Report

Current Biology

Learning to Associate Orientation with Color in Early Visual Areas by Associative Decoded fMRI Neurofeedback

Highlights

- There has been no evidence of associative learning of features in early visual areas
- Neurofeedback induced signals for red paired with an achromatic vertical grating
- Such paired presentations led to associative learning of orientation and color
- The results show that early visual areas may create associative learning

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In Brief

Amano et al. demonstrate that pairing of fMRI signals for red induced by decoded neurofeedback with an achromatic vertical grating created associative learning of orientation and color, most likely in early visual areas.

Amano et al., 2016, Current Biology *26*, 1861–1866
July 25, 2016
http://dx.doi.org/10.1016/j.cub.2016.05.014

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Report

Learning to Associate Orientation with Color in Early Visual Areas by Associative Decoded fMRI Neurofeedback

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http://dx.doi.org/10.1016/j.cub.2016.05.014

SUMMARY

Associative learning is an essential brain process where the contingency of different items increases after training. Associative learning has been found to occur in many brain regions [1–4]. However, there is no clear evidence that associative learning of visual features occurs in early visual areas, although a number of studies have indicated that learning of a single visual feature (perceptual learning) involves early visual areas [5–8]. Here, via decoded fMRI neurofeedback termed "DecNef" [9], we tested whether associative learning of orientation and color can be created in early visual areas. During 3 days of training, DecNef induced fMRI signal patterns that corresponded to a specific target color (red) mostly in early visual areas while a vertical achromatic grating was physically presented to participants. As a result, participants came to perceive "red" significantly more frequently than "green" in an achromatic vertical grating. This effect was also observed 3–5 months after the training. These results suggest that long-term associative learning of two different visual features such as orientation and color was created, most likely in early visual areas. This newly extended technique that induces associative learning is called "A-DecNef," and it may be used as an important tool for understanding and modifying brain functions because associations are fundamental and ubiquitous functions in the brain.

RESULTS AND DISCUSSION

The complete experiment consisted of four stages: retinotopic mapping [10], color classifier (decoder) construction, associative decoded fMRI neurofeedback (A-DecNef) training, and post-test stages (see the Supplemental Experimental Procedures). In the color classifier construction stage, we measured blood-oxygen-level-dependent (BOLD)-signal multi-voxel patterns in the primary and secondary visual areas (V1/V2) evoked by the presentation of red-black, green-black, and gray-black gratings of both vertical and horizontal orientations (Figure S1) and constructed a color classifier [11]. The outputs of the classifier represented the calculated likelihood of red color presented to the participants. The classifier's mean percentage of correct color classification was approximately 70%, which was significantly above chance (50%, $t_{11} = 13.66$, $p < 0.001$ for red; $t_{11} = 11.60$, $p < 0.001$ for green; one-sample t test with Bonferroni correction).

The color classifier construction stage was followed by 3 days of the A-DecNef training stage (Figure 1). Participants were unknowingly trained to create an internal association between a physically presented achromatic vertical grating and the neural activation for a specific target color (red), although no chromatic stimulus was presented in the display. Participants were asked to do the following: "Maintain your gaze at the fixation point at the center of the display. While the achromatic grating is being presented, try to somehow regulate your brain activity to make a to-be-presented solid gray disk as large as possible." The participants were not informed that the size of the disk was proportional to the red likelihood. In short, participants were trained to induce the activation patterns for red in V1/V2 without having any real red stimulus presented. By pairing such activation patterns with a physically presented vertical grating, we tested whether associative learning of vertical orientation and red occurred.

Figure 2 shows the red likelihood change due to A-DecNef training. The red likelihood on days 1, 2, and 3 was significantly higher than the red likelihood on day 0 (the red likelihood for the achromatic vertical grating during the color classifier construction stage). These results suggest that BOLD-signal patterns similar to those evoked by the red-black grating in V1/V2 were successfully induced during A-DecNef training. None of participants reported that they had the target color in mind during A-DecNef training (Table S1).

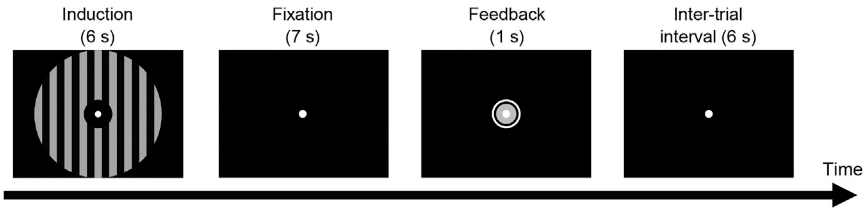

Figure 1. Procedure of a Trial in the A-DecNef Training Stage

An achromatic (gray-black) vertical grating was presented during the induction period (6 s), during which participants were trained to induce BOLD-signal multi-voxel patterns in V1/V2 corresponding to the color red, unbeknownst to participants. Immediately after the fixation period (7 s), a feedback disk was presented for 1 s. The disk size roughly represented how similar the BOLD-signal patterns in V1/V2 induced during the induction period were to the patterns evoked by the target color stimuli (red-black gratings) presented in the color classifier construction stage.

See also Figure S1.

Next, we tested whether associative learning between the orientation and color was indeed created as a result of A-DecNef. We conducted a psychophysical measurement during the post-test stage where a two-alternative-forced-choice task was performed to construct chromatic psychometric functions for each participant. Vertical, horizontal, and oblique gratings were used (Figure 3A). Assuming that A-DecNef training should have no effect on oblique stimuli, the oblique stimuli were used as control orientations for the vertical orientation. The color of the inner grating was tinted from green to red in eight steps, passing through a neutral gray. Participants were instructed to judge whether the inner grating was red or green. Figures 3B and 3C show the mean red response percentage in the A-DecNef group and the control group (see the Supplemental Experimental Procedures), who did not participate in A-DecNef training, respectively. Results of a three-way mixed-design ANOVA (group as a between-participants factor, and orientation and color as within-participants factors) on the red response percentage indicated a significant main effect of color ($F_{2.6,42.1}$ = 142.82, $p < 0.001$; $\varepsilon = 0.38$), and a significant three-way interaction ($F_{7.1,113.5}$ = 2.18, $p = 0.040$; $\varepsilon = 0.51$). Testing for a simple

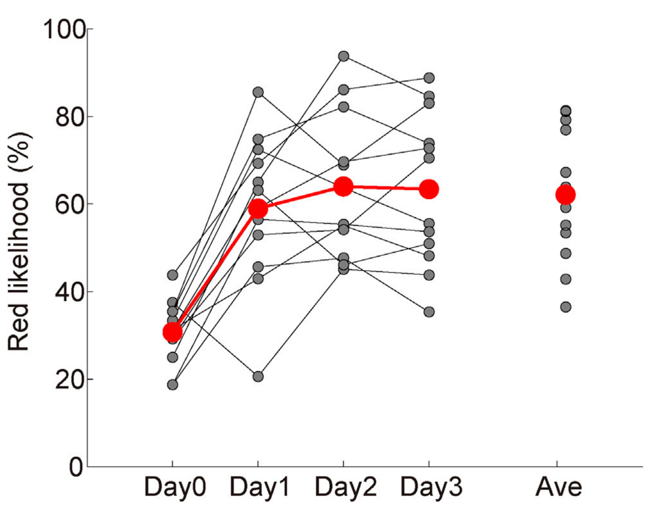

Figure 2. Change in the Red Likelihood by A-DecNef Training

On day 0 the color classifier was constructed, and on days 1, 2, and 3 the A-DecNef training (N = 12) was conducted. Gray dots represent individual data, and red dots represent the average across participants. The red likelihoods on days 1, 2, and 3 were significantly higher than on day 0 ($p < 0.001$ for all 3 days and the average; $t_{11} = 5.64$ for day 1; $t_{11} = 7.25$ for day 2; $t_{11} = 7.07$ for day 3; $t_{11} = 7.42$ for the average across the 3 days; paired t test with Bonferroni correction). The average value is for days 1–3.

interaction for each group showed that the interaction between orientation and color was significant for the A-DecNef group ($F_{14,224}$ = 2.41, $p = 0.004$), indicating that A-DecNef training resulted in an orientation-specific shift of the chromatic psychometric function. In contrast, a simple interaction between orientation and color was not significant for the control group ($F_{14,224}$ = 1.32, $p = 0.20$). Thus, it is suggested that A-DecNef training, which targeted V1/V2, created perception of a color associated with an orientation.

