

## Context-enabled learning in the human visual system

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**Training was found to improve the performance of humans on a variety of visual perceptual tasks<sup>1,2</sup>. However, the ability to detect small changes in the contrast of simple visual stimuli could not be improved by repetition<sup>3</sup>. Here we show that the performance of this basic task could be modified after the discrimination of the stimulus contrast was practised in the presence of similar laterally placed stimuli, suggesting a change in the local neuronal circuit involved in the task. On the basis of a combination of hebbian and anti-hebbian synaptic learning rules compatible with our results, we propose a mechanism of plasticity in the visual cortex that is enabled by a change in the context.**

Practice is known to improve the ability of humans to detect small changes in a variety of visual attributes such as position, orientation, motion, depth, spatial phase, hyper-acuity and texture segmentation<sup>1,2</sup>. For these kinds of tasks, repetitions have resulted in a gradual improvement in the performance (perceptual learning), until a performance plateau (saturation) is reached at a new level. The specificity of these learning effects to the spatial position, to the orientation of the stimuli and to the eye that receives the stimuli has served as evidence of long-lasting plasticity in the primary visual cortex of human adults<sup>4–6</sup>. Accumulating evidence<sup>7,8</sup> shows changes in the primary visual cortex of the monkey that are correlated with learning effects, supporting the psychophysical results.

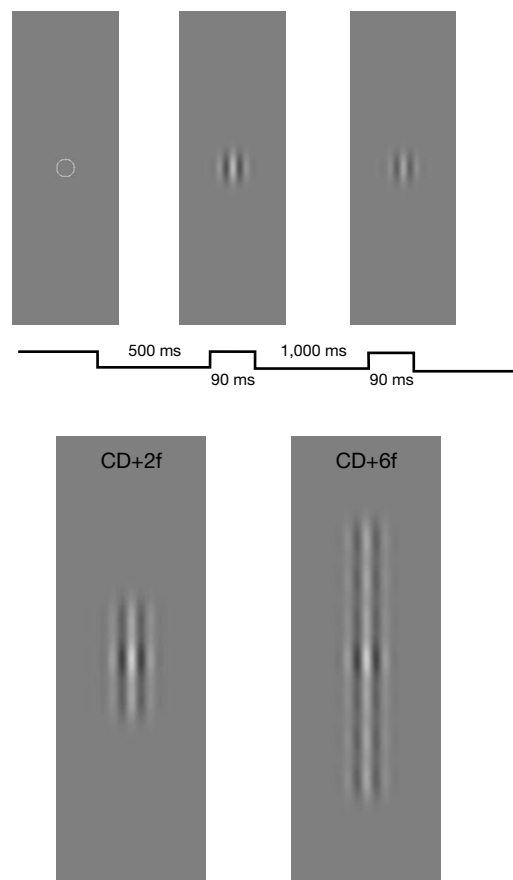
Assuming that adults retain plasticity at low levels of visual processing, we would expect that practising the ability to notice small changes in the stimulus contrast (contrast-discrimination task, or CD) would also lead to an improvement. However, CD is an example of a task where practice does not ‘make perfect’. In refs 3 and 9, observers repeated CD experiments over a long period of time (over 40 sessions), without any improvement. In fact, the only observable effect of the practice was a slight deterioration in the performance, indicating that this basic task<sup>10</sup> might have reached its optimal performance either during normal development or within the first 500 trials that composed a testing session (that is, during ‘fast-learning processes’<sup>6,11</sup>).

The saturation of perceptual learning for most of the tasks, as well as the absence of learning for the CD task, indicates that not all the activations of the primary visual cortex result in long-term modifications. Moreover, it appears that any particular pattern of stimulation ceases to become effective in evoking modifications when it becomes ‘familiar’ to the visual system. Thus, the saturated performance following repetitions may not necessarily reflect the best possible performance of a task. To explore this possibility, we searched for practice conditions that would improve the seemingly saturated performance of the CD task. We introduced a set of CD practice sessions in which the target stimulus was surrounded by chains of similar stimuli of fixed high contrast and varying length<sup>12</sup> (Fig. 1b). We then compared the CD performance for isolated target stimuli, measured before and after the practice sessions.

