

Adaptation to left–right reversed vision rapidly activates ipsilateral visual cortex in humans

Satoru Miyauchi ^{a,*}, Hiroyuki Egusa ^b, Masahiro Amagase ^c, Kaoru Sekiyama ^d,
Toshihide Imaruoka ^a, Takara Tashiro ^e

^a Brain Information Group, Kansai Advanced Research Center, National Institute of Information and Communications Technology, 588-2 Iwaoka, Iwaoka-cho, Nishi-ku, Kobe-shi, Hyogo 651-2492, Japan

^b Department of Human and Psychological Studies, Soai University, 4-4-1 Nankoh-naka, Suminoe-ku, Osaka 559-0033, Japan

^c Department of Psychology, Nara Women's University, Kitauwoyanishimachi, Nara 630-8506, Japan

^d School of Information Science, Future University-Hakodate, Kameda Nakano, Hakodate-shi 041-8655, Japan

^e Department of Psychology, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

Abstract

The brain mechanisms of adaptation to visual transposition are of increasing interest, not only for research on sensory–motor coordination, but also for neuropsychological rehabilitation. Sugita [Nature 380 (1996) 523] found that after adaptation to left–right reversed vision for one and a half months, monkey V1 neurons responded to stimuli presented not only in the contralateral visual field, but also in the ipsilateral visual field. To identify the underlying neuronal mechanisms of adaptation to visual transposition, we conducted fMRI and behavioral experiments for which four adult human subjects wore left–right reversing goggles for 35/39 days, and investigated: (1) whether ipsilateral V1 activation can be induced in human adult subjects; (2) if yes, when the ipsilateral activity starts, and what kind of behavioral/psychological changes occur accompanying the ipsilateral activity; (3) whether other visual cortices also show an ipsilateral activity change. The results of behavioral experiments showed that visuomotor coordinative function and internal representation of peripersonal space rapidly adapted to the left–right reversed vision within the first or second week. Accompanying these behavioral changes, we found that both primary (V1) and extrastriate (MT/MST) visual cortex in human adults responded to visual stimuli presented in the ipsilateral visual field. In addition, the ipsilateral activity started much sooner than the one and a half months, which had been expected from the monkey neurophysiological study. The results of the present study serve as physiological evidence of large-scale, cross-hemisphere, cerebral plasticity that exists even in adult human brain.

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1. Introduction

Since Stratton first reported that he himself wore up-down inverting prisms and could adapt to the visually inverted world [37], numerous studies on visual transposition using animals and humans have followed from the viewpoint of sensory–motor coordination. They revealed that the capability to adapt to a visually transposed world generally depends on phylogenetic order: there are a plenty of evidence that humans can adapt

almost perfectly [9,22,23]; monkeys follow humans [8,40]; there are split results in birds [13,32]; and no adaptation in amphibians [35], fishes [36] and insects [14]. These phylogenetic reviews suggest that the capacity for adaptation to visual transposition is associated with higher cerebral functions and plasticity, which only mammals and especially primates possess.

In addition, Sugita [39] demonstrated that left–right reversed vision can induce functional reorganization of the brain even within early visual processing. Namely, after adaptation to left–right reversed vision for one and a half months using prisms, V1 neurons in the monkey responded to stimuli presented not only in the contralateral visual field, but also in the ipsilateral field. This study is notable in two respects. First, it demonstrated

* Corresponding author. Tel.: +81-78-969-2162; fax: +81-78-969-2269.

E-mail address: miyauchi@po.nict.crl.go.jp (S. Miyauchi).

that V1, the earliest cerebral cortex for visual information processing, can be reorganized across hemispheres. Second, the reorganization was observed not in infants but in adult subjects, which were believed to lack this kind of large-scale cerebral plasticity.

Apart from this, it has recently been established that visual transposition using prisms or mirrors is a useful technique not only for research, but also for neuropsychological rehabilitation. For instance, prism adaptation to a rightward optical deviation rapidly improves left hemispatial neglect [31]; seeing a phantom hand as a normal hand via a mirror induces feeling of the phantom hand, and relieves phantom limb pain [26]. In most visual transposition studies using human subjects, however, psychological and behavioral experiments, which rely on a subject's introspective data, are predominant. As a natural consequence, there are few studies which have succeeded in finding changes in brain activity [15,38]. Possible reasons are that there was no method to detect subtle changes in human brain activity with high spatial resolution, and that the period for visual transposition might have been too short.

Fortunately, recent advances in functional magnetic resonance imaging (fMRI) have brought us several benefits. First, fMRI can measure human brain activity with high enough spatial resolution that we can distinguish the activity of V1 from other visual cortices. Second, its non-invasiveness enables us to repeat measurements. Third, while the unit recording obtains data from a single cell, fMRI can record brain activity data from almost all brain areas in an experiment. These features make fMRI the best tool for investigating human brain function, especially changes in brain activity accompanying long-term learning and adaptation for which repetitive measurements are indispensable.

Thus, to identify the underlying neuronal mechanisms of adaptation to visual transposition, we conducted a series of fMRI and behavioral/psychological experiments for which human subjects wore left–right reversing goggles for more than five weeks and examined:

- (1) Whether ipsilateral V1 activation can be induced in adult human subjects.
- (2) If yes, when the ipsilateral activity starts, and what kind of behavioral/psychological changes occur accompanying the ipsilateral activity.
- (3) Whether other visual cortices also show an ipsilateral activity change.

2. Methods

2.1. Subjects

Four normal volunteers (two males and two females) participated in the experiments. Their mean age was 22

years (range 21–23 years). All subjects were determined to be right-handed by the Edinburgh Handedness Inventory [21]. They underwent optometry, and any refractive anomaly was corrected using trial glasses for fMRI experiments. Informed consent was acquired from all subjects following procedures consistent with the Declaration of Helsinki and approved by the Ethical Committee of the Communications Research Laboratory.

