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Original Paper

Differential Activation Patterns in the Prefrontal Cortex during Top-down and Bottom-up Behavioral Adaptations in Reversal Learning: A Functional Near-infrared Spectroscopy Study

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Abstract

To investigate the neural mechanisms underlying top-down/bottom-up behavioral adaptation, we recorded cortical hemodynamics in the prefrontal cortex (PFC) by functional near-infrared spectroscopy (fNIRS) while a subject performed a behavioral task in which the subject learned stimulus-response associations and was required to adapt his/her response when the relationships between the stimulus and the response changed (reversal learning). In this task, we employed two reversal conditions: whole and partial reversal conditions. Under the whole reversal condition, the stimulus-response associations changed for all stimuli so that the subjects were able to prospectively adapt their behavior after the reversal on the basis of their knowledge of prior stimulus-response associations. This type of reversal learning corresponds to top-down behavioral adaptation. Under the partial reversal condition, only a portion of stimuli changed their contingency so that the subjects needed to relearn the stimulus-response associations after the reversal. This type of reversal learning corresponds to bottom-up behavioral adaptation. We found a significant increase in the oxyhemoglobin (oxy-Hb) concentration in the first block after the whole reversal, and a significant decrease in the first block after the partial reversal. These results indicate that the PFC is especially important for top-down behavioral adaptation.

1. Introduction

Since the environment that we live in is continuously changing, an adaptive behavior at a certain time would be maladaptive at another time. Therefore, we need to change our behavior in accordance with the situation. Generally, there are two types of behavioral adaptation: top-down and bottom-up adaptations[1-3]. In top-down behavioral adaptations, cognitive information, such as knowledge, expectation, or thoughts, guides the behavior. In bottom-up behavioral adaptations, on the other hand, incoming information, such as sensation, guides the behavior. Developmental psychologists such as Piaget and Bruner indicated that the ability to form and use categories is the seeds of abstraction and can serve as a benchmark of higher intelligence in cognitive development[4,5]. Category-based reasoning enables predictive adaptation[6], which is

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one kind of top-down behavioral adaptation. Many neurophysiological studies suggest that the prefrontal cortex (PFC) is involved in decision-making based on category[7-11]. Patients with damage to the PFC have impairments in category-based reasoning[12,13]. It has been reported that the PFC plays an important role in the adaptation of behavior in response to changes in situations[14-16]. On the other hand, it has also been reported that a PFC lesion does not impair the performance in a reversal task[17]. In this study, we aimed to investigate how the PFC is involved in different types of behavioral adaptation. To this end, we recorded the activation of the PFC by a functional near-infrared spectroscopy (fNIRS) and compared the PFC activity when the subjects performed a task with the strategy of top-down behavioral adaptation with that when they did the task with the strategy of bottom-up behavioral adaptation.

To investigate the neural mechanisms underlying top-down/bottom-up behavioral adaptation, we used a group reversal task[6,18,19]. In this task, the subject learned stimulus-response associations between six visual stimuli and either a left or right click of the mouse. The subjects learned these stimulus-response associations on a trial-and-error basis. After the subjects learned these associations, the stimulus-response associations were changed (reversal learning). We employed two types of reversal condition: whole reversal and partial reversal. Under the whole reversal condition, the stimulus-response associations changed for all stimuli so that the subjects were able to prospectively adapt their behavior after the reversal on the basis of their knowledge of prior stimulus-response associations (i.e., a category-based inference). This type of reversal learning corresponds to top-down behavioral adaptation. Under the partial reversal condition, on the other hand, the stimulus-response associations changed in only some of the stimuli so that the subjects were unable to predict which stimuli changed their contingency and needed to relearn the stimulus-response associations after the reversal. This type of reversal learning corresponds to bottom-up behavioral adaptation. We recorded the hemodynamics of PFC by fNIRS while the subjects performed the group-reversal task. We hypothesized that if the PFC is involved in behavioral adaptation in general, it should be activated both under the whole and the partial reversal conditions. On the other hand, if the PFC is involved in prospective (top-down) behavioral adaptation, but not the bottom-up one, it should be activated only under the whole reversal condition.

2. Methods

2.1 Participants

Fifteen adults without a history of any neurological disorders participated in the experiments (3 males and 12 females; mean age, 22.2 ± 3.3 years; range, 20-34 years). The experiments were conducted in accordance with the Declaration of Helsinki. This project was approved by the Ethical Committee of Kawasaki University of Medical Welfare (approved number: 19-005). All the subjects were informed of the nature of the experiment, and written informed consent was obtained from them. A subject was seated on a chair with a headrest to minimize body movement in a dimly lit room. A 19-inch liquid crystal display (LCD) monitor (P1917S, Dell Computer, Round Rock, Texas, USA) was placed in front of each subject. The distance between the subject and the monitor was approximately 65 cm.

