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Review article

Self-reorganization of neuronal activation patterns in the cortex under brain-machine interface and neural operant conditioning

Hiroyuki Ito[a,*], Soichiro Fujiki[b], Yoshiya Mori[a,1], Kenji Kansaku[b,c]

[a] Faculty of Information Science and Engineering, Kyoto Sangyo University, Kyoto, Japan
[b] Department of Physiology, Dokkyo Medical University School of Medicine, Mibu, Japan
[c] Center for Neuroscience and Biomedical Engineering, The University of Electro-Communications, Chofu, Japan

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ABSTRACT

In this review, we describe recent experimental observations and model simulations in the research subject of brain-machine interface (BMI). Studies of BMIs have applied decoding models to extract functional characteristics of the recorded neurons, and some of these have more focused on adaptation based on neural operant conditioning. Under a closed loop feedback with the environment through BMIs, neuronal activities are forced to interact directly with the environment. These studies have shown that the neuron ensembles self-reorganized their activity patterns and completed a transition to adaptive state within a short time scale. Based on these observations, we discuss how the brain could identify the target neurons directly interacting with the environment and determine in which direction the activities of those neurons should be changed for adaptation. For adaptation over a short time scale, the changes of neuron ensemble activities seem to be restricted by the intrinsic correlation structure of the neuronal network (intrinsic manifold). On the other hand, for adaptation over a long time scale, modifications to the synaptic connections enable the neuronal network to generate a novel activation pattern required by BMI (extension of the intrinsic manifold). Understanding of the intrinsic constraints in adaptive changes of neuronal activities will provide the basic principles of learning mechanisms in the brain and methodological clues for better performance in engineering and clinical applications of BMI.

Contents

* Corresponding author.
E-mail address: hiro@cc.kyoto-su.ac.jp (H. Ito).
[1] Present address: Department of Integrated Science and Technology, National Institute of Technology, Tsuyama College, Tsuyama, Japan

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1. Introduction

In traditional studies of information processing in the brain, we investigate the neuronal activities associated with the perception of stimuli or movement of our body. In practice, we explore the neural correlate between physical events inside of the brain (such as activation patterns of a neuron ensemble) and physical events outside of the brain (such as presentation of a visual stimulus). In a mature brain, learning of the correspondences between two physical events is already complete. Therefore, however far we examine those correspondences in the brain, we are no longer able to know by what design principle the brain self-organized its neural networks to establish the correspondence between those two physical events. Recently, a novel experimental method of brain-machine interface (BMI) has attracted much attention for its engineering (Hatsopoulos and Donoghue, 2009; Rao, 2013; Shenoy and Carmena, 2014; Levedev and Nicolelis, 2017) and clinical applications (Wolpaw et al., 2000; Chaudhary et al., 2016; Sitaram et al., 2017). BMI has been used to control other external devices or computers using signals from the brain. In addition, BMI also represents a powerful tool to address the design principle of the brain (Fetz, 2007; Orsborn and Carmena, 2013; Sakurai et al., 2014; Moxon and Foffani, 2015; Orsborn and Pesaran, 2017). In BMI, we make the brain interact directly with the environment by a closed loop feedback between neuronal activities and external variables such as amount of rewards or cursor movement. In principle, we can impose any causality relationship between activities of the recorded neurons and external variables by mediating our designed decoding model. By imposing a perturbation (mismatch) to the established consistency between the brain and the environment, we can observe transient dynamics of self-reorganization of the neural network to adapt to the perturbation.

Adaptive changes of the brain by interaction with the environment have been one of the main research interests in neuroscience. Since we cannot observe activities of all the neurons in the brain, we cannot completely identify the neurons engaging in the interaction with the environment. In BMI, we select small numbers of neurons and impose the decoding model in which only those *direct neurons* are the control variables of the interaction with the environment. Therefore, we subdivide the recorded neurons into two groups: direct neurons, and indirect neurons having an indirect causality with the interaction. The indirect neurons interact with the environment only through interaction with the direct neurons. BMI provides an exploratory neural system that enables us to observe how the network activities of both the direct neurons and the indirect neurons self-reorganize in a closed loop feedback with the environment. By examining the adaptive changes of neural activities to the perturbation of the decoding model, we can know how the brain solves a *credit assignment problem*: under only the feedback of macroscopic variables such as rewards, how the brain can identify the neurons in a microscopic scale responsible for the mismatch and the adequate directions of the change to compensate for the perturbation.

In all BMI experiments introduced in this review, the feedback information on the misfit between the actions and the target (e.g., cursor position or amount of rewards) was conveyed to the brain by the natural sensation of the reward (visual, auditory, or food intake). While we restrict the interaction with the environment to the direct neurons, we do not impose any restriction on the neurons receiving the feedback information from the environment. In other approaches, complete restriction of the closed feedback loop to the neuron level has been examined. For example, by direct stimulations of the somatosensory neurons, Nicolelis and colleagues constructed bi-directional interactions between the neural activities and the environment (Shokur et al., 2013).

Before introducing experimental reports of BMI, we clarify the differences between the two experimental protocols: BMI based on decoding model versus BMI based on neural operant conditioning. Examples of schematic representations of the two BMI experimental protocols are shown in Fig. 1A and B. The diagram of each experimental protocol consists of several blocks with numbers such as "STEP1″ representing different experimental steps explained in text in the following sections. The two diagrams illustrate different logics between the two BMI experiments.

1.1. BMI based on decoding model

STEP 1: We first identify functional characteristics of the recorded neurons in the innate and/or obtained interaction with the environment. A typical example is direction tuning properties of the neurons in the motor cortex during arm movement in different directions.

STEP 2: The decoding model is constructed based on intrinsic functional characteristics of the neurons and translates the activities of the neuron ensemble to the control variables of external devices (e.g., positions of a robotic arm or computer cursor). During the body control mode, the decoding model is trained to reproduce the actual body movement by controlling the external device from the activities of the recorded neurons.

STEP 3: Once the decoding model has been trained, the control of the external device is switched to BMI control mode (Carmena et al., 2003). Now, the neuronal activities interact with the environment by controlling the device mediated by the decoding model.

STEP 4: In the closed loop feedback between the brain and the environment, the recorded neurons need to modify their functional characteristics for better adaptation (i.e., better performance to get more rewards) to the imposed and fixed decoding model.

Since we trained the decoding model as biomimetic, we expect that the neuronal activities can successfully control the external device as in the body control mode. In BMI based on decoding model, the main interest is a construction of a more biomimetic decoding model to attain better performances in controlling the external devices. Therefore, it seems that not enough attention has been paid to subsequent changes in functional characteristics of the neurons after switching to BMI control mode. Actually, in engineering and clinical applications of BMI, stable functional characteristics of the neurons are preferable for maintaining the performance for a longer duration. However, some animal BMI experiments have suggested that the recorded neurons exhibited different firing properties when performing BMI tasks as opposed to the natural body movement (Ganguly and Carmena, 2009; Heliot et al., 2010). Therefore, studies of BMI based on decoding model inevitably engage in the investigation of self-reorganization of the neuronal activity patterns under the closed loop feedback interaction with the environment. Recent BMI experiments have been exploring this basic problem further. By imposing intentional perturbations to the learned decoding model, a part of the recorded neurons is assigned different functional characteristics from their intrinsic characteristics. This enables us to observe how the neuron ensembles self-reorganize their activity patterns to compensate for the perturbation.

1.2. BMI based on neural operant conditioning

STEP 1: In BMI based on neural operant conditioning, the intrinsic functional characteristics of the recorded neurons are not taken into account. Instead, we set the activities of the recorded neurons (increased firing rates, oscillatory activities, or synchronous activities) as conditioned responses to the action in controlling environmental variables (such as amount of rewards or cursor position to target).

