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Does physical exercise and congruent visual stimulation enhance perceptual learning?

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Abstract

Purpose: There is currently great interest in methods that can modulate brain plasticity, both in terms of understanding the basic mechanisms, and in the remedial application to situations of sensory loss. Recent work has focussed on how different manipulations might be combined to produce new settings that reveal synergistic actions. Here we ask whether a prominent example of adult visual plasticity, called perceptual learning, is modified by other environmental factors, such as visual stimulation and physical exercise.
Methods: We quantified the magnitude, rate and transfer of perceptual learning using a peripheral Vernier alignment task, in two groups of subjects matched for a range of baseline factors (e.g. age, starting Vernier threshold, baseline fitness). We trained subjects for 5 days on a Vernier alignment task. In one group, we introduced an exercise protocol with congruent visual stimulation. The control group received the same visual stimulation, but did not exercise prior to measurement of Vernier thresholds.
Results: Although the task generated large amounts of learning (~40%) and some transfer to untrained conditions in both groups, there were no specific benefits associated with either the addition of an exercise schedule or congruent visual stimulation.
Conclusion: In adults, short periods of physical exercise and visual stimulation do not enhance perceptual learning.

Introduction

There is both theoretical and practical interest in methods that enable or enhance the expression of plasticity in the adult brain.[1,2] On the one hand, there is considerable intrinsic curiosity in understanding how changes to anatomical pathways, neurochemical cascades and network dynamics remodel brain circuits to enhance or extend the behavioural repertoire of the owner.[3-5] While on the other, manipulations of brain plasticity present an opportunity to correct functional deficits arising during development, or mitigate loss associated with ageing and neurological disease.[6-9] Over the last few decades a range of approaches has been developed with the potential to modify sensory, motor and cognitive capacity in the adult brain across a wide range of species. This activity has focussed on a number of levels of description, from genetic, cellular and molecular through to systems and behaviour. In the visual system, examples include pharmacological manipulation,[10-14] cortical stimulation,[15-21] environmental enrichment,[22-24] removal of light stimulation,[25-27] aerobic exercise[28] and behavioural training such as perceptual learning and video game play.[3,29-33] The relative success of these different approaches varies considerably (see Bavelier *et al.*, for review[2]). At present, there is generally little data available on the combination of techniques to heighten visual plasticity, perhaps with the notable exception of perceptual learning and electrical stimulation of the visual cortex.[15-19]

Over and above the well-documented effects on cardiovascular health, moderate amounts of physical exercise are known to exert a positive influence on the neuroplasticity of a range of brain systems.[34] This link was originally based on the early observation that good behavioural performance on cognitive and motor tasks was associated with regular patterns of physical activity.[35,36] Since then, interest has focussed on establishing a direct causal link, revealing the structural and functional mechanisms that mediate exercise-based neuroplasticity, and finding ways to optimise it with a view to deployment in neuro-rehabilitative strategies.[37] With therapeutic use in mind, studies have set out to establish whether different forms of physical exercise promote brain plasticity, the extent to which they modify behaviour, and to ask how the benefits are moderated by other factors such as age, behavioural task, baseline fitness and duration or intensity of physical activity. Animal studies point to a central role for brain-derived neurotrophic factor (BDNF) - a key mediator of synaptic plasticity.[38] In adult rats, physical activity increases the level of BDNF and nerve growth factors (NGF) across a broad range of brain areas, including the cerebellum and cortex.[39] These changes in the circulating level of BDNF, and those of other molecules such as vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-I), stimulate gliogenesis, neurogenesis, synaptogenesis and angiogeneisis.[37] The modified activity of neurotrophins play an important role in mediating plasticity, and a key area of interest in behavioural neuroscience is the enhancement of learning. Rodent studies have revealed improvements in route finding,[40] avoidance[41] and object recognition[42] associated with physical exercise. In humans, there is increasing evidence that physical activity enhances cognitive and brain function.[34,43] This has led to the suggestion that exercise, by promoting neuroplasticity, may create a more permissive neural environment for the application of behavioural training programs.[44]