Six adult observers, with typical contrast-discrimination abilities<sup>13</sup> participated in the experiments. After measuring their performance in the contrast discrimination of an isolated foveal Gabor signal<sup>14,15</sup>, the observers practised the same task in the presence of chains of high-contrast lateral Gabor signal flankers (Fig. 1). The practice was organized in subsequent cycles of three daily sessions each, with 500–1,000 trials a day. During each

experimental sub-session, the contrast of the target stimulus was varied from 0 to 50%, while the length of the chain of flankers was held constant; this length was increased (2–10) from one sub-session to another. After 2–3 practice cycles, all observers had improved their discrimination performance. Most importantly, the CD thresholds for isolated target stimuli, tested after each practice cycle, were significantly reduced (Fig. 2a). Specifically, there was a marked decrease in the just-noticeable difference in contrast (the threshold) with reference contrasts above 10%. On average ( $N = 6$  observers), the CD threshold for a reference contrast of 50% decreased to about half of its initial value (by  $0.28 \pm \text{s.d.} = 0.03$  logunits; s.d., standard deviation). This decrease was highly significant ( $P < 0.0002$ ,  $N = 6$ ). A significant decrease ( $P < 0.002$ ,  $N = 6$ ) was also found in the CD threshold for a reference contrast of 25%, where the threshold decreased to 0.58 of its initial value ( $0.24 \pm \text{s.d.} = 0.04$  logunits).

The effect of the lateral flankers used in our learning procedure could be merely to increase the overall excitation at the target location. To control for this possibility we used the following procedure: two observers practised the discrimination of a partial range of high contrasts for a number of trials similar to that of the



**Figure 1** Experimental conditions. **a**, In the contrast-discrimination (CD) task we measured the just-noticeable difference in contrast needed to discriminate the two Gabor signals. The observers report which of the two stimuli appears to have a higher contrast. A temporal two-alternative forced-choice procedure was used, as described by the time sequence in the figure, and in more detail in the Methods. **b**, Examples of stimuli used during the ‘practice with flankers’ sessions, in which the thresholds for contrast-discrimination for the central Gabor signal were measured in the presence of chains of collinear flankers. Here we show a chain of two flankers (2f), and a chain of six flankers (6f).

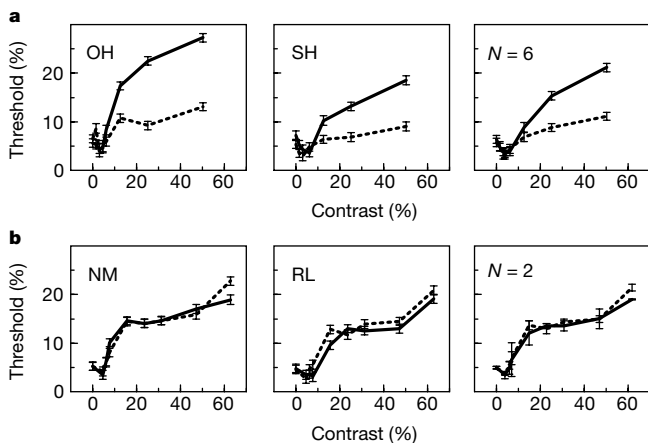
first experiment. This learning procedure did not result in any statistically significant change in the performance of the CD task (Fig. 2b), which implies that the lateral input from the proximal flankers is not equivalent to direct input to the target location<sup>16,17</sup>.

The time course of the learning process can be evaluated by monitoring the changes in the CD performance after subsequent practice cycles. As illustrated in Fig. 3, most of the learning effect took place after one cycle (three sessions taken on different days) of practice in the presence of a chain of lateral GS flankers. We note that a similar time course of learning was found with other perceptual tasks where the new level of performance was reached after 4–6 sessions taken on different days<sup>11</sup>. The learning effect was found to last for at least eight months (Fig. 3), indicating long-lasting modifications in the human visual cortex<sup>4,11</sup>.