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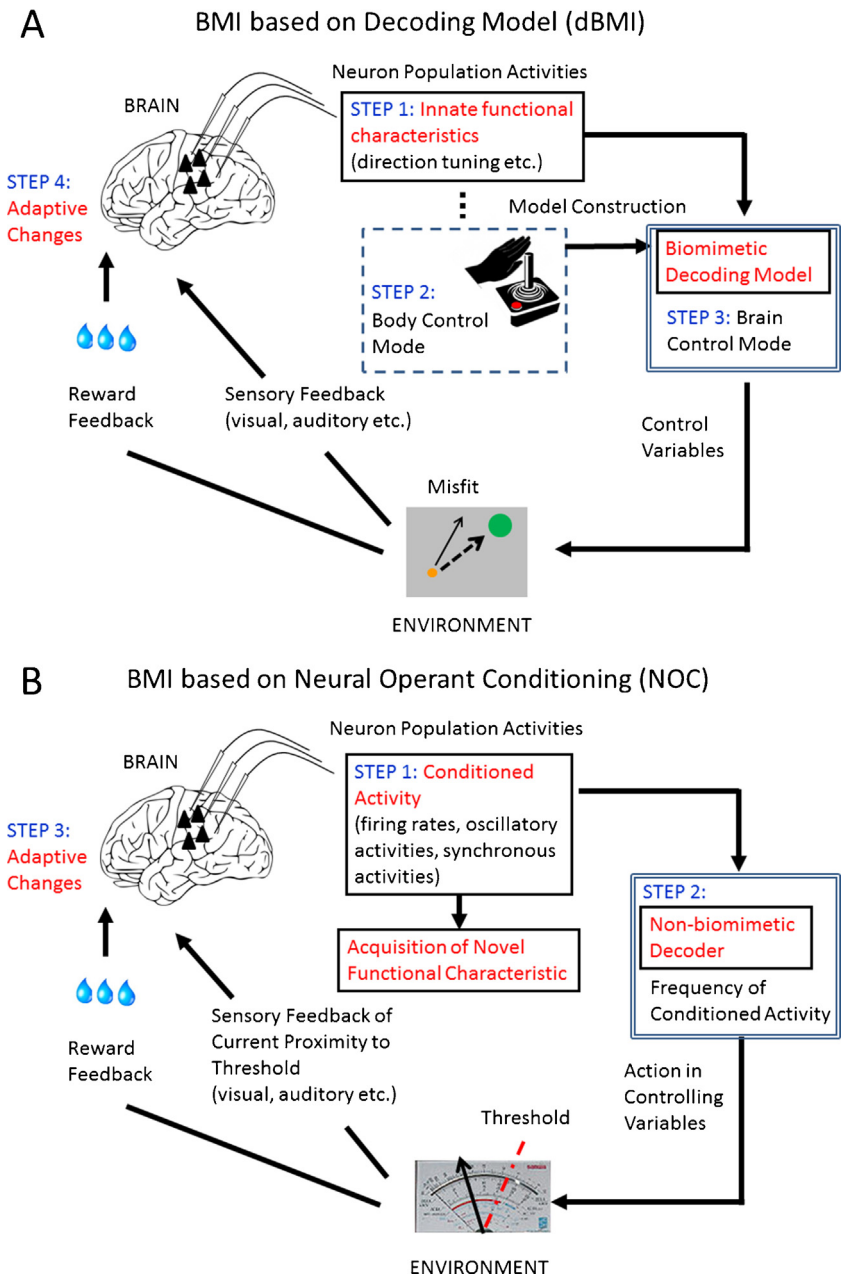

Fig. 1. Examples of schematic representations of two BMI experimental protocols. A: BMI based on decoding model (dBMI). B: BMI based on neural operant conditioning (NOC). See text for detailed explanation of the components in the diagram of each experimental protocol.

STEP 2: Also in this BMI protocol, we need a decoding model that transforms the neuronal activities to the variables controlling the environment. However, contrary to BMI based on decoding model, the decoding model is not biomimetic based on intrinsic functional characteristics of the neurons.

STEP 3: In a closed loop feedback between the brain and the environment, the neuronal ensemble self-reorganizes its activities to acquire novel functional characteristics. The main interest is the adaptive changes of recorded neurons under the causal interaction with the environment.

In principle, in BMI based on neural operant conditioning, we can set up arbitrary neuronal activities (arbitrary realizable physical events in the brain) as conditioned responses. Therefore, there is no guarantee of successful adaptation of the neuronal ensemble into a non-biomimetic decoding model accompanied by acquisitions of novel functional characteristics. Even if accomplished, we expect a long training time to achieve control over the decoding models, especially when the conditioned response is a complex activity pattern in multiple neurons.

The two types of BMIs are further subdivided to invasive BMI and non-invasive BMI depending on the implementation of the recording sensors. Hereafter, we represent BMI based on decoding model and BMI based on neural operant conditioning simply as dBMI and NOC, respectively. Recently, decoded neurofeedback (DecNef) was proposed as a novel NOC protocol based on fMRI signals of human subjects (Watanabe et al., 2017). In DecNef, with the aid of a machine learning algorithm (e.g., sparse logistic regression), high-dimensional voxel data are reduced to moderate numbers of relevant variables needed for classification of category labels, such as different orientations of the visual gratings. Since the exploration of the adequate activity pattern is constrained in the configuration space spanned by those relevant variables, the subject can attain the target activity pattern efficiently.

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In this review we first focus on NOC experiments, which have applied a direct interaction between neuronal activities and environmental variables with a simple decoding model. We introduce several experimental reports of NOC in Section 2 and those of dBMI in Section 3. Some theoretical models have been proposed to reproduce the experimental observations of adaptive changes. In Section 4, we introduce those models and discuss how they could be constructed based on the common mechanisms, that is, the activation-reward covariance rule and exploration induced by neural noise. NOC and dBMI studies of human subjects and their clinical applications are briefly introduced in Section 5. Finally we will discuss the experimental observations and the simulated results of the models in Section 6. Throughout this review, we continue to ask three of the most puzzling questions in NOC and dBMI:

1) Can we condition the brain to generate arbitrary neuronal activity patterns?
2) Is there any intrinsic and endogenous restriction of neural network to adaptive changes of the brain?
3) What neural mechanism guides the brain toward the adequate direction to reach the adaptive state in a short time?

An extensive survey of recent progress of BMIs is not the purpose of this review. Instead, we highlight some of the key experimental reports and attempt to summarize the current understanding on the nature of adaptive changes in neuronal activities in BMI. For a more systematic survey of NOC and dBMI, consult alternate review articles (NOC: Fetz, 2007; Sakurai et al., 2014; dBMI: Hatsopoulos and Donoghue, 2009; Rao, 2013; Shenoy and Carmena, 2014; Levedev and Nicolelis, 2017; BCI and Neurofeedback of human subject: Wolpaw et al., 2000; Chaudhary et al., 2016; Sitaram et al., 2017). Moxon and Foffani (2015) discussed that BMI paradigm is characterized by two main aspects: self-observation of neural activities and brain-behavior causality. They concluded that those two characteristics make BMI paradigm particularly appealing for investigation of fundamental questions on how information is encoded and decoded by neural circuit in real time.

In order to provide a global view of BMI experiments, in Fig. 2 we categorized main BMI experiments introduced in this review. Each experiment is placed in the map based on its degree of biomimesis in the decoder and its degree of adaptive changes. We need to point out that the degree of adaptive change depends on both external factor and internal factor. Experimental design provides the external factor: a degree of freedom (dimensionality of adjustable parameters) in the imposed decoding model that was allowed the neuron ensemble to modify for a better adaptation to the environment. On the other hand, the internal factor is intrinsic ability of neuron ensemble in plastic changes of their activity patterns. For example, when the decoding model is constructed based on only the firing rate of a single neuron, the neuron ensemble need not to increase synchronous firing activities over multiple neurons. In contrast, even when the decoding model requires synchronous firing activities in neuron ensemble, a structure of neuronal network may inhibit such a plastic change of activities. For more systematic categorization, the axis of the degree of adaptive change should be replaced by the two dimensional space representing the two different factors.

2. Adaptations in BMI based on neural operant conditioning (NOC)

In most NOC experiments, one of the recorded neurons is selected as a target neuron and its firing rate controls the environmental variable, such as amount of reward or one-dimensional cursor position. This simple closed loop feedback enables us to explore the most basic principle of adaptive change in the brain under the interaction with the environment. A pioneering NOC experiment was reported by Fetz in 1969 (Fetz, 1969; Fetz and Baker, 1973). They isolated two adjacent neurons from the spike signals recorded in the monkey motor cortex by a single microelectrode. One of the neurons was selected as a target neuron and the increase of its firing rate above the threshold led to delivery of a reward. Current proximity to the threshold was indicated to the monkey by the meter arm. They reported that the monkey learned to volitionally increase the activity of the target neuron within a few minutes. Since no significant change was observed in the activity of the adjacent neuron (non-target neuron), they concluded that the brain specifically identified the target neuron having a causality with the reward. When they stopped the conditioning, the firing rate of the target neuron settled back to the baseline activity. When a decrease of firing rate was conditioned, the target neuron showed a lower activity. When the target neuron was switched to another adjacent neuron, only the new target neuron changed its activity. We wonder by what neuronal mechanism the brain could identify the target neuron within a short time out of huge numbers of neurons in the brain; that is, how the brain can solve this credit assignment problem. Adaptive increases and decreases in firing rate were observed in a target neuron in the monkey lateral prefrontal cortex (Kobayashi et al., 2010). Many experimental reports suggested that, for successful conditioning of the neural activities, the proximity to the target should be continuously indicated to the subject. The indication was given by meter arm (Fetz, 1969), position of the water bottle (Arduin et al., 2013), tone pitch (Koralek et al., 2012), bar length (Kobayashi et al., 2010), or size of a disk (Shibata et al., 2011). For the control of robotic arm or cursor position by the motor cortical neurons in BMI, the subject receives continuous visual feedback of the deviation from the target.