We further tested whether A-DecNef successfully created the orientation-specific color perception in the A-DecNef group. If A-DecNef successfully associates the vertical orientation with red BOLD-signal patterns, we should observe the following two aspects in the A-DecNef group. First, the point of subjective equality (PSE) to produce 50% red responses (and therefore 50% green as well) for the vertical orientation should be significantly more greenish in terms of the tinted color level in the inner gratings than for the other orientations. Second, the red response percentage should be significantly higher than chance when the vertical orientation was at the neutral gray, which is defined as the PSE for the control oblique orientation.

First, a cumulative Gaussian function was fitted to the data from each individual participant, and the PSE for each orientation was defined as the stimulus level with the 50% red response. We applied one-way repeated-measures ANOVA (orientation as a within-participants factor) to the PSE for each orientation. The ANOVA showed that a main effect of orientation on the PSE was significant ($F_{1.3,14.2}$ = 7.28, $p = 0.013$; $\varepsilon = 0.65$). The PSE for the vertical orientation was significantly different from those for the horizontal (t_{11} = 2.87, $p = 0.015$) and the oblique orientation (t_{11} = 2.77, $p = 0.018$), indicating a significant shift of PSE for the orientation used in A-DecNef training.

Next, we obtained the red response percentage for the vertical orientation at the neutral gray. Perception of the neutral gray for the oblique (control) grating was not significantly affected by A-DecNef, because two-way mixed-design ANOVA (group as a between-participants factor, and color as a within-participants factor) on the chromatic psychometric function of the oblique grating showed no significant effect of group ($F_{1,16}$ = 2.51, $p = 0.133$). The red response percentage for the vertical orientation was defined as the fitted value of a cumulative Gaussian function at this neutral gray. The red response percentage for the vertical grating was significantly higher than chance (t_{11} = 3.70, $p = 0.004$). These results suggest that A-DecNef created red perception in an achromatic vertical grating.

Is the effect of associative learning temporary or long-lasting? To test this, the chromatic psychometric functions for vertical,

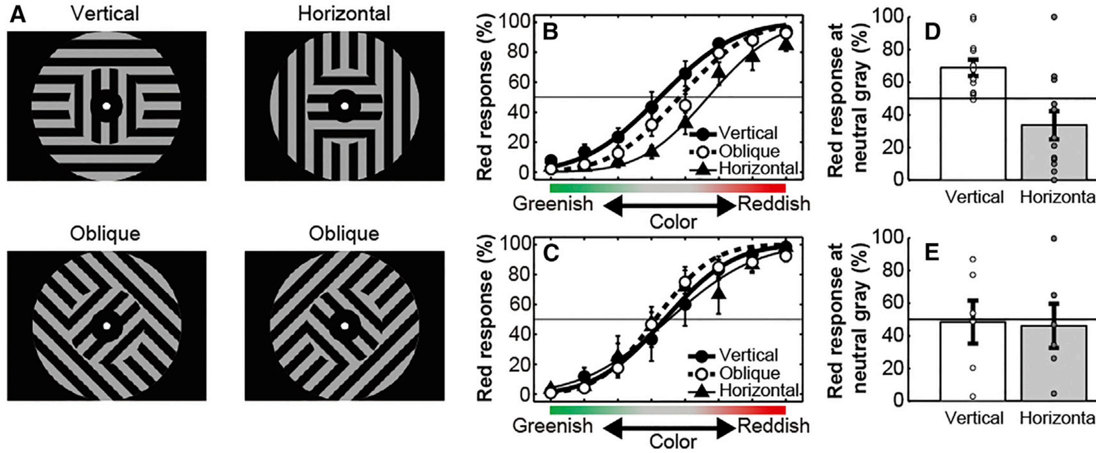

Figure 3. Stimuli and Results of the Post-test Stage

(A) Stimuli. The color in the inner gratings varied in eight steps between a reddish tint (x = 0.323, y = 0.310, Y = 17.9) and greenish tint (x = 0.313, y = 0.323, Y = 17.9), passing through a neutral gray, while the outer grating was kept achromatic.

(B) Mean (±SEM) chromatic psychometric functions for the vertical (black circles), oblique (white circles), and horizontal (black triangles) gratings for the A-DecNef group (N = 12).

(C) Mean (±SEM) chromatic psychometric functions for the vertical (black circles), oblique (white circles), and horizontal (black triangles) gratings for the control group (N = 6).

(D and E) Individual and mean (±SEM) red response percentage for the vertical and horizontal gratings at the neutral gray for the A-DecNef group (D) and the control group (E).

See also Figures S2 and S4.

horizontal, and oblique orientations for the A-DecNef group were measured after 3–5 months and compared with those of the control group. The results of detailed analyses (Figure S2; Table S2) indicate that psychometric functions were significantly different between the groups and that the vertical grating continued to be perceived as reddish in the A-DecNef group even several months later, and that the A-DecNef group showed significant differences in the PSE between vertical and other orientations even after 3–5 months. These results show that the association between orientation and color is long-lasting, as has been reported for other types of associative learning [12, 13].

It is worth noting that the green perception tends to increase for the horizontal gratings after A-DecNef training. In Figure 3B, the PSE for the horizontal grating was significantly different from that for the oblique grating ($t_{11} = 2.25$, $p = 0.046$), whereas in Figure 3D, there was the tendency that the red (or green) response percentage for the horizontal grating at the neutral gray was lower (or higher) than chance ($t_{11} = -1.89$, $p = 0.086$). Three to five months later (Figure S2A), the same tendency was observed. The PSEs for the horizontal and oblique gratings were significantly different from each other ($t_8 = 5.56$, $p < 0.001$), and the red (or green) response percentage was significantly lower (or higher) than chance ($t_8 = -7.84$, $p < 0.001$).

A-DecNef training was specifically based on BOLD-signal patterns in V1/V2. However, we thought that it was necessary to test whether similar neural activities in different areas other than V1/V2 had occurred by A-DecNef and contributed to the association between the orientation and color. If A-DecNef training induced color-specific brain activities in areas other than V1/V2, then BOLD-signal patterns in those areas should in turn properly predict the red likelihood in V1/V2 on a trial-by-trial basis. The results of a searchlight analysis [14] that explored the whole brain utilizing an L_1 regularized least-square regressor (Supplemental Experimental Procedures) indicated the following results. First, during the color classifier construction stage, in which participants were presented with the chromatic gratings, the colors were accurately classified based on BOLD-signal patterns in V1/V2 and in ventral areas including the fourth visual area (V4) (Figure 4A). Second, during the color classifier construction stage, the red likelihood in V1/V2 was best predicted by BOLD-signal patterns in V1/V2 and moderately by those in ventral areas including V4 (Figure 4B). However, during the A-DecNef training, the BOLD-signal patterns in areas other than V1/V2 including V4 were very poor predictors of the red likelihood in V1/V2 (Figure 4C). These results collectively indicate the following points. The result of the color classification accuracy (Figure 4A) indicates the ability of the classifier to extract chromatic information in V4 when there is chromatic information in V4. Furthermore, multi-voxel patterns in V4 can predict chromatic information in V1/V2 by the regressor during the color classifier construction stage (Figure 4B). Thus, the result that the same regressor did not predict chromatic information in V1/V2 from multi-voxel patterns in V4 during the A-DecNef training (Figure 4C) suggests that there was little chromatic information in V4 and other areas during the A-DecNef training. These results further suggest that the A-DecNef predominantly modified BOLD-signal patterns and the red likelihood in early visual areas.

