Report

Current Biology

Perceptual Learning of Contrast Detection in the Human Lateral Geniculate Nucleus

Highlights

- Contrast learning shows specificity to the trained eye and visual hemifield
- Contrast learning boosts the activity of the M layers of the LGN
- Perceptual learning in human adults can occur as early as at the thalamic level

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In Brief

Yu et al. reveal that perceptual learning of contrast detection leads to an eye- and hemifield-specific neural response increase to low contrast in the M layers of the LGN and suggest that visual training can induce plasticity in subcortical nuclei.

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Perceptual Learning of Contrast Detection in the Human Lateral Geniculate Nucleus

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SUMMARY

The brain is continuously modified by perceptual experience throughout life. Perceptual learning, which refers to the long-term performance improvement resulting from practice, has been widely used as a paradigm to study experience-dependent brain plasticity in adults [1, 2]. In the visual system, adult plasticity is largely believed to be restricted to the cortex, with subcortical structures losing their capacity for change after a critical period of development [3, 4]. Although various cortical mechanisms have been shown to mediate visual perceptual learning [5–12], there has been no reported investigation of perceptual learning in subcortical nuclei. Here, human subjects were trained on a contrast detection task for 30 days, leading to a significant contrast sensitivity improvement that was specific to the trained eye and the trained visual hemifield. Training also resulted in an eye- and hemifield-specific fMRI signal increase to low-contrast patterns in the magnocellular layers of the lateral geniculate nucleus (LGN), even when subjects did not pay attention to the patterns. Such an increase was absent in the parvocellular layers of the LGN and visual cortical areas. Furthermore, the behavioral benefit significantly correlated with the neural enhancement. These findings suggest that LGN signals can be amplified by training to detect faint patterns. Neural plasticity induced by perceptual learning in human adults might not be confined to the cortical level but might occur as early as at the thalamic level.

RESULTS

Behavioral Learning Effects

Twenty subjects underwent 30 daily training sessions (1,200 trials per session) to perform a monocular contrast detection task with a faint checkerboard pattern presented in the left or right visual hemifield (Figure 1A). The trained eye and hemifield was fixed throughout training. On a trial, the checkerboard was presented in one of two intervals (Figure 1B). Subjects were asked to indicate which of the two intervals contained the checkerboard. A QUEST staircase was used to control the contrast of the checkerboard adaptively to estimate subjects' contrast detection thresholds at 75% accuracy.

Throughout training, subjects' contrast detection thresholds decreased gradually and significantly ($F(29, 551) = 15.136$; $p < 0.001$) (Figure 1C). Before and after training, we measured subjects' contrast detection thresholds and fMRI contrast response functions in four test conditions: the trained hemifield in the trained eye (THTE), the trained hemifield in the untrained eye (THUE), the untrained hemifield in the trained eye (UHTE), and the untrained hemifield in the untrained eye (UHUE). Subjects' performance improvement was quantified as percent change in detection threshold after training, relative to the thresholds measured before training (Figure 1D). Performance improvements were submitted to a repeated measures two-way ANOVA, with eye and hemifield as within-subject factors. We found a significant main effect of eye ($F(1, 19) = 23.983$, $p < 0.001$) and hemifield ($F(1, 19) = 42.331$, $p < 0.001$). The interaction between eye and hemifield was also significant ($F(1, 19) = 3.664$, $p < 0.05$). The strongest learning effect occurred in the THTE condition (one-sample t test, $t(19) = 5.539$, $p < 0.001$), and it was significantly larger than the learning effects in the other three conditions (paired t test, all $ts(19) > 4.573$, $p < 0.001$, Bonferroni corrected). The learning effect in the THUE condition was marginally significant (one-sample t test, $t(19) = 2.638$, $p = 0.065$), but little learning took place in the other two conditions (one-sample t test, both $ts(19) < 2.100$, $p > 0.197$). These psychophysical results demonstrated that training led to a significant learning effect on contrast detection, which was specific to the trained eye and the trained hemifield.