Since the pioneering experiment by Fetz more than 40 years ago, the development of recording technology enabled us to monitor activities of a large number of neurons simultaneously in the cortex of awake behaving animals. It enables us to examine the changes in activities of the non-target neurons having no direct causal relationship with the macroscopic feedback. Arduin et al. succeeded in controlling the position of a water bottle via the firing rate of a single target neuron in rat motor cortex (Arduin et al., 2013). They reported that 88 % of the target neurons could be successfully conditioned and the rats could drink the water by moving the bottle on a one-dimensional rail to their mouth. They further succeeded in bidirectional control of the position by increasing or decreasing the firing rate (Arduin et al., 2014). The target neuron showed significantly shorter reaction time and a larger increase in the firing rate than non-target neurons separated by more than 250 μm. Although the changes were not completely localized at the target neuron, the brain identified the target neuron through the direct interaction with the environment. Adaptive change of the target neuron was attained after 5∼10 training sessions (one session lasted 10∼15 min). They observed an increase of trial-to-trial variability in the activity of the target neuron during the waiting period between successive tasks. In the early stage of the adaptation, variability was greater but gradually settled back to the baseline as the adaptation progressed. Interestingly, increased trial-to-trial variabilities (noise activities) were commonly observed during the adaptation period in many experiments and are believed to facilitate exploration of the adaptive state. This possibility will be discussed in Sections 4 and 6. By using two-photon Ca imaging of the neuron population in motor cortex, Prsa et al. (2017) trained mice to activate a single neuron. Mice were rewarded when Ca-dependent activity of the target neuron exceeded a threshold level. In addition to this standard closed loop feedback, another feedback of the activity level of the target neuron was continuously provided by proportion-

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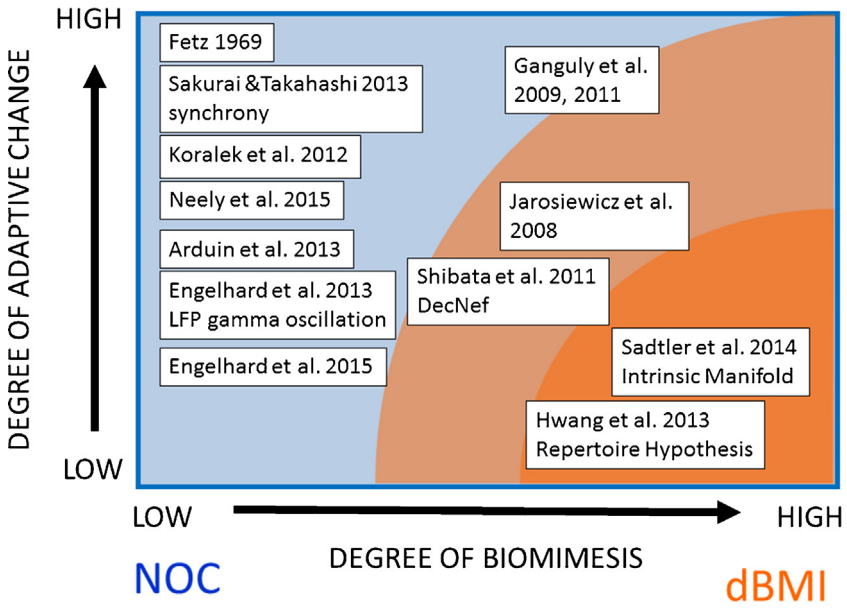

Fig. 2. Schematic categorization of BMI experiments introduced in this review. Each experiment is placed based on its degree of biomimesis in the decoder and its degree of adaptive change. While dBMI applies a biomimetic decoding model based on innate functional characteristics of individual neurons, non-biomimetic decoder applied in NOC transforms the frequency of the conditioned activity into control variables of the environment. For the highest degree of adaptive change, neuronal population can adapt to any conditioned activity in NOC or any imposed decoding model in dBMI. For a lower degree of adaptive change, neuronal adaptation is restricted by intrinsic structure of neuronal network. Since each BMI experiment is characterized by multiple factors, strict categorization is not adequate. Graduations in the map represent that the categorization is continuous rather than discrete.

ally stimulating somatosensory cortex by optogenetic stimulation. They found that the cortical stimulation facilitated a rapid increase of the target activity and learning-related activity changes were observed in the conditioned cell only.

Since a neuron forms a neural network with other neurons, conditioning of the target neuron should lead to associated changes in the non-target neurons reflecting their interconnections. Engelhard et al. (Engelhard, 2015; Engelhard et al., 2019) recorded multiple neurons in the monkey motor cortex and carried out NOC experiments targeting the increased activity of a single neuron. They carefully examined the changes occurring at the non-target neurons and found that those changed their activities depending on their spike count correlation with the target neuron. Their experimental sessions consisted of four blocks: 1) the movement state of a center-out reaching task to one of the eight directions. 2) the observation-state in which the monkey passively observed the cursor movement generated by the computer. The distance of the cursor from the origin to the target was chosen randomly every 100 ms, so rewards were delivered randomly. 3) the BMI state, in which the position of the cursor depended on the firing rate of a single target neuron. 4) a repeat of the movement state after BMI learning. Although the conditioning targeted the activity of a single neuron, the entire network exhibited extensive changes in both firing rates and functional connectivity patterns. In addition to increased activity of the target neuron, increased activities and decreased activities were balanced over the population of the non-target neurons. Neuronal activity patterns during the BMI task were markedly different from the patterns in the movement state. These changes appeared not to be related to either sensory stimuli or physical movements. They found that the patterns in the BMI state were initially similar to those in the observation-state and evolved to produce an increase in the firing rate of the target neuron. They further found that the non-target neurons having negative spike count correlations with the target neuron during the observation-state tended to decrease their firing rate, whereas those having positive correlations with the target neuron tended to increase their firing rate. It is not clear what information processing the activity pattern during the observation-state represented. We suppose that they might represent the on-going activity when not engaging in any movement.

Dopaminergic neurons in the basal ganglia are related to the reward system and are considered to play a significant role in reinforcement learning (Schultz, 2015). Neurons of the striatum in the basal ganglia have dopamine receptors. Koralek et al. (2012) investigated the functional role of the striatum in adaptive neuronal changes in NOC. Microelectrodes were implanted in the rodent motor cortex (M1) and the dorsal striatum (DS) and activities of the neuron ensemble in M1 were set to control the one-dimensional position of an auditory cursor. When the cursor reached the target, a reward was delivered. Proximity to the target was continuously indicated to the animals by auditory feedback of the changes in tone pitch. As the success rate increased, the neurons in DS increased their activities. Increases in activities of DS neurons were dominant during the period a few seconds before the cursor reached the target. The contribution of the long-term potentiation in the DS to the adaptive changes was confirmed by the fact that mutant mice lacking NMDA receptors in their striatum neurons failed to improve the success rate. They further investigated the temporal relation between the neural activities in the M1 and DS (Koralek et al., 2013). They observed that increased success rate was associated with an increase in the coherence of the local field potentials (LFPs) in the low-frequency bands between the M1 and DS. Although the mechanism during the learning phase remains unclear, their results suggested that M1 or DS spikes in one region induce oscillatory LFP in the other region and lead to synchronous oscillatory LFPs in the corticostriatal network. Recently, the same NOC task was applied to neurons in the rodent primary visual cortex (V1) (Neely et al., 2018). The firing rates of two neurons (direct neurons) were used for controlling an auditory cursor. The authors observed improved performance exceeding the chance rate. Correlations between the two direct neurons significantly increased over the course of the session. No such change was observed between

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the indirect neurons or between a direct neuron and the indirect neurons. It was therefore suggested that only the direct neurons were modulated. The authors further investigated the interaction between V1 and DS neurons by optogenetic inhibition of mice DS neurons during the training. Inhibition during the training prevented improvement of the success rate while the inhibition after completion of the learning did not affect the already improved performance. This result further confirmed the importance of the corticostriatal loop in NOC. The findings suggested the possibility that volitional controls of neural activities could occur even in the sensory cortex, which engages in information processing of sensory stimuli. The authors claimed that rats and mice can learn to produce arbitrary patterns of neural activity to control an auditory cursor and obtain a reward. As we have defined in the Introduction, in NOC, intrinsic functional characteristics of the recorded neuron are not taken into account in the decoding model. We can set the arbitrary activities of the recorded neurons as conditioned responses to the action in controlling environmental variables. The neuronal ensemble self-reorganizes their activities to acquire novel functional characteristics. Moritz and Fetz (2011) reported NOC experiment targeting high or low firing rates of a single neuron in the monkey motor cortex. The neurons were conditioned equally well independently of any directional tuning. They suggested that arbitrary single cortical neurons, regardless of the strength of directional tuning, are capable of controlling cursor movements in a one-dimensional BMI.

The target neural event of NOC is not necessarily the firing rate of a single neuron. There have been several attempts to extend the target events to oscillatory activities or synchronous spike firings between neurons. Engelhard et al. (2013) recorded LFPs in the monkey motor cortex by a two-dimensional electrode array (Utah probe). The electrode grid spanned an area of 4 mm × 4 mm on the cortical surface. Initially, the monkey was trained to perform a center-out reaching task to one of eight directions. The task was then switched to a NOC task in which distance of the cursor from the center was controlled by the power strength of the gamma band in the LFP of a selected recording site. The monkey successfully increased the gamma power to move the cursor to the target and received a reward. Increase of the gamma power was also observed in a wider area of 500 μm from the target recording site. The authors reported that the gamma power in the LFP decreased with distance from the target recording site. Although LFP is a signal of lower special resolution than the single unit activity, the localized increase of gamma power suggested that the brain identified the target activity having a direct causality with the reward. They also recorded spike activities of the neurons and observed that neural firings were tightly synchronized with oscillations in the LFP. Therefore, conditioning of the LFP led to synchronous firings of large numbers of neurons around the target recording site. Since the gamma power was calculated by the mean power in the frequency range of 30–43 Hz, the conditioning did not require oscillatory LFP with a sharp spectrum peak. However, induced oscillatory LFP had very narrow peak around 34 Hz. This property suggests that adaptive change of the neuron ensemble (oscillation frequency of the LFP) was restricted by intrinsic properties of the neural network.