2.2. Procedures

Fig. 1 shows the time line of five fMRI experiments; the control experiment (PRE) was conducted just before the subjects put on the goggles, and three (first, second and third experiment) were conducted during the adaptation period. A final one (POST) was performed five months after removal of the goggles. In parallel with the fMRI experiments, psychological/behavioral test batteries consisting of more than 20 experiments (see Appendix A) were conducted almost every day. The subjects continuously wore handmade goggles (Fig. 2) for 35 (two of four) or 39 days except while they slept. In all the psychological experiments except for Experiment 19 (see Appendix A), the subjects were tested with reversing goggles on. In addition, they were blindfolded while they slept. They were always required to close their eyes before they took off the goggles to perform tasks for the fMRI and the psychological experiments during the adaptation period. They wore only the frame of the goggles for the pre- and post-test. During the adaptation period, the subjects were required to live their lives as normally as they could; for example, they performed everyday tasks like shopping, operating a computer, and reading. All experiments were performed in compliance with relevant laws and institutional guidelines. The goggles, in which a right-angle prism was set in front of each eye, reversed the subject's view about the vertical meridian (left–right reversal). Two goggles were prepared for each subject; one for vision of extrapersonal space, the other for vision of peripersonal space. The subjects used both goggles properly. The field of view

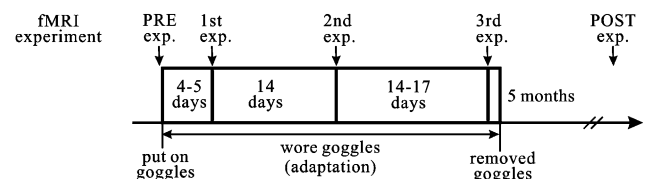


Fig. 1. Time line of fMRI experiments. The PRE fMRI experiment was conducted just before wearing the goggles, and the third fMRI experiment was conducted a few days before removing the goggles. The last one (POST) was performed five months after removal. In parallel with the fMRI experiments, visually guided reaching experiments were conducted seven times, and map discrimination experiments were conducted four times.



Fig. 2. Left–right reversing goggles (left) and one of the four subjects who wore the goggles (right). They wore the goggles for more than five weeks, except while they slept.

was restricted to 65–96° (goggles for extrapersonal space) and 35–60° (goggles for peripersonal space) on the horizontal meridian and 68–78° (goggles for extrapersonal space) and 60–72° (goggles for peripersonal space) on the vertical meridian.

2.3. fMRI experiments

2.3.1. Stimuli

Three kinds of fMRI experiment were conducted. One was for examining activity changes in primary visual cortex and extrastriate cortex accompanying adaptation to left–right reversed vision (Experiment 1); the other two were for identifying the location of V1 and V2/V3 (Experiment 2), and MT/MST (Experiment 3).

2.3.2. Experiment 1

To activate the visual cortices, a computer generated a reversing (7 Hz) checkerboard pattern (subtended 3.5° of visual angle, 15 cd/m² for white, 0.4 cd/m² for black) which was presented in either the lower-left or lower-right quadrant avoiding a central foveal area (1.1° radius) with a fixation cross for the test condition (Fig. 4). Only the fixation cross was presented for the control condition. The subjects were required to fixate on the fixation cross. The visual stimuli were presented on a rear-projecting screen near the subject's head with a high-luminance CRT projector (SONY VPH-1272QJ, Tokyo, Japan). The subjects viewed the stimuli binocularly via a tilted mirror without the reversing goggles. Since the subjects were asked to close their eyes before taking off the goggles and the mirror was tilted about 45° from horizontal in the headward direction, the subjects could not see their hands in non-reversed vision.

2.3.3. Experiment 2

To separate V1 functionally from the other visual cortices, flickering (7 Hz) wedge-shaped checkerboard patterns were presented along the horizontal meridian in the test condition (0.8–7.0° eccentricity, 20° wedge angle) and along the vertical meridian in the control

condition (0.8–6.0° eccentricity, 20° wedge angle) with a fixation cross. While horizontal-meridian stimulation should activate the lateral depths of the calcarine fissure and the V2/V3 border, vertical stimulation should activate the V1/V2 border. Thus pixels located between the area activated by horizontal-meridian stimulation and the area activated by vertical stimulation can be defined as V1. Other activated areas around the V1 area were defined as “V2/V3”. Otherwise, the conditions were the same as in Experiment 1.

2.3.4. Experiment 3

To identify MT/MST areas functionally, a coherently moving (6.5°/s of visual angle) white dot pattern was presented in either the right or left visual hemifield (subtended 11°×7° of visual angle) for the test condition, and a stationary dot pattern was presented for the control condition. During the test condition, the direction of the coherent movement changed randomly every 1–2 s. Subjects were required to fixate on a stationary fixation cross. The activated area around the meeting point of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus was defined as “MT/MST” [43]. Otherwise, the conditions were the same as in Experiment 1.

2.4. Visually guided reaching experiment

To evaluate changes in visuomotor coordinative function accompanying adaptation to left–right reversed vision, a visually guided reaching experiment was conducted seven times: the control experiment (PRE) was conducted just before the subjects wore the goggles, and four were conducted during adaptation (day 2, day 11, day 20, and days 26–29). The last two were performed just after removal of the goggles (POST1) and on the next day (POST2). In the experiment, the subject wearing left–right reversing goggles sat in front of a touch display. The subject's head was placed on a chin rest, which prevented head movements, at a viewing distance of 45 cm so that the tested eye was located just

in front of the center of the display. The other eye was covered. The fixation cross was presented at the center of the screen. After a variable period from extinction of the fixation cross, a target circle (16 mm in diameter) appeared at one of eight radial positions (81 mm from the center), or at the fixation point for 500 ms. The subject was required to hold down a button located in front of the computer screen, and when the target appeared, to touch the target circle with his/her preferred (right in all the subjects) index finger as quickly and accurately as possible. Error (distance between target position and location where the subject's index finger touched) and movement latency (time between target onset and releasing the button) were measured.

2.5. Map discrimination experiment

To evaluate the adaptive changes in the subject's internal representation of living spaces which were familiar to the subjects, a map discrimination experiment was conducted four times (day 3, day 15, day 25, and days 33/34) while the subjects wore left–right reversing goggles. An experimenter asked the subjects wearing left–right reversing goggles to close their eyes and turned the subjects' body twice or thrice to remove their sense of which direction they faced (north, south, east or west). Then the subject sat in front of a CRT screen with a viewing distance of 100 cm. The CRT was placed in a room and surrounded with a cylindrical curtain. The direction of the entrance into the room and the direction of the CRT screen were randomized for each experiment. The following maps ($\approx 20 \times 20$ cm) depicting their university's campus were presented on the screen under computer (Apple Macintosh Performa 5220) control: (1) four true maps (north-top, south-top, east-top, and west-top; the same locations shall apply hereafter) of a small student common room (Fig. 3a, $\approx 6 \times 4$ m) where all the

subjects spent most of their time for resting and meals during the experimental period, and their four mirror-image maps, (2) four maps of a floor plan of the building including an L-shaped corridor (Fig. 3b, $\approx 30 \times 20$ m), the common room, a rest room and other rooms, and their four mirror-image maps, (3) four maps of a courtyard (Fig. 3c, $\approx 100 \times 60$ m) including the building, and their four mirror-image maps, and (4) four maps of the university campus (Fig. 3d, $\approx 500 \times 500$ m) including the courtyard and their four mirror-image maps. The subjects were all very familiar with these areas before the experiments. During the adaptation period, they walked around these areas almost every day. Either a true map or a mirror image map was presented in each trial for 10 s, and the subject was required to answer verbally whether the presented map matched his/her present internal representation of the space or not. Thus, 32 maps (4 areas \times true or mirror image \times 4 orientations) were successively presented in random order within a session, and the session was repeated three times in an experiment.