fMRI Learning Effects in Visual Areas

The regions of interest (ROIs) in visual areas 1–3 (V1–V3) and the lateral geniculate nucleus (LGN) were defined as a set of contiguous voxels ($2 \times 2 \times 2$ mm^3) that responded significantly to the full-contrast checkerboard stimuli. Identification of the LGN

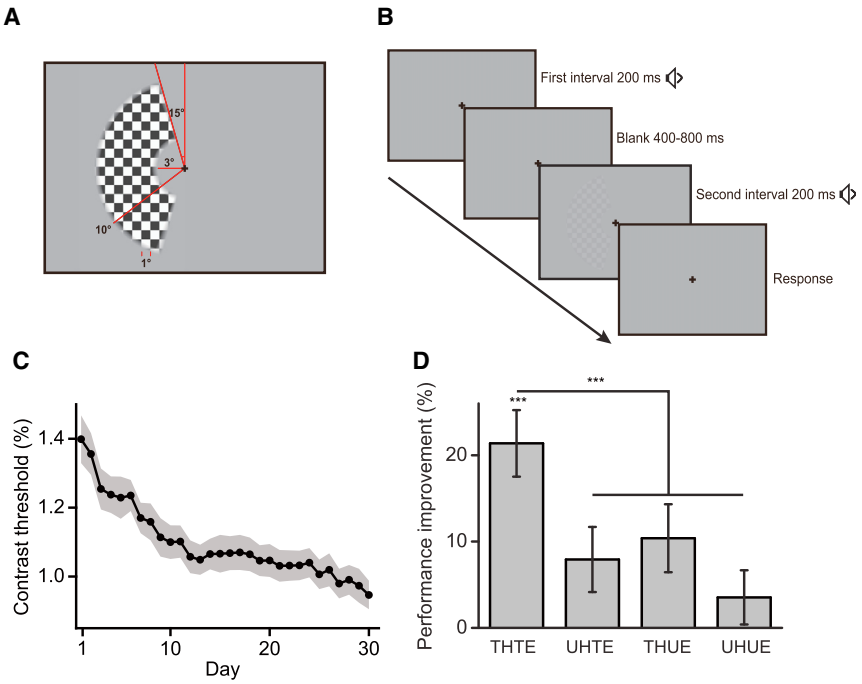

Figure 1. Methods and Behavioral Results

(A) A sample checkerboard stimulus presented in the left visual hemifield.

(B) Schematic description of a two-alternative forced-choice (2-AFC) trial in a QUEST staircase for measuring contrast detection threshold.

(C) Learning curve. Contrast detection thresholds are plotted as a function of training day.

(D) Percent improvements in contrast detection threshold after training in the four test conditions. The asterisks indicate a significant improvement in the THTE condition or significant differences among the test conditions (***$p < 0.001$). Error bars and shade regions denote 1 SEM across subjects.

voxels was further constrained by the anatomical locations of the LGN based on high-resolution T1 images. On the T1 images in Figure 2A, which shows the LGN from a representative subject, the LGN appeared darker relative to surrounding brain tissues. The LGN is the thalamic component in the retinocortical projection and has been traditionally viewed as a passive relay station for retinal signals on their way to the primary visual cortex, or V1 [13]. This view has been challenged recently. There is growing evidence from human fMRI and monkey neurophysiology studies that neural responses in the LGN are influenced by perceptual and cognitive tasks (see [14] for a review).