2.2 Procedures

2.2.1 Group reversal task

The subjects performed a task in which they had to learn the stimulus-response associations between abstract visual stimuli and either left or right click of a computer mouse (Figures 1A and B). We used six novel visual stimuli in each session. Three of the six stimuli were associated with a left click, whereas the other three were associated with a right click. The subject needed to learn these stimulus-response associations on a trial-and-error basis. In every trial, a visual stimulus was presented to the subject on the monitor. A stimulus was chosen pseudorandomly in such a way that each of the six stimuli was used once in a block of six trials. The time sequence of the task events was as follows. (1) At the beginning of a trial, a small white square (fixation spot) appeared at the center of the LCD for 1 s. (2) A visual stimulus

was presented at the center of the LCD for 2 s. (3) After the visual stimulus disappeared, a delay period intervened for 1 s. (4) At the end of the delay period, the fixation spot turned from white to green, which was a signal for the subject to click either the left or right button of the mouse. (5) Immediately after the subject responded, the response was indicated as correct or incorrect on the monitor for 1 s. (6) Then, the monitor cleared and a progress bar was shown on the monitor during the intertrial interval (ITI) of 10 s.

After the subjects learned the stimulus-response associations, we reversed the relationships between the stimuli and responses. We employed two types of reversal: whole and partial reversals. In the whole reversal, all stimuli changed their stimulus-response associations: the three stimuli that were associated with a left click in the initial learning (before the reversal) were associated with a right click after the reversal, and vice versa. That is, the functional equivalence of each of the three stimuli was preserved even after the reversal (i.e., each stimulus was associated with the same correct response before and after the reversal). Thus, the subjects can prospectively adapt their behavior after the reversal on the basis of their knowledge of the stimulus-response associations learned before the reversal. This type of behavioral adaptation corresponds to top-down processing. In the partial reversal, on the other hand, not all stimuli in each group (i.e., only one or two stimuli) changed their contingency so that the subjects were unable to predict which stimuli changed their contingency, and they needed to relearn the stimulus-response associations for all stimuli after the reversal. This type of behavioral adaptation corresponds to bottom-up processing.

Before the experimental sessions started, we informed the subjects of whether the reversal type would be a whole or partial reversal in the forthcoming session so that the subject knew in advance whether they should switch the responses (whole reversal) or relearn the stimulus-response associations (partial reversal) at the time of reversal. The order of whole and partial reversal sessions was counterbalanced across subjects. The criteria for the reversal was that the subject made correct responses for all 6 stimuli in two consecutive blocks (i.e., 12 consecutive correct trials). The subjects were not informed of the criteria nor timing of the reversal. Because we presented a stimulus whose association had changed in the first trial after the reversal, the subject inevitably made an error if he/she made a response that had been correct before the reversal. We used different stimulus sets for the whole reversal and partial reversal conditions so that the subjects needed to learn the stimulus-response associations for novel stimuli in each session. We finished the experimental session when the subject made correct responses for all six stimuli in two consecutive sessions after the reversal.

2.2.2 Measurements

Cerebral oxygenation changes were measured using Spectratech OEG-17APD (Spectratech Inc., Yokohama, Japan) at a sampling frequency of 12.2 Hz. The Spectratech OEG-17APD employs two wavelengths of approximately 770 and 840 nm. The NIRS equipment was attached to the subject's head. Seventeen channels were measured with a 3 x 4 optode probe set consisting of six light emitters and six photodetectors. The optodes were affixed to a probe set at an inter-optode distance of 3 cm. The probe set was fastened to the subject's head with elastic straps.

The NIRS probes were attached to the forehead in accordance with the international 10-10 electrode system, such that the center of the lowest probe line (i.e., channel 10) was positioned on Fpz (Figure 1C). Our measurement area covered Fp1, Fpz, Fp2, AF3, AFz, AF4, F3, F1, Fz, F2, and F4.

2.3 Data analysis

The raw data on oxyhemoglobin (oxy-Hb) from each channel was digitally band-pass filtered between 0.01-0.3 Hz to attenuate low-frequency drift and cardiac oscillations. We then converted the data by the hemodynamic signal separation method described by Yamada et al.[20]. This method reduces the influence of systemic physiological signals by separating the hemodynamic signal into estimated functional and systemic components on the basis of the fact that the changes in oxy-Hb and deoxyhemoglobin (deoxy-Hb) concentrations are negatively correlated in the functional cerebral response, but positively correlated in the