2.6. fMRI data acquisition and analysis

All fMRI experiments were carried out with a 1.5 Tesla MR scanner (Siemens Vision) with a standard CP (circular polarized) head coil. Functional images were acquired using a T2*-weighted echoplanar imaging (EPI) sequence (echo time = 66 ms, flip angle = 90° , number of slices = 10, inter scan interval = 4 s). The pixel size was 2.34×2.34 mm for Experiments 1 and 3, 2.0×2.0 mm for Experiment 2. The slice thickness was 5 mm for Experiments 1 and 3 (slice gap = 2 mm), and 3 mm for Experiment 2 (slice gap = 1 mm). The slice orientation was almost perpendicular to the calcarine fissure for Experiments 1 and 2, and transverse for Experiment 3. Visual stimulus presentation was controlled by a computer (NEC PC-9821), and synchronized with functional

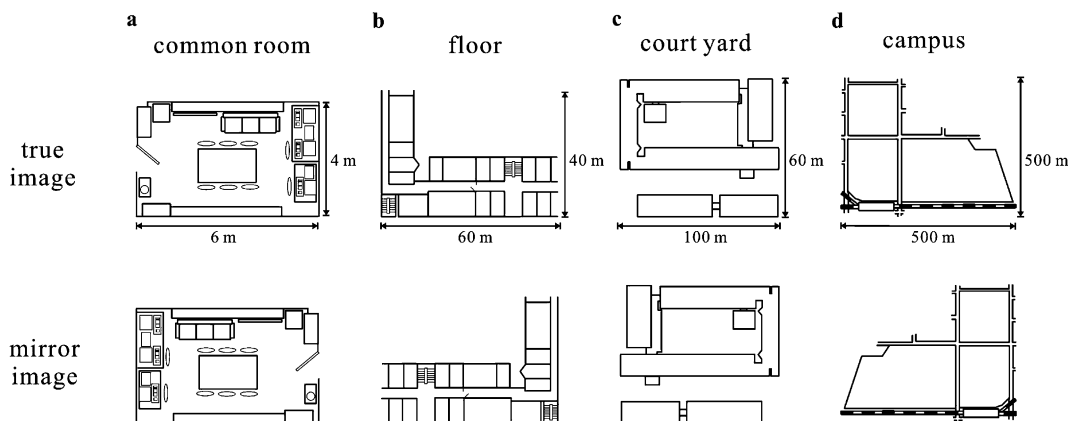


Fig. 3. Examples of maps presented in the map discrimination experiment. (a) The student common room where subjects spent most of their time during the experiment (upper) and its mirror image (lower). (b) The floor containing the common room (upper) and its mirror image (lower). (c) The courtyard containing the floor (upper) and its mirror image (lower). (d) The university campus containing the courtyard (upper) and its mirror image (lower).

image acquisition. An fMRI experiment consisted of six repetitions of 10-scan test and control blocks (120 scans total). Two scans were added at the beginning, and discarded, to eliminate magnetic saturation effects. For all experiments, high-resolution T1-weighted structural images were also acquired at the same location as the functional images (repetition time = 240 ms, echo time = 6 ms, flip angle = 90°, pixel size = 1.1 × 1.1 mm, slice thickness = 5 mm) to provide detailed anatomical information. For all subjects, a T1-weighted 3D MP RAGE scan (repetition time = 9.7 ms, echo time = 4 ms, flip angle = 12°, voxel size = 1.0 × 1.0 × 1.0 mm, slice orientation = sagittal) that covered the whole brain was also recorded to identify brain sulci in each subject.

To prevent head movement and to obtain images in the same position for the five measurements extending over a six-month period, each subject used an adjustable impression of his/her teeth which was fixed firmly to the head coil. Eye movements were monitored using a remote infrared eye tracking system (NAC ST-564). Since the subject's task was just to view stimuli passively, the subject was required to press a button after each scan in all fMRI experiments to keep the subject's arousal level constant. In addition, to eliminate contamination by left–right confusion which can frequently be observed in subjects wearing reversing goggles, all the button presses were done with both left and right index fingers together, and the direction of the press was “footward” or “headward”.

After motion correction [46], the functional images were analyzed using the pixel-by-pixel cross-correlation method, in which the cross-correlation coefficient (CC) between the signal time course and a reference function was calculated for each pixel. The reference function took a value of 1 for the test condition and –1 for the control condition and was delayed by 1 scan interval (4 s) to maximize the CC. Pixels with a significance level of 0.0001 or higher were accepted. Data from V1/V2 border areas, defined by the results of Experiment 2, were eliminated from the analysis to avoid confusing V1 activation with V2 activation. We did not use any software for transforming the subject's brains into a standardized coordinate system, because the calcarine sulcus usually has a complicated winding shape, and errors in registration might cause confusion of V1 activation with V2 activation. In the same way, to avoid confusion due to distortion of the T2*-weighted functional images compared to T1-weighted images, all analyses and identification of visual cortex were done only with T2*-weighted functional images, not with T1-weighted structural images.

3. Results

During the study, one of the four subjects definitely showed maladaptation to left–right reversed vision.

That is, compared with the other three subjects, he was much more inactive and showed more severe confusion when he was required to perform left–right discrimination. In addition, during the fMRI experiment he reported double vision which was fatal for observation of ipsilateral activation. Thus, his data were excluded from further analysis.