We also examined A-DecNef-related brain activation by a conventional generalized linear model (GLM) analysis (Figure S3A) to test whether V1/V2 is the main locus of the A-DecNef. Although we found significant activation in nine areas during the A-DecNef training stage, the activation in these areas was negligibly correlated with the perceptual change, except for V1/V2 (Figure S3B). Note that the searchlight analysis was based on classification

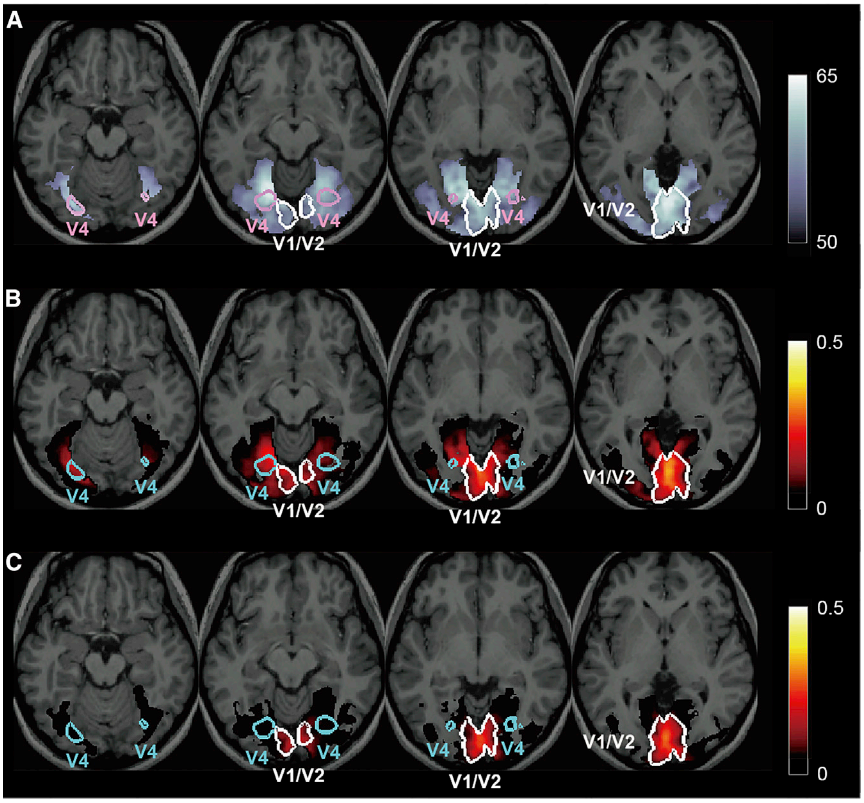

Figure 4. Accuracy of the Color Classifier and Predictability of the Red Likelihood in V1/V2 Using a Searchlight Analysis

(A) Distribution map of the color classifier accuracy during the color classifier construction stage. The accuracy was computed by moving a sphere region of interest (ROI) across the whole brain. The classifier has the ability to extract information for the red likelihood in both V1/V2 and ventral areas including V4. The color scale bar indicates the accuracy (%).

(B) Distribution map of the predictability of the red likelihood in V1/V2 during the color classifier construction stage. The predictability was the highest in V1/V2 and to a moderate degree in ventral areas including V4. The color scale bar indicates a coefficient of determination between the V1/V2 red likelihood predicted by BOLD-signal patterns within an ROI and the actual V1/V2 red likelihood (based on the V1/V2 BOLD-signal patterns) in the searchlight analysis. See the Supplemental Experimental Procedures for technical details.

(C) Distribution map of the predictability of the red likelihood in V1/V2 during the A-DecNef training stage. Not much significant predictability was found outside V1/V2. The color scale bar indicates a coefficient of determination, as in (B). See the Supplemental Experimental Procedures for technical details.

Color-coded voxels correspond to $p < 0.05$. See also Figure S3.

performance of "red" versus "green," whereas the GLM analysis was conducted on BOLD-signal amplitudes, which could be caused by multiple factors. Considering these differential aspects of the analyses, it is suggested that during the A-DecNef training stage, activations not only involved in red perception but also in the training procedure occurred.

These results together suggest that early visual areas, rather than the higher areas including V4, are most likely to be the main locus of the associative learning of the orientation and color in the current study. However, we need to say that we cannot completely reject the possibility of the contribution of other areas to the current associative learning. Future studies to test whether induced associative learning transfers between eyes or between retinal locations may be helpful to clarify the roles of the higher visual areas in the current associative learning.

There are neurons that respond to a specific combination of orientation and color in V1 [15–18]. Does this invariably indicate that associative learning of orientation and color should occur in V1? The answer is negative. For example, it is well known that there are neurons in V1 that best respond to a specific orientation. However, this does not necessarily mean that learning of the orientation occurs in V1. In a similar manner of logic, the existence of neurons that respond best to a specific combination of orientation and color does not necessarily indicate that learning to associate a specific combination of orientation and color occurs in V1. There has been no study, to our knowledge, that indicates that neurons responding to a specific combination of orientation and color learned to induce perception of the color when the orientation was presented as a cue.

What is a possible neural mechanism for the current associative learning? As mentioned above, A-DecNef training resulted in not only reddish perception on an achromatic vertical grating but also greenish perception on an achromatic horizontal grating. Simple pairing of a vertical orientation and red color would not produce greenish perception on the horizontal grating [19]. Because of the nature of A-DecNef training, which uses the red-versus-green output of the classifier, it is likely that the A-DecNef training created a neural state that biases toward a "more likely to be red, not green" state as opposed to an absolute red state. We therefore suggest that A-DecNef changed the balance of mutual inhibition between the neuronal populations that process red and green (Figure S4; see [18, 20]). This suggests that for the current associative learning to occur, mere activation of the population for red paired with a vertical grating is not sufficient. The neurofeedback training that leads to the more likely to be red, not green state, which is perhaps due to changes in the balance of mutual inhibition between neuronal populations for red and green, may be necessary. This may be why associative learning between orientation and color as a result of pairing of a real colored stimulus with an achromatic grating has never been reported. Future studies have to test the validity of the model. One good way is to use a grating in a different color (e.g., blue) during the DecNef training to test shifts in psychometric functions after association of a given color and achromatic grating.

One may wonder whether the McCollough effect [19] is compelling evidence of associative learning in early visual areas. In some cases, the McCollough effect has been discussed as a possible manifestation of associative learning of orientation and color in early visual areas. However, there is no clear evidence for such a claim. First, it is a matter of great controversy whether the McCollough effect occurs in early visual areas [21–24]. In addition to the studies that advocate the V1 origin hypothesis of the effect [25, 26], there are a substantial number of studies that are against this view. One fMRI study found BOLD activity changes in multiple areas and concluded that the McCollough effect is created through top-down processing from a high-cognitive area [27]. Another fMRI study found that the left anterior portion of the color-selective area in the ventral occipital cortex, presumably V4 alpha, was significantly activated in association with the McCollough effect [28]. Second, in the McCollough effect, the induced color is *complementary* to the exposed color. This indicates that in contrast to the associative learning in the present study, the McCollough effect is not due to a simple form of association but rather reflects the complexity of the underlying neural mechanism, including adaptation processes [29]. Some studies have suggested that the McCollough effect is not due to associative learning [30].