Conditioning of synchronous spike firings was examined by Sakurai and Takahashi (2013). They recorded multiple neurons from the rat hippocampus CA1 region and successfully trained rats in two operant conditioning tasks. In the first task, the target event was to increase the firing rates of a group of neurons. In the second task, the target event was switched to achieve synchronous spike firings among the same group of neurons. They observed that a larger number of neuron pairs showed synchronous firing in the second task than the first task. Non-target neurons did not show a significant increase of their firing rates.

3. Adaptations in BMI based on decoding model (dBMI)

Contrary to NOC, in which particular neuronal activities are trained to become a conditioned response to control the interaction with the environment, the interaction in dBMI is mediated by the decoding model of neuronal activities constructed based on their intrinsic functional characteristics such as direction tuning properties of arm movement. Therefore the selection of the decoding model strongly influences the adaptive behavior of neuron ensemble activities. We can explore how the activities of a neuron ensemble self-reorganize to compensate for the perturbations imposed on the learned decoding model. Hwang et al. (2013) discussed two possible mechanisms of adaptation in dBMI:

1) *Individual neuron*: A learning mechanism that facilitates independent adaptation of individual neurons. There is no change in activities of the non-target neurons. The brain could learn to produce virtually any arbitrary activity pattern.
2) *Intrinsic variable*: Since neural networks are functionally structured to manipulate an intrinsic variable of natural movements such as target direction, independent adaptation of individual neurons is difficult because a global network of neurons is sensitive to the manipulated variable. Learning of arbitrary patterns is not guaranteed because of the limited repertoires of activity patterns associated with natural movements.

In order to distinguish the two possibilities, the authors recorded multiple neurons in the monkey parietal reach region and imposed a BMI task based on one of the neurons (trained neuron). The recorded neurons had their own directional tuning of the hand movement. After training of a target pointing task by hand to two targets in opposite directions, the task was successfully switched to a BMI task in which pointing directions were determined by the firing rate (high or low) of the trained neuron during the delay period before the GO signal. They observed that, during the BMI task, not only the trained (target) neuron but also the untrained (non-target) neurons showed similar direction tuned activity profiles as in the hand movement task. Following their notations, here we call trained neuron and untrained neuron rather than target neuron and non-target neuron. Then, a BMI decoding model was modified (BMI-anti) so that the pointing directions were anti-correlated with the intrinsic direction tuning of the trained neuron. High firing rates led to pointing in the opposite direction of its preferred direction. They observed that the trained neuron did flip its direction tuning property to succeed in the BMI-anti-pointing task. However, they also observed that other untrained neurons also flipped their tuning properties. They concluded that the observation of such global re-aiming did not support the individual-neuron scheme.

They further extended the BMI decoding model to population activities of the two neurons. At first, the authors made a two-dimensional scatter plot of the joint firing rates of the two neurons in the same trial. The plot showed two isolated clusters of multiple trial data corresponding to the hand movement to two opposite directions (red and black dots in Fig. 3A). They set up a linear boundary separating the two clusters and a BMI decoder determined a pointing direction depending on which side of the boundary the joint activity fell in (black lines in Fig. 3A and B). Under this decoder (BMI-pro), movement to one of the directions S1 was attained by higher firing rates of neuron 1 and lower firing rates of neuron 2. In addition, lower firing rates of neuron 1 and higher firing rates of neuron 2 led to the movement to the opposite direction S2. The two neurons successfully generated adequate joint activities for correct pointing directions. They modified a BMI decoding model (BMI-mix) by setting a different linear boundary (red lines in Fig. 3A and C). For correct pointing directions, only neuron 2 needed to flip its direction tuning. The monkey immediately produced appropri-

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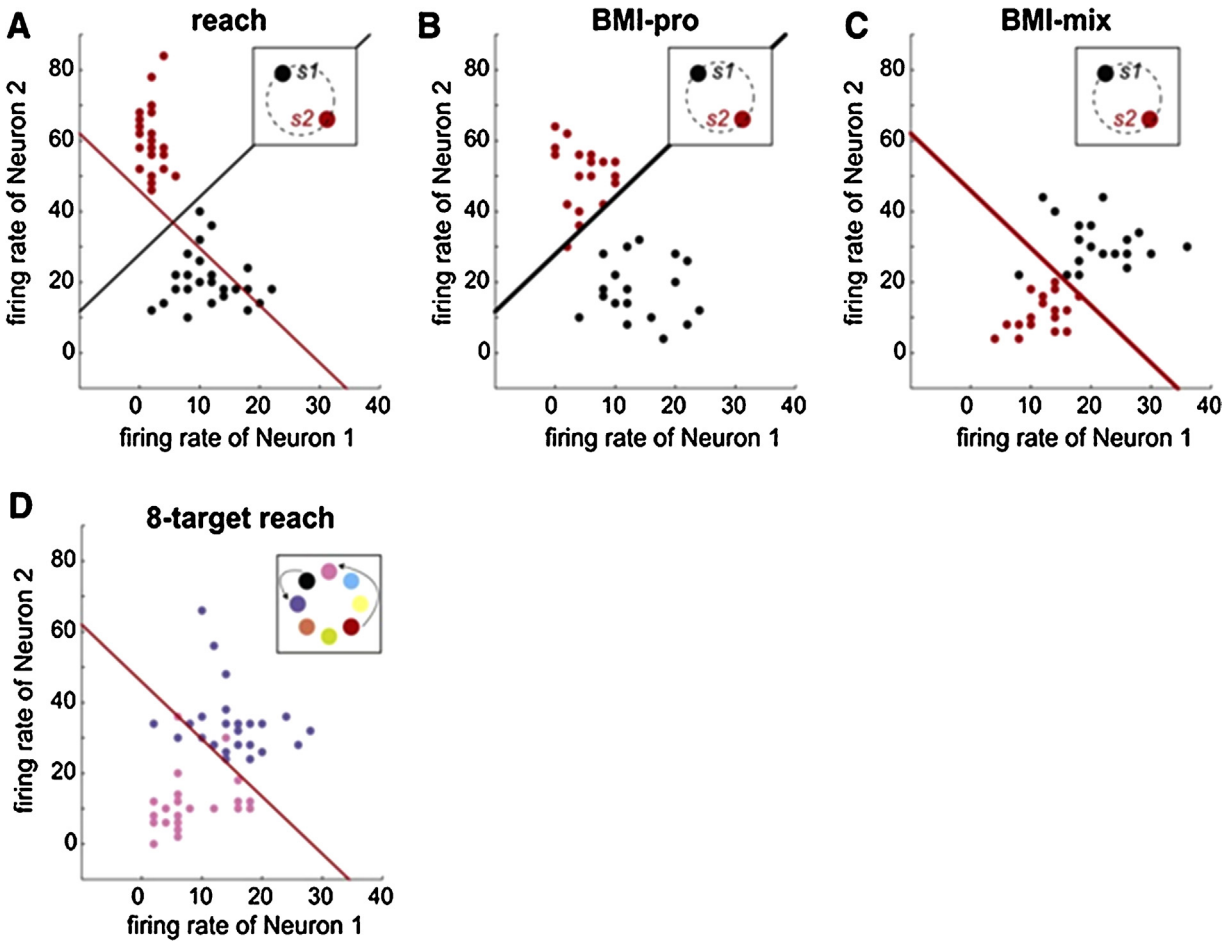

Fig. 3. BMI task based on joint firing rates of two neurons. A-C: Joint firing rates of two trained neurons in response to two pointing directions (color coded) in the reach, BMI-pro, and BMI-mix tasks. Unit of the firing rates in the plots is spikes/s. The black and red lines represent the linear boundary used for decoding in the BMI-pro and BMI-mix tasks, respectively. The insets show the location of the two pointing directions. D: Joint firing rates of the same two neurons for reach to two of the eight target directions (purple and pink in the inset). From, Hwang et al. (2013) with permission.

ate joint activity patterns. They pointed out that each of imposed joint activity pattern (Fig. 3C) was similar to the activity pattern in natural reach task to one of the eight targets (Fig. 3D). These observations led them to conclude that the neurons in the parietal reach region could adapt their activity pattern to an imposed BMI model, but those patterns were limited within the activity repertoire associated with the natural movement.

We think that their experimental results do not necessarily support their conclusion. First of all, the two target directions in BMI-mix task (red and black in inset of Fig. 3D) and the directions of the actual reach task that produce similar activity patterns to those in BMI-mix task (pink and purple in inset of Fig. 3D) did not have any systematic relationship such as global re-aiming. By plotting joint activities of the two neurons in the scatter plot, combinations of the tuning properties of the two neurons lead to different placements of the clusters for eight different movement directions. It is probable that we could find the activity pattern (cluster, repertoire) similar to the target activity pattern in BMI-mix task. For the validation of the intrinsic-variable scheme, we need to impose the target activity patterns that cannot be generated by the natural movements. Recently, they executed the same experiment on the human anterior intraparietal cortex (AIP) (Sakellaridi et al., 2019). In addition to reproduction of the previous results of the monkey experiment (Hwang et al., 2013), the authors extended the previous BMI-mix task to BMI-non-feasible task. They set a linear boundary such that the subject could not compensate for the BMI decoder by any remapping strategy to preexisting joint activities of the two neurons over eight directions. The subject could not learn to produce rule-complying activity patterns. They concluded that AIP neurons could not generate novel activity patterns, independent of the preexisting neuronal structure. Therefore, they reached at basically the same paradigm as Sadtler et al. (2014) that there is a constraint on learning imposed by the existing neural structure (intrinsic manifold) or more extensive training is required to generate entirely novel neuronal activity patterns. The idea of an intrinsic manifold will be discussed later in this section.