3.1. Behavioral/psychological experiments

As for the other subjects, behavioral adaptation to left–right reversed vision improved considerably within two weeks. As shown in Fig. 4, the error in visually guided reaching, which increased dramatically in every location in the early phase of the adaptation (Fig. 4, day 2), settled down by day 11 and returned to the PRE level by day 20. The recovery from left–right reversed vision after removing the goggles was much faster than the adaptation. Although the error increased just after removing the goggles (POST1), especially when the targets appeared on the left side of the screen, it reverted to the PRE level within two days (POST2). In the map discrimination experiment, a mirror image map seen with left–right reversing goggles looks non-reversed. Thus, it matches the subject's view before wearing

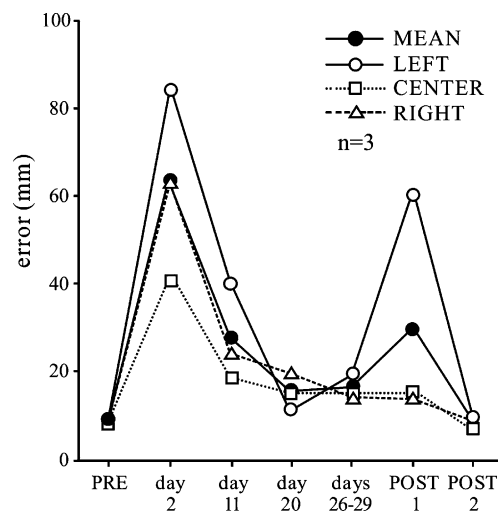


Fig. 4. Change in error (distance between target position and location where the subject's index finger touched) for the visually guided reaching experiments. The errors are displayed separately depending on the target locations. LEFT: Average of errors for three targets which appeared on the left side of the screen. RIGHT: Average of errors for three targets which appeared on the right side. CENTER: Average of errors in three targets which appeared at the fixation point, just above the fixation cross and just beneath the fixation cross. MEAN: Average of LEFT, RIGHT and CENTER. While all subjects showed low values in the control session conducted just before wearing goggles (PRE), all of them showed definite increase at day 2. At day 11, however, the error was considerably decreased, and returned to the PRE level on day 20 and days 26–29. Just after removing the goggles, the error increased noticeably (POST1). However, it returned to normal by the next day (POST2).

goggles and does not match the subject's view while wearing goggles. In the same way, a true map does not match the subject's view before wearing goggles and matches the subject's view while wearing goggles. As expected, when a map of the building floor plan was presented, the rate that a mirror image map was judged to match the subject's internal representation was high (>90%) in the first experiment, and decreased rapidly (<60%) by the end of the second week (Fig. 5b). On the contrary, the rate that a true map was judged to match the subject's internal representation was approximately 50% in the first experiment, after which it increased rapidly and reached 100% within the first two weeks. In the case of a map of a larger space (the courtyard or the university campus), the rate that a mirror-image map was judged to match the subject's internal representation remained high across the experiments. The rate that a true map was judged to match gradually increased (Fig. 5c and d). In the case of the map with the most limited space, the common room, the rate that the true map was judged to match the subject's internal representation was almost 90% in the first experiment, and stayed high across the experiments. Though the rate that a mirror-image map was judged to match was also high in the first experiment, it gradually decreased (Fig. 5a). Among the more than 20 behavioral/psychological experiments, only the results of the map discrimination experiments distinctively showed adaptive changes within a few days.

3.2. fMRI experiments

No discernible eye movement was observed during Experiments 1 and 3 for all the subjects. Though a small amount of saccadic movements were observed during Experiment 2 accompanying the change in motion direction, the frequency showed no marked change across the experiments. Fig. 6a shows the checkerboard pattern we employed for activation of the visual corti-

ces, Fig. 6c shows the change in ipsilateral V1 activation accompanying adaptation to left–right reversed vision in a representative subject and Fig. 6b shows the location of the slice shown in Fig. 6c. V1 showed no ipsilateral activation before the reversing goggles were put on. During adaptation, ipsilateral activation appeared in a small posterior area within V1; it disappeared within five months after removing the goggles. One of the three subjects showed ipsilateral V1 activation in the first adaptation experiment, two of three in the second experiment, and all three in the third experiment. Compared with activation by a contralateral stimulus, the ipsilateral activation was noticeably restricted to a small posterior area within V1 where the contralateral stimulus activated most vigorously.

The number of significant pixels, however, does not necessarily increase with increased brain activity, because the threshold used to determine each voxel's statistical significance introduces a non-linearity [1]. Thus, to evaluate the ipsilateral activity more quantitatively, we calculated the average cross-correlation coefficients (CCs) obtained from the 10 pixels which showed the highest CCs in response to the stimulus in both contralateral and ipsilateral V1 (Fig. 7a), V2/V3 (Fig. 7b), and MT/MST (Fig. 7c) areas. Only the four most posterior slices were analyzed for V1 and V2/V3, because the V1/V2 border was ambiguous in the anterior part of the occipital cortex. To avoid confusing V1 activation with V2 activation, areas which were defined as the V1/V2 border by the experiment for V1/V2 functional separation were not included in the calculation. As a result, ipsilateral V1 showed slightly negative values at PRE and POST, and showed a statistically significant increase in the first experiment (days 4/5), which then increased gradually to a maximum positive value just before taking off the goggles (days 32–35). On the contrary, contralateral V1 showed conspicuously high CCs and was almost constant across the experiments. Compared with V1, the V2/V3 areas showed less marked changes. Al-

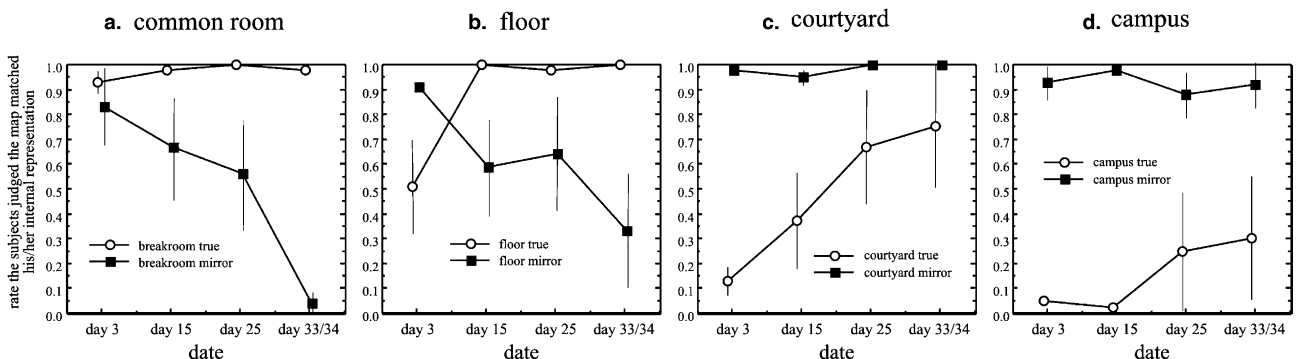


Fig. 5. Mean rates and standard deviations at which the subjects judged that the map matched his/her present internal representation of the living space or not. There were four map categories according to the scale of the living space. (a) The small common room where all the subjects spent most of their time for resting and meals during the experimental period. (b) The floor plan of the building including the break room, a rest room and other rooms. (c) The courtyard including the building. (d) The university campus including the courtyard.

