

# Chapter 23

## Multipotentiality of the Brain to Be Revisited Repeatedly

Yoshio Sakurai, Tomoya Ohnuki, Ryo Shiroshita, Yukitoshi Sakaguchi, Kazuki Shiotani, and Chi Jung Lee

**Abstract** The brain is a unified entity that cannot realize any functions in its isolated regions. It is also so dynamic that the functions of its regions and neurons are not necessarily fixed. Historically, this natural notion has been confirmed repeatedly by several experimental findings and theoretical considerations including those by Sherrington, Lashley, Hebb, Olds, and John. However, this notion, which typically can be called “multipotentiality” of the brain proposed by E. R. John, has been repeatedly ignored. Most studies in modern neuroscience are searching for fixed and peculiar regions responsible for individual, even any higher, functions and trying to detect treasured single neurons. This article emphasizes again the multipotentiality and raises promising strategies to investigate such unique features of the brain. First, we introduce the historical background and revisit the pioneering studies and consider the impacts of their views on our understanding of brain structures and functions. The second section emphasizes that the brain-machine interfaces has been presenting the multipotentiality of the brain’s regions and neurons. The third section considers the clinical relevance of the multipotentiality, particularly in relation to neurorehabilitation and the recovery of function after brain damage. Finally, we introduce recent neuroimaging findings indicating the multipotentiality and suggest an adequate experimental strategy to investigate the brain functions based on the view of multipotentiality, in which the assumption of cell-assembly coding is necessarily involved.

**Keywords** Multipotentiality • Plasticity • Functional map • Brain-machine interface • Neurorehabilitation • Cell assembly

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## 23.1 Introduction

Unlike a man-made machine, the brain is a unique and enigmatic organ not completely elucidated yet. Although the brain can be classified to many small regions, each with their individual functions and structures, it also works as a unified organ, and individual constituent regions cannot realize any functions in isolation. In addition, the brain exhibits dynamism to such an extent that the functions of its regions are not necessarily fixed. This view of the brain has been repeatedly confirmed by many researchers within experiments and theoretical considerations. However, such view has been often ignored, although almost all neuroscientists more or less understand it. Very many researchers have been focusing on regional separation and searching for specific regions responsible for individual, even any higher, functions and trying to detect the treasured and task-related individual neurons. This article once again emphasizes that the brain is not a mosaic of functionally independent regions and neurons and supports the multipotentiality theory, to which cell-assembly theory is related, and suggest that we should revisit it repeatedly in the present and future researches. This article additionally raises the issues of adequate experimental studies, brain-machine interfaces (BMIs), and real plasticity for clinical treatments in relation to the multipotentiality of the brain.