The orientation-color association in the present study is also distinguishable from the anti-McCollough effect [31], in which the exposed color rather than the complementary color is perceived in a configuration similar to the McCollough effect [31]. First, the anti-McCollough effect shows 100% interocular transfer, suggesting that it takes place in higher areas than in V1. Second, the anti-McCollough effect lasts less than a day, whereas the orientation-color association in the present study lasts at least 3–5 months. These lines of evidence indicate that neither the McCollough effect nor the anti-McCollough effect has provided any clear evidence that associative learning occurs in early visual areas.

To summarize, using A-DecNef, we created long-lasting associative learning of orientation and color in early visual areas. These results suggest that early visual areas are most likely to be the main locus of the associative learning, although we cannot completely reject the possibility of the contribution of other areas to the associative learning.

EXPERIMENTAL PROCEDURES

A total of 18 participants were employed in the study. All participants had normal or corrected-to-normal color vision and gave their written informed consent to participate. All experimental procedures were approved by the institutional review board at Advanced Telecommunications Research Institute International. See the Supplemental Experimental Procedures for more details.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.05.014.

AUTHOR CONTRIBUTIONS

K.A., K.S., M.K., Y.S., and T.W. conceived and designed the experiments. K.A. performed the experiments and analyzed the data. K.A., K.S., M.K., Y.S., and T.W. wrote the manuscript.

CONFLICTS OF INTEREST

The authors are the inventors of patents related to the neurofeedback method used in this study, and the original assignee of the patents is Advanced Telecommunications Research Institute International, with which the authors are affiliated.

ACKNOWLEDGMENTS

We thank Drs. Ben Seymour, Naotsugu Tsuchiya, and Ryota Kanai for critical discussions and comments on an early draft. We also thank Dr. Hiroshi Ban for technical assistance, and Drs. Jonathan Dobres and Aaron Berard for editing. This study is the result of a contract with the National Institute of Information and Communications Technology entitled "Development of Network Dynamics Modeling Methods for Human Brain Data Simulation Systems." K.S. was partially supported by JSPS, T.W. by NIH R01EY019466 and R01AG031941, Y.S. by R01MH091801 and NSF BCS 1539717, and M.K. by Japan MIC "Novel and Innovative Brain R&D" and "Development of BMI Technologies for Clinical Application" of the Strategic Research Program for Brain Sciences supported by Japan Agency for Medical Research and Development (AMED).

Received: November 24, 2015
Revised: April 4, 2016
Accepted: May 4, 2016
Published: June 30, 2016

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Current Biology, Volume *26*

Supplemental Information

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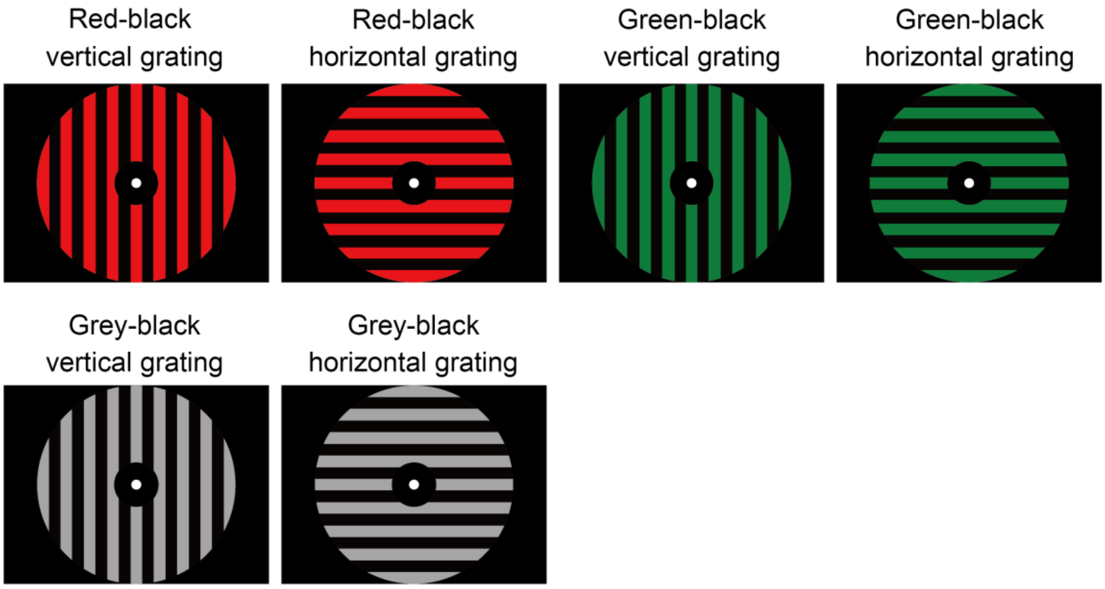


Figure S1. Grating stimuli used in the color classifier construction stage, related to Figure 1.

Stimuli used in the color classifier construction stage were red-black, green-black and gray-black gratings whose orientation was either vertical or horizontal.

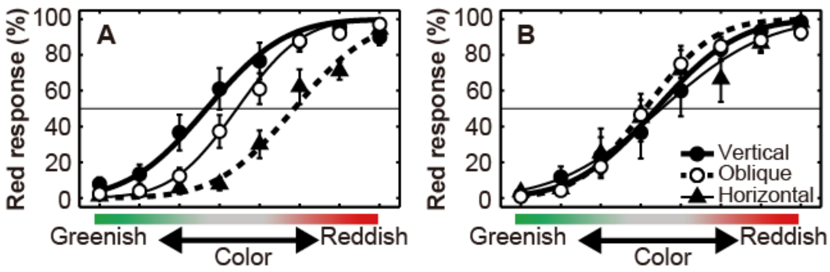
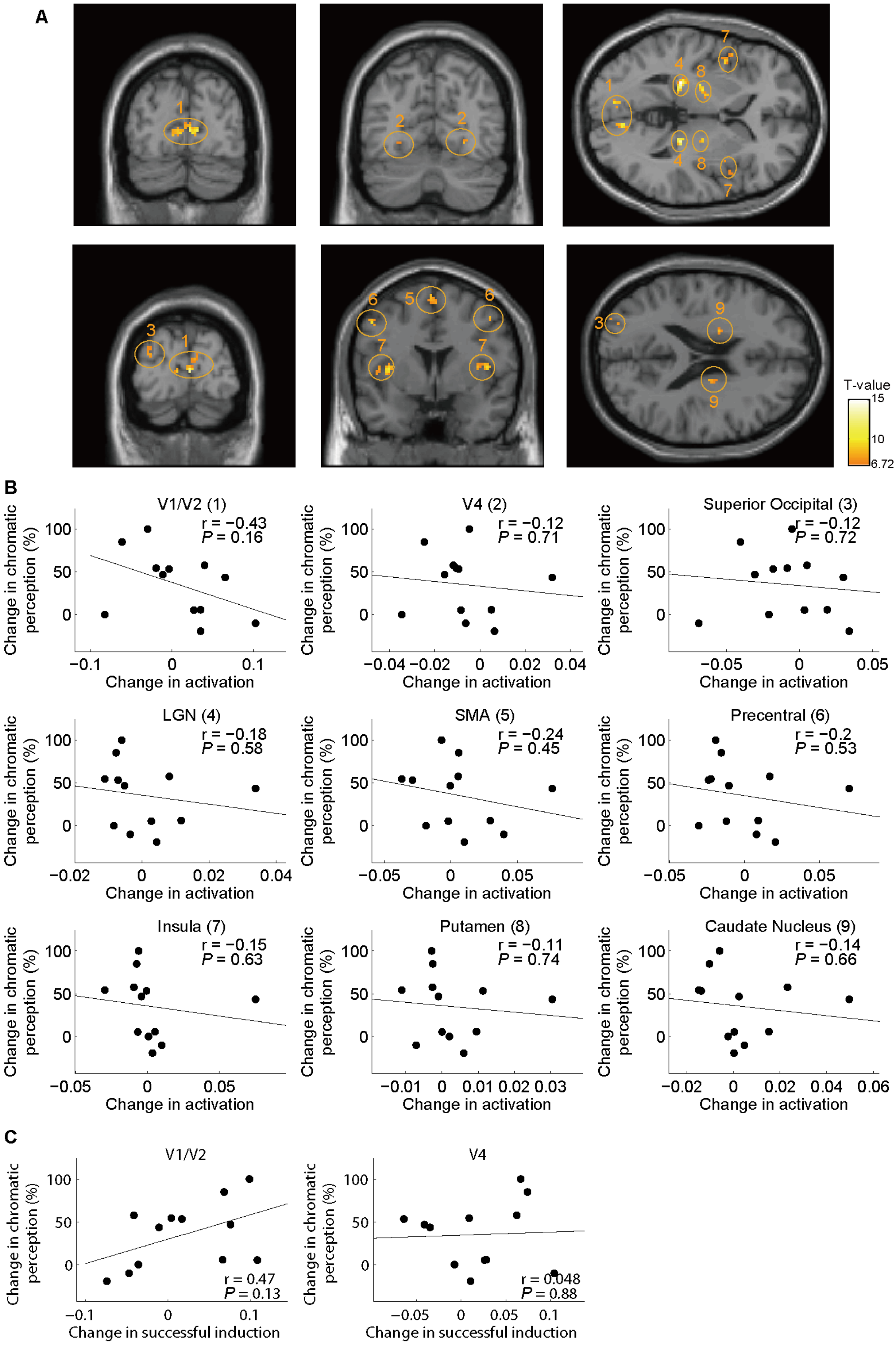