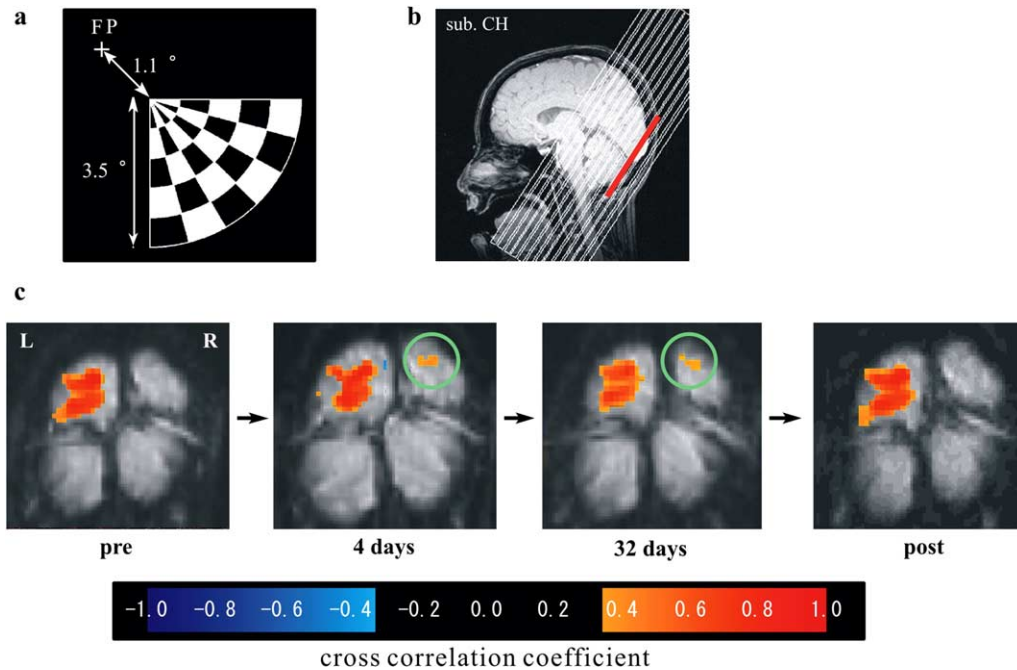


Fig. 6. Change of ipsilateral V1 activation accompanying prism adaptation in a representative subject. (a) The flickering (7 Hz) checkerboard pattern which was presented in the lower-right quadrant for the test condition. Only the fixation cross was presented for the control condition. (b) The location of the slice shown in (c). (c) Before wearing the goggles (pre), V1 showed no ipsilateral activation; during adaptation, ipsilateral V1 activation appeared in a small posterior area within V1 (enclosed by circles); it disappeared within five months after removing the goggles. Note that the subjects viewed the stimuli binocularly without the reversing goggles.

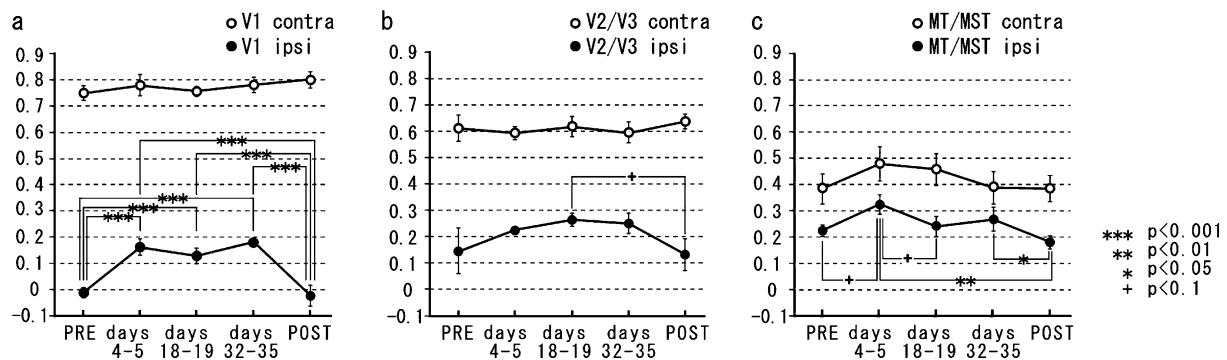


Fig. 7. Time course of average CCs in contralateral and ipsilateral visual cortices accompanying prism adaptation. We calculated the average CC obtained from the 10 pixels showing the highest CC in V1 (a), V2/V3 (b), and MT/MST (c). For V1, the analysis of variance across the blocks showed highly significant main effects for ipsilateral V1 ($F(4, 25) = 11.900, p < 0.0001$), but no main effect for contralateral V1 ($F(4, 25) = 0.454, n.s.$). Post-hoc comparisons with a Fisher's test revealed that ipsilateral CCs during the adaptation were significantly higher than those at PRE and POST ($p < 0.001$ for all comparisons). For V2/V3, the analysis of variance showed no main effect for both ipsilateral V2/V3 ($F(4, 25) = 1.414, n.s.$) and contralateral V2/V3 ($F(4, 25) = 0.239, n.s.$). Post-hoc comparisons with a Fisher's test revealed that ipsilateral CCs of days 18/19 tended to be higher than that of POST ($t = 0.132, p < 0.10$). For MT/MST, the main effect for ipsilateral MT/MST did not achieve statistical significance but rather had a tendency ($F(4, 25) = 2.341, p < 0.10$), while that for contralateral MT/MST did not ($F(4, 25) = 0.611, n.s.$). Post-hoc comparisons with a Fisher's test were conducted to explore differences in ipsilateral activation, and statistically significant differences were found for days 4/5 vs. POST ($t = 0.143, p < 0.01$). In addition, comparisons between PRE and days 4/5, days 4/5 and days 18/19, days 32–35 and POST tended to be different ($t = -0.101, p < 0.10; t = 0.084, p < 0.10; t = 0.086, p < 0.10$, respectively).