Jarosiewicz et al. reported a BMI experiment based on multiple neurons (median of the number of recorded neurons was 26) in the monkey motor cortex (Jarosiewicz et al., 2008; Chase et al., 2012). The monkey performed center-out reaching task to eight directions in 3D virtual reality (VR) space by the population vector computed by the vector sum of preferred directions of the recorded neurons weighted by their normalized activities. After the monkey had adapted to the BMI model, they perturbed the decoding model. The decoding-preferred directions of a randomly selected subset of units (rotated neurons, 25 % or 50 % of the recorded units) were altered from their measured value by rotating them 90° around one of the x, y, z axes. The preferred directions of all the perturbed neurons were rotated around a common axis. They discussed three possible strategies to compensate for the errors caused by the perturbations: 1) Re-aiming: aiming for a virtual target location that offsets the visuomotor rotation. 2) Reweighting: selectively

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suppressing the modulation depths of the activities (tuning amplitudes) of the rotated neurons. 3) Remapping: selectively changing the directional tunings of the rotated neurons. While re-aiming is a global strategy over all the recorded neurons, reweighting and remapping are local strategies requiring selective change to the rotated neurons. Although they observed all the adaptation strategies in their data, the dominant strategy employed by the subjects was global re-aiming, accounting for ~86 % of the total error reduction. The remaining 14 % of the error reduction could be attributed to local changes in tuning curves (reweighting and remapping). Rotated neurons tended to shift their preferred directions towards the decoding-preferred direction rotation. Changes in the preferred directions of nonrotated neurons were weaker and significantly less strongly biased toward the direction of rotation than the preferred directions of rotated neurons. The authors suggested that global adaptation strategy is a suboptimal response to these perturbations, implying that there are constraints on the network's ability to rapidly identify the optimal solution to a given perturbation.

Ganguly and Carmena (2009) imposed a fixed BMI decoding model to the monkey motor cortex for a long duration (up to 19 days) and observed long-term adaptation of the recorded neurons. Initially, they trained monkeys to perform a center-out reaching task to eight directions and constructed a linear regression model that predicted the motion of the cursor from firing rates of multiple recorded neurons (10–15 neurons). A stable level of performance was obtained after 8 days. The authors found that an increase in the performance was strongly associated with changes in the direction tuning properties of the recorded neurons. Once stable performance was obtained, the tuning properties of the neurons were also stabilized. They further examined whether the ensemble of neurons could learn an arbitrary fixed decoding model. The decoding model was perturbed by shuffling the coefficients of the linear regression model. Surprisingly, the neuron ensemble adapted to this nonbiomimetic decoder after several days. Furthermore, they reported that the neuron ensemble could adapt to multiple decoding models. After the neuron ensemble had adapted to a decoding model, they imposed another decoding model. On each day, a BMI task with the new decoding model was suddenly switched to a BMI task with the old decoding model. They observed that, while it took several days for the neuron ensemble to adapt to the new decoder, the neuron ensemble immediately adapted upon reversion to the old decoding model. Therefore, the neuron ensemble could rapidly reorganize its activity patterns to the pre-learned model accompanied by corresponding changes of tuning properties of the neurons. Since those neurons also participated in the control of natural arm movement for a greater part of the day, the neuron ensemble could switch into one of the three different modes in a context dependent manner based on the change in decoding model.

Ganguly et al. (2011) further examined the changes in activities of the indirect neurons, that is, recorded but not used in the decoding model. Those neurons have an indirect causality relationship with the cursor movement only through interaction with the direct neurons. The authors trained monkeys to adapt to the BMI decoding model which was obtained by a linear regression of firing rates of the direct neurons to predict the natural arm movement. They found that the indirect neurons also experienced a change in their preferred directions similar to that of the direct neurons. They subdivided the indirect neurons into two groups (near and far) by their distance from the direct neurons. There was no significant difference in the percentage and the extent of changes in the preferred direction between the two groups. Although there were large-scale changes in the preferred direction of both direct and indirect neurons, the indirect neurons had a more significant reduction in the modulation amplitude of the direction tuning (tuning amplitude) than the direct neurons. Therefore, to some extent the neuron ensemble was sensitive to the causality with the cursor movement and solved credit assignment problem. As their previous experimental reports indicate (Ganguly and Carmena, 2009), both the preferred directions and the modulation amplitudes settled back to their original values when the task was switched to the manual arm movement.

While Ganguly et al. (2009, 2011) demonstrated that a neuron ensemble can perform flexible adaptation even to a nonbiomimetic decoder over a long-term training period, Sadtler et al. (2014) discussed the existence of constraints for adaptive change of neuronal activity patterns over a short-time training period. Sadtler et al. recorded multiple neurons (85–91 units) in the monkey motor cortex and introduced the idea of *intrinsic manifold,* which is a geometrical subset in the configuration space of joint activities of the recorded neurons. In statistical analysis of multiple neurons, we often consider a high-dimensional activity space in which each axis corresponds to the firing rate of an individual neuron (see Fig. 3 for the case of two neurons). By plotting the joint firing rates of all the neurons recorded in the same trials in the rat auditory cortex, Luczak et al. (2009) found that even on-going (spontaneous) activities under a no stimulus condition were restricted within a limited geometrical structure. Finite spike count correlations among the neurons restricted independent activity of each neuron and such geometrical restriction reduced effective dimensionality of the ensemble activities. Sadtler et al. examined how the constraint in the activity space influenced adaptive changes of the neuron ensemble to the BMI decoding model. The authors applied a dimensional reduction by factor analysis to the activities of multiple neurons during the calibration session. High-dimensional activity patterns were described in terms of a low dimensional set of factors, and named this low dimensional subspace intrinsic manifold. They set up a one-dimensional subspace on the intrinsic manifold (BMI control space) and imposed a BMI decoding model (intuitive mapping) so that the cursor position was controlled by the position of the neuron activities in the BMI control space. Intuitive mapping was constructed by a modified version of the standard Kalman filter. Fig. 4A schematically depicts an intrinsic manifold in the activity space of three neurons. For simplicity, the intrinsic manifold is represented by a plane and the joint activities in each trial (dots in Fig. 4A) are restricted to this plane. One-dimensional BMI control space is shown by a line on the intrinsic manifold, which restricts the joint activities of the three neurons. For example, suppose that along this line neuron 1 has a positive spike count correlation with neuron 2 and a negative correlation with neuron 3; in this case, an increase in the firing rate of neuron 1 should be associated with an increase and decrease in neuron 2 and neuron 3, respectively.

Sadtler et al. at first defined a BMI control space and trained a monkey in a BMI decoding model along this line. After the monkey had adapted to the model, they perturbed BMI model by imposing joint activities along different BMI control space (Fig. 4B). There are two kinds of perturbations. For within-manifold perturbation, BMI control space remains on the intrinsic manifold (dashed line in Fig. 4B). For outside-manifold perturbation, BMI control space departs from the intrinsic manifold (red line in Fig. 4B). They found that the neuron ensemble rapidly adapted to within-manifold perturbation. A new BMI control space was still on the intrinsic manifold and the neuron ensemble can change their activity pattern satisfying spike count correlations along the BMI control space. On the other hand, the neuron ensemble could not adapt to outside-manifold perturbation in training over a short time scale. We consider that in order to generate the required correlated activities, the neural network needed to modify its anatomical structure by changing synaptic connections and to extend/deform the intrinsic manifold such that the imposed BMI control space would be included on the intrinsic manifold.

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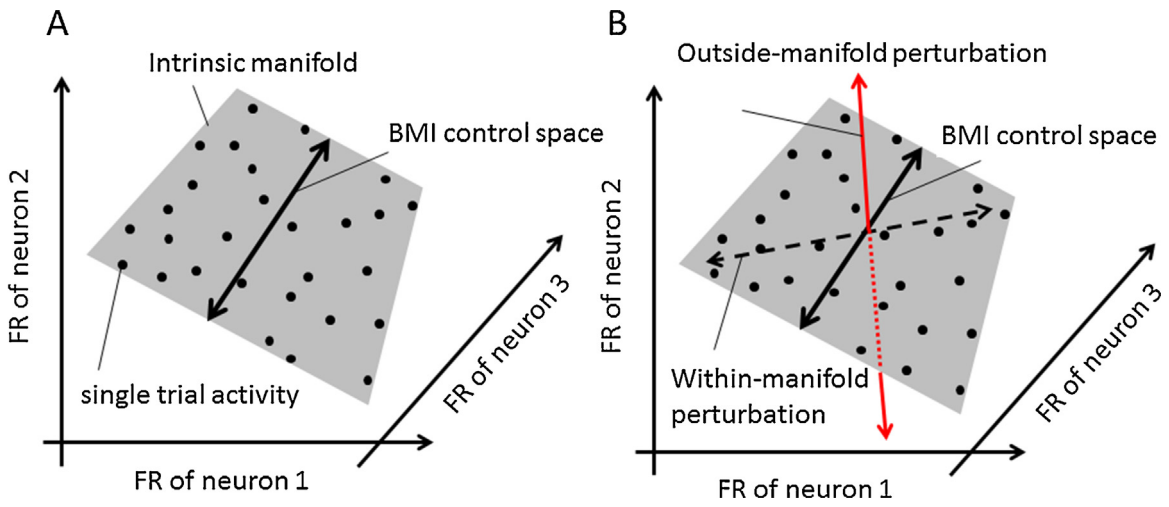

Fig. 4. Schematic view of intrinsic manifold and adaptations to two kinds of perturbations. A: The activity space of three neurons. Each axis represents the firing rate (FR) of an individual neuron. Each dot represents the joint activity of three neurons in a single trial. Spike count correlations restricted the joint activities to the intrinsic manifold (grey plane). The cursor position is controlled by the location of the joint activity along one-dimensional BMI control space (solid line). B: After the neuron ensemble has adapted to a BMI decoding model, the BMI model is perturbed by imposing the joint activities along the different BMI control space (dashed line and red line). For within-manifold perturbation, BMI control space remains on the intrinsic manifold (dashed line). For outside-manifold perturbation, BMI control space departs from the intrinsic manifold (red line) (adapted from [Sadtler et al., 2014]).