To account for the learning effect that was found here, we have assumed that the CD performance involves the activation of an interconnected local neural network<sup>18,19</sup>, with synaptic connections that are modified in an activity-dependent manner. Because the performances were found to be stable after repetitions with different contrasts, but improved after practising the task with a new context, we looked for a plasticity mechanism that is activated by a change of context. Such a mechanism can be sub-served by the properties of long-term synaptic modification analysed recently<sup>20</sup>. In studying the implications of spike-time-dependent synaptic plasticity<sup>21–23</sup>, the following approximate expression for changing the probability of neurotransmitter release ( $P_r$ ; equivalent to the ‘strength’) for a synaptic connection was formulated

$$\frac{dP_r}{dt} = r_1 P_r f_{pre} f_{post}^2 - r_2 (P_r f_{pre})^2 f_{post} \quad (1)$$

This function of the pre- and post-synaptic instantaneous firing frequencies ( $f_{pre}(t)$  and  $f_{post}(t)$ ) combines nonlinear hebbian and anti-hebbian terms<sup>24</sup> that determine the up- and downregulation of the release probability, and thus the effectiveness of the synaptic connection. (Here  $r_1$  and  $r_2$  denote the corresponding rate constants). By rewriting equation (1) in a slightly different way, we obtain



**Figure 2** Changes in the contrast-discrimination curves. Data were obtained after **a**, practising contrast-discrimination in the presence of chains of flankers (a new context) and **b**, practising discrimination of high-contrast stimuli (the same context). For each condition the graph shows the data for two individual observers, and the average across  $N$  observers. Each datum point in the observers’ data is the average of 2–4 threshold estimates taken on different days. The solid curves represent the data before the practice. The dotted curves represent the after-practice data.

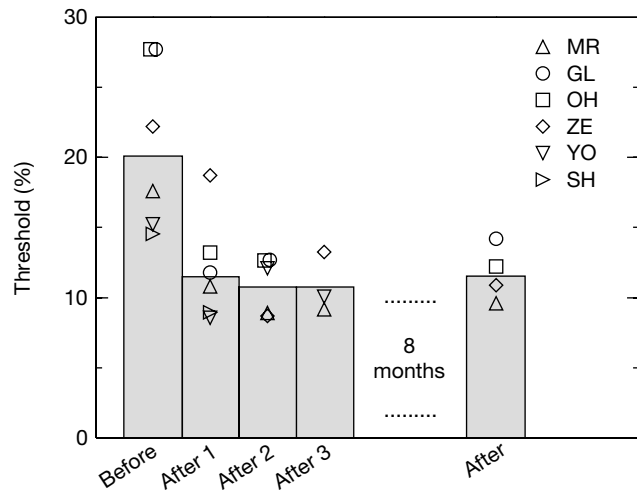
$$\frac{dP_r}{dt} = r_1 P_r f_{pre} f_{post} (f_{post} - P_r \epsilon f_{pre}) \quad (2)$$

where  $\epsilon$  is defined as  $r_2/r_1$ . According to this equation, a steady state is reached when

$$P_r = \frac{f_{post}}{\epsilon f_{pre}} \quad (3)$$

Thereafter, the release probability will remain steady as long as the ratio between the post- and pre-synaptic rate remains constant. However, when the rates deviate from this relation, the release probability begins to change until a new equilibrium point is reached (Fig. 4a). The release probability of the synapse can therefore serve as a memory for the expected relation between the pre- and post-synaptic firing rates. We next show how such a mechanism can explain the stability of human CD performance when practised with stimuli of different contrasts, and the change in the performance when a new stimulus configuration is introduced.