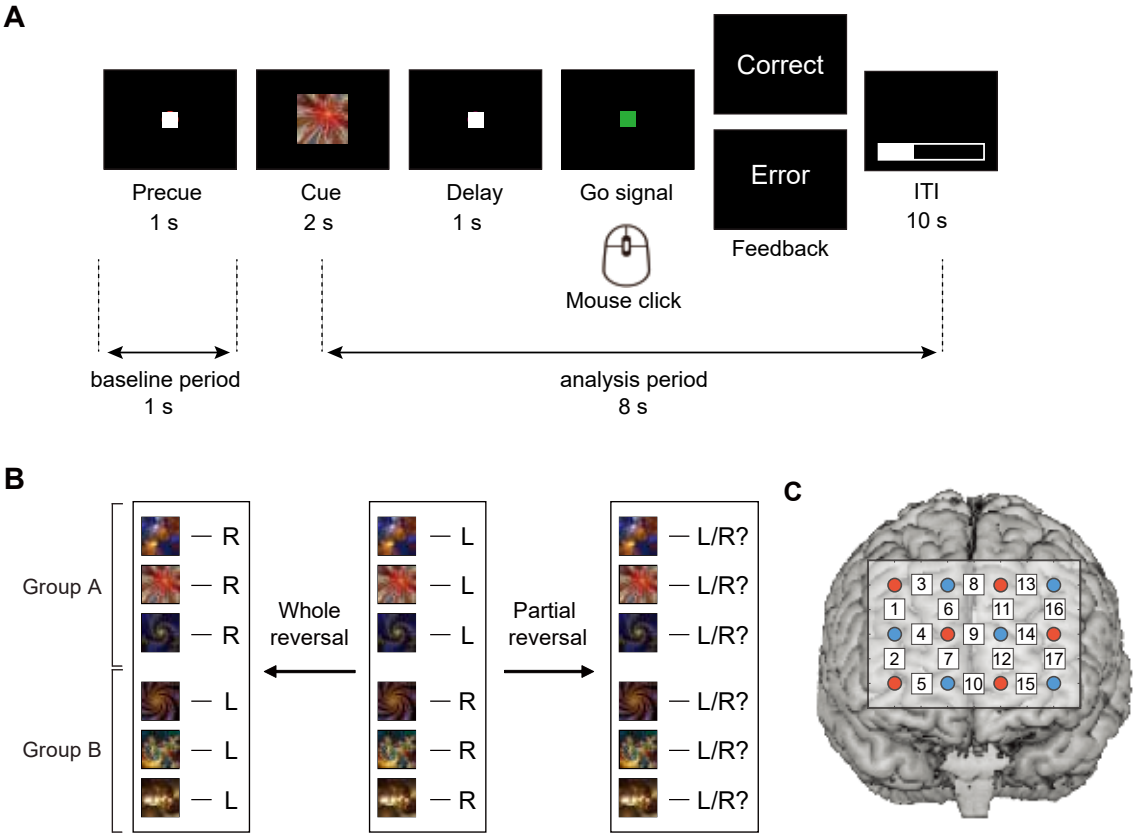


Figure 1 Group reversal task (A, B) and arrangements of fNIRS probes (C)

(A) Sequence of events in a trial of the group reversal task. Each visual cue was associated with either a left or right mouse click. The subjects learned the associations between each visual cue and the correct response on a trial-and-error basis. The baseline period and analysis period are shown below the task sequence. (B) Examples of stimuli used in the group reversal task. Each stimulus set consisted of six abstract figures. Three figures formed a group, which was associated with the same correct response (a click of the mouse: L, left button; R, right button). After the whole reversal, the stimulus-response contingency changed for all of the stimuli. After the partial reversal, on the other hand, the stimulus-response contingency changed in only a portion of stimuli, and it was unpredictable which stimuli changed its contingency. In each trial, a stimulus was selected from the stimulus set pseudorandomly in such a way that each stimulus in a set was presented once in a block of six trials. (C) Schematic arrangement of fNIRS probes was superimposed on a standard brain surface. Red and blue circles represent near-infrared emitters and detectors, respectively. Numbers refer to the recorded NIRS channels.

systemic fluctuations[20,21]. We used the functional component of oxy-Hb in statistical analyses. We defined a period of 1 s before the cue onset in each trial as the baseline period, and the period from 1 to 9 s after the cue onset as the analysis period. We subtracted the mean activity in the baseline period from that in the analysis period, then analyzed the subtracted mean activity by one-tailed t-tests (significance level was set at 0.05). As a result, positive t-values indicate an increase in oxy-Hb concentration, whereas negative t-values indicate a decrease in oxy-Hb concentration.

