsequent reaction times.[32] Furthermore, functional interactions between large-scale networks such as the executive control network and ventral visual stream contribute to subsequent reaction times.[33] Thus, it is reasonable that reaction times are controlled through a more complex network than the direct mesocortical pathway. This possibility should be clarified in future studies. Second, does VM activity determine the strength of the force generation independent of incentive motivation? Incentive motivation improves both reaction time[2-4] and force exertion[34,35] and is associated with the activity of dopaminergic neurons in the VM.[13,36,37] Based on these findings, it has been hypothesized that VM activity mediates motivation-dependent performance improvements. However, there is no evidence of a relationship between VM activity and motor parameters, although the striatal activity projecting from the VM is linked to saccade movements.[38,39] Considering that our behavioral paradigm requires participants to respond faster to obtain monetary rewards, the strength of the force generation is involuntarily affected by motivational states. As mentioned above, electrical stimulation of the VM can induce muscle activity in anesthetized monkeys.[26] Thus, it is possible that the subsequent peak grip force depends on the VM activity even without external rewards. Despite recent achievements in noninvasive deep brain stimulation,[40,41] it remains difficult to manipulate deep brain nuclei in healthy humans. One promising approach involves real-time fMRI.[42-45] Real-time fMRI neurofeedback can modulate the VM activity.[42,43] However, the impact of VM activity on behavior remains unknown. Future neurofeedback studies should test the effect of VM modulation on motor performance in humans to demonstrate whether a causal link exists between VM activity and motor performance independent of external rewards.

Our recent neuroimaging study provides novel evidence for the functional role of the mesocortical pathway in human motor control in the context of existing incentive motivation. The mesocortical pathway seems to be crucial for understanding mind–motor interactions in humans. This finding may facilitate the development of psychophysiological therapeutic approaches in sports and clinical domains. The neural mechanisms underlying mind–motor interactions are of interest to many scientists in psychology, sports sciences, neurophysiology, and neuroanatomy who investigate motor control, motor learning, and motivational behavior, as well as people with a desire to enhance motor performance.

Author Contributions

S.K.S. and Y.N. wrote the paper.