Figure S2. Long-lasting effect of the A-DecNef training on chromatic perception, related to Figure 3.

(**A, B**) Mean (±SEM) chromatic psychometric functions measured 3-5 months after induction for the A-DecNef group who were available for the follow-up experiment (**A**, N=9) and for the control group (**B**, N=6, the same data as **Figure 3C**). See **Table S2** for detailed results of three-way mixed-design ANOVA (group as a between-participants factor, and orientation and color as within-participants factors) on chromatic psychometric functions, and one-way repeated measures ANOVA (orientation as a within-participants factor) on the PSE for each orientation.



A
1
2
2
7
4
8
1
4
8
7
3
1
6
5
6
7
7
3
9
9
T-value
15
10
6.72
B
V1/V2 (1)
r = −0.43
P = 0.16
V4 (2)
r = −0.12
P = 0.71
Superior Occipital (3)
r = −0.12
P = 0.72
LGN (4)
r = −0.18
P = 0.58
SMA (5)
r = −0.24
P = 0.45
Precentral (6)
r = −0.2
P = 0.53
Insula (7)
r = −0.15
P = 0.63
Putamen (8)
r = −0.11
P = 0.74
Caudate Nucleus (9)
r = −0.14
P = 0.66
Change in chromatic perception (%)
Change in activation
C
V1/V2
r = 0.47
P = 0.13
V4
r = 0.048
P = 0.88
Change in chromatic perception (%)
Change in successful induction

Figure S3. A-DecNef related brain activation, related to Figure 4.

(**A**) Significant activations (*P*<0.005) during A-DecNef training (see **Supplemental Experimental Procedures** for details) were found in the nine regions: (1) V1/V2, (2) V4, (3) the superior occipital area, (4) the lateral geniculate nucleus (LGN), (5) the supplementary motor area (SMA), (6) the precentral area, (7) the insula, (8) the putamen, and (9) the caudate nucleus. The names of the areas are according to an anatomy toolbox [S1]. Note that the V4 activation here extends into the fusiform area.

(**B**) Scatter plots between the chromatic perceptual change and the neural changes, which were estimated using the activation amplitudes in each of the nine regions during A-DecNef training (see **Supplemental Experimental Procedures** for details). The number next to the area name corresponds to the region number shown in (**A**). The change in the chromatic perception was defined by the sum of the percentage of red response for the vertical grating and that of green response for the horizontal grating in the post-test. The correlation coefficient for V1/V2 was the strongest among the nine regions (see below for more details). One possible reason for the negative correlation for V1/V2 could be that the current associative learning is at least partially due to an overall increase in inhibition. If our model of changes in mutual inhibition is correct (see **Figure S4**), the amount of inhibition from RV (neural population for red & vertical) to GV (neural population for green & vertical) might be larger than the amount of inhibition from GV to RV, which could cause the overall increase in inhibitory signals. Future research is necessary to test this possibility.

(**C**) Scatter plots between the chromatic perceptual change and the neural changes, which were estimated using the number of successful inductions in V1/V2 and V4 during A-DecNef training (see **Supplemental Experimental Procedures** for details). These two areas were chosen based on their relatively high color classification accuracy (**Figure 4A**). The correlation coefficient for V1/V2 was stronger than V4 (see below for more details). See (**B**) for the change in the chromatic perception.

The GLM analysis showed A-DecNef-related activations in the nine regions. However, based on the correlation analyses with chromatic perceptual changes (**Figure S3B** and **S3C**) as well as the results of the searchlight analysis (**Figure 4**), we suggest that not all of A-DecNef related activations are involved in the change of the red likelihood (**Figure 2**). The results as in the **Figure S3B** shows that only V1/V2 showed the moderate strength of correlation (r = -0.43), although not statistically significant, whereas other areas showed little correlation (correlation coefficients ranging r = -0.24 to -0.11) with the chromatic perceptual changes. This suggests that V1/V2 is most related to the change in color perception among these nine regions. While the searchlight analyses (**Figure 4**) suggested that the red likelihood may be represented in V4 as well as in V1/V2, the results as in **Figure S3C** indicate that V1/V2 has stronger correlation coefficient, again supporting the idea that V1/V2 is likely to be the main locus for the association between orientation and color.

We speculate that A-DecNef-related activations (Figure S3A) may correspond to visual processing and skill learning in addition to the red likelihood information, which is likely to be represented in V1/V2. We will describe our interpretations of activations other than V1/V2 below. First, we speculate that the significant activations in the LGN, V4 and the superior occipital area correspond to visual processing since a visual stimulus (achromatic vertical grating) was presented during A-DecNef. Second, the significant activations in the remaining regions (the SMA, the precentral gyrus, the insula, the putamen and the caudate nucleus) have been implicated in motor sequence or skill learning (for instance, [S2-5]). We speculate that A-DecNef involves skill learning because participants learn to modulate their brain activations. Interestingly, in a brain-computer interface (BCI) study [S6], the SMA has been shown to be involved. BCI is a neurorehabilitation technology [S7] that requires participants to learn to move external devices without using normal motor output (for instance, to move a cursor which receives the motor command from the motor cortex without using a hand). Thus, participants have to learn to modulate activation of their motor cortex. A-DecNef also required a participant to learn to change activation patterns of the early visual cortex (although it was not clear to the participant). Regarding the activations of the putamen and caudate nucleus, alternative interpretation may be possible, because they have been shown to be involved in instrumental conditioning [S8]. Since A-DecNef can be considered to be an instrumental conditioning, the activation of putamen and caudate nucleus may correspond to an instrumental conditioning component. Together, the present A-DecNef recruits areas including those involved in visual and motor functions, whose roles in A-DecNef have yet to be revealed.