3. Results

3.1 Behavioral data

In each session, a novel stimulus set (six stimuli) was introduced and the subjects learned the relationship between the stimulus and the correct response on a trial-and-error basis. The mean numbers of blocks that the subjects needed to reach the reversal criterion (correct responses to all six stimuli in two consecutive

blocks; 12 trials) in the initial learning phase (i.e., before the reversal) were 5.6 ± 0.6 in the whole reversal condition and 4.5 ± 0.2 in the partial reversal condition. After the performance reached the criterion, the relationship between the stimulus and the correct response was reversed. Figure 2 shows the average performance in the initial learning epoch and after the reversal. Because the subjects did not know the timing of the reversal and because a stimulus whose contingency had been changed was presented in the first trial after the reversal, the subjects inevitably made an error in the first trial after the reversal. In the whole reversal condition, however, the subjects made a correct response in the second and later trials after the reversal. In the partial reversal condition, on the other hand, the subjects required more trials to adapt their response after the reversal. The mean numbers of first blocks in which the subjects made correct responses to all stimuli after the reversal were 2.2 ± 0.1 in the whole reversal condition and 3.2 ± 0.6 in the partial reversal condition. These results indicate that the subjects adapted their response in a top-down manner on the basis of the prior stimulus-response associations in the whole reversal condition, whereas they adapted their response in a bottom-up manner in the partial reversal condition.

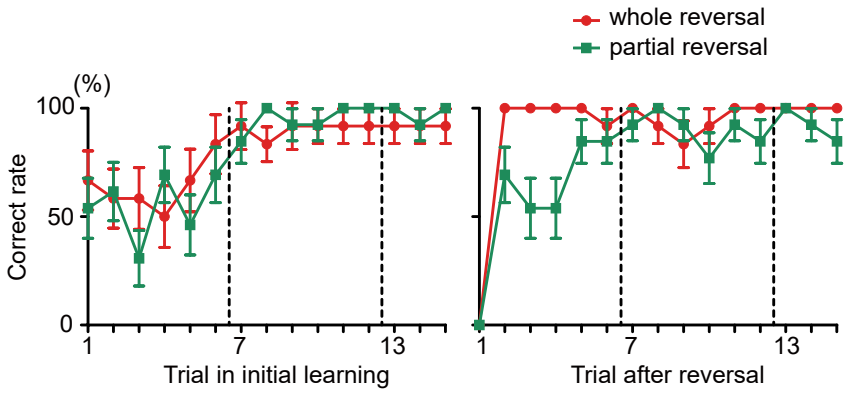


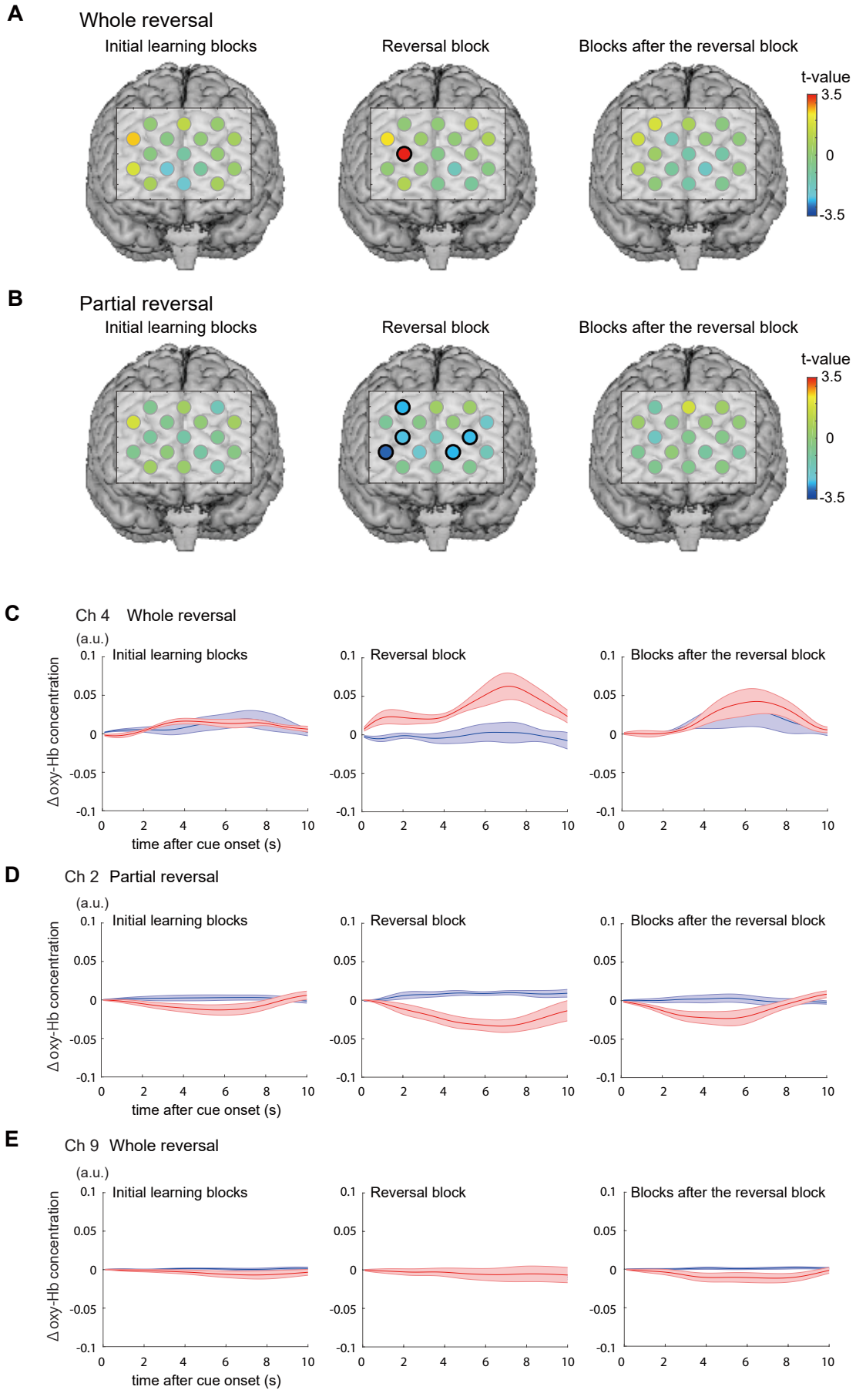
Figure 2 Behavioral performance in the group reversal task

