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Short Communication

Continuous membrane potential fluctuations in motor cortex and striatum neurons during voluntary forelimb movements and pauses

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ABSTRACT

Theoretical simulations suggest that spike rate is regulated by varying both membrane potential and its fluctuation. We investigated whether membrane potential fluctuation functionally changes in motor cortex and striatum neurons during discrete forelimb movements and pauses, or at rest, using whole-cell recording in task-performing rats. Membrane potential fluctuation was diminished by task performance, but maintained overall in the alpha/beta and gamma bands during forelimb movements and pauses. By contrast, membrane potential itself was correlated with spike rate in task-related neurons. Thus, membrane potential, but not its fluctuation, is a critical determinant of execution and pausing of discrete movements.

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Primates skillfully perform discrete voluntary movements of the head, body, and limbs that are controlled by spike outputs from neurons in the primary motor cortex (Evarts, 1968; Georgopoulos et al., 1982). Rodents can also perform discrete movements of each limb (Iwaniuk and Whishaw, 2000), which are distinct from automatic repetition of stereotyped motion of all limbs (i.e., locomotion), the tongue (licking), and whiskers (whisking) under the control of subcortical pattern generator(s) (Kjaerulff and Kiehn, 1996; Travers et al., 1997; Gao et al., 2003). Recently, we observed that in task-performing rats under a head-fixed condition, the primary motor cortex neurons exhibit increases in spike activity during either discrete movements of one forelimb (e.g., pushing/pulling a lever; referred to as Movement-type neurons) or intended pauses between these movements (e.g., keeping a lever in the hold position; Hold-type neurons) (Isomura et al., 2009, 2013; Saiki et al., 2014). Movement-type neurons are distributed in superficial and deep layers of the motor cortex, whereas the Hold-type neurons are mostly in deep layers (Igarashi et al., 2013). We observed similar Movement-type and Hold-type activations in direct and indirect pathway neurons of the dorsolateral striatum into which the motor cortex neurons send axonal projections (Isomura et al., 2013). Moreover, the motor cortex changes the power of electrocorticographic or local field synchronous oscillations including theta, beta, and gamma bands depending on voluntary limb movements (Igarashi et al., 2013; Boulay et al., 2015; von Nicolai et al., 2014). Typically, active movements diminish beta and other slow oscillations and augment gamma oscillations in the motor cortex. The motor information can indeed be decoded by gamma-band activity (>30 Hz; Khorasani et al., 2016). The spike activities of motor cortex neurons are phase-locked to gamma and theta oscillations (Igarashi et al., 2013) and are often synchronous among neurons (Kimura et al., 2017) in the behaving state.

How, then, do these neurons generate functional spike outputs depending on different behavioral situations? So far, in vivo membrane potential analyses have been performed with the goal of elucidating the subcellular mechanism by which spike signals are generated to convey functional information optimally in each neuron. Importantly, the membrane potential of cortical neurons fluctuates below the spike threshold in behaving animals (Matsumura, 1979; Chen and Fetz, 2005), which could be synchronized or desynchronized with the electrocorticographic activity

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depending on behavioral states. In theoretical simulations, a gain change in membrane potential fluctuation, along with a steady shift in membrane potential (depolarization/hyperpolarization), can optimize the responsiveness of spiking neurons to synaptic inputs (Hô and Destexhe, 2000; Chance et al., 2002; Murphy and Miller, 2003). In rodents, somatosensory cortex neurons depolarize the membrane potential and decrease its fluctuation during spontaneous whisker movements in comparison to quiet wakefulness with no whisking (Poulet and Petersen, 2008; Yamashita et al., 2013). Likewise, motor cortex neurons reduce membrane potential fluctuation when running or walking relative to quiet sitting, whether they increase or decrease their spike activity (Schiemann et al., 2015). Some motor cortex neurons diminish their fluctuation and spike activity prior to licking responses (Zagha et al., 2015). Thus, cortical neurons commonly lessen the membrane potential fluctuation, accompanied by steady depolarization or hyperpolarization, during repetitive movements such as locomotion, licking, and whisking. Striatum neurons also depolarize the membrane potential in relation to licking movements (Sippy et al., 2015). It is, therefore, possible that motor information in each neuron could be encoded directly by the change in power of its membrane potential fluctuations. However, due to technical difficulties in behavioral and electrophysiological experiments, it remains unknown whether the membrane potential fluctuation of motor cortex and striatum neurons functionally changes during discrete forelimb movements, relative to the situation during intended pauses of these movements.

To test this possibility, we performed in vivo whole-cell recordings to characterize the membrane potential fluctuation in the motor cortex and striatum neurons during discrete forelimb movements and pauses in rats (Fig. 1A; pulling and holding a lever, respectively; see Kimura et al., 2012; Saiki et al., 2014 for details). Briefly, Long-Evans rats ($N = 32$, 150–243 g, male; Institute for Animal Reproduction, Japan) had a head-attachment surgically attached to the skull with anchor screws and dental resin cement (Super-Bond C & B, Sun Medical, Japan; Panavia F2.0, Kuraray Medical, Japan; Unifast II, GC Corporation, Japan) under 2.0–2.5% isoflurane anesthesia (Univentor 400 anesthesia unit, Univentor, Malta); body temperature was maintained at 37 °C during the surgery (BWT-100, Bio Research Center, Japan). Two silver-wire electrodes (Teflon-coated, 180 μm in diameter, A-M systems, USA) were implanted above the cerebellum as a reference and ground. After recovery from the surgery, the rats were deprived of drinking water in their home cage, but sufficient water was provided as a reward for their task performance in the laboratory. An agar block (15 ml water) was given to them, when necessary, to maintain >80% of body weight. The rats operantly learned a forelimb movement task in an automatic task-control system (TaskForcer, O'hara & Co., Ltd., Japan) in 3 training days (2–5 h/day). In this task, they started each trial spontaneously by pushing a spout-lever and holding it for >0.5 s (hold period) with the right forelimb under head fixation. If they pulled the spout-lever toward his mouth after the hold period, they received reward water (0.1% saccharin, 10 μl) from the spout with a 0.2–0.8 s delay.