## 23.2 History of Instable Functional Maps and Multipotentiality of the Brain

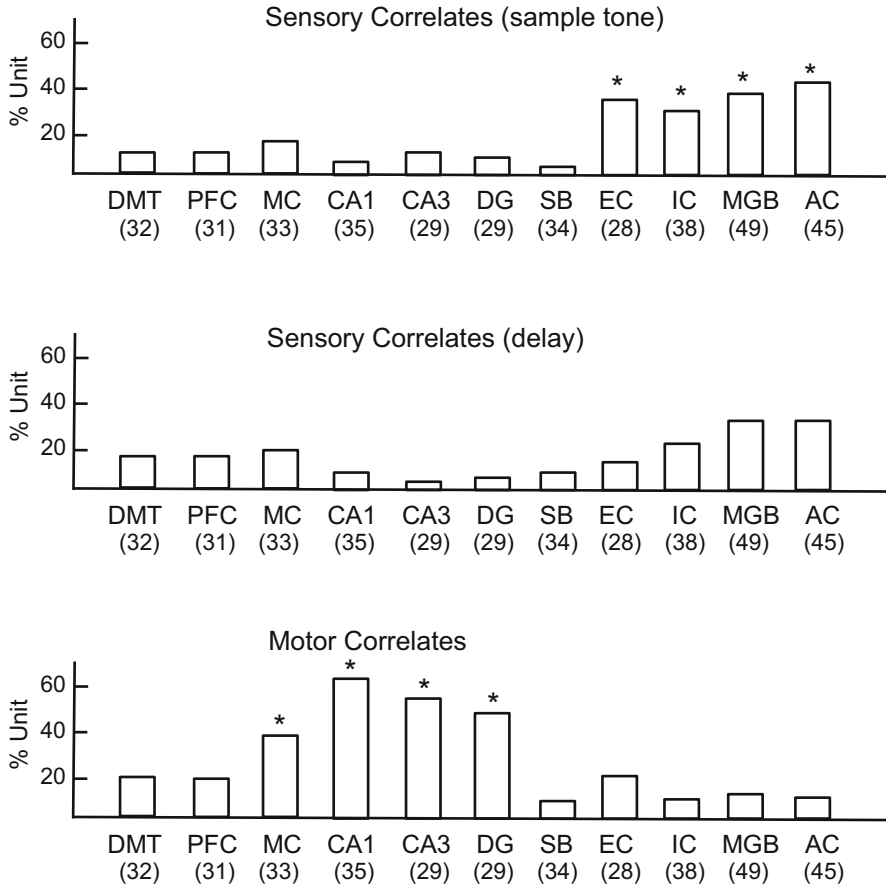
Controlling body movements is a primary function of the brain, and the primary motor cortex (M1) is regarded as containing clearly established functional maps, in which individual regions and neurons fulfill specific roles to activate specific muscles of the body. However, even during the early twentieth century, repeated electrical stimulation to identical points in M1 did not necessarily generate identical muscle movements, and the generated muscle movements varied among the animals and from day to day (Brown and Sherrington 1912; Lashley 1923). These pioneering studies conducted approximately 100 years ago suggested that region–muscle or neuron–muscle connections in M1 are not fixed and often changed by time and experience. Recently, Fetz and his colleagues have reported such dynamic and learning-dependent connections between M1 neurons and muscles (see Fetz 2007 for review). Moreover, they have demonstrated that motor-unrelated neurons in the monkey M1 have the ability to control limb muscles with FES (Functional Electronic Stimulation) (Moritz et al. 2008). The implications by these studies are that functional maps can undergo change readily, even in M1 which has been considered to contain many well-defined borders separating the maps.

When we examine the brain in its entirety instead of specific regions, the functional maps become more flexible and the notion of well-defined borders becomes meaningless. Within the memory function, a typical example of higher functions,

the region–memory or neuron–memory correspondence varies and shows flexibility. The pioneering study by K. Lashley in 1920s found that the memory engram of mazes was consolidated not in any specific regions but in widely distributed regions covering almost all neocortices. Lashley stated “Somehow, equivalent traces are established throughout the functional area . . . within a functional area the cells throughout the area acquire the capacity to react in certain definite patterns . . .” (Lashley 1950, p. 502). Though this “equipotentiality theory” (Lashley 1921) might be too radical and the varying parts of the brain are not completely homogeneous in ability of memory retention, the notion that cells throughout the regions are able to acquire capacity and ability to react in certain definite patterns was the pioneering work emphasizing broad plasticity of the brain.

E. R. John has emphasized such broad plasticity and suggested that any neuron and region may contribute to mediating a diversity of functions and that many neurons and regions contribute to every function (John 1980). He called this assumption “multipotentiality theory”. The theory does not imply that different neurons and regions are functionally equivalent or that different functions are equally dependent on diverse neurons and regions. John (1972) actually reported that the patterns of evoked electrical potentials in many different regions distributed in the brain started changing simultaneously when the animal was acquiring the discriminative avoidance task, though the shapes of patterns and the points in time when the shapes changed differed among the regions. He suggested that the brain employs plastic and statistical processing in distributed areas rather than switchboard-like processing in specific areas. J. Olds, another pioneering researcher, demonstrated learning-related multipotentiality in the brain (Olds 1975). He showed that multiple neurons in many regions started changing their firing rates almost simultaneously, although the regions showed somewhat different firing latencies when the animal was acquiring the discriminative reward-approaching task (e.g., Olds et al. 1972). Both the studies by John and Olds surely indicate that many neurons distributed across many regions have a capacity to change their activity during learning, which is a typical operation to induce plasticity in the brains. Y. Sakurai confirmed that the multipotentiality notion was valid when learning was accomplished. He examined multineuronal activities in several brain regions of the rat when performing a working memory task (Sakurai 1990a, b). The results showed that all regions demonstrated all types of task-related neurons during performance of the task (Fig. 23.1). The implications are that all regions have the ability to be involved in the memory process and each region has the ability to contribute to the different functions. The proportions of involvement were somewhat different among the regions, suggesting that the results support the notion not of equipotentiality but of multipotentiality of the brain.