4. Model simulations of adaptive changes of neuronal activity patterns

Several computational models have been proposed to reproduce the adaptive changes of neuronal activity patterns observed in the experiments. The point of the modeling is determine how we can implement a learning mechanism to solve the credit assignment problem: based on only the global feedback of cursor movement, the neuronal network needs to identify which subset of neurons contribute more to cursor error and how those direct neurons needs to be changed. Most of the proposed models adopted learning algorithms of synaptic strength based on the activity-reward covariance rule. The same kind of learning rule has been well studied in dopamine-dependent plasticity of corticostriatal synapses in the model of reinforcement learning (Reynolds and Wickens, 2002).

Legenstein et al. (2010) proposed a network model to reproduce the experimental observations in the monkey motor cortex by Jarosiewicz et al. (2008). As explained in the previous section, a BMI model of the population vector was perturbed by rotating the decoding-preferred directions of a part of the neuron population. The network adapted to the perturbation both by a global strategy of re-aiming and by a local strategy of changes in their direction tunings (reweighting and remapping). Legenstein et al. successfully reproduced those adaptive changes in simulations of two layered feed-forward networks composed of an input layer and a motor cortex layer (Fig. 5). The input layer consists of m = 100 neurons with activities $x_1(t), \ldots, x_m(t)$. The motor cortex layer receives inputs from the input population and consists of n_{total} = 340 neurons with activities $s_1(t), \ldots, s_{n_{\text{total}}}(t)$. All of the modeled motor cortical neurons were used to determine the monkey arm velocity in their model; however, only n = 40 of these (the "recorded" neurons) were used for cursor control. The total synaptic input $a_i(t)$ to the cortical neuron i was modeled as a noisy weighted linear sum of its inputs:

$$a_i(t) = \sum_{j=1}^{m} w_{ij} x_j(t) + \xi_i(t),$$

where w_{ij} is the synaptic efficacy from input neuron j to cortical neuron i and $\xi_i(t)$ models an additional noise input. The activity $s_i(t)$ of neuron i was modeled as a rectified linear function (ReLU) of the total synaptic input $a_i(t)$. The cursor velocity $\boldsymbol{y}(t)$ was computed as the vector sum of the decoding-preferred directions (dPDs) weighted by the baseline activity subtracted and normalized activities of $s_i(t)$ over all the recorded neurons. The adaptation of the network to the perturbation proceeded by the changes in synaptic efficacy w_{ij} according to the activity-reward covariance learning rule,

$$\Delta w_{ij}(t) \propto x_j(t)[a_i(t) - \overline{a_i(t)}][R(t) - \overline{R(t)}]$$

where $\overline{a_i(t)}$ and $\overline{R(t)}$, respectively, denote the low-pass filtered version of the total synaptic input to cortical neuron i and that of the reward signal. The changes of activities in the postsynaptic cortical neurons were induced by the noise inputs (the exploratory signals).

Heliot et al. proposed a computational/engineering model, which was not a network model of neurons. Firing rates of the recorded neurons are the system variable and the decoder function transforms a vector of the firing rates to a cursor position. Learning of the system toward the adaptive state is guided by an error descent (ED) learning algorithm developed in machine learning (Cauwenberghs, 1993). Change of the firing rates induced by noise inputs leads to change of the error in the cursor position. The ED algorithm calculates a gradient of the error to the change of the firing rates and changes the firing rates of the neurons toward the direction of the steepest descent. Same as the back propagation algorithm in artificial multi-layer neural network, in order to solve the credit assignment problem, the ED algorithm transmits the error signal in the macroscopic level back to the microscopic variables of the firing rates. Since the gradient of the error in the cursor position to the change of firing rates represents interdependence between the two variables, this learning algorithm is essentially based on the same mechanism as the activity-reward covariance rule adopted by Legenstein et al. In addition to the activity-reward covariance rule, the two models share another mechanism - that is, exploration of the adaptive state is driven by structureless noises added to the neural activities. Increases in neuronal noise, or trial-to-trial variabilities, during the adaptation period were reported in many experiments (Arduin et al., 2013; Mandelblat-Cerf et al., 2009).

Ganguly and Carmena (2009) constructed a decoding model in which movement of the cursor in manual control was predicted by

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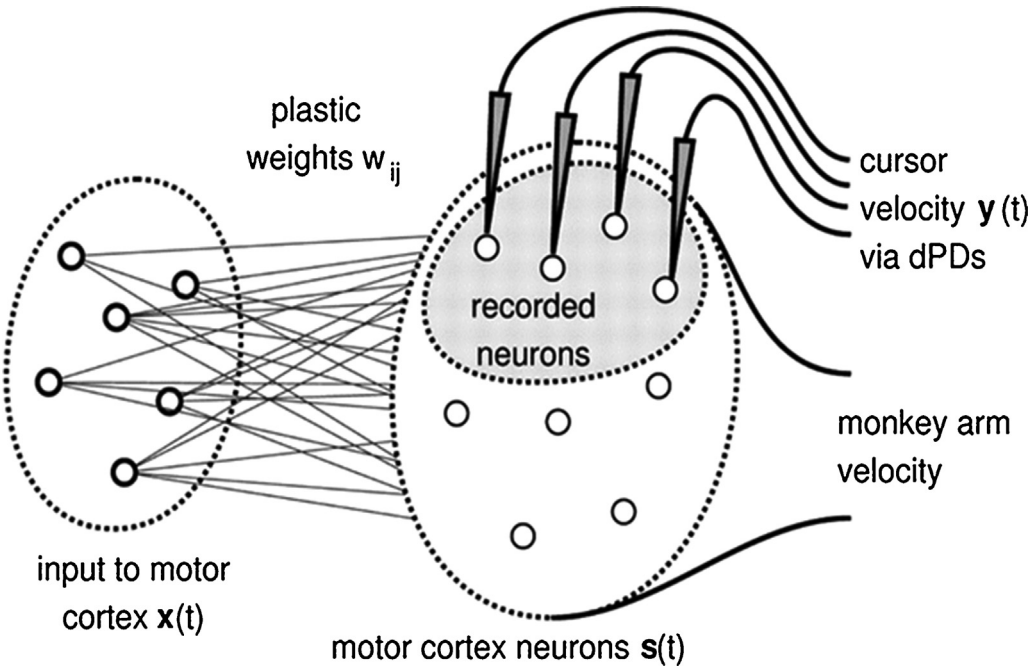

Fig. 5. Schematic view of the network model used for the cursor control task. A set of neurons in input pool project to noisy neurons in motor cortex. Arm movement was modeled by a fixed linear mapping from the activities of the modeled motor cortex neurons to the 3D velocity vector of the monkey arm. A subset of neurons in the simulated motor cortex was recorded for cursor control. The velocity of the cursor movement was given by the population vector, which is the vector sum of decoding-preferred directions of the recorded neurons weighted by their normalized activities. Learning was proceeded by updating the synaptic weight from the input neurons to the cortical neurons. From Legenstein et al. (2010) with permission.

the linear regression of instantaneous firing rates of direction tuned neurons in a monkey. They then imposed the perturbed linear regression model which randomly shuffled the linear coefficients. Contrary to the global adaptation strategy reported by Jarosiewicz et al. (2008), they observed a change in preferred direction in individual neurons (local strategy) to compensate for the perturbation. Heliot et al. successfully reproduced those experimental observations by simulations of their model. They also simulated the adaptive changes of the neuron population in response to the perturbation tested by Jarosiewicz et al. (2008). Both the experimental results and the model simulation by Legenstein et al. showed non-optimal adaptation by global re-aiming of all the neurons. Heliot et al. also showed that in the early stage of learning, there was a shift in tuning directions of all neurons to compensate for the perturbation. However, after those early responses, the system identified the rotated neurons with perturbed decoding-preferred direction and changed their preferred directions accordingly (local strategy). At the end, only the rotated neurons changed their preferred direction by 90 degrees and the preferred directions of the nonrotated neurons settled back to their original value.

Engelhard et al. (Engelhard, 2015; Engelhard et al., 2019) reported their NOC experiment in which a monkey received rewards by increasing the firing rate of a single motor cortical neuron (see Section 2). They also reproduced many of their experimental observations by simulations of the balanced network model (van Vreeswijk and Sompolinsky, 1996). Due to balanced interconnections of excitation and inhibition, the model realizes the basic characteristics of cortical activities, low firing, and weak spike count correlation between the neurons. The authors prepared another neuron pool sending weak, plastic, feed-forward connectivity to the balanced network. Except for the balanced network, their model is similar to the two-layer network model proposed by Legenstein et al. (2010). A target neuron was chosen randomly from the balanced network, and feed-forward synapses from the input neuron pool to the neurons in the balanced network were updated according to the activity-reward covariance rule. The synapse was strengthened (weakened) when the mean-subtracted firing rate of the postsynaptic neuron had positive (negative) covariance with the presence of the reward. Their model is also based on the two mechanisms which guide adaptive change: the activity-reward covariance rule and noise for exploration. Engelhard et al. stressed that, contrary to the previous models by Legenstein et al. and Heliot et al., artificial noise input was not necessary in their model because chaotic behavior of the balanced network itself produced variability.