We model the CD task as mediated by a local cortical column consisting of two interconnected subpopulations of excitatory and inhibitory neurons<sup>12,25</sup> (Fig. 4b and see the Methods). The activity of the excitatory ( $E$ ) and the inhibitory ( $I$ ) subpopulations is determined by the external inputs, which are increasing functions of the stimuli contrast, and the recurrent interactions in the local network. When the contrast of the visual stimulus is increased, the resulting activity ( $E$ ) also increases, enabling the discrimination between the contrasts. The CD threshold is controlled by the steepness of the relation between the activity ( $E$ ) and the contrast. Our psychophysical results could be explained in this model if synaptic connections are modified according to the principles presented above. Assume that the network receives stimulus-driven thalamic inputs ( $e$  and  $i$ ) that are divided between the excitatory and inhibitory subpopulations in a certain fixed proportion that is,  $i = ke$  (ref. 12). We can show that in the linear approximation, the ratio between the average firing rates  $E$  and  $I$  is contrast independent (see Methods). Thus, according to the above analysis of synaptic



**Figure 3** The time course of the context-induced learning. The figure shows the development with practice of the changes in the contrast-discrimination thresholds with a reference contrast of 50%. Thresholds measured before and after consecutive cycles of practice are shown for six observers, with their average represented by the histogram bars. Observers practised the collinear configurations, except observer MR, who practised the parallel configurations, obtaining similar results. Each ‘after- $N$ ’ measurement was taken on the day after the  $N$ th practice cycle. Four observers were tested after about 8 months to check the retention of their learning effect. The average of their average thresholds is represented with the rightmost bar (‘after’). The symbols represent the thresholds obtained for each of the six observers.

plasticity, the strength of the connections, when reaching equilibrium levels, will not change further when the same local visual stimulus is repeatedly shown at various contrasts (Fig. 4a). If, however, a new stimulus configuration is presented, such as the one with the laterally placed flankers, synaptic modification will be rekindled. This is because the lateral input from the flankers may be distributed differently between the excitatory and inhibitory subpopulations and this will change the  $E/I$  ratio. According to equation (3), the equilibrium values for the corresponding connections ( $J_{ei}$  and  $J_{ie}$ ) will change after the presentation of the flankers. To make the analysis simpler we assume that only one type of connection undergoes modification. In particular, if the lateral input is more biased towards inhibition ( $\Delta i = k_1 \Delta e$ ;  $k_1 > k$ ), which is compatible with our previous results<sup>12</sup> and with physiological findings<sup>26</sup>, then the overall ratio between the inputs to inhibitory and excitatory subpopulations ( $k$ ) will be larger

$$k \rightarrow \frac{i + \Delta i}{e + \Delta e} = k + (k_1 - k) \frac{\Delta e}{e + \Delta e} \quad (4)$$

Calculations show that in this case the new stationary value of  $J_{ei}$  (or  $J_{ie}$ ) will be lower (Methods), resulting in a steeper dependency of the activity of the excitatory subpopulation  $E$ , on the contrast. The CD threshold is therefore lowered, as demonstrated by the model simulations (Fig. 4c).

Our psychophysical findings show that the seemingly stable contrast discrimination (CD) performance could be modified after practising the task in the presence of similar flankers. The system is thus capable of long-term adjustments in its local gain, according to changes in the relevant environment. This result demonstrates that the visual system possesses a mechanism for

context-induced learning. This mechanism allows the visual system to distinguish between stimulus changes that are irrelevant for object recognition and learning (for example, stimulus contrast), and changes affecting object shape (for example, stimulus configuration). Inspired by recent physiological results<sup>21–23</sup>, we suggest that this type of learning is mediated by a synaptic modification rule that combines hebbian and anti-hebbian types of plasticity and is activated by changes in the relative proportions of the excitatory and inhibitory activities in the local visual circuits. Our data suggest that the specific context that was practised here leads to decreased inhibitory influences. We expect that other practice contexts will be found which will lead to an opposite change in the relative excitatory-inhibitory activities, and thus to higher inhibitory influences.