The multipotentiality theory suggests that any region may contribute to mediating a diversity of functions. However, there have been several disputes to allocate a specific and only function to a region. An example of such disputes is spatial/nonspatial controversy about the hippocampal function. Although it is historically well-established that the hippocampus is involved in processing of spatial information, several studies have reported hippocampal contribution to both



**Fig. 23.1** Proportions of task-related neurons during an auditory working memory task in rats in a previous study (Sakurai, 1990a, b). *Upper panel* Proportions of neurons with sensory correlates, i.e., differential activation between the discriminative tones, during presentation of the sample tones to be retained during the delay periods. *Middle panel* Proportions of neurons with sensory correlates during the delay periods. *Lower panel* Proportions of neurons with motor correlates, i.e., differential activation between go and no-go responses, immediate prior to the responses. The asterisk (\*) signifies a statistically significant difference ( $p < 0.05$ ) among the regions. DMT, dorsomedial thalamus; PFC prefrontal cortex, MC motor cortex, CA1 hippocampal CA1 subfield, CA3 hippocampal CA3 subfield, DG dentate gyrus, SB subicular complex, EC entorhinal cortex, IC inferior colliculus, MGB medial geniculate body, AC auditory cortex. Numbers in parentheses are the total neurons recorded in each region (Reconstructed from Sakurai 1990b)

spatial and nonspatial functions (e.g., Hampson et al. 1999). D. S. Olton stated “Is the hippocampus a spatial or a mnemonic processor? The answer is clearly yes. Comparison of these two approaches might proceed best if the question was changed, perhaps to: ‘How does the hippocampus process both spatial and nonspatial, mnemonic information?’” (Olton et al. 1989).

The above brief history demonstrates that the brain is not a precision machine but rather a plastic and integrated organ characterized by many distributed regions, each of which shows multipotentiality for multiple functions. However, the main stream of modern neuroscience has been attempting to clarify unique functions of individual regions and neurons as well as to classify the regions into even more detailed and smaller components. According to this dominant but outdated paradigm, classification of each region's and neuron's unique functions, if any, is regarded as "clarification of the brain".

### 23.3 Multipotentiality and Brain-Machine Interfaces

Approximately 15 years ago, an innovative research method, termed "brain-machine interface (BMI)," was introduced to neuroscience (Chapin et al. 1999). This method has once again moved the focus to multipotentiality of the brain (Lebedev and Nicolelis 2006; Nicolelis and Lebedev 2009; Moran 2010; Lebedev and Nicolelis 2011; Nicolelis 2012; Lebedev 2014). In some BMI studies (Wessberg et al. 2000; Carmena et al. 2003), the neurons not only in the precentral (motor) cortical areas but also in the postcentral (parietal) had ability to predict motor movements and the neurons whose activities were used as signals representing information of motor movements were randomly distributed in the motor cortex. Even the neurons which were randomly selected from the non-motor area and were unrelated to motor movement in nature actually attributed to the accuracy of movement prediction when the number of the neurons used for the BMIs were increased (Wessberg et al. 2000; Carmena et al. 2003). These clearly indicates that the information on motor movements and forces is widely distributed in cortical neurons.

These conclusions from the BMI studies are explicitly challenging the classical view of functional localization based on the assumption of rigid functional maps and have suggested that the functional boundaries are not strictly definite but rather obscure and dynamic. Some BMIs do not necessarily require the selection of functionally specific motor neurons (e.g., Moritz et al. 2008) or, as described above, a specific motor area to improve their performance in brain control of devices. Therefore, BMI research is surely contradictory of the view of extremely rigid and subdivided functional maps and clearly supports the theory of multipotentiality of the brain, suggesting that any neuron and region can mediate diverse functions and that many neurons and regions can contribute to many functions, although different neurons and regions do not always have complete equivalence of functions or different functions are not always equally dependent on diverse neurons and regions. It is advantageous within the use of a BMI as a neuroprosthetic system to have the potential to utilize any neuron and any brain region unrelated to the target functions replaced by the BMI.