Using the counterphase flickering checkerboard stimuli, we measured fMRI contrast response functions in the ROIs at three contrast levels (6%, 24%, and 96%). During scanning, subjects performed a demanding task to detect the color change of the fixation point (Figure 2B). Therefore, the peripheral checkerboard stimuli were task irrelevant. The fMRI contrast response functions are shown in Figure 2C. For each ROI and each test condition, blood-oxygen-level dependent (BOLD) amplitudes were submitted to a repeated measures ANOVA, with training (pre- and post-training) and contrast (6%, 24%, and 96%) as within-subject factors. The main effects of contrast were significant (LGN: all $Fs(2, 38) > 82.82$, $p < 0.001$; V1: all $Fs(2, 38) > 142.77$, $p < 0.001$; V2: all $Fs(2, 38) > 168.93$, $p < 0.001$; V3: all $Fs(2, 38) > 122.98$, $p < 0.001$, Bonferroni corrected). The BOLD responses increased with contrast. The main effects of training were not significant (LGN: all $Fs(2, 19) < 3.195$, $p > 0.36$; V1: all $Fs(2, 19) < 0.378$, $p = 1$; V2: all $Fs(2, 19) < 0.445$, $p = 1$; V3: all $Fs(2, 19) < 1.217$, $p = 1$). The interaction effect between training and contrast was only significant in the THTE condition in the LGN (THTE: $F(2, 38) = 6.839$, $p < 0.05$; UHTE: $F(2, 38) = 0.567$, $p = 1$; THUE: $F(2, 38) = 0.350$, $p = 1$; UHUE: $F(2, 38) = 1.408$, $p = 1$, Bonferroni corrected). Furthermore, post hoc t tests showed that the BOLD response after training was significantly larger than that before training only at the 6% contrast level (6%: $t(19) = 3.639$, $p < 0.01$; 24%: $t(19) = 0.667$, $p = 1$; 96%: $t(19) = 0.281$, $p = 1$, Bonferroni corrected). In V1–V3, no significant interaction was found (V1: all $Fs(2, 38) < 3.09$, $p > 0.23$; V2: all $Fs(2, 38) < 2.83$, $p > 0.28$; V3: all $Fs(2, 38) < 2.55$, $p > 0.36$). These results showed that training resulted in an eye- and hemifield-specific BOLD response increase to the low-contrast stimuli in the LGN. However, we failed to find such an increase in V1, V2, or V3.

In the aforementioned analysis, the ROIs in V1–V3 and the LGN contained 388, 378, 362, and 24 voxels (averaged across subjects), respectively. Relative to the LGN, many more voxels in V1–V3 were included, which might have diluted the learning effect (if there is any) in these cortical areas and caused the negative results described earlier. To examine this possibility, for each of these cortical areas, only the 24 most responsive voxels (or the 24 least responsive voxels) in the ROI of the area (see Supplemental Experimental Procedures) were included to measure fMRI contrast response functions. However, no significant learning effect was found in these areas, even with less voxels (Figures S1 and S2). Another potential way to improve the detectability of the learning effect in V1 is using high-spatial-resolution fMRI to map ocular dominance columns [15]. Since the contrast learning showed eye specificity, ocular dominance columns corresponding to the trained eye might exhibit a more detectable learning effect. However, because of the fMRI spatial resolution limit in the present study, we cannot test this idea.

fMRI Learning Effects in the M and P Layers of the LGN

The LGN consists of six main layers, each of which contains a retinotopic map of the contralateral visual hemifield as seen through one eye (contralateral or ipsilateral). The four dorsal layers contain small parvocellular (P) neurons, and the two ventral layers contain large magnocellular (M) neurons. The M and P layers are responsible for processing different aspects of visual inputs. The M layers are sensitive to higher temporal frequency, lower spatial frequency, and lower contrast; and vice versa for the P layers. The P layers exhibit strong responses to chromatic stimuli, while the M layers are color blind [16, 17].