Trialwise behavioral performance in the initial learning epoch (left) and after the reversal (right). Mean performance across the subjects is shown (mean ± SEM). The red line indicates the mean performance in the whole reversal condition, and the green line indicates that in the partial reversal condition. Vertical dashed lines indicate the boundary of blocks (1 block = 6 trials).

3.2 NIRS data

First, to observe the overall change in PFC activity during the course of the group reversal task, we determined the topographical activation patterns of the PFC in different phases while the subjects performed the group reversal task (Figures 3A and B). In the initial learning phase (i.e., blocks before the reversal), we observed no significant changes in the oxy-Hb concentration at any channel in either type of reversal session (Figures 3A left and 3B left). However, in the first block (6 trials) after the whole reversal, we found a significant increase in the oxy-Hb concentration in the right PFC (channel 4; one-sample t-test, $p < 0.05$) (Figure 3A middle). On the other hand, in the first block after the partial reversal, we found a significant decrease in the oxy-Hb concentration in the PFC (channels 2, 3, 4, 12, and 14; one-sample t-test, $p < 0.05$) (Figure 3B middle). None of the channels showed a significant increase in the oxy-Hb concentration in the first block after the partial reversal. In the second and later blocks after the reversal, these significant changes in the oxy-Hb concentration disappeared in either type of reversal (Figures 3A right and 3B right).

Then, we focused on the representative channels where oxy-Hb concentration significantly changed when the subject adapted their response (i.e., in the reversal block). Figure 3C shows the temporal change of the oxy- and deoxy-Hb concentration in the whole reversal condition at channel 4, where the maximum increase


A
Whole reversal
Initial learning blocks
Reversal block
Blocks after the reversal block
t-value
3.5
0
-3.5
B
Partial reversal
Initial learning blocks
Reversal block
Blocks after the reversal block
t-value
3.5
0
-3.5
C
Ch 4 Whole reversal
(a.u.)
Initial learning blocks
Reversal block
Blocks after the reversal block
Δ oxy-Hb concentration
time after cue onset (s)
D
Ch 2 Partial reversal
(a.u.)
Initial learning blocks
Reversal block
Blocks after the reversal block
Δ oxy-Hb concentration
time after cue onset (s)
E
Ch 9 Whole reversal
(a.u.)
Initial learning blocks
Reversal block
Blocks after the reversal block
Δ oxy-Hb concentration
time after cue onset (s)