Some studies have reported that the use of BMIs clearly induced changes in the plasticity of neuronal activities and functions (e.g., Zacksenhouse et al. 2007; Ganguly et al. 2011). Moreover, BMIs can induce the changes in neuronal activity

in the regions not used for device control (Koralek et al. 2012, 2013). Therefore, BMIs can be actively applied to research on the extent to which the brain can change and to determine how the brain can be changed more efficiently. The implications of the former are that BMI studies are able to classify the actual plasticity of the brain. A recent paper (Oweiss and Badreldin 2015) reviews the development process of BMIs and emphasizes the relationships between BMIs and neuroplasticity. The latter suggests that the development of BMIs will lead to the development of better methods of neurorehabilitation to induce changes in neuronal activities and connections facilitating functional compensation (Dobkin 2007; Fetz 2007; Jackson and Fetz 2011; Miller and Weber 2011). Actually, another recent paper (Gulati et al. 2015) reported that learning with BMI operation enhanced neuronal activity in the regions near the structure damaged by stroke in the rat, which had shown disability of motor movements due to the brain damage. These findings and theories can contribute to clinical treatments for patients with impaired brain function and are certainly related to multipotentiality of the brain regions.

### 23.4 Multipotentiality and Neurorehabilitation

The basic paradigm for BMIs is identical with that for neuronal operant conditioning (neural biofeedback) (Fetz 2007). As it has been pointed out (Dobkin 2007; Fetz 2007; Sakurai et al. 2014; Sakurai and Song 2016), neuronal operant conditioning is a core mechanism of BMI control and can elucidate the potential of neuronal plasticity. Such elucidation necessarily contributes to progress of neurorehabilitation methods (Raskin 2011). In order to allow applicability of neuronal operant conditioning to clinical use, it should be shown that the conditioning does not require selection of functionally specific neurons or regions. In patients with motor deficits, for example, it would be impossible to enhance inherent motor neurons for compensation of motor deficits as very many inherent motor neurons are already lost. Therefore, it should be necessary for neuronal operant conditioning to have the potential to enhance any neuron and hopefully any brain region unrelated to the target functions to be compensated (Sakurai et al. 2014). This is again related to the theory of multipotentiality of the brain.

We actually reported in our previous study (Sakurai and Takahashi 2013) that the neurons showing rapid enhancement in firing rates and synchrony during the neuronal operant conditioning originally manifested no behavior-related activity responsible for motor responses and had been randomly selected from the hippocampus. This result indicates that neurons not initially involved in adaptive behavioral performance can be enhanced by the conditioning and can be subsequently utilized to compensate for loss of motor functions responsible for adaptive behavior. Moritz et al. (2008) had previously indicated such a notion from their findings that the monkeys could learn to use task-unrelated neurons to control an external device when they were enhanced by operant control training. An issue to be addressed is whether any neuron and region can be available for the conditioning

to enhance the higher functions in the sensory and higher brain regions, such as motor functions. Addressing this issue involves testing the validity of the view of multipotentiality of the brain.