Using the method developed by Zhang et al. [18, 19], we identified the M and P layers of the LGN with stimuli designed

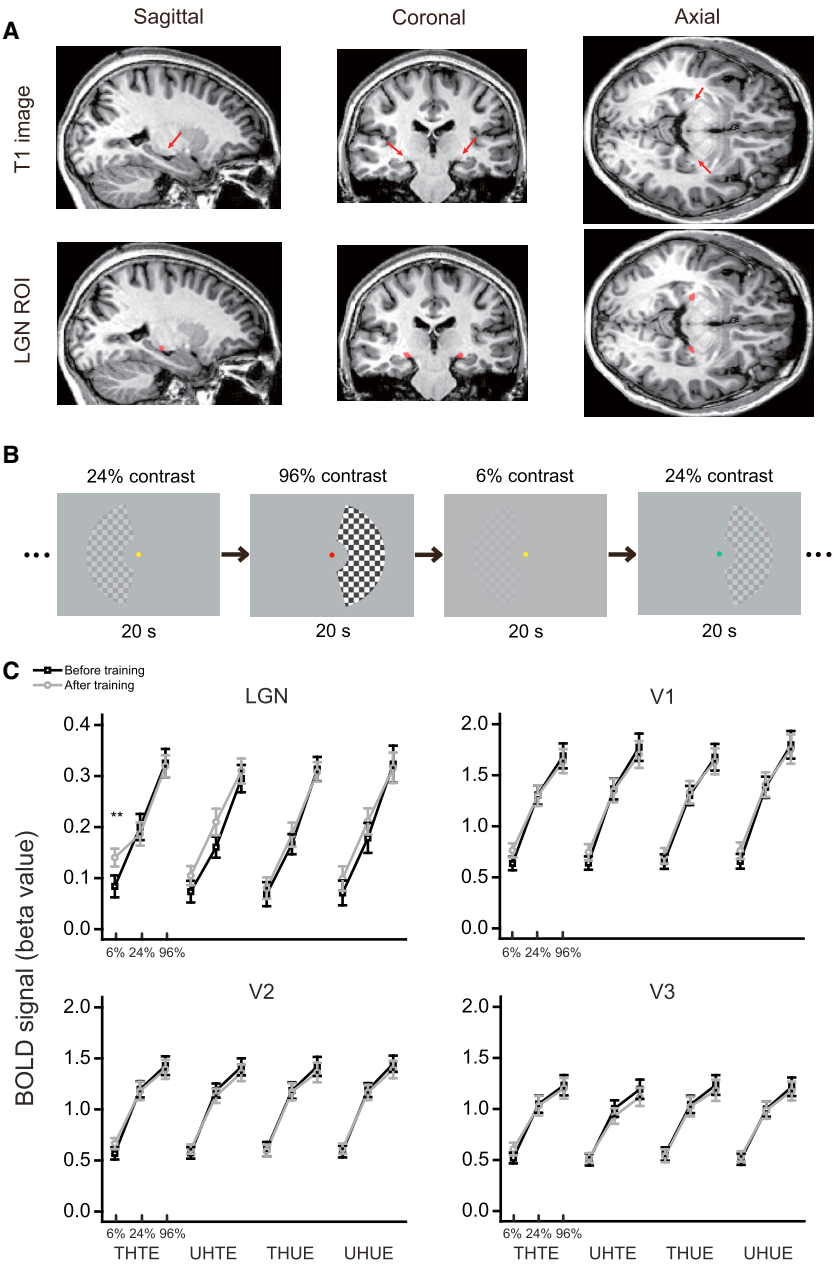

Figure 2. FMRI Protocol and Results

(A) The first row shows the locations of the LGN in a representative subject's brain (T1 images) from sagittal, coronal, or axial views, as indicated by the red arrows. The second row shows the ROIs (red areas) of the subject's LGN for analysis.

(B) Counterphase flickering checkerboards at three contrast levels (6%, 24%, and 96%) were presented in the left or right visual hemifield alternately. Subjects viewed the checkerboards with either the trained or the untrained eye.

(C) FMRI contrast response functions in the LGN, V1, V2, and V3 before and after training. The asterisks indicate a significant difference before and after training (**$p < 0.01$).