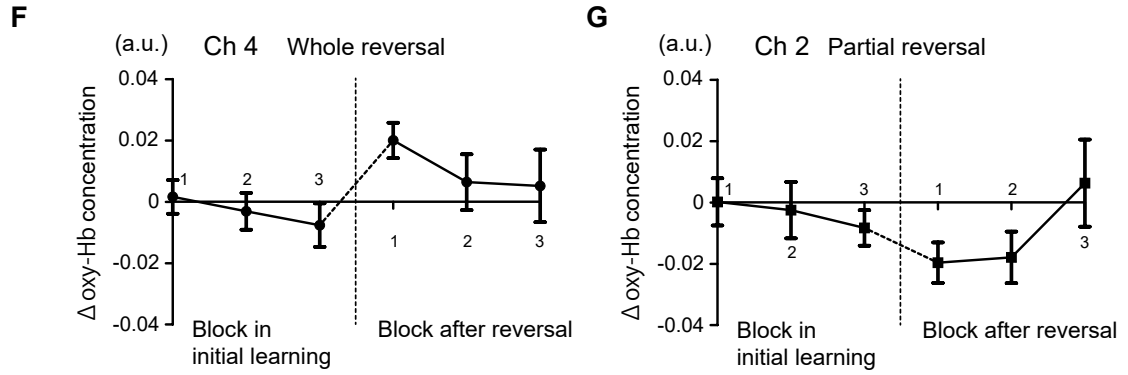


Figure 3 Topographical activation patterns in the group reversal task

(A) Topographical maps of brain activation (oxy-Hb signals) in the whole reversal condition. Statistical maps (t-values) for the data in the blocks before the reversal (left), for the data in the reversal block (middle), and for the data in the second and later blocks after the reversal (right) are shown. T-values show increases and decreases in relative oxy-Hb concentration against zero (one-sample t-test). The red and blue circles indicate the channels with increases and decreases in oxy-Hb concentration, respectively. Channels with significant increase or decrease in oxy-Hb concentration are indicated by a black line. (B) Topographical maps of brain activation (oxy-Hb signals) in the partial reversal condition. The configuration is the same as that in (A). (C) Time course of blood flow after the cue onset at channel 4 in the whole reversal condition. The panel on the left shows the mean signals (mean ± SEM, red: oxy-Hb, blue: deoxy-Hb) in the blocks before the reversal. The middle panel shows that in the reversal block. The panel on the right shows that in the blocks after the reversal block. The activity is aligned to the cue onset. (D) Time course of blood flow after the cue onset at channel 2 in the partial reversal condition. The configuration is the same as that in (C). (E) Time course of blood flow after the cue onset at channel 9 in the whole reversal condition. The configuration is the same as that in (C). (F) Mean oxy-Hb concentrations in channel 4 in each block of the whole reversal condition. The mean relative oxy-Hb concentrations in the three blocks from the start of the session is shown on the left side of the dashed vertical line, and that in the three blocks after the reversal is shown on the right side of the vertical dashed line. Note that some subjects required more than three blocks to reach the reversal criteria before the reversal. (G) Mean oxy-Hb concentrations in channel 2 in each block of the partial reversal condition. The configuration is the same as that in (F).

in the oxy-Hb concentration was observed in the reversal block under the whole reversal condition. In the reversal block (middle panel), the oxy-Hb signal increased after the cue onset and returned to the baseline by the end of ITI. We did not find any significant change in the blood flow in either blocks before or after the reversal block (left and right panels in Figure 3C), although the oxy-Hb signal was still high relative to the baseline in the blocks after the reversal (right panel). Figure 3D shows the temporal change of the oxy- and deoxy-Hb concentration in the partial reversal condition at channel 2, where the maximum decrease in the oxy-Hb concentration was observed in the reversal block under the partial reversal condition. The oxy-Hb signal significantly decreased after the cue onset only in the reversal block (middle panel in Figure 3D). As a comparison, we showed the temporal change of the oxy- and deoxy-Hb concentrations in the whole reversal condition at channel 9, where we did not find significant change in the oxy- or deoxy-Hb concentration in any block during the task (Figure 3E).

Figure 3F shows the blockwise change in the oxy-Hb concentration at channel 4 in the whole reversal condition. The relative oxy-Hb concentration increased in the first block, and returned to the baseline level in the second block after the reversal. Likewise, Figure 3G shows the blockwise change in the oxy-Hb concentration at channel 2 in the partial reversal condition. The relative oxy-Hb concentration was lower in the first and second blocks after the reversal, and returned to the baseline level in the third block after the reversal. These results indicate that PFC activity increased when the subjects adapted their response in a top-down manner (whole reversal), whereas it decreased in the case of a bottom-up manner (partial reversal).

4. Discussion

In this study, we examined whether or not the involvement of the PFC in reversal learning may vary depending on the strategy that the subjects adopted; top-down or bottom-up behavioral adaptation. We found that the subjects adopted different strategies between the whole and partial reversal conditions. We also found different patterns of PFC activity between the whole and partial reversal conditions in the first reversal block: a significant increase in PFC activity in the whole reversal condition, and a significant decrease in PFC activity in the partial reversal condition. The results indicate that the PFC is differently involved in behavioral adaptation depending on whether the strategy was top-down or bottom-up.

In this study, we used the group-reversal task under two reversal conditions: whole reversal and partial reversal. In whole reversal, the subjects were able to adapt their behavioral response on the basis of their knowledge of the stimulus-response associations learned before the reversal. This corresponded to a top-down behavioral adaptation. In partial reversal, on the other hand, the subjects needed to relearn the stimulus-response associations after the reversal because the subjects were unable to predict which stimuli changed their contingency. Since the subjects were informed of whether the reversal type of the impending session was whole or partial, they were able to select an appropriate strategy at the time of reversal in advance (i.e., switch responses for all stimuli after whole reversal, or forget the prior stimulus-response associations and relearn them after partial reversal). Actually, the subjects made correct responses in the second and later trials after whole reversal, whereas they required more trials before they were able to adapt their behavior after partial reversal. These results indicate that the subjects used a top-down strategy in the whole reversal condition, and a bottom-up one in the partial reversal condition.