5. NOC and dBMI of human subjects and their clinical applications

Invasive implantations of recording electrodes have been limited to some pilot trials. The most developed clinical applications are the controls of a robotic arm by the multiple neurons recorded by an electrode array (Utah probe) implanted in the motor cortex of patients (spinal cord injury, tetrariplegia) (Hochberg et al., 2006, 2012). Recently, wide band EEG signals can be recorded by subdural ECoG electrodes implanted in epilepsy or stroke patients. Clinical applications of ECoG-based BMI and NOC have been used to develop therapies for neuro-rehabilitation (Leuthardt et al., 2004; Hirata and Yoshimine, 2015).

Most of NOC experiments introduced in this review set up a closed loop feedback between the brain and the environment. For clinical application, adaptive changes of neural activities have been studied in a closed loop feedback between the two brain areas. By implanting artificial neural connections, Moritz et al. (2008) demonstrated that a monkey could directly control stimulation of muscles using the activity of neurons in the motor cortex. Nishimura et al. (2013) also implanted artificial neural connections to a monkey with a unilateral spinal cord lesion. By bridging the impaired spinal lesion, the monkey drove spinal stimulation through volitionally controlled power of high-gamma activity in either the premotor or motor cortex. Although the clinical applications of closed loop feedback between the two brain areas have

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been still in an early stage, there were some pilot human studies of nerve stimulations associated with the body movements. Sasada et al. (2014) succeeded in initiating the walking-like behavior by an artificial neural connection, in which the EMG activities of the rhythmic voluntary movements of the shoulder muscle were converted to the transcranial magnetic stimuli (TMS) at the lumbar vertebra. Koganemaru et al. (2019) reported a significant increase in the speed of self-paced gait by the stroke patient, under oscillatory transcranial direct current stimulation (tDCS) to the primary motor cortex synchronized with individual gait rhythm.

Many NOC and dBMI experiments on human subjects have been based on surface EEG signals. Research focus in this subject has been developed by some of pioneering studies (Wolpaw et al., 2000) rather independently from animal NOC and dBMI experiments. Historically, the corresponding experiments using human subjects were collectively named Brain-Computer Interface (BCI). Previous BCI studies have been reviewed in Sitaram et al. (2017). For example, in stroke patients with hand movement paralysis, a neurofeedback treatment via EEG was examined, for which the target score was designed to increase activity in the lesion area (Mottaz et al., 2018). The patients were instructed to increase the score displayed on a monitor without moving their hands. The training induced changes in activities in the lesion area and, moreover, Fugl-Meyer Assessment scores improved after the training. Keizer et al. (2010) reported a neurofeedback experiment by surface EEG recorded at the occipital and frontal sites. They observed that volitionally increased gamma band activity led to improved performance on cognitive tests of sensory binding and memory.

Magnetoencephalography (MEG) was also used for neurofeedback to reduce phantom limb pain (Yanagisawa et al., 2016). Phantom limb pain is not a motor dysfunction, but it is sometimes induced by missing limbs. Although the mechanism of phantom limb pain remains unclear, according to the results of mirror therapy (Ramachandran et al., 1995), it seems to be related to a mismatch between the motion and sensory representations in the brain. To reduce pain, the effect of neurofeedback via MEG was investigated, in which patients were instructed to control the virtual reality (VR) hands on a monitor (Yanagisawa et al., 2016). Contrary to mirror therapy, the patients were told to control the VR hands based on MEG signals from their motor cortex of the affected side. The training successfully increased activity of the motor cortex corresponding to the affected hand. However, contrary to their initial expectation, they reported that training increased the pain score as well.

Decoded Neurofeedback (DecNef) is regarded as one of the most successful NOC protocols in human subjects. Shibata et al. (2011) collected fMRI voxel data from the visual areas under visual presentations of three gratings with different orientations. By applying dimensional reduction using the sparse logistic regression algorithm, they developed a decoder that classified the voxel patterns into one of the three orientations. The decoder computed the correlation coefficient between the input voxel pattern and each of the three voxel patterns corresponding to different gratings, and then selected the orientation having the maximum correlation. The subjects were instructed to increase a radius of the disk presented on the monitor by modifying their brain activity; they were not informed that the radius was related to the correlation coefficient between the current voxel pattern and the voxel pattern of one of the selected orientations. After the subjects had successfully increased the radius, their visual abilities in orientation identification were measured by presentations of the three gratings of low contrasts. Interestingly, the orientation identifications were significantly improved only for the orientation used in the DecNef training. DecNef has been mainly used for intervention into visual perception and emotion in humans (Watanabe et al., 2017). Neural activities in the early visual area during viewing of the color red were scanned by fMRI, and based on these voxel data, the DecNef was designed (Amano et al., 2016). After presentation of a vertical achromatic grating, the subjects were trained to increase the radius of the disk on the monitor by modifying their brain activities. The radius represented the correlation coefficient between the current voxel pattern and the voxel pattern under presentation of the color red. After three days of training, the subjects came to perceive red color significantly more frequently than green color in an achromatic vertical grating. They suggested that associative learning of orientation and color was successfully trained by DecNef. In a similar way, the potential in clinical applications has been shown that emotions such as fear could be modulated by DecNef (Koizumi et al., 2016).

6. Discussion

We have reviewed several experimental observations and model simulations in the research subject of BMI. We classified studies of BMIs into two categories depending on their protocols; BMI based on decoding model and BMI based on neural operant conditioning. In this review, the two categories were represented simply by dBMI and NOC, respectively. In those experimental protocols, neuronal activities in the brain are forced to interact directly with the environment. Under a closed loop feedback with the environment, the neuron ensemble self-reorganized their activity patterns and completed a transition to an adaptive state within a short time. Many experiments have suggested that the brain could solve a credit assignment problem; that is, the brain can identify the target neurons having a direct causality with the environment and determine in which direction the activities of those target neurons should be changed for adaptation. Since these research subjects have attracted much attention, there have been many recent experimental reports. As discussed in the previous sections, there still exist contradicting debates on the nature of adaptive changes observed in NOC and dBMI. At the end of this review, we summarize the current common understandings on the three basic questions that we addressed in Introduction:

1) *Can we condition the brain to generate arbitrary neuronal activity patterns?* NOT LIKELY for adaptation over a short time scale. The changes of neuron ensemble activities seem to be restricted by the intrinsic correlation structure of the neuronal network (constraint by intrinsic manifold).

LIKELY for adaptation over a long time scale. Modifications of synaptic connections enable the neuronal network to generate a novel activation pattern as required by NOC and dBMI (deformation/extension of intrinsic manifold).

2) *Is there any intrinsic and endogenous restriction of neural network to adaptive changes of the brain?* YES. The adaptive changes of neuron ensemble activities seem to be restricted by the intrinsic correlation structure of the neuronal network (constraint by intrinsic manifold).
3) *What neural mechanism guides the brain toward the adequate direction to reach the adaptive state within a short time?* Exploration of the adaptive activation pattern seems to be facilitated by restriction within a lower dimensional activation space (intrinsic manifold). Exploration is likely to be induced by temporal increase of neural noises (trial-to-trial variabilities) during the adaptation period. Although many computational models assumed learning occurred using the activation-reward covariance rule, the physiological mechanism of such inter-scale interactions (between microscopic neural activities and macroscopic reward) needs to be discussed.

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6.1. Constraint by correlation structure of network activities – intrinsic manifold

Since the intrinsic manifold is a novel concept, researchers seem to interpret their experimental results by their own definitions of the intrinsic manifold. Currently, there are at least two possible definitions. Firstly, we can define the intrinsic manifold by the set of all the activity patterns of the recorded neurons (repertoires) over natural movements, such as hand movement to eight directions. As explained in Section 3, Sakellaridi et al. reported that a human subject could not generate novel patterns of activity independent of the preexisting neuronal repertoires in natural movements. An alternate definition of the intrinsic manifold is the set of all possible activity patterns of the recorded neurons realized in the neuronal network, including the on-going activities (Luczak et al., 2009). It is well known that the neuronal network can generate diverse activity patterns even under fixed anatomical connections (Luczak et al., 2009; Sporns, 2011). There were several experimental reports and model simulations showing context dependent changes of the correlation structure in a neuron ensemble (effective connectivity by Aertsen et al., 1989). Spike count correlations between two neurons in the visual cortex showed significant orientation dependence and some of the neuron pairs changed the direction of the correlation (Maruyama and Ito, 2013). In this definition, the intrinsic manifold is the union of all the possible dynamical states of the recorded neuron ensemble in the activity pattern space (phase space in dynamical system, see Fig. 3 for a space of the joint firing rates of two neurons). Luczak et al. (2009) found that the activity patterns in the rat auditory cortex induced by different tone stimuli were subsets of the possible activity patterns realized in the on-going activity.