Error bars denote 1 SEM across subjects. See also Figures S1 and S2.

to differentially activate the M (M stimulus) and P (P stimulus) neurons in 15 of the 20 subjects. The P stimulus was a high-spatial-frequency isoluminant red/green square wave pattern and was counterphase flickered at 1 Hz. The M stimulus was a low-spatial-frequency sine wave pattern, with 30% luminance contrast, and was counterphase flickered at 7.5 Hz (Figure 3A). The M layers of the LGN were identified as voxels showing a greater response to the M stimulus than to the P stimulus, and vice versa for the identification of the P layers. It should be noted that, due to the spatial resolution limit of fMRI, some voxels in the identified M or P layers might contain both M and P neurons (see [20], in which M layers and P layers are approximately 2 and 4 mm thick, respectively). However, it is safe to claim that voxels identified as located in the M and P layers were dominated by M and P neurons, respectively.

To validate the spatial topography of the M and P layers, for all subjects, their right LGN was mirror flipped to the left, and all LGNs were registered to their center of mass. Relative to the center of the P layers, the center of the M layers were located more anteriorly, inferiorly, and slightly more medially, which is in accordance with the anatomy of human LGN (see the brain slices obtained by autopsy in Figure 3B). This finding is also consistent with previous studies [18, 19, 21]. The mean responses of the M and P layers to the M and P stimuli are shown in Figure 3C, which exhibited an evident bias to the M and P stimuli, respectively.

To examine how training modulated the responses of the M and P layers, we performed the same statistical analysis as described earlier with their responses (Figure 4A). The main effects of contrast in all the four test conditions in both the M and P layers were significant (all $Fs(2, 28) > 36.772$, $p < 0.001$, Bonferroni corrected). The main effects of training were not significant (all $Fs(2, 28) < 0.992$, $p > 0.335$). Only the interaction between training and contrast in the THTE condition in the M layers was significant (M layers, THTE: $F(2, 28) = 6.727$, $p < 0.05$; other conditions: all $Fs(2, 28) < 1.75$, $p > 0.776$; P layers: all $Fs(2, 28) < 3.202$, $p > 0.224$, Bonferroni corrected). Furthermore, post hoc t tests showed that, in the THTE condition, the BOLD signal of the M layers after training was significantly larger than that before training only at the 6% contrast level, but not at the 24% or 96% contrast levels (6%: $t(14) = 3.249$, $p < 0.05$; 24% and 96%: both $ts(14) < 0.533$, $p > 0.05$, Bonferroni corrected).

To further evaluate the role of the LGN in contrast detection learning, we calculated the correlation coefficients between the behavioral learning effect ((threshold on the first training day × threshold on the last training day)/threshold on the first training