Our learning procedure resulted in an increased sensitivity to changes in contrast, and so it may be used to improve the contrast discrimination ability in humans. A challenging study would be to apply variations of our learning technique to improve the sensitivity of other sensory attributes. □

Methods

Apparatus

Stimuli were displayed as grey-level modulation on a Philips colour monitor, using a personal computer with an Intel Pentium II processor. For full details see ref. 16.

Stimuli

The stimuli consisted of one target signal (at the fixation point), one reference signal (at the target location) and 0, 2, 4, 6, 8 or 10 lateral masks (flankers). The spatial luminance distribution of each of the target, reference and mask signals was described by a Gabor function (a cosine grating multiplied by a gaussian envelope<sup>27</sup>, with a vertical orientation, and  $\sigma = \lambda = 0.15^\circ$ ). The reference-signal amplitude,  $C_r$ , was changed from 0 up to 63% during the experimental conditions. The amplitude of the Gabor signal was taken to represent its contrast. The target and masks were aligned with  $2\lambda$  ( $0.3^\circ$ ) spacing.

Experimental procedure

A temporal two-alternative forced choice procedure was used (Fig. 1a). A staircase method<sup>3</sup> was used to determine the contrast threshold at a level of 79% correct. For full details see ref. 16.

Psychophysical experiments

Observers practiced the CD task using either the ‘practice with flankers’ or the ‘practice without flankers’ learning procedures (see below). The results were described by a threshold versus contrast (TVC) function. After measuring the initial TVC curve for each observer (2–4 repetitions), observers practised CD tasks using a specific learning procedure. Practice was taken in cycles. Each practice cycle was taken on three successive days. Observers participated in 2–3 practice cycles. One TVC curve was taken for each observer the day after each practice cycle. We used the following learning procedures.

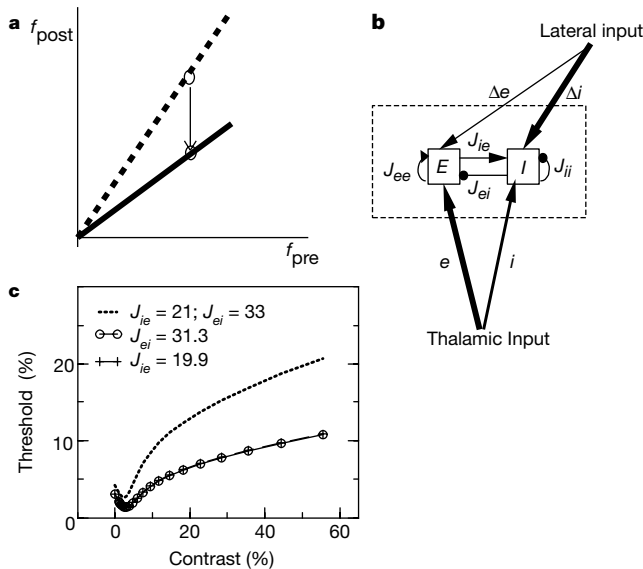
In experiment 1 (practice with flankers), contrast-discrimination thresholds were measured for a foveal Gabor signal flanked on each side by either 1, 2, 3, 4 or 5 high-contrast (30%) Gabor signal masks. The reference contrast varied from zero to 50% ( $C_r = 0, 1.5, 3, 6, 12.5, 25$  and 50%) during each experimental sub-session, whereas the flankers’ contrast ( $C_m = 30\%$ ) and the number of flankers were fixed. Observers usually participated in two 20-min experimental sub-sessions each time they came to the laboratory. They had a 20-min break between the successive sub-sessions. One cycle of practice consisted of five experimental sub-sessions (each with a different number of flankers) and was taken on three successive days. Six adult observers (17–24 years old) participated in this experiment. Five observers practised with collinear flankers and one observer practised with parallel flankers. An observer (S.H.) practised the discrimination of just two reference-contrasts (0 and 30%) in the presence of either two or four high-contrast lateral flankers.