though ipsilateral V2/V3 showed slightly positive values at PRE, reached a maximum in the second experiment (days 18/19), and returned to the initial level at POST, there were no statistically significant differences among the experiments. Contralateral V2/V3, like contralateral

V1, showed high CCs and was almost constant across the experiments. MT/MST showed slightly different timecourses from V1 and V2/V3; both contralateral and ipsilateral MT/MST areas already showed conspicuously positive values at PRE; both reached their

maximum in the first experiment (days 4/5), and then gradually decreased. In addition, whereas the ipsilateral cortex showed an increase in activity after the subjects put on the goggles (days 4–5, days 18–19 and days 32–35) and a decrease in activity after the taking them off (POST), the contralateral cortex showed almost constant activation in the V1 and V2/V3 areas. In contrast, both contralateral and ipsilateral MT/MST areas seemed to covary through time.

4. Discussion

The results of the fMRI experiments suggest that, not only contralateral V1, but also ipsilateral V1 in human adults responds to visual stimuli during adaptation to left–right reversed vision. The ipsilateral activation might also be induced if the subjects could not fix their eyes on the fixation point. The actual accuracy of our eye tracking system ($\approx 1^\circ$ in visual angle) is not so high that we can definitely establish that the subjects looked at the fixation point throughout the experiment. However, the stimulus configuration of Experiment 1 was quite simple; a checkerboard pattern flickered at the same location, and no psychological task was required. It was quite easy for the subjects to keep their eyes on the fixation point. Slightly negative values in the ipsilateral V1 at PRE and POST, indeed, indicate that the ipsilateral activation was not due to the misfixation. Thus, our result, combined with that of the monkey neurophysiological study [39], suggests that V1 in Primates, at least, can be reliably activated by ipsilateral stimulation during adaptation to left–right reversed vision. In addition, our present study adds the following two findings: first, a more quantitative analysis revealed that not only V1, but also MT/MST showed significant activity changes during adaptation to left–right reversed vision. In other words, the functional reorganization caused by left–right reversed vision is not restricted to the earliest stage of visual processing, but rather occurs in much more extended areas of the human brain. Second, ipsilateral V1 activation became significant within only four or five days of wearing the goggles, which is much sooner than expected from monkey neurophysiology.

4.1. Anatomical structures which activate the ipsilateral visual cortices

There are three candidate anatomical structures which can activate the ipsilateral visual cortices: (1) bilateral projections from the retina to V1, which extend from 0.6° to 3° across the vertical meridian in humans [42], and 1.5° at the fovea in monkeys [2]; (2) homotopic commissural connections between visual cortices in both hemispheres. These connections are lacking in V1 except

for the V1/V2 border which corresponds to the vertical meridian of the visual field [4]; (3) backward connections which project from a higher cortex to lower cortices in both hemispheres. The distance between the fixation point and the visual stimulus which we employed (1.1°) was not enough to discard the first and second possibilities. As described in the results, however, the experiment for V1/V2 functional separation identified V1/V2 border areas where both the bilateral projection and the commissural connection are concentrated. Data from these areas were eliminated from the analysis of the ipsilateral activation to avoid confusing V1 activation with V2 activation. The absence of ipsilateral activation of V1 before wearing and after removing reversing goggles in the present study is consistent with the result of an earlier study which also measured the ipsilateral activity of visual cortices using fMRI [41], and demonstrates that the V1 area we analyzed did not include the callosal band along the V1/V2 border. Therefore, the most prominent candidate is backward connectivity from a higher cortex to lower visual cortices of both hemispheres. Furthermore, while ipsilateral V1 showed activity changes accompanying putting on and taking off the reversing goggles, and the contralateral side showed almost constant activation, both contralateral and ipsilateral MT/MST areas showed coincidental change. This discrepancy indicates that the underlying neuronal mechanism for adaptation of the MT/MST area may be different from that of V1. Namely, not only backward connections, but also the homotopic commissural connections, which are prevalent throughout the MT/MST area, might play a major role in the activation of ipsilateral MT/MST areas.

4.2. Why did the ipsilateral activation appear so rapidly?

Sugita [39] reported that monkey V1 neurons responded to stimuli presented not only in the contralateral visual field, but also in the ipsilateral visual field one and a half months after putting on reversing goggles. Although the notion has been widely accepted that mature brain, even in a primary sensory area, is more plastic than previously believed, few studies have reported that functional plasticity could occur rather rapidly; for example, Weiss et al. [45] reported that functional plasticity in the human primary somatosensory cortex occurs within a period of 10 days after amputation.

One possible explanation for the rapid generation of the ipsilateral activity is the difference in the subject's activity, particularly during the initial phase of wearing reversing goggles. That is, many studies on visual transposition suggest that active movements which manipulate the environment facilitate adaptation to reversed vision [10–12]. In the monkey experiment, however, “The disruption of visually guided behavior was

much more severe than expected from human studies. The animals could not even move by themselves for the first two weeks” [39]. On the contrary, our human subjects were encouraged to conduct their daily lives as normally as possible after putting on the reversing goggles, and they actually did so. Consistent with this view, the results of the behavioral experiments showed rapid adaptation to left–right reversed vision: errors in the visually guided reaching task decreased considerably by day 11; the results of the map discrimination experiment revealed that internal representation of relatively small living spaces also reversed within the first two weeks. In particular, reversed internal representation of the common room in which the subjects spent most their time during the experiment was already dominant over the non-reversed one by day 3. These results suggest that visuomotor coordinate function and internal representation of peripersonal space adapted, or at least started to adapt, within the first week. Thus, the prompt adaptation to left–right reversed vision resulting from active behaviors is probably associated with generation of the ipsilateral activity. A second possibility is, while our human subjects underwent the fMRI experiment in an alert state, the neuronal activity of the monkeys was recorded in an anesthetized state. Though the influence of anesthesia on neuronal activity is still unclear, anesthesia might weaken the activity especially when it is under the top-down influence of higher cortical areas.