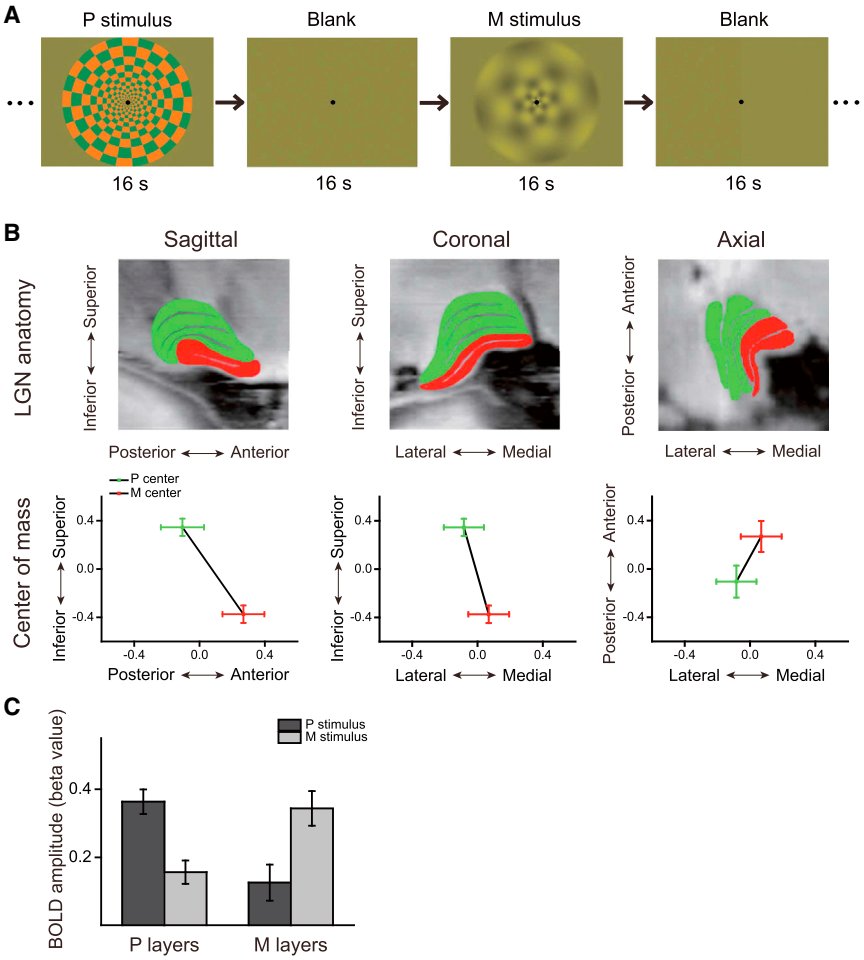

Figure 3. Localization of the M and P Layers in the LGN

(A) Stimuli and procedure for the functional localizer to identify the M and P layers.

(B) Topographies of the M and P layers of the LGN. The first row shows the LGN anatomy as a reference, derived from human brain autopsy (the M and P layers are rendered in red and green, respectively). The second row shows the locations of mass centers for the M and P layers in sagittal/coronal/axial planes.

(C) BOLD responses of the M and P layers to the M and P stimuli.

Error bars denote 1 SEM across subjects.

day × 100%) and the BOLD signal change at the 6% contrast level. The correlation was significant in the M layers ($r = 0.636$, $p < 0.05$), but not in the P layers ($r = -0.104$, $p = 0.712$), suggesting a fundamental role of the M layers in this learning (Figure 4B).

DISCUSSION

One month of training on a near-threshold contrast detection task led to a significant improvement in human subjects' contrast sensitivity, which was specific to the trained eye and the trained visual hemifield. Parallel to the behavioral learning effect, training also resulted in an eye- and hemifield-specific response increase to low contrast in the M layers of the LGN, but not in the P layers, V1, V2, or V3. Remarkably, the neural response enhancement in the M layers was closely associated with the contrast sensitivity improvement. Though it is traditionally believed that perceptual learning is underpinned by plasticity mechanisms at the cortical level, our findings demonstrate that, even at the thalamic level, neural circuits are not hardwired, and perceptual learning can modify receptive field properties of the LGN neurons.

It has been shown that perceptual learning can change cortical processing of trained stimuli in various ways, such as sharpening tuning curves [6, 12, 22], improving the stability of neural activation patterns [11, 23], enhancing neural response [24, 25], and reweighting sensory signals for decision making [7, 9, 26]. Notably, the perceptual learning literature has shown that subtle differences in the trained tasks and stimuli can generate dramatically different results [6, 27]. Nevertheless, a consistent observation is that training to detect a near-threshold weak stimulus usually increases brain responses to the stimulus [28–30]. In human subjects, Furmanski et al. [28] demonstrated that training on an oriented grating detection task reliably increased the BOLD signal in V1. The same training task was also found to increase the amplitude of C1, the earliest component of the visual evoked potentials (VEPs), which is believed to arise from V1 [29]. Furthermore, in cats, Hua et al. [30] showed that contrast detection training increased the contrast gain of V1 neurons that responded preferentially to stimuli presented via the trained eye and with spatial frequency near the trained spatial frequency. These neurophysiological findings are resonant with psychophysical measures by Sowden and colleagues [31], which showed that contrast detection learning was tuned to spatial frequency, specific to retinal location, and could be specific to the trained eye but was not selective for orientation. Taken together, these findings point to the proposition that neural plasticity mediating contrast detection learning occurs at the earliest stage of cortical processing, where the monocular organization of the visual inputs are still retained.