In experiment 2 (practice without flankers), two 17-year-old observers participated in this learning procedure. During each session, the reference contrast was varied over a limited range of supra-threshold contrasts ( $C_r = 0, 30\%, 47\%$  and 63%). A session consisted of 10 blocks of CD experiments, followed by two blocks of CD experiments ( $C_r = 0, 30\%$ ) that were performed about 20 min after the end of the daily session. The last block of the daily session used a high-contrast reference stimulus (30%). One cycle of practice contained three sessions taken on three successive days.

Network model of contrast discrimination

The network model is illustrated in Fig. 4b. Assuming the threshold-linear gain functions for both subpopulations, for given input ( $e, i = ke$ ), the activities converge to a steady-state solution of the following equations<sup>12,28</sup>

$$\begin{aligned} E &= e - J_{ei}I + J_{ee}E \\ I &= ke - J_{ii}I + J_{ie}E \end{aligned} \quad (5)$$



**Figure 4** Putative synaptic mechanism and model simulations. **a**, Linear relationship between pre- and post-synaptic frequencies for which synaptic modification does not occur. The slope of the line depends on the synaptic strength (probability of release). Deviating from the linear relationship initiates a modification of the release probability, until it reaches a new stable value. **b**, A schematic representation of a cortical hyper-column<sup>12</sup>, consisting of two interconnected subpopulations: excitatory ( $E$ ) and inhibitory ( $I$ ). The symbols  $e$  and  $i$  denote the strength of the thalamic sensory inputs to these two subpopulations;  $\Delta e$  and  $\Delta i$  are lateral inputs. The width of the corresponding lines illustrates the assumed differences in the relative distribution of inputs to excitatory and inhibitory subpopulations. **c**, Performance of the model on the CD task before (dotted) and after (solid) modifications in either of the connections  $J_{ei}$  or  $J_{ie}$  (which led to practically the same effect). See Methods for details; compare with Fig. 2a.

where  $J_{ei}$  denotes the average strength of I to E connections (analogously for the other connections), and is an increasing function of the stimulus contrast (see below). We have assumed that the steady-state solution of equation (5) is stable and both  $E$  and  $I$  are positive for a positive  $c$ , which imposes certain conditions on the values of the connection strengths (see for example, ref. 29). In particular, if recurrent excitation exceeds the destabilizing level ( $J_{ee} > 1$ ), it has to be offset by strong enough inhibition. Under these conditions, the CD is determined by the dependency of the activity  $E$  on the contrast

$$E = e \frac{1 + J_{ii} - kJ_{ei}}{J_{ei}J_{ie} - (J_{ii} + 1)(J_{ee} - 1)} \quad (6)$$

Simple algebra shows that this dependency becomes steeper when the strength of either the inhibitory connection  $J_{ei}$  or the excitatory connection  $J_{ie}$  decreases, thus leading to better CD performance. We assume that one of these connection types undergoes modification according to equation (1). For example, for the connection between the subpopulations  $I$  and  $E$  we write explicitly  $f_{pre} = I, f_{post} = E$  and  $J_{ei} = P_i W_{ei}$ , where  $W$  is a constant factor. It follows from equation (5) that the ratio between the rates of the subpopulations is independent of the input  $e$  (that is, on the stimulus contrast)

$$\frac{E}{I} = \frac{1 + J_{ii} - kJ_{ei}}{J_{ie} - k(J_{ee} - 1)} \quad (7)$$

Thus, according to equations (3) and (7), if the strength of the connections is at the equilibrium values, activation of the network at different contrasts does not lead to synaptic modifications. However, the modification will occur if the value of  $k$  is changed. Calculations show that when  $k$  increases owing to laterally placed flankers (equation (4)), a new equilibrium is reached at which the strength of the connection that undergoes the modification (either  $J_{ei}$  or  $J_{ie}$ ) is weaker. In order for the equilibrium to be stable, the sign of the rate constants ( $r_1, r_2$ ) in equation (1) have to be positive for  $J_{ei}$  and negative for  $J_{ie}$ ; that is, these different types of connections should obey modification rules with exchanged powers of the corresponding hebbian and anti-hebbian terms.