4.3. What caused the ipsilateral V1 activity?

When wearing reversing goggles, one finds that the right hand, which is usually in the right visual field, appears in the left visual field as if it were the left hand, and vice versa. To assimilate the new, reversed images of the hands in the context of proprioceptive signals and/or efferent copies of motor commands which are not reversed, the subjects may need to create new reversed hand representations. On the basis of some psychophysical experiments (hand identification experiment and visual localization experiment, see Appendix A, Experiments 11 and 14, respectively) and an fMRI experiment using our subjects, Sekiyama et al. [34] reported generating new reversed hand representations after more than three weeks of adaptation to left–right reversed vision. The result of the fMRI experiment for which the subjects performed a hand identification task (almost the same as Experiment 11 in Appendix A) revealed that using implicit motor imagery of the new reversed hand activated the parietal cortex (BA7/39) as well as the frontal cortex (BA44, 47, 46, 9). These results are consistent with those of a previous imaging study which reported that the posterior parietal cortex is responsible for the recalibration of hand–eye coordination for wedge prism adaptation [5]. Verbal reports obtained from one of our subjects vividly express the

process generating the new reversed hand representations: “I found that the visual image of my hands frequently alternated; sometimes my right hand was located on the right side of my body, and my left hand was located on the left like before wearing reversing goggles; sometimes, however, my right hand was located on the left side of my body and my left hand was located on the right; sometimes both non-reversed and reversed images of my hands coexisted. As time went on, the reversed images of my hands became predominant. In other words, when I move my right hand with my eyes closed, I feel like my left hand is moving. . .”. However, the distinct development of the new reversed hand representation (more than three weeks) was much slower than the appearance of the ipsilateral activation in V1 and MT/MST area (four or five days).

This temporal discrepancy between the generation of the new reversed hand representation and the appearance of the ipsilateral activation of visual cortices led us to an idea that there are at least two types of adaption processes to left–right reversing goggles. Subjects wearing wedge prisms, which cause lateral optical deviation, usually show rapid adaptation [5,22,23,31]. It has been suggested that there are two types of adaption process in this kind of wedge prism adaptation: faster strategic (top-down) perceptual-motor control to coordinate sensorimotor systems and slower spatial realignment among several sensorimotor coordinate systems (spatial maps) [27–29]. Though it is still unclear that adaptation to left–right reversing goggles and rapid adaptation to wedge prisms share common underlying neuronal mechanisms, psychological and neurological changes observed in the early phase of adaptation to left–right reversing may be associated with the process of the faster strategic perceptual-motor control. One of the most crucial actions for a subject with left–right reversed vision is controlling the hands to pick up and point at objects in the personal/peripersonal space. For example, when the subjects wearing left–right reversing goggles pick up an object located in the left visual field, they have to use their right hand which is normally located in the right visual field and whose visual information is normally projected to left V1 (ipsilateral to the visual field in which the object appears). To perform such actions, the subjects in the early phase of adaptation must change their strategic (top-down) perceptual-motor control. It is well-known that top-down visual imagery alone can activate primary visual cortex with a topographical representation [16,17], especially when a task requires high-resolution imagery [17,18]. In addition, there are several pieces of evidence which suggest that tactile and proprioceptive perception involve visual imagery and activate visual cortices [6,20,24,25,33,48]. In particular, normal sighted subjects who were visually deprived for five days showed enhanced activation of visual cortices including the primary visual cortex

during the tactile stimulation on the second and the fifth day, though the activation in the somatosensory cortex decreased [25]. It can be easily expected that our subjects, as is the case with the visually deprived subjects, required high-resolution visual images and top-down perceptual-motor control for picking up and pointing at objects in left–right reversed personal/peripersonal space. These strategic exertions and crossmodal links between visual and somatosensory cortices might be a cause of the activation in the ipsilateral visual cortex and the reverse internal representation of peripersonal space in the early phase of adaptation.

Linden et al. reported that wearing upside-down inverting and left–right reversing goggles (180° rotation) for 7–10 days did not induce any functional change in early visual cortical areas, though the subjects showed rapid adaptation of visuomotor functions [19]. This discrepancy between the result of our left–right reversed vision experiment and that of the 180°—rotated one suggests that the brain mechanism for adaptation to left–right reversed vision is essentially different from that for adaptation to upside-down inverted vision. This conclusion is probable from the following psychological and physiological findings. First, most objects we see in our lives have “mono-orientedness” in the upper-lower dimension of the visual field, and “bi-orientedness” in the left–right dimension [44,47] (e.g. inverted pictures of human faces look very odd, but it is difficult to discriminate left–right reversed pictures of human faces from non-reversed ones). Second, anatomical and physiological asymmetries are larger between visual cortices corresponding to the upper and lower visual fields than between those corresponding to the left and right visual fields. For example, while V3, which is located in dorsal extrastriate cortex, has reciprocal connections with V1, VP, located in ventral extrastriate cortex, has no connection. While V3 is more motion sensitive than VP, VP is more color sensitive [3,7]. In addition, visually responsive pattern-selective neurons in the inferotemporal cortex of macaque monkeys responded more similarly to members of a lateral mirror-image pair than to members of a vertical mirror-image pair [30]. These anisotropies of our visual world and anatomical/functional asymmetries of our brain may promote changes in brain activation more easily for left–right reversed vision than for up-down inverted vision.

5. Conclusion

In conclusion, we found that left–right reversed vision rapidly activates ipsilateral visual cortices in humans. The ipsilateral activity started much sooner than the one and a half months which were expected from the monkey neurophysiological study. The most prominent

anatomical candidate which induced the ipsilateral activity is backward connectivity from a higher cortex to lower visual cortices of both hemispheres. It is suggested that there are at least two types of adaptation processes to left–right reversing goggles: faster strategic (top-down) perceptual-motor control to coordinate sensorimotor systems and slower spatial realignment among several sensorimotor coordinate systems. The activation of ipsilateral visual cortices in the early phase of adaptation may correspond to the faster process for which top-down perceptual-motor control and crossmodal links activated the primary visual cortex ipsilateral to the hemivisual field where objects appeared through backward connection from higher visual cortices or association cortices to the primary visual cortex. The results of the present study serve as physiological evidence of the large-scale, cross-hemisphere, cerebral plasticity that exists even in adult human brain. However, the functional role of the parietal cortex, which seems to be essentially associated with this type of somatovisual and somatomotor adaptation, is still unclear. In addition, there is no clear evidence that adaptation to left–right reversing goggles and rapid adaptation to wedge prisms share common underlying neuronal mechanisms. Further research is needed to clarify these issues.

Note

Movie files in which the subjects struggle with left–right reversing goggles over the course of the five-week experiment can be downloaded from our lab’s homepage (<http://www-karc.nict.go.jp/d333/english/movie/index.html>).