ORCID iD

Sho K. Sugawara https://orcid.org/0000-0002-1417-5325

REFERENCES

1. Hollerman JR, Tremblay L, Schultz W. Influence of reward expectation on behavior-related neuronal activity in primate striatum. *J Neurophysiol*. 1998;80:947-963.
2. Hassani OK, Cromwell HC, Schultz W. Influence of expectation of different rewards on behavior-related neuronal activity in the striatum. *J Neurophysiol*. 2001;85:2477-2489.
3. Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JDE. Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron*. 2006;50:507-517.
4. Mir P, Trender-Gerhard I, Edwards MJ, Schneider SA, Bhatia KP, Jahanshahi M. Motivation and movement: the effect of monetary incentive on performance speed. *Exp Brain Res*. 2011;209:551-559.
5. Kapogiannis D, Campion P, Grafman J, Wassermann EM. Reward-related activity in the human motor cortex. *Eur J Neurosci*. 2008;27:1836-1842.
6. Thabit MN, Nakatsuka M, Koganemaru S, Fawi G, Fukuyama H, Mima T. Momentary reward induce changes in excitability of primary motor cortex. *Clin Neurophysiol*. 2011;122:1764-1770.
7. Klein P-A, Olivier E, Duque J. Influence of reward on corticospinal excitability during movement preparation. *J Neurosci*. 2012;32:18124-18136.
8. Galaro JK, Celnik P, Chib VS. Motor cortex excitability reflects the subjective value of reward and mediates its effects on incentive-motivated performance. *J Neurosci*. 2019;39:1236-1248.
9. Salamone JD. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav Brain Res*. 1994;61:117-133.
10. Salamone JD, Correa M. The Mysterious motivational functions of mesolimbic dopamine. *Neuron*. 2012;76:470-485.
11. Berridge KC, Robinson TE. What is the role of dopamine in reward. *Brain Res Rev*. 1998;28:309-369.
12. Schultz W. Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol*. 1997;7:191-197.
13. Matsumoto M, Hikosaka O. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature*. 2009;459:837-841.
14. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*. 2010;35:4-26.
15. Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *Neuroimage*. 2003;18:263-272.
16. Knutson B, Taylor J, Kaufman M, Peterson R, Glover G. Distributed neural representation of expected value. *J Neurosci*. 2005;25:4806-4812.
17. Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Düzel E. Reward-related fMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron*. 2005;45:459-467.
18. Carter RMK, MacInnes JJ, Huettel SA, Adcock RA. Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. *Front Behav Neurosci*. 2009;3:1-15.
19. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*. 2011;35:1219-1236.
20. Gaspar P, Stepniewska I, Kaas JH. Topography and collateralization of the dopaminergic projections to motor and lateral prefrontal cortex in owl monkeys. *J Comp Neurol*. 1992;325:1-21.
21. Williams S M, Goldman-Rakic PS. Widespread origin of the primate mesofrontal dopamine system. *Cereb Cortex*. 1998;8:321-345.
22. Hosp JA, Nolan HE, Luft AR. Topography and collateralization of dopaminergic projections to primary motor cortex in rats. *Exp Brain Res*. 2015;233:1365-1375.
23. Zubair M, Murris SR, Isa K, et al. Divergent whole brain projections from the ventral midbrain in macaques. *Cereb Cortex*. 2021;31:2913-2931.
24. Hosp JA, Coenen VA, Rijntjes M, et al. Ventral tegmental area connections to motor and sensory cortical fields in humans. *Brain Struct Funct*. 2019;224:2839-2855.
25. Sugawara SK, Yamamoto T, Nakayama Y, et al. Premovement activity in the mesocortical system links peak force but not initiation of force generation under incentive motivation. *Cereb Cortex*. 2023;33:11408-11419.
26. Suzuki M, Inoue K, Nakagawa H, et al. A multisynaptic pathway from the ventral midbrain toward spinal motoneurons in monkeys. *J Physiol*. 2022;7:1731-1752.
27. Ramnani N, Miall RC. Instructed delay activity in the human prefrontal cortex is modulated by monetary reward expectation. *Cereb Cortex*. 2003;13:318-327.
28. Jaeger D, Gilman S, Aldridge JW. Primate basal ganglia activity in a precued reaching task: preparation for movement. *Exp Brain Res*. 1993;95:51-64.
29. Ohata R, Ogawa K, Imamizu H. Single-trial prediction of reaction time variability from MEG brain activity. *Sci Rep*. 2016;6:1-11.
30. Nashef A, Cohen O, Israel Z, Harel R, Prut Y. Cerebellar shaping of motor cortical firing is correlated with timing of motor actions. *Cell Rep*. 2018;23:1275-1285.
31. Miyachi S, Lu X, Inoue S, et al. Organization of multisynaptic inputs from prefrontal cortex to primary motor cortex as revealed by retrograde transneuronal transport of rabies virus. *J Neurosci*. 2005;25:2547-2556.
32. Clithero JA, Reeck C, Mckell Carter R, Smith DV, Huettel SA. Nucleus accumbens mediates relative motivation for rewards in the absence of choice. *Front Hum Neurosci*. 2011;5:1-11.
33. Utevsky AV, Smith DV, Young JS, Huettel SA. Large-scale network coupling with the fusiform cortex facilitates future social motivation. *eNeuro*. 2017;4:1-12.
34. Pessiglione M, Schmidt L, Draganski B, et al. How the brain translates money into force: a neuroimaging study of subliminal motivation. *Science*. 2007;316:904-906.
35. Schmidt L, Lebreton M, Cléry-Melin ML, Daunizeau J, Pessiglione M. Neural mechanisms underlying motivation of mental versus physical effort. *PLoS Biol*. 2012;10:e1001266.
36. Schultz W. Predictive reward signal of dopamine neurons. *J Neurophysiol*. 1998;80:1-27.
37. Takakuwa N, Kato R, Redgrave P, Isa T. Emergence of visually-evoked reward expectation signals in dopamine neurons via the superior colliculus in V1 lesioned monkeys. *Elife*. 2017;6:1-17.
38. Lauwereyns J, Watanabe K, Coe B, Hikosaka O. A neural correlate of response bias in monkey caudate nucleus. *Nature*. 2002;418:413-417.
39. Nakamura K, Hikosaka O. Role of dopamine in the primate caudate nucleus in reward modulation of saccades. *J Neurosci*. 2006;26:5360-5369.
40. Grossman N, Bono D, Dedic N, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell*. 2017;169:1029-1041.e16.
41. Wessel MJ, Beanato E, Popa T, et al. Noninvasive theta-burst stimulation of the human striatum enhances striatal activity and motor skill learning. *Nat Neurosci*. 2023;26:2005-2016.
42. Sulzer J, Sitaram R, Blefari ML, et al. Neurofeedback-mediated self-regulation of the dopaminergic midbrain. *Neuroimage*. 2013;83:817-825.
43. MacInnes JJ, Dickerson KC, Chen N, Adcock RA. Cognitive neurostimulation: Learning to volitionally sustain ventral tegmental area activation. *Neuron*. 2016;89:1331-1342.
44. Sitaram R, Ros T, Stoeckel L, et al. Closed-loop brain training: the science of neurofeedback. *Nat Rev Neurosci*. 2017;18:86-100.
45. Chew B, Hauser TU, Papoutsi M, Magerkurth J, Dolan RJ, Rutledge RB. Endogenous fluctuations in the dopaminergic midbrain drive behavioral choice variability. *Proc Natl Acad Sci U S A*. 2019;116:18732-18737.