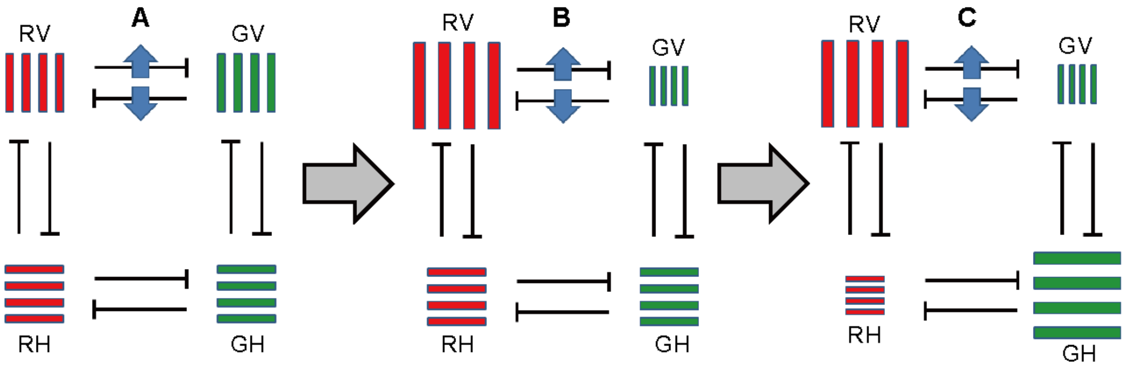


Figure S4. Possible neural mechanisms underlying the change in chromatic perception by A-DecNef, related to Figure 3.

Here we assume four populations for the sake of simplicity. Each population has sensitivity toward both orientation (vertical or horizontal) and color (red or green). They could jointly be sensitive to both orientation and color, as binding features [S9, 10], or they could contain two sub-populations each of which has sensitivity towards either color or orientation alone but they are associated. The assumed four populations are red-vertical (RV), green-vertical (GV), red-horizontal (RH) and green-horizontal (GH) gratings. We propose that the populations mutually inhibit between opposing values of orientation (vertical vs. horizontal) or color (red vs. green).

(**A**) In the model, first, A-DecNef both increases inhibition from RV to GV and decreases inhibition from GV to RV. (**B**) Second, the imbalance in mutual inhibition results in larger response of RV than GV, which leads to reddish perception on the vertical grating (**C**) Third, inhibition from increased response of RV to RH leads to decreased response of RH, whereas inhibition from decreased response of GV to GH leads to increased response of GH. Larger response of GH than RH leads to greenish perception on the horizontal grating.

Table S1, related to Figure 1. At the end of each A-DecNef session, participants were queried regarding any techniques, strategies, or particular thoughts they employed to increase the size of the feedback disk. Responses were as follows (Japanese responses were translated into English by the authors).

Participant	Day1	Day2	Day3
1	"I concentrated on the fixation point and attended to the vertical grating."	"I imagined a situation where I behaved violently."	"I sometimes tried to focus on, or at other times defocused from, the stimulus."
2	"I tried to concentrate on the task sometimes, or relaxed at other times. I also rotated the attended area slowly (several seconds per rotation) while maintaining fixation at the center."	"I imagined that the black area around the fixation point was contracting. I also moved the attended location in a circular trajectory."	"I moved the attended location in a circular trajectory."
3	"I tried to remember scenes shown on TV or video games. I also imagined watching music videos."	"I tried to remember scenes in video games. Then I imagined music of promotional films."	"I tried to remember scenes in video games."
4	"I attended to the anterior part of the brain. Then I tried to control activity in the occipital area. I also focused attention on the fixation point."	"I focused attention on the grating."	"I focused attention on the grating."
5	"I imagined that I was singing or running. I also made calculations	"I imagined visual and auditory images"	"I imagined scenes in promotional films."

	on some things or remembered some sentences.”		
6	“I tried to remember what I did yesterday. I also tried to recall memories of exciting incidences during my last summer vacation.”	“I tried to remember what I was impressed with.”	“I tried to remember memories of exciting incidences during my last summer vacation.”
7	“I did mental multiplication. I also imagined several things including a zebra and building. I also imagined a uniform gray circle.”	“I imagined a uniform gray circle.”	“I imagined a zebra. I also imagined a disk.”
8	“I imagined myself to be a hero. I also imagined actions including lighting a cigarette or getting in a car.”	“I imagined actions including lighting a cigarette or getting in a car. I also mentally counted, or remembered the lyrics of songs. ”	“I imagined actions including lighting a cigarette or getting in a car. I also imagined the movements of a bus driver.”
9	“I first calculated, and then remembered what I did yesterday, and the day before yesterday. I also planned what I will do today.”	“I added up figures in my head.”	“I added up figures in my head.”
10	“I just focused my attention on the fixation point.”	“I imagined translational movement of an afterimage. I also thought about something.”	“I mentally drew a circle within the black region around the fixation point. I also imagined translational movement of an afterimage or mentally let out a

			voice.”
11	“I imagined a gymnastic match in which I performed well. I also imagined simple actions including running.”	“I imagined a gymnastic match in which I performed well. I also imagined simple actions including running.”	“I imagined simple actions including running or bicycling.”
12	“I mentally moved a dot along the annulus aperture of the grating.”	“I mentally moved a dot along the annulus aperture of the grating.”	“I mentally moved a dot along the annulus aperture of the grating.”

Table S2. ANOVAs for long-term effect of A-DecNef, related to Figure 3. (A) Results of three-way ANOVA on the red response percentage. (B) Results of one-way ANOVA on the PSE for each orientation. (C) Results of t-test on the red response percentage at the neutral gray.

A: Three-way mixed-design ANOVA (group as a between-participants factor, and orientation and color as within-participants factors) on the red response percentage

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Orientation	14821.20	1.2	12505.30	8.59	.008
Orientation × Group	13234.54	1.2	11166.56	7.67	.011
Error (Orientation)	22436.57	15.4	1456.21		
Color	415965.19	4.4	94510.58	146.69	<.001
Color × Group	1836.30	4.4	417.22	.648	.645
Error (Color)	36863.43	57.2	644.28		
Orientation × Color	9908.43	8.7	1136.64	3.86	<.001
Orientation × Color × Group	10330.65	8.7	1185.07	4.03	<.001
Error (Orientation × Color)	33367.13	113.3	294.44		

Simple interaction between orientation and color for each group of participants

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Orientation × Color (A-DecNef)	20825.93	14	1487.57	8.11	<0.001
Orientation × Color (Control)	2981.94	14	213.00	1.16	0.308
Error (Orientation × Color)	33367.13	182	183.34		

B: One-way repeated measures ANOVA (orientation as a within-participants factor) on the PSE for each orientation

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Orientation	19.34	1.2	15.53	20.94	0.001
Error (Orientation)	7.39	10.0	0.74		

Multiple comparisons for the PSE

Pair	df	t	Sig.
Vertical vs. Horizontal	8	-4.74	0.002
Vertical vs. Oblique	8	-3.11	0.015
Horizontal vs Oblique	8	5.56	<0.001

C: T-test on the red response percentage at the neutral gray

Source	df	t	Sig.
Vertical vs 50%	8	4.22	0.003
Horizontal vs 50%	8	-7.84	<0.001

Supplemental Experimental Procedures

Participants

Data from 18 participants (18 to 27 years old) are included in the present experiments. Twelve participants took part in the main experiment, nine of whom took part in the experiment that tested the long-lasting effect. Another six participants took part in the control experiment, which consisted only of the post-test stage, without A-DecNef training. All participants had normal or corrected-to-normal color vision and gave their written informed consent to participate. All experimental procedures were approved by the institutional review board at Advanced Telecommunications Research Institute International (ATR).