Clinical treatment taking into account multipotentiality should be seriously considered, and the classical view of the brain as a complex but rigid organ does patients with brain damage a disservice. The modern imaging technique of functional magnetic resonance imaging (fMRI) has demonstrated broad plastic changes in the brain after injuries and neural defects and has suggested the possibility of functional recovery by adequate treatment to induce the plasticity (Ungerleider et al. 2003; Rocca and Filippi 2006). A recent study employs a novel method of BMI based on real-time fMRI (rtfMRI) and has succeeded self-regulation of the functional connectivity between different brain areas and of distributed brain networks (Ruiz et al. 2014). They emphasize the significance of their methodology to achieve self-regulation of brain functions and applicability of it for potential alleviation of neuropsychiatric disorders. Clinical research within the field of neurorehabilitation has also indicated that some well-devised treatments, such as selected behavioral manipulation, multimodal stimulation, and repetitive transcranial magnetic stimulation (rTMS) could induce experience-dependent plasticity in the nervous system and broad reorganization of cortical functional maps (Pekna et al. 2012). Chapman and Mudar (2014) and Chapman et al. (2015) introduces growing evidence suggesting training-induced enhancement of cognitive brain performance by engaging efficient communication across the widespread neural networks, e.g., the Default Mode Network (DMN) and the Central Executive Network (CEN), in normal and clinical populations. In addition, recent experimental studies using animals are revealing cellular and trans-regional mechanisms underlying temporal plasticity and functional recovery (Murata et al. 2015); these studies support the notion of multipotentiality theory, which will contribute to further development of clinical treatments and progress within experimental research.

## 23.5 Conclusion

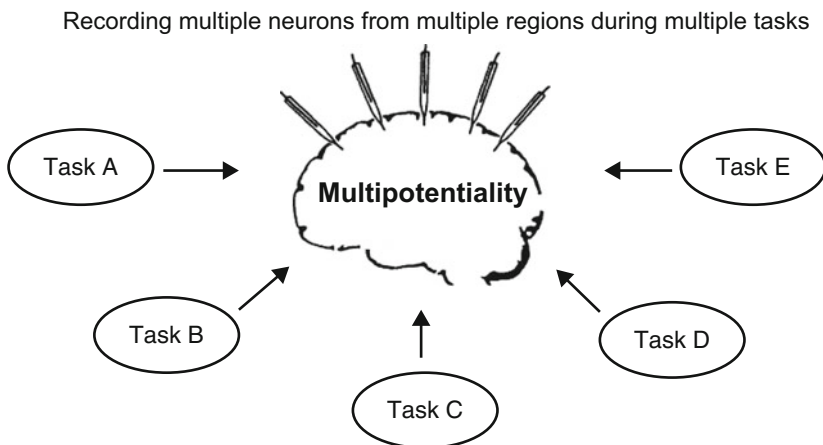
It has been reported that the human brain can reorganize the sensory deprivations by cross-modal neuroplasticity in visual-related cortices (Bedny et al. 2011). In blind individuals, visual processing regions can be activated by auditory and tactile stimuli. Recently Ortiz-Terán et al. (2016) investigated functional reorganization in regional and distributed neural-systems in late-onset blind (LB) and congenitally blind (CB) cohorts. They revealed the critical role of recipient multi-sensory integration areas in network reorganization and cross-modal plasticity in blind individuals and suggest that cross-modal neuroplasticity and adaptive sensory-motor functions may potentially occur through reorganization in multimodal integration regions.

Regarding attentional processing, the view of multipotentiality is becoming prominent. Although many studies have showed that the various particular brain

areas are related to the process of attention, Rosenberg et al. (2016) recently revealed that the extent of attentional abilities depend on the functional connectivity in whole brain, not only in specific regions in human. They conducted the sustained attention task and analyzed functional connections between 268 distinct brain regions using fMRI. The result showed that a specific brain connection was not always needed for the task and whole brain network is more important for higher attention. Their findings contribute to understanding how the whole brain networks comprehensively work for higher brain functions.

Those recent findings and the historical studies introduced in this article confirm that the brain demonstrates multipotentiality of its regions and neurons in particular in learning and higher functions including cognition and attention. This means that finding a peculiar functional localization and a peculiar function of a single neuron can not contribute to clarifying how the brain is functioning. This is consistent to the suggestion by a recent review article (Hampshire and Sharp 2015), which states “a more holistic approach that considers how common network mechanisms support diverse cognitive processes to fully understand the neural basis of behavioral control.”

The view of multipotentiality and the holistic approach on it inevitably requires an adequate experimental strategy of recording multiple neurons from multiple regions during multiple tasks (Fig. 23.2) rather than the recording single neurons from a single region during a single task. Such a strategy should be the standard and used in present and future recording experiments. It could uncover unique features of the brain to be distinguished from precision machines, and concurrently, unique features of information coding in the brain, such as coding by closing loops in microcircuits in prefrontal cortex and hippocampus (Opris et al. 2012, 2013, 2015b).