Once the rats completed the behavioral task learning, they were subjected to a second surgery under isoflurane anesthesia to open a tiny hole in the skull and dura mater above the left primary motor cortex (forelimb area) and the dorsolateral striatum (Fig. 1B; 1.0 ± 0.5 mm anterior, 2.5 ± 0.5 mm lateral from bregma, cf. Paxinos and Watson, 2007; the hole was covered with 1.5–2.0% agarose gel). Glass electrodes (GC150F-7.5, Harvard Apparatus, USA), prepared by a puller (PC-10, Narishige, Japan), were filled with an internal solution containing (in mM): 140 K-gluconate, 2 NaCl, 1 $MgCl_2$, 10 HEPES, 0.2 EGTA, 2 5′-ATP Na_2, and 0.5 GTP Na_2, 10 biocytin (pH 7.4, 5–10 MΩ; Fujiwara-Tsukamoto et al., 2010). While the rats were awake (i.e., several hours later), the electrode was inserted near vertically into the motor cortex, and to the striatum, with a water hydraulic microdrive manipulator (MWS-1B, Narishige) on a stereotaxic frame (SR-8N, Narishige) to blindly search for target neurons. The membrane potential of healthy neurons (resting membrane potential, <−50 mV; spike amplitude, >40 mV at $I = 0$) was measured in I-clamp mode with a patch-clamp amplifier (Axopatch 1D, Axon Instruments, USA, and EX4-400, Dagan, USA; final gain, x25; high-cut filter, 5 kHz) during task performance and quiet resting. If necessary, the neurons were slightly hyperpolarized by injecting constant current in order to obtain occasional trials with no spikes for wavelet analysis. The position of the spout-lever was tracked by an angle encoder in the task-control system. In some experiments, we performed electrocorticography (ECoG) on the surface of motor cortex via an additional silver-wire electrode (EX4-400; final gain, x2000; band-pass filter, 0.5 Hz–10 kHz). The rats were perfused intracardially with fixative solution under urethane anesthesia (2–3 g/kg, i.p.) after the recording experiments (only one session for each rat), to histologically confirm the location of recorded neurons (Koshimizu et al., 2008; Unzai et al., 2015). All the recorded data (membrane potential, lever position, task events, and ECoG) were digitized at 20 kHz and saved in a hard-disc recorder (LX-120, TEAC, Japan). All the experiments were approved by the Animal Research Ethics Committee of Tamagawa University (H22/27–32), and carried out with all efforts to minimize suffering in accordance with the Guidelines for Animal Experimentation in Neuroscience (Japan Neuroscience Society, 2015) and the Guidelines for the Care and Use of Laboratory Animals established by the Committee for Animal Care and Use of Doshisha University.

The recorded data were analyzed using MATLAB (The MathWorks, USA). Task-related membrane potential was defined as the median value of membrane potential aligned with pull onset across trials (>15 trials), which should not be affected by action potentials. For statistical analysis, we evaluated task-related membrane potential change by comparing the averaged median membrane potential in a pull time-window (250 ms; 0 to +250 ms from pull onset) with that in a hold time-window (250 ms; −500 to −250 ms from it) as a baseline. Task-related spike rate change was also evaluated by comparing averaged spike rate between the hold and pull time-windows (using neurons with >100 spikes and >15 trials). Instantaneous amplitude of ECoG or membrane potential fluctuation was computed by convolving the ECoG or membrane potential signal (using >15 trials with no spikes) with a complex Morlet wavelet function (Lachaux et al., 1999; Kajihara et al., 2015; $n_{CO} = 3$, spanning 1–80 Hz in 1 Hz steps). Wavelet transform was applied to a 6 s epoch of data (−3500 ms to +2500 ms from pull onset). We evaluated task-related amplitude changes in delta (1–5 Hz), alpha/beta (10–30 Hz), and gamma (30–80 Hz) band components by comparing averaged amplitudes between the hold and pull time windows. In some neurons, we also analyzed data from quiet resting periods by setting time points randomly (>15 points, during no lever movement lasting for >5 s), instead of at the pull onsets in task-performing periods.

We obtained membrane potential data from a total of 13 motor cortex neurons (resting membrane potential, -63.8 ± 11.1 mV) and 9 striatum neurons (-73.8 ± 10.6 mV) while rats were performing the forelimb movement task (Fig. 1C; $N = 20$ rats). We analyzed the data of these neurons, behaving similarly, all together unless otherwise stated. Some of them were also recorded while the rats were resting quietly (Fig. 1D; 7 motor cortex and 5 striatum neurons). Consistent with previous studies (e.g., Poulet and Petersen, 2008), the delta and alpha/beta components of the membrane potentials of these 12 neurons were much larger in the quietly resting state than in the task-performing state (delta, $+23.1 \pm 34.8\%$, $n = 12$, t-test, $p < 0.05$; alpha/beta, $+20.2 \pm 28.2\%$, $p < 0.04$; see Figs. 2 D and 3 D), whereas gamma components did not differ significantly between the two states ($+5.9 \pm 34.5\%$, $p = 0.57$). The large delta

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