To simulate our psychophysical data, we chose the widely used<sup>18,19,30</sup> Naka–Rushton function<sup>31</sup> to describe the thalamic input

$$e = \frac{C^p}{C^q + A^q} \quad (8)$$

where  $C$  represents the stimulus contrast. In the simulations (Fig. 4c) we used  $p = 3.5$ ,  $q = p - 0.5$ , and  $A = 3.5$ . The thalamic input to the  $I$  node was  $i = 0.3e$ . The simulations for the 'before' practice curve were obtained using equation (5) with  $J_{ee} = J_{ie} = 21$ ,  $J_{ii} = 30$  and  $J_{ei} = 33$ . The 'after' simulations were obtained using either  $J_{ei} = 31.3$ , or  $J_{ie} = 19.9$ . All the other parameters were the same as in the 'before' simulations. We have assumed that any two contrasts,  $C_1$  and  $C_2$ , can be discriminated if  $E(C_1) - E(C_2) \geq 0.4$  (the criterion for discrimination was fixed according to the value of the CD at zero contrast).

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1. Sagi, D. & Tanne, D. Perceptual learning: learning to see. *Curr. Opin. Neurobiol.* **4**, 155–159 (1994).
2. Karni, A. The acquisition of perceptual and motor skills: a memory system in the adult human cortex. *Brain Res. Cogn. Brain Res.* **5**, 39–48 (1996).
3. Dorais, A. & Sagi, D. Contrast masking effects change with practice. *Vision Res.* **37**, 1725–1733 (1997).
4. Karni, A. & Sagi, D. Where practice makes perfect in texture discrimination-evidence from primary visual cortex plasticity. *Proc. Natl Acad. Sci. USA* **88**, 4966–4970 (1991).
5. Polat, U. & Sagi, D. Spatial interactions in human vision: from near to far via experience-dependent cascades of connections. *Proc. Natl Acad. Sci. USA* **91**, 1206–1209 (1994).
6. Fahle, M., Edelman, S. & Poggio, T. Fast perceptual learning in hyperacuity. *Vision Res.* **35**, 3003–3013 (1995).
7. Schoups, A., Vogels, R. & Orban, N. Q. G. Practicing orientation identification improves orientation coding in V1 neurons. *Nature* **412**, 549–553 (2001).
8. Crist, R. E., Li, W. & Gilbert, C. D. Learning to see: experience and attention in primary visual cortex. *Nature Neurosci.* **4**, 519–525 (2001).
9. Zenger, B. & Sagi, D. in *Textbook on 'Perceptual Learning'* (eds Fahle, M. & Poggio, T.) Ch. 10, 177–196 (MIT Press, Boston, 2002).
10. Boynton, G. M., Demb, J. B., Glover, G. H. & Heeger, D. J. Neuronal basis of contrast discrimination. *Vision Res.* **39**, 257–269 (1999).
11. Karni, A. & Sagi, D. The time course of learning a visual skill. *Nature* **365**, 250–252 (1993).
12. Adini, Y., Sagi, D. & Tsodyks, M. Excitatory-inhibitory network in the visual cortex: psychophysical evidence. *Proc. Natl Acad. Sci. USA* **94**, 10426–10431 (1997).
13. Legge, G. E. A power law for contrast discrimination. *Vision Res.* **21**, 457–467 (1981).
14. Marcelja, S. Mathematical description of the responses of simple cortical cells. *J. Opt. Soc. Am.* **70**, 1297–1300 (1980).
15. Pollen, D. A. & Romer, S. F. Visual cortical neurons as localized spatial frequency filters. *IRRR Trans. Syst. Man Cybern. SMC-13*, 907–916 (1983).
16. Adini, Y. & Sagi, D. Recurrent networks in human visual cortex: psychophysical evidence. *J. Opt. Soc. Am. A* **18**, 2228–2236 (2001).
17. Zenger-Landolt, B. & Koch, C. Flanker effects in peripheral contrast discrimination—psychophysics and modeling. *Vision Res.* **41**, 3663–3675 (2001).
18. Wilson, H. R. & Humanski, R. Spatial frequency adaptation and contrast gain control. *Vision Res.* **33**, 1133–1149 (1993).
19. Foley, J. M. Human luminance pattern-vision mechanisms: Masking experiments require a new model. *J. Opt. Soc. Am. A* **11**, 1710–1719 (1994).
20. Senn, W., Markram, H. & Tsodyks, M. An algorithm for modifying neurotransmitter release probability based on pre- and postsynaptic spike timing. *Neur. Computat.* **13**, 35–67 (2001).
21. Markram, H., Lübke, J., Frotscher, M. & Sakmann, B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* **275**, 213–215 (1997).