The NIRS data show differential patterns of activation of the PFC in the first reversal block depending on whether the subjects made a prospective top-down behavioral adaption or bottom-up adaptation. In the first block after the whole reversal, there was a significant increase in the oxy-Hb concentration in the PFC. In previous studies, it was shown that the PFC is involved in the processing of category information[18,22-26] and in reversal learning[14-16]. PFC neurons responded strongly at the point of reversal in a reversal task[27]. These observations indicate that the PFC plays a critical role in adapting behavior in a top-down manner using category information. The increase in the oxy-Hb concentration was observed only at a single channel in the right PFC after the whole reversal. Many studies have shown functional differences between the left PFC and the right PFC, and the right PFC has some specific functions[28]. Aron and coworkers argued that the right PFC plays a critical role in motor inhibition (i.e., stop or override motor responses)[29,30]. When the whole reversal occurred, the subjects needed to inhibit the response that had been associated with the cue stimulus before the reversal and to reverse the response (i.e., left to right, and right to left). Thus, it is possible that the increase in the oxy-Hb concentration in the right PFC may reflect the motor inhibition that was necessary for the behavioral adaptation in the whole reversal.

In the first block after the partial reversal, on the other hand, there was a significant decrease in the oxy-Hb concentration in a wide area of the PFC. Previous studies suggest that an increase in attentional load to visual stimuli cause a decrease in the oxy-Hb concentration in the PFC[31,32]. Unlike under the whole reversal condition, the subjects could not predict which stimuli changed their response contingency and needed to pay more attention about the contingency changes to adapt their behavioral response under the partial reversal condition. This increase in the attentional demand in the partial reversal condition may have induced a decrease in the oxy-Hb concentration in the PFC. It is known that the oxy-Hb concentration decrease reflects neural inhibition[33]. Moreover, there is a passive hemodynamic change that induces decrease in the blood flow, which is called the 'vascular steal' phenomenon[32,34]. The phenomenon is interpreted as blood draining from neighboring areas to active areas, which induces a decrease of the blood flow in the neighboring areas. In fNIRS recording, if brain areas outside the recording area have been more activated, the blood flow in the recording area could decrease. Thus, it is plausible that the PFC is not active in the partial reversal condition relative to the whole reversal condition, which in turn implies that

the PFC may not mainly be engaged in the processing for bottom-up behavioral adaptation.

It remains unclarified which part of the brain plays a critical role in bottom-up behavioral adaptation. Interestingly, we also did not find any increase in the PFC activity in the initial learning blocks. The subjects needed to learn the stimulus-response associations in both the initial learning blocks and the blocks after the partial reversal. These results indicate that the PFC is not important for simple association learning. Further studies will be required to elucidate which parts of the brain are involved in the process of the initial learning and in that after the partial reversal. One candidate is the inferotemporal cortex, which is reported to be involved in the processing of long-term association memory[35,36].

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References

1. Köhler W (translated by Winter E) : *The mentality of apes*. Harcourt Brace & Co, New York, 1925.
2. Thorndike E : Some experiments on animal intelligence. *Science*, 7(181), 818-824, 1898.
3. Bobrow DG and Norman DA : *Some principles of memory schemata*. In *Representation and understanding*. Morgan Kaufmann, San Francisco, 131-149, 1975.
4. Bruner JS, Olver RR and Greenfield PM : *Studies in cognitive growth*. Wiley & Sons, New York, 1966.
5. Piaget J, Cook M and Norton WW : *The origins of intelligence in children (Vol. 8)*. International Universities Press, New York, 1952.
6. Hosokawa T, Honda Y, Yamada M, Romero MdC, Iijima T and Tsutsui K-I : Behavioral evidence for the use of functional categories during group reversal task performance in monkeys. *Scientific Reports*, 8(1), 15878, 2018.
7. Freedman DJ, Riesenhuber M, Poggio T and Miller EK : Categorical representation of visual stimuli in the primate prefrontal cortex. *Science*, 291(5502), 312-316, 2001.
8. Freedman DJ, Riesenhuber M, Poggio T and Miller EK : A comparison of primate prefrontal and inferior temporal cortices during visual categorization. *Journal of Neuroscience*, 23(12), 5235-5246, 2003.
9. Cromer JA, Roy JE and Miller EK : Representation of multiple, independent categories in the primate prefrontal cortex. *Neuron*, 66(5), 796-807, 2010.
10. Roy JE, Riesenhuber M, Poggio T and Miller EK : Prefrontal cortex activity during flexible categorization. *Journal of Neuroscience*, 30(25), 8519-8528, 2010.
11. Antzoulatos EG and Miller EK : Differences between neural activity in prefrontal cortex and striatum during learning of novel abstract categories. *Neuron*, 71(2), 243-249, 2011.
12. Robinson AL, Heaton RK, Lehman RA and Stilson DW : The utility of the Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. *Journal of Consulting and Clinical Psychology*, 48(5), 605, 1980.
13. Gershberg FB and Shimamura AP : Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia*, 33(10), 1305-1333, 1995.
14. Budhani S, Marsh AA, Pine DS and Blair RJ : Neural correlates of response reversal: considering acquisition. *Neuroimage*, 34(4), 1754-1765, 2007.
15. Cools R, Clark L, Owen AM and Robbins TW : Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *Journal of Neuroscience*, 22(11), 4563-4567, 2002.
16. Ghahremani DG, Monterosso J, Jentsch JD, Bilder RM and Poldrack RA : Neural components underlying behavioral flexibility in human reversal learning. *Cerebral Cortex*, 20(8), 1843-1852, 2010.
17. Hornak J, O'doherty J, Bramham J, Rolls E, Morris R, Bullock P and Polkey C : Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *Journal of*