The experimental design for the main experiment

The main experiment consisted of four stages: (1) retinotopic mapping (one day), (2) color classifier construction (one day), (3) A-DecNef training (three days), and (4) post-test stages. The color classifier construction stage and the first day of the A-DecNef training stage were separated by at least ten days. The post-test was conducted immediately after the conclusion of the A-DecNef training stage.

MRI parameters

Participants were scanned in a 3T MRI scanner (Verio, Siemens) with a head coil at the ATR Brain Activation Imaging Center. FMRI signals were acquired using a gradient EPI sequence. In all fMRI experiments, 33 contiguous slices (TR = 2 s, voxel size = $3 \times 3 \times 3.5$ mm^3, 0 mm slice gap) oriented parallel to the AC-PC plane were acquired, covering the entire brain. T1-weighted MR images (MP-RAGE; 256 slices, voxel size = $1 \times 1 \times 1$ mm^3, 0 mm slice gap) were also acquired.

Apparatus and stimuli

In the MRI scanner, visual stimuli were presented using an LCD projector (DLA-G150CL, Victor) on a translucent screen. Measurement of chromatic psychometric functions in the post-test stage was conducted outside the scanner using a CRT display (P275, IBM). Both the projector and CRT spanned 20 × 15 deg of visual angle (800 × 600 resolution) and had a 60 Hz refresh rate. All visual stimuli were generated using Psychtoolbox 3 [S11] running on Matlab.

Retinotopic mapping

Before the color classifier construction stage, we measured retinotopic maps [S12] using conventional rotating wedge and expanding ring stimuli presented within a circular region of 7.5 deg in radius, allowing us to define V1, V2, and V4 for each participant. In addition, participants were presented with a localizer stimulus to define the subregions (1.5-7.5 deg in eccentricity) of V1, V2, and V4. The localizer stimulus was a flickering colored checkerboard, which was presented alternatively between one visual field (an annulus region; 1.5-7.5 deg in radius) for 8 s and another (a central circle region; 0-1.5 deg in radius) for 8 s. The 16 s block was repeated 14 times per run for at least 3 runs. To ensure the maintenance of gaze at the fixation point presented at the center of the screen, during both the retinotopic mapping and localizer scans, participants were asked to press a button with their right hand if they detected changes in the color of the fixation point.

Color classifier construction stage

In the color classifier construction stage, we measured BOLD-signal multi-voxel patterns evoked by the presentation of red-black, green-black, and gray-black gratings oriented both vertically and horizontally (**Figure S1**). The grating stimulus, presented within an annular aperture (1.5-7.5 deg in radius), was defined by a square-wave modulation between either red, green, or gray and black at 1 cycle/deg. The phase of the grating was fixed across all trials, runs, and participants, so that the position of the black segments of the grating was constant. To construct a classifier based on color difference rather than on luminance difference, the red, green and gray colors were adjusted to be iso-luminant to each other. The red luminance was fixed at the maximum output of the red gun ([255 0 0], x=0.643, y=0.326, Y=22.3 in CIE xyY color space). The green luminance ([0 Green 0]) and the gray luminance ([Gray Gray Gray]) were matched to the red luminance for each participant using flicker photometry [S13]. During flicker photometry, red/green or red/gray flicker patterns were presented at 30 Hz, and participants were instructed to minimize flicker by adjusting green/gray luminance with a keyboard. Measurements were repeated ten times for each color, and the resulting green and gray colors, perceptually iso-luminant to red, were used for the color classifier construction stage.

In each trial of the color classifier construction stage, the grating flickered at 0.5 Hz for 6 s (3 repetitions of 1.5 s on and 0.5 s off) and was followed by a black screen for 6 s. The orientation (vertical or horizontal) and color (red, green, or gray) of the grating were selected randomly from the six possible combinations. For the purpose of maintaining fixation, participants performed a fixation task in which they were asked to press a button with their right hand if they detected changes in the luminance (from white to gray) of the fixation point at the center of the screen. The difficulty of the fixation task was manipulated with a QUEST procedure [S14] so that the hit ratio asymptotically approached 50%.

Within a run, each combination of orientation and color was presented 4 times. Fixation periods for 10 s and 6 s were placed before and after the stimulus presentations, respectively (1 run = 304 s). Twelve runs were repeated for each participant. A brief break period was provided after each run upon a participant's request.

Measured BOLD signals were preprocessed using the mrVista software developed at Stanford University (http://vistalab.stanford.edu/software/). All functional images underwent 3D motion correction. No spatial or temporal smoothing was applied. Rigid-body transformations were performed to align the functional images to the structural image for each participant. A gray matter mask was used to extract BOLD signals only from gray matter voxels for further analyses. A reference region within V1/V2 that corresponded to the size of the grating stimulus (1.5-7.5 deg in radius) was defined by intersecting V1/V2 and the area activated by the localizer. Once we identified the reference region, the time-course of BOLD signals in the color classifier construction stage was extracted from each voxel in that region. After removing the linear trend, the time-course was *z*-score normalized for each voxel for each run to minimize baseline differences across the runs. The data samples for computing the classifier were created by averaging the BOLD-signal amplitudes of each voxel across the 3 TR corresponding to the 6 s grating periods. Six s (3 TR) of hemodynamic delay was taken into account.

We used sparse logistic regression (SLR) [S15] to construct a red-black vs. green-black (red vs. green) classifier for live use during the A-DecNef training stage. SLR automatically selected the voxels relevant for the discrimination of grating color from the voxels in the reference region within V1/V2. We trained the classifier to classify BOLD-signal multi-voxel patterns into one of the two colors using 192 data samples obtained from 192 trials during the 12 runs. The classifier did not contain orientation information because BOLD-signal multi-voxel patterns from both vertical and horizontal gratings were pooled for the analysis. The mean (±SEM) number of voxels in V1/V2 selected by SLR was 194±28.

After we built the classifier, we also calculated the target color (red) likelihood based on the BOLD-signal multi-voxel patterns evoked by the vertical gray-black grating. This likelihood is shown as on Day 0 in **Figure 2**, and works as a baseline likelihood for the A-DecNef training.

In a separate analysis, we tested whether two different colors can be differentiated based on different BOLD-signal multi-voxel patterns in V1/V2. A leave-one-run-out cross-validation procedure was conducted for each participant. In each cross-validation cycle, the classifier was trained using 176 data samples obtained from 11 runs and tested using 16 data samples obtained from the remaining run. This cycle was repeated 12 times. The mean classification accuracy for the test data across the 12 cycles was regarded as decoding accuracy.

A-DecNef training stage

During the A-DecNef training stage, participants were trained to create an internal association between the presentation of an achromatic vertical grating and the neural activity corresponding to a specific target color (red).

A-DecNef training stage always spanned 3 consecutive days (1 session per day). Each day consisted of a maximum of 12 runs. The mean (±SEM) number of runs on each day was 11.9±0.1 across days and participants. A brief break period after each run was provided upon a participant's request to minimize fatigue.

Each run was 330 s long and consisted of 15 trials (1 trial = 20 s) preceded by a 30 s fixation period. Each trial consisted of an induction period (6 s), a fixation period (7 s), a feedback period (1 s), and an inter-trial interval (6 s), in that order (**Figure 1**). During the induction period, an achromatic (gray-black) vertical grating, identical to the one used in the color classifier construction stage (**Figure S1**), was presented with a fixation point at the center of the screen. The grating flickered at 0.5 Hz for 6 s (3 repetitions of 1.5 s on and 0.5 s off). During the fixation period and inter-trial interval, only a fixation point was presented on a black background. Participants were instructed to somehow regulate their brain activity during the presentation of the achromatic grating to make the size of the solid gray disk presented during the subsequent feedback period as large as possible. Participants were also instructed to maintain fixation on the fixation point for the whole experiment period. The experimenters provided no further instructions or strategies.