At the earliest cortical stage, monocular cells have been reported in layers 4A, $4C_\alpha$, and $4C_\beta$ of V1 [32, 33]. Monocular cells in layer 4 receive their input from the LGN magnocellular division that is tuned for the low contrast of the trained stimuli here [34]. Therefore, it is possible that the neural response enhancement in V1 following contrast detection training in previous studies [28–30] might be inherited from earlier brain regions along the visual pathway. This is exactly what we found here. Note that contrast detection learning is not the only kind of perceptual learning that is suggested to be mediated by monocular neurons. Schwartz et al. [25] found that texture detection learning increased V1 responses in corresponding retintoptoic areas only for targets presented to the trained eye, compared with

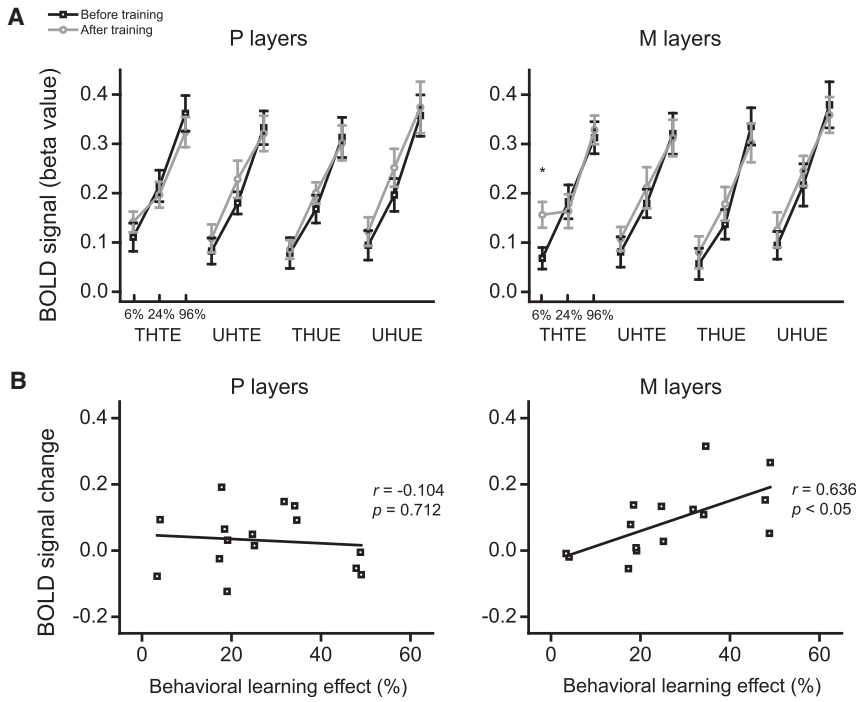

Figure 4. FMRI Results in the M and P Layers of the LGN

(A) FMRI contrast response functions in the M and P layers before and after training. The asterisk indicates a significant difference before and after training (*$p < 0.05$).

(B) Correlations between the behavioral learning effect and the training-induced BOLD signal changes in the M and P layers at the 6% contrast level.

Error bars denote 1 SEM across subjects.

targets presented at the same retinal location to the untrained eye, which is in line with the eye specificity property of this kind of behavioral learning [5].

Is this LGN response enhancement a long-lasting change, and does it serve as a long-term mechanism of contrast detection learning? One recent study [35] measured the dynamics of subjects' behavioral performance with a texture detection task [5] and their V1 activation over a long time course of perceptual learning. Within the first few weeks of training, V1 activation in a subregion corresponding to the trained location and task performance both increased. However, while the improved performance was maintained 2 weeks after training, the V1 activation decreased to the level observed before training. Similar transient response enhancements were also found in the fusiform face areas immediately after training on a face discrimination task [11]. Both of the studies challenged the role of the transient response enhancements immediately after training in perceptual learning. In the present study, we did not measure brain signals after the post-training test to examine the persistence of the response enhancement to the low contrast. Nevertheless, the significant correlation between the behavioral and neural enhancements provides deterministic evidence for the crucial role of the M layers in the contrast detection learning, at least in the learning effect immediately after training.