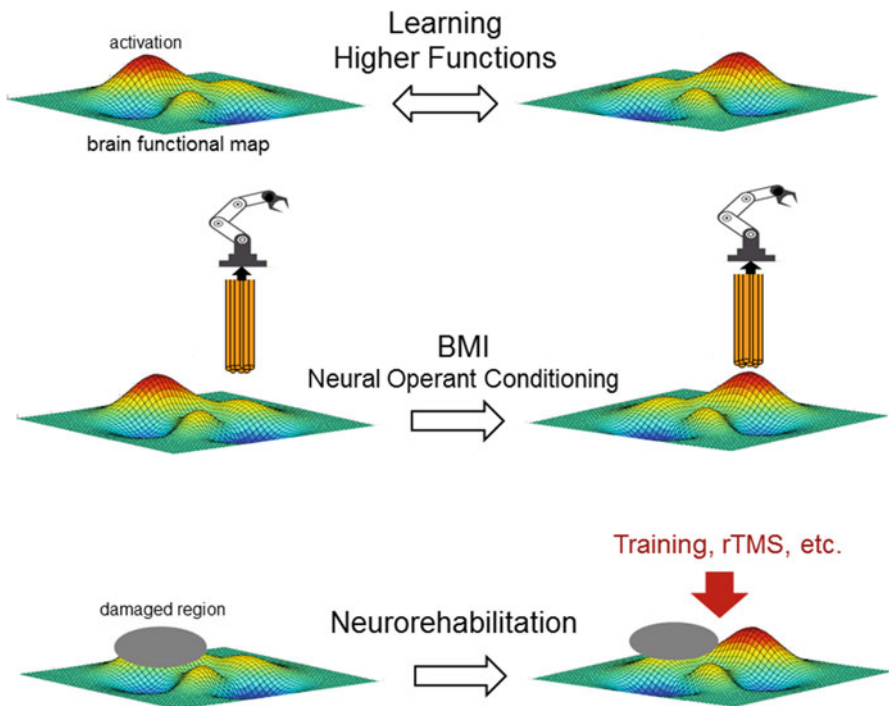
**Fig. 23.2** The standard strategy to be used in recording experiments based on the view of multipotentiality of the brain (Reconstructed from Sakurai 1999)



Clarification of coding in the microcircuits can contribute to implementation of BMIs (Opris et al. 2015a).

The strategy is also particularly related to research of coding by cell assemblies (Hebb 1949). As many researchers have defined (Eichenbaum 1993; Sakurai 1996, 1999; Harris 2005; Sakurai and Takahashi 2008; Buzsaki 2010; Wallace and Kerr 2010; Sakurai et al. 2013), the cell assembly is a group of functionally connected neurons and represents neuronal information in the working brain. Figure 23.2 is essentially identical with that to detect cell assemblies (Sakurai 1999). In addition, the cell-assembly coding is related to development of BMIs (Nicolelis 2003; Nicolelis and Lebedev 2009). The theory of multipotentiality, therefore, is strongly combined with the assumption of cell-assembly coding (Sakurai 2014) and should be further verified by present and future neuroscience research, including BMI and neurorehabilitation studies.

Figure 23.3 briefly illustrates the concept of multipotentiality based on the descriptions in this article. The brain functional map dynamically changes especially in learning and higher functions (top in Fig. 23.3). BMI and neural operant conditioning often cause the change of functional map to control external devices



**Fig. 23.3** Brief illustration of the concept of multipotentiality in relation to learning and higher functions, BMI and neural operant conditioning, and neurorehabilitation (Some parts of the figure are reconstructed from Microsoft Clip Arts)

efficiently (middle in Fig. 23.3). Training for recovery and the recent techniques, e.g., rTMS, in neurorehabilitation often facilitate the change of functional map to compensate the damaged brain region (bottom in Fig. 23.3). Though the illustration is too simple to suggest detailed mechanisms underlying the dynamic changes of functional maps, we should at least recognize that the brain functional localization is not absolute and can be easily modified by the normal actions and the recently developing techniques.

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