The size of the gray disk presented during the feedback period represented how much the BOLD-signal multi-voxel patterns in V1/V2 during the induction period corresponded to the patterns evoked by the presentation of the red-black gratings in the color classifier construction stage. The size of the gray disk was determined by the following procedures. First, newly obtained functional image data underwent 3D head motion correction using Turbo-Brain Voyager (Brain Innovation, The Netherlands). Second, time-course of BOLD signals was extracted from each voxel in the reference region within V1/V2. Third, a linear trend was removed from the time-course. The time-course was then z-score normalized for each voxel using a 20 s time-course of BOLD-signal amplitudes collected starting from 10 s after the start of each run. Fourth, the BOLD signals measured during the first 6 s of the fixation period were averaged for each voxel, so that the resultant BOLD-signal multi-voxel patterns would reflect neural activities that were induced during the 6 s of the induction period (hemodynamic delay was assumed to be 6 s). Finally, the red likelihood was calculated by multiplying the BOLD-signal multi-voxel patterns with the weights determined in the color classifier construction stage, and by passing this weighted sum through a logistic function (likelihood estimates could range from 0 to 100%). The size of the gray disk was proportional to the red likelihood and the disk was always enclosed by a circle (1.5 deg in radius) that represented the disk's maximum size.

At the end of each run, the amount of the monetary bonus reward for that run, as well as the accumulated bonus amount, was shown on the screen. The amount of the reward for each run was proportional to the size of the feedback disk averaged across trials. Participants were informed that they would receive bonus rewards proportional to the total size of the disk, but were not informed as to how the size of the disk was determined or what the size represented. Participants were paid a maximum bonus of up to 3,000 JPY per day, in addition to a fixed amount for participation in the experiment.

Immediately after the conclusion of each day of the A-DecNef training stage, participants were asked about how they had manipulated their brain activity (**Table S1**).

Post-test stage

A chromatic psychometric function was measured outside the scanner. In each trial of the psychometric function measurement, a grating of one of four orientations (vertical, horizontal and 2 oblique orientations, **Figure 3A**) in one of eight possible colors (32 configurations in total) was presented. The grating was a square-wave modulation between a color and black at 1 cycle/deg. The color in the inner gratings varied in 8 steps between a reddish tint (x=0.323, y=0.310) and greenish tint (x=0.313, y=0.323), passing through a neutral gray, keeping the luminance constant (Y=17.9). The outer grating was a square-wave modulation between gray and black at 1 cycle/deg. The phase of the grating was the same as the phase of the grating used in the color classifier construction stage (**Figure S1**). Participants were asked to report whether the inner grating was tinted red or green. Gratings were presented for 0.5 s, and each combination of orientation and color was repeated 10 times in a random order. A next trial started immediately after participant's response.

The psychophysical experiment was not conducted prior to the A-DecNef training stage. This is because we wished to avoid the possibility that participants would notice the relation between the orientation and color, and explicitly associate orientation with color during the induction periods in the subsequent A-DecNef training stage.

Searchlight analysis

We tested whether other areas than V1/V2 contributed to the association between orientation and color. We conducted a searchlight analysis [S16] by moving a sphere (r=15 mm) region of interest (ROI) across the whole gray matter voxels (~30000 voxels). We calculated (1) color classification accuracy during the color classifier construction stage (**Figure 4A**), (2) the predictability of the red likelihood of V1/V2 during the color classifier construction stage (**Figure 4B**), and (3) the predictability of the red likelihood of V1/V2 during the A-DecNef training stage (**Figure 4C**), using the searchlight method [S16].

First, for color classification accuracy, we constructed a color classifier for each sphere ROI using the BOLD-signal patterns measured in the color classifier construction stage and evaluated the classifier performance (percent correct) using the leave-one-run-out cross-validation procedure. The same leave-one-run-out cross-validation procedure was used as for the color classifier construction stage (see above), except that linear support vector machine rather than SLR was employed here for its time efficiency. The searchlight analysis demonstrated that both V1/V2 and ventral areas including V4 enjoyed high classification accuracy of color (**Figure 4A**).

Second, the predictability of the red likelihood of V1/V2 by BOLD-signal patterns in each sphere ROI during the color classifier construction stage was computed as below. The red likelihood ranging from 0 to 100%, which was computed by SLR from V1/V2 BOLD-signal patterns (see Color classifier construction stage section), was predicted by L_1-regularized least-square regressor (α=1, λ=0.024) from BOLD-signal patterns within each sphere ROI. A hyper parameter λ, which decides the balance between the residual and L_1 norm of the weights, was defined by the geometric mean of the optimal λ across three sphere ROIs (centered at V1/V2, left V4 and right V4) for all of the participants (36 ROIs in total). Prediction accuracy was defined as a coefficient of determination between the likelihoods in V1/V2 and the likelihoods calculated using BOLD-signal patterns in the sphere ROI on a trial-by-trial basis. The accuracy was evaluated by a leave-one-run-out cross-validation procedure. The pairs of the red likelihood on one run were used for test data, while the pairs obtained on the remaining runs were used for training the sparse linear regression model.

Third, the predictability of the red likelihood of V1/V2 by BOLD-signal patterns in each sphere ROI during A-DecNef training stage was computed. The L_1-regularized least-square regressor model of V1/V2 red likelihood was built using the data during the classifier construction stage as described above, and was applied to the data during the A-DecNef training stage consisting of three days. The accuracy of prediction was again evaluated as a coefficient of determination between the actual red likelihood within V1/V2 and its regressed value from a sphere ROI.

The above analyses using the searchlight method were calculated in the native coordinate of each participant, normalized into a MNI template and were averaged across participants. A permutation test was conducted on the classification accuracy (**Figure 4A**) and on the correlation coefficient (**Figures 4B and 4C**) [S17]. *P*-values were corrected for multiple comparisons using threshold-free cluster enhancement [S18]. The values significantly above chance (P<0.05) were plotted.

GLM analysis

We conducted a conventional GLM analysis to find areas activated during the A-DecNef training stage (**Figure S3**) using the SPM8 package [S19]. We calculated the contrast between the induction period (6 s) and the blank periods (fixation period and inter-stimulus interval). The group analysis was performed on the data of all 12 participants, and the areas showing significant activation (P<0.005, corrected for family wise error) were identified based on the Gaussian random field theory.

Correlation analysis

For the purpose of elucidating the brain area contributing to the orientation specific chromatic perception, we calculated the correlation coefficients between the change of chromatic perception due to A-DecNef and two types of changes in neural activities (**Figure S3**).

As the change of chromatic perception, we calculated the sum of the percentage of red response for the vertical grating and that of green response for the horizontal grating in the post-test stage.

As for the measure of neural changes, we have 2 ways. We utilized change in activation amplitude for the first measure, and the number of successful induction (the red likelihood higher than 90%) across all 36 runs in three days of A-DecNef training for the second measure. First, we calculated the slope of the best fitted line to the estimated BOLD-signal amplitude (beta value) during the induction period of 36 runs in the 9 ROIs identified by the GLM analysis (**Figure S3A**), and obtained correlation coefficients with the chromatic perceptual change for each of 9 regions (**Figure S3B**). Second, we calculated the slope of the best fitted line to the number of successful inductions of 36 runs in V1/V2 and V4, which showed relatively high color classification accuracy (**Figure 4A**), and obtained correlation coefficients with the perceptual changes for V1/V2 and V4 (**Figure S3C**).

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