22. Bell, C. C., Han, V. Z., Sugawara, Y. & Grant, K. Synaptic plasticity in a cerebellum-like structure depends on temporal order. *Nature* **387**, 278–281 (1997).
23. Bi, G. Q. & Poo, M. M. Synaptic modifications in cultured hippocampal neurons: dependence on spike timing, synaptic strength, and postsynaptic cell type. *J. Neurosci.* **18**, 10464–10472 (1998).
24. Abbott, L. F. & Nelson, S. B. Synaptic plasticity: taming the beast. *Nature Neurosci.* **3**, 1178–1183 (2000).
25. Somers, D. C. *et al.* A local circuit approach to understanding integration of long-range inputs in primary visual cortex. *Cereb. Cortex* **8**, 204–217 (1998).
26. Walker, G. A., Ohzawa, I. & Freeman, R. D. Suppression outside the classical cortical receptive field. *Vis. Neurosci.* **17**, 369–379 (2000).
27. Gabor, D. Theory of communication. *J. Inst. Elect. Eng. (Lond.)* **93**, 429–457 (1946).
28. Wilson, H. R. & Cowan, J. D. A mathematical theory of the functional dynamics of cortical and thalamic nervous tissue. *Kybernetik* **13**, 55–80 (1973).
29. Tsodyks, M. V., Skaggs, W. E., Sejnowski, T. J. & McNaughton, B. L. Paradoxical effects of external modulation of inhibitory interneurons. *J. Neurosci.* **17**, 4382–4388 (1997).
30. Albrecht, D. G. & Hamilton, B. Striate cortex of monkey and cat: contrast response function. *J. Neurophysiol.* **48**, 217–237 (1982).
31. Naka, K. I. & Rushton, W. A. H. S-potentials from luminosity units in the retina of fish (cyprinidae). *J. Physiol. Lond.* **185**, 587–599 (1966).

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**Competing interests statement**

The authors declare that they have no competing financial interests.

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**Excitatory glycine receptors containing the NR3 family of NMDA receptor subunits**

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The N-methyl-D-aspartate subtype of glutamate receptor (NMDAR) serves critical functions in physiological and pathological processes in the central nervous system, including neuronal development, plasticity and neurodegeneration<sup>1,2</sup>. Conventional heteromeric NMDARs composed of NR1 and NR2A–D subunits<sup>3,4</sup> require dual agonists, glutamate and glycine, for activation. They are also highly permeable to Ca<sup>2+</sup>, and exhibit voltage-dependent inhibition by Mg<sup>2+</sup>. Coexpression of NR3A with NR1 and NR2 subunits modulates NMDAR activity<sup>5–7</sup>. Here we report the cloning and characterization of the final member of the NMDAR family, NR3B, which shares high sequence homology with NR3A. From *in situ* and immunocytochemical analyses, NR3B is expressed predominantly in motor neurons,