In addition to the credit assignment problem, we face another problem in the curse of dimensionality (Watanabe et al., 2017) - that is, how the neuron ensemble can find an optimal state in a short time by exploration of a very-high-dimensional activity space. Many experiments reported adaptations over a rather short time scale (a few minutes to a few hours). It is probable that the neuron ensemble could find an optimal state because exploration is restricted within a relatively low dimensional space on the intrinsic manifold. In order to facilitate systematic discussions on the mechanism of adaptive changes in neuron ensembles, a mathematical definition of the intrinsic manifold should be discussed.

6.2. Discussion for unified understanding of different experimental results

The two experiments by Hwang et al. (2013) and Engelhard et al. (2019) enforced increased activity of a single cortical neuron. As introduced in Sections 2 and 3, the authors commonly succeeded in the conditioning of target neuron and observed extensive changes in non-target neurons. However, they observed different adaptive changes in the network activities. Hwang et al. reported that the network adapted to perturbations by globally re-aiming to the preexisting activity repertoire of the natural movements. On the other hand, Engelhard et al. reported that activity patterns during the BMI task were markedly different from those during the movement state. These changes appeared not to be related to either the sensory stimulus or physical movements. They found that the patterns in the BMI state were initially similar to those of the passive observation-state and evolved to produce an increase in the firing rate of the target neuron. We suppose that the inconsistency between the two experiments derives from the different methods of conditioning the target neuron. Hwang et al. imposed a dBMI task on the target neuron such that the movement of a cursor was controlled by the decoding model based on the directional tuning property of the target neuron. Therefore, the target neuron tried to adapt to the perturbation within the context of its functional characteristics. On the other hand, Engelhard et al. imposed a NOC task on the target neuron, in which simply an increase of the firing rate was conditioned and the target neuron tried to adapt to the perturbation without regard to its intrinsic functional properties. Since adaptive change in the neuronal network seems to be very flexible, it is probable that the system sensitively recognizes different causality contexts in the experimental setup and self-reorganizes accordingly. In order to understand the general mechanism of neuronal adaptations, we need to analyze what constraints we impose on the neural system and compare different experimental findings carefully and systematically.

Ganguly and Carmena (2009) observed long-term adaptive change in a neuron ensemble to a BMI decoding model. The neuron ensemble adapted even to a nonbiomimetic decoder after several days. Once the adaptation to the new BMI decoder was completed, the neuron ensemble could immediately adapt to either BMI decoder upon a switch between the two decoders. The neuron ensemble could rapidly reorganize its activity patterns to the pre-learned decoder accompanied by corresponding changes in the tuning properties of the neurons. We think those experimental results could be in concord with the idea of intrinsic manifold proposed by Sadtler et al. Rapid changes in the activity patterns of a neuron ensemble are not likely to be explained by changes in anatomical synaptic connections. We have defined the intrinsic manifold as the union of all possible dynamical states realized in the anatomically fixed neural network. A rapid change of the activation pattern could correspond to a transition to some other dynamical state satisfying the condition imposed by the given decoding model. In the experiment by Ganguly and Carmena, for adaptation to the new decoding model, the neuron ensemble needed to generate a novel activation pattern that could not be realized in the current neuronal network (outside of manifold perturbation). Therefore, the network needed a few days to modify its synaptic connections in order to generate the novel activation pattern. We note that this was an extension of the intrinsic manifold, because the network preserved its ability to generate activity patterns corresponding to the old decoding model. Once the novel repertoire of the dynamical state was added to the intrinsic manifold, the neuron ensemble could rapidly change its activity patterns in response to a switch between the two decoding models.

Engelhard (2015, 2019) trained a monkey to increase the firing rate of a single target neuron to receive a reward and observed extensive changes in the non-target neurons. The adaptation of the activity patterns of the network strongly depended on the neuronal correlation structure in the observation-state (possibly, on-going activity). The authors discussed that such constraint of the network dynamics was different from the constraint by the intrinsic manifold observed by Sadtler et al. (2014). They claimed that, in adaptive changes within the intrinsic manifold, the correlation pattern was fixed and therefore imposed a fixed constraint on learning. However, their experimental results and model simulations showed that the neural correlation structure that constrained the learning process was not fixed; instead, it could change dramatically depending on the action-perception state that precedes learning (observation-state). Still, we think that their experimental observations are consistent with constraint by the intrinsic manifold. As introduced in Section 2, after completion of the NOC task they repeated the natural movement task and confirmed that the network activity showed similar patterns to those in the same task before the NOC task. Again, those rapid changes were not likely to be associated with changes in synaptic connections. Those changes could be regarded as a transition to a dynamical state within the intrinsic manifold.

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6.3. Physiological plausibility of computational models

All the computational models introduced in Section 4 have been proposed to reproduce adaptive changes of neuronal activity patterns observed in the experiments. Both models by Legenstein et al. (2010) and Engelhard et al. (2019) were composed of two layered neural networks and adaptive changes of the neuron ensemble in the cortical layer were induced by the learning of feed-forward synaptic weights from the input layer. On the other hand, the computational/engineering model proposed by Heliot et al. (2010) was not a network model of neurons. Firing rates in the recorded neurons were the system variable and the decoder function transformed a vector of the firing rates to a cursor position. Learning of the system toward the adaptive state was guided by an error descent (ED) learning algorithm, which calculated a gradient of the error in cursor position to the change in firing rates and modified the firing rate of each neuron toward the direction of the steepest descent.

It is worth noting that, because of the lack of gradient knowledge, the ED algorithm required two time samples to compute the feedback adjustment. Two evaluations of the error term, hence two movements, were needed. The mechanism of the adaptation was based on the algorithm of machine learning and we need to discuss how that algorithm could be implemented in the actual neuronal network in the brain. The network models by Legenstein et al. and Engelhard et al. are physiologically more plausible, whereby adaptive changes proceed through self-reorganization of the neural network induced by the changes of local synaptic weights. However, their activity-reward covariance learning rule relies on a direct interaction between the microscopic variables, activities of neurons, and the macroscopic variable, amount of the reward. The information on the reward needs to be transmitted back to all the neurons in the motor cortex. A physiological mechanism of such cross-scale interaction should be discussed. In the research of reinforcement learning, global transmission of the reward signal is assumed to be mediated by dopamine. We wonder if there could exist any neural mechanism solving the credit assignment problem by identifying the target neuron more specifically. We need to explore a novel physiological mechanism that transmits macroscopic information to the microscopic neurons through cascades of physical events at different system scales. As introduced in Section 2, Carmena's group discussed a more specific neuronal mechanism guiding adaptive change. They reported that the development of adaptive change in the cortex required synchronized activities between the cortex and the striatum in the basal ganglia (Koralek et al., 2012, 2013, Neely et al., 2018).

6.4. Exploration of adaptive activity patterns induced by noises

Many experimental observations suggested that trial-to-trial variabilities of the neuron activities increased temporally during the adaptation period and settled back to the baseline upon achievement of adaptation. Other than NOC and dBMI tasks, an increase in trial-to-trial variabilities was reported in both the monkey primary motor cortex and the supplementary motor area during adaptation to the rotational visuomotor task (Mandelblat-Cerf et al., 2009). Traditionally, trial-to-trial variabilities have been regarded as stochastic noises which inevitably derive from fluctuations at multiple synaptic transmissions. They were assumed to have no functional role and degrade the fidelity of information transmissions in the brain. However, it is known now that trial-to-trial variabilities do not occur independently at each neuron, but there is a weak correlation of the variabilities between the neurons (spike count correlation). Recent experimental observations suggested possible functional significance of variabilities and spike count correlation (Cohen and Kohn, 2011). In all computational models introduced in Section 4, exploration for adaptive activity patterns was induced by neuronal noises. It is probable that the increase in variability during learning reflects a wider range search for a new appropriate configuration. However, this may be a teleological argument. We need to discuss a neuronal mechanism that induces an increase in variability when the current activities of the neuron ensemble no longer agree with the environment under the imposed perturbation.

7. Conclusion

This review covered several experimental observations and model simulations in the research subject of BMI. Studies of BMIs are classified into two categories depending on their protocols; BMI based on decoding model (dBMI) and BMI based on neural operant conditioning (NOC). Under a closed loop feedback with the environment, neuronal activities are forced to interact directly with the environment. Many experiments suggested that the neuron ensemble self-reorganized their activity patterns and completed a transition to an adaptive state within a short time period. The brain could identify the target neurons having a direct causality with the environment and found in which direction the activities of those target neurons should be changed for adaptation. Through integrations and comparisons of several experimental observations and model simulations, we attempted to summarize the current understanding on the nature of adaptive changes in the activation patterns. For adaptation over a short time scale, the changes of neuron ensemble activities seem to be restricted by the intrinsic correlation structure of the neuronal network (constraint by intrinsic manifold). However, for adaptation over a long time scale, the modifications of synaptic weights enable the neuronal network to generate a novel activation pattern required by NOC and dBMI (deformation/extension of intrinsic manifold). Exploration of adaptive activation patterns seems to be facilitated by restriction within a lower dimensional activation space of the intrinsic manifold. Exploration is likely to be induced by a temporal increase in neural noises during the adaptation period. Although many computational models assumed learning occurred by the activation-reward covariance rule, a physiological mechanism of such inter-scale interaction needs to be discussed. Understanding of the intrinsic constraints of adaptive changes in neuronal activities will provide basic principles of learning mechanisms in the brain and methodological clues for better performance in engineering and clinical applications of BMI.

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