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Appendix A

The following is a list of behavioral/psychological experiments which were conducted before, during and after adaptation to the left–right reversing goggles. In all the experiments except for Experiment 19, subjects were tested with reversing goggles on, except for the pre- and post-test, for which they wore only the frame of the goggles.

Experiment 1 (*Visually guided reaching*). See Section 2.

Experiment 2 (*Map discrimination*). See Section 2.

Experiment 3 (*Writing characters*). The subject was required to write on paper an English character/word and a Kanji character/word with his/her eyes open and eyes closed. The frequency of occurrence of mirror-image characters was measured.

Experiment 4 (*Reading an English character*). The subject was required to read aloud a series of English characters which were successively presented at the center of a computer display in random order. Half of the characters were laterally asymmetric (b, d, p and q), the other half were laterally symmetric (A, H, M, and T). The latency and the number of errors were measured.

Experiment 5 (*Reading a clock without numbers on the clockface*). The latency and the number of errors were measured.

Experiment 6 (*Sense of equilibrium-A*). The subject was required to walk as quickly as possible on a series of thirteen blocks (12 cm in width, 12 cm in height and 60 cm in length) which were arranged in an S-shaped pattern. Time to reach the goal and number of falls from the blocks were measured.

Experiment 7 (*Sense of equilibrium-B*). The subject was required to stand on one leg on a stabilometer with eyes open and eyes closed. Total shift in the center of gravity swayed for a minute and the time in which the subject could balance on one leg were measured.

Experiment 8 (*Stereogram observation*). The subject observed a random dot stereogram and two types of line-contoured stereogram which simulated different depth orders and depth magnitudes through the reversing goggles. The frequency of depth-order perception which was consistent with binocular disparity was measured for each type of stereogram.

Experiment 9 (*Depth cue integration*). The subject observed stereograms through the reversing goggles. In these stereograms, binocular disparity and monocular cue (motion parallax, or texture size) simulated different depth orders and depth magnitudes. Apparent depth order and depth magnitude were measured.

Experiment 10 (*Apparent distance*). The subject was required to observe a luminous disc by binocularly fusing them, or to observe monocularly an LED by translating her/his head, in a completely darkened room

through the reversing goggles. The disc and LED were located at different positions. Apparent viewing distances to the stimuli were measured.

Experiment 11 (*Hand identification*). Stimuli consisted of three line drawings of a hand that were presented as either a left or right hand in one of eight orientations (0°, 45°, 90°, 135°, 180°, 225°, 270° and 315°) in the picture plane. A stimulus stayed visible until the onset of the subject's voice. The subjects were instructed to identify each hand as left or right and reported the handedness verbally. The reaction time was measured, and the number of errors was counted.

Experiment 12 (*Playing darts*). The subject threw darts at a round board located at a distance of 2 m. The distance between the center of the board and the position of the dart was measured.

Experiment 13 (*Walking a maze*). The subject was required to walk a simple T-shaped (4.5 × 3 m) maze. Time to reach the goal, the speed of walking, and the trace of the walk were recorded.

Experiment 14 (*Visual localization*). The subject sat in front of a display with a viewing distance of 105 cm. He/she placed both hands on a switch box that was hidden from view on the subject's knees. A fixation point was presented for 500 ms at the center of the display. After a 100-ms period with no display, a target cross was presented for 200 ms at either 10.5 cm to the left or right of the center. The subjects were required to indicate whether the target was perceived at the left or the right of the center by pressing the button with the left hand (left side) or the button with the right hand (right side) as fast as possible. The reaction time was measured, and the number of errors was counted.

Experiment 15 (*Auditory localization*). Instead of visual stimuli, the subject listened to auditory tones which were presented for 200 ms to the left or the right ear. Otherwise, the conditions were the same as in the visual localization task.

Experiment 16 (*Tactile localization*). Small vibrators were attached to both sides of the subject's head, left and right shoulders, left and right hands, and left and right feet. Instead of visual stimuli, a tactile stimulus was delivered to one of the above regions for 200 ms. Otherwise, the conditions were the same as in the visual localization task.

Experiment 17 (*Stimulus-response compatibility effect*). Reaction time to a visual target in the left or right hemispace was measured. The subject sat in front of a

display at a viewing distance of 57 cm. A square or a circle was presented at 3 cm to the upper-left, upper-right, lower-left or lower-right of the fixation at the center of the display. Two buttons were placed side by side in front of the display. The subjects were required to indicate whether the square or the circle appeared by pressing either the left button with the left hand or the right button with the right hand as fast as possible.

Experiment 18 (*Vection (visually induced self-motion sensation)*). The subject stood on a stabilometer holding a push button in each hand and observed horizontally moving random dots which were projected on a screen at a distance of 75 cm from the subject. He/she pushed the button to indicate the direction of the visually induced self-motion. The shifts in the gravity center of the subject's body were measured.

Experiment 19 (*Motion perception accompanying head movements*). The subject took off the goggles and put on a head mounted display in a completely darkened room. Then he/she was required to turn his/her head from side to side in time to the auditory click (0.25 and 0.4 Hz). Coherently moving (from left to right) random dots were presented on the head mounted display at various velocities. The subject judged the motion perception when he/she turned his/her head from right to left.

Experiment 20 (*Binocularly fusional area*). A light-emitting diode (LED) was presented at variable viewing distances (25–265 cm) under completely darkened or illuminated conditions. The subject observed the LED binocularly and judged whether she/he saw a single fused image or a double image. The smallest viewing distance with which the subject could binocularly fuse the LED was measured.

Experiment 21 (*Representation of small living space*). The subject was required to explain the layout of the small living space by drawing a sketch or making a verbal report (e.g. "The shower head in the shower room is located at the right side when I face the door of the room").

Experiment 22 (*Object recognition with different modalities*). The subject perceived an L-shaped bar visually, tactually (eyes closed), and visually and tactually. After that, the other L-shaped bar was presented. He/she was asked to recognize the bar by sight, by touch with eyes closed, and by touch with eyes opened. Dissociation of the object recognition between different modalities was checked.

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Further reading

Parts of the results of these experiments appear in the following articles:

- [1] K. Sekiyama, S. Miyauchi, T. Imaruoka, H. Egusa, T. Tashiro, Body image as a visuomotor transformation device revealed in adaptation to reversed vision, *Nature* 403 (2000) 192–195.
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