Unlike previous studies [28–30], we did not observe training-induced response increase at the cortical level (i.e., V1). Here are several possible reasons. First, the fMRI measurement is not sensitive enough to detect such small changes (if there are any) that might be also specific to the trained eye and M neurons. In V1–V3, BOLD signals from individual voxels reflect mixed neural signals from left and right eye neurons and from M and P neurons, which could not be separated due to the limit of the current fMRI spatial resolution. Second, subjects were trained for 30 days in our study. There might be cortical changes at some point during the training course, but the changes disappeared after the long training. Indeed, a very similar phenomenon has been reported by Yotsumoto et al. [35]. Third, neurons in visual cortex might integrate and normalize LGN signals so that, after training, the low-contrast stimuli produce more reliable, less noisy neural signals (e.g., spike trains), but the average neural signals do not change. This possibility was proposed by Furmanski et al. [28] to explain their finding that perceptual learning of contrast detection enhanced activities in V1 but not in V2 and V3. Fourth, in the fMRI experiment, subjects performed a demanding fixation task (i.e., the test task), rather than the contrast detection task (i.e., the training task). The lack of cortical response changes might be due to the difference between the training task and the test task. Shibata et al. [36] have shown that cortical response changes induced by perceptual learning in some cortical areas (e.g., V1) reflected task-based plasticity, which manifested only when subjects performed the training task during fMRI measurement. When subjects performed the fixation task, their attention was directed away from the peripheral stimuli. Feedback signals from higher to lower visual areas, which are enabled by attention, have been shown to play a pivotal role in the expression of perceptual learning at the cortical level [37] (but see also [23]). Nevertheless, one advantage of using a fixation task while measuring fMRI signal is the capacity to rule out the attentional explanation of our finding in the LGN. If the response enhancement in the LGN was ascribed solely to attention, we should have observed such an effect at the cortical level. Furthermore, subjects performed the fixation task equally well across scanning sessions and contrast levels, presumably holding effort and attention constant at fixation across all the conditions, which makes the attentional explanation even more unlikely.

The plasticity of the LGN has been investigated by comparing the consequences of temporary monocular eyelid closure and pharmacological inactivation of one retina with those of normal visual experience. This kind of research is usually carried out with animals during their early postnatal life, and the plasticity has been well characterized [38, 39]. A recent breakthrough in this area is the identification of a robust form of plasticity in the LGN of adult cats [40]. This study used intraocular injections of

the glutamate receptor agonist to block visual responses in on-center retinal ganglion cells and found that the inactivation led to a rapid emergence of off-center responses from on-center neurons in the LGN. A significant stride we made in the present study is that, without such abnormal visual experience (i.e., eyelid closure or pharmacological inactivation), even regular practice could profoundly change local receptive field properties of the LGN neurons in human adults. Recently, it has been recognized that the LGN and other thalamic structures actively regulate information transmission to the cortex and between cortical areas using various mechanisms, thereby contributing to perception and cognition much more than we previously believed [14, 41]. Exploring the functional plasticity of the subcortical structures induced by training is an important research topic in the future, which is necessary for us to fully understand the adaptive nature of perceptual and cognitive information processing in the brain.

EXPERIMENTAL PROCEDURES

The procedures and protocols used in this study were approved by the human subject review committee of Peking University. Complete procedures can be found in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two figures and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.09.034.

AUTHOR CONTRIBUTIONS

Q.Y. and F.F. designed the study. Q.Y. and J.Q. conducted the experiments. Q.Y., P.Z., and F.F. analyzed the data and wrote the manuscript.

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