Cognitive Neuroscience, 16(3), 463-478, 2004.
18. Tsutsui K, Hosokawa T, Yamada M and Iijima T : Representation of functional category in the monkey prefrontal cortex and its rule-dependent use for behavioral selection. *Journal of Neuroscience*, 36(10), 3038-3048, 2016.
19. Yamada M, Pita MC, Iijima T and Tsutsui K : Rule-dependent anticipatory activity in prefrontal neurons. *Neuroscience Research*, 67(2), 162-171, 2010.
20. Yamada T, Umeyama S and Matsuda K : Separation of fNIRS signals into functional and systemic components based on differences in hemodynamic modalities. *PLoS One*, 7(11), e50271, 2012.
21. Cui X, Bray S and Reiss AL : Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. *Neuroimage*, 49(4), 3039-3046, 2010.
22. Antzoulatos EG and Miller EK : Increases in functional connectivity between prefrontal cortex and striatum during category learning. *Neuron*, 83(1), 216-225, 2014.
23. DeGutis J and D'Esposito M : Distinct mechanisms in visual category learning. *Cognitive, Affective, & Behavioral Neuroscience*, 7(3), 251-259, 2007.
24. Pan X and Sakagami M : Category representation and generalization in the prefrontal cortex. *European Journal of Neuroscience*, 35(7), 1083-1091, 2012.
25. Ranganath C, DeGutis J and D'Esposito M : Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. *Brain Research, Cognitive Brain Research*, 20(1), 37-45, 2004.
26. Wutz A, Loonis R, Roy JE, Donoghue JA and Miller EK : Different levels of category abstraction by different dynamics in different prefrontal areas. *Neuron*, 97(3), 716-726 e718, 2018.
27. Hampshire A, Chaudhry AM, Owen AM and Roberts AC : Dissociable roles for lateral orbitofrontal cortex and lateral prefrontal cortex during preference driven reversal learning. *Neuroimage*, 59(4), 4102-4112, 2012.
28. Levy BJ and Wagner AD : Cognitive control and right ventrolateral prefrontal cortex: reflexive reorienting, motor inhibition, and action updating. *Annals of the New York Academy of Sciences*, 1224, 40-62, 2011.
29. Aron AR and Poldrack RA : Cortical and subcortical contributions to stop signal response inhibition: Role of the subthalamic nucleus. *Journal of Neuroscience*, 26(9), 2424-2433, 2006.
30. Aron AR, Robbins TW and Poldrack RA : Inhibition and the right inferior frontal cortex. *Trends in Cognitive Science*, 8(4), 170-177, 2004.
31. Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houde O, Crivello F, Joliot M, Petit L and Tzourio-Mazoyer N : Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Research Bulletin*, 54(3), 287-298, 2001.
32. Matsuda G and Hiraki K : Sustained decrease in oxygenated hemoglobin during video games in the dorsal prefrontal cortex: A NIRS study of children. *Neuroimage*, 29(3), 706-711, 2006.
33. Stefanovic B, Warnking JM and Pike GB : Hemodynamic and metabolic responses to neuronal inhibition. *Neuroimage*, 22(2), 771-778, 2004.
34. Hu D and Huang L: Negative hemodynamic response in the cortex: Evidence opposing neuronal deactivation revealed via optical imaging and electrophysiological recording. *Journal of Neurophysiology*, 114(4), 2152-2161, 2015.
35. Naya Y, Sakai K and Miyashita Y : Activity of primate inferotemporal neurons related to a sought target in pair-association task. *Proceedings of the National Academy of Science of the United States of America*, 93(7), 2664-2669, 1996.
36. Naya Y, Yoshida M and Miyashita Y : Forward processing of long-term associative memory in monkey inferotemporal cortex. *Journal of Neuroscience*, 23(7), 2861-2871, 2003.