Recently, new studies have begun to investigate whether exercise influences one of the most common forms of behavioural plasticity associated with the human visual system - perceptual learning. This term describes the improvements in sensory performance, regularly found in adults, which result from repeatedly performing a demanding visual task. This form of plasticity is profound and omnipresent in the human visual system, occurring across a multitude of different tasks.[45,46] Although perceptual learning shows some selectivity to the behavioural task, location in the visual field or stimulus complexity, repeated exposure to near-threshold stimuli invariably results in systematic improvements in sensory performance that are retained over considerable periods of time. The cortical mechanisms that underpin perceptual learning remain unresolved, but appear to operate at multiple levels across the visual hierarchy.[47] Results so far on the interaction between visual sensitivity, perceptual training and aerobic exercise have produced rather contradictory findings. Woods and Thomson[48] reported that cycling, jogging and stair running had no effect on a range of oculomotor control functions or contrast sensitivity. Therefore, exercise does not appear to influence baseline visual sensitivity. More recently, Perini *et al.*,[49] examined the ability of a single bout of aerobic exercise to influence both magnitude and rate of perceptual and motor learning using an orientation discrimination task and thumb abduction task. They reported improved discrimination thresholds for both tasks and concluded that a single-session of moderate physical activity enhanced both visual and motor learning for a period lasting around 30 min after exercise cessation. In contrast, Connell and colleagues[50] examined perceptual learning using a motion direction discrimination task over a more prolonged period (5 days). They concluded that daily periods of moderate exercise did not influence either the rate of learning or its transfer to untrained conditions. In a further divergence from Perini and colleagues, they reported that when exercise was delivered prior to the perceptual learning task, it impaired learning rather than enhanced it.

Here we revisit this issue to try and resolve discrepancies with previous work. We quantify the magnitude, rate and transfer of perceptual learning using a peripheral Vernier alignment task. This stimulus arrangement typically generates large threshold improvements, and the constraints on behavioural performance are neural, rather than optical. We asked subjects to train each day on the Vernier alignment task. In one group, we introduced an exercise protocol with congruent visual stimulation. The control group received the same visual stimulation, but did not exercise. We did this as recent work on mouse visual cortex has shown recovery of visual function (following a period of monocular deprivation) when locomotor activity is coupled to visual stimulation, suggesting that both might be necessary to generate behavioural improvements.[51,52] Kaneko and Stryker performed intrinsic signal optical imaging under four different conditions following re-opening of the deprived eye. First, 4 h of daily running with visual stimulation. Second, 4 h of daily running in the dark. Third, running for the same period without visual stimulation (viewing a blank grey screen) and finally, visual stimulation without running. The visual stimulation consisted of either dynamic sequences of contrast-modulated noise or drifting bars spanning the full range of orientations. Relative to control animals housed in standard conditions (i.e. no specific running or visual stimulation), the results showed that neural response gain and visual recovery were significantly enhanced when visual stimulation was provided during locomotion, but was not observed for either locomotion or visual stimulation alone. Further, the recovery was specific to the stimulus the animal viewed during locomotion.[51]

Methods

Participants

Forty adults with normal, or corrected-to-normal, vision were recruited to this study. The general health of participants was evaluated using an institutionally developed general health questionnaire. Participants with known cardiovascular problems, metabolic disease or respiratory problems were excluded from the study. Other exclusion criteria included clinical depression, use of antipsychotics and antidepressants, hormone replacement therapy and the use of any drugs affecting the dopaminergic system. Informed written consent was obtained from all participants before starting the experiment. The experimental procedures complied with the Declaration of Helsinki and were approved by the local Ethics Committee (School of Psychology, University of Nottingham, UK).

Apparatus

Stimuli were generated on a PC using custom software written in Python[53] and presented on a LaCie Electron 22-inch Blue IV colour CRT monitor (www.lacie.com) at a refresh rate of 85 Hz and display resolution of 2048 × 1536 pixels. During measurements of visual thresholds, participants had their heads held in a fixed position using a forehead and chinrest. Testing was carried out in a darkened and quiet room at a viewing distance of 2.75 m. Fixation was maintained on a small illuminated external fixation spot that was external (adjacent) to the display. Stimuli either consisted of vertically or horizontally oriented abutting Vernier lines - each line element was 4.92 arcmin long and 0.492 arcmin wide, presented at an eccentricity of 15 deg. in the nasal peripheral field of the right eye while the left eye was occluded with a patch. The luminance of the Vernier lines was 83 cd/m^2 while that of the background was 0.29 cd/m^2.

To deliver acute periods of aerobic activity we used a road bike mounted on a stationary trainer (VR Fortius Multiplayer Trainer; www.tacx.com). Tacx Trainer Software 4 (www.tacx.com) was used to control the bike resistance via an Apple Mac computer. The computer was connected to a Panasonic TH-42PZ81B screen (www.panasonic.com) placed in front of the bike at a viewing distance of 1.35 meters. During the aerobic activity phase, a Tacx Real Life Video (www.tacx.com) was shown on the viewing screen and a Garmin Forerunner 15 (www.garmin.com) GPS running watch was used to monitor the heart rate. Participants could control the bicycle gears in order to maintain the required intensity of the physical activity. The Tacx software provides access to over 100 Km of virtual road network. For this study, we used a 30-min route set in Corsica, France. The advantage of this approach is that for the active condition, visual stimulation (i.e. optic flow field) is directly coupled to activity on the bike. The same video sequence, played at a constant rate and viewed from the same distance, was used for the control condition.

Health and physiological assessments

A demographic and general health questionnaire was administered to collect general information on date of birth, gender, health history and habits related to health, such as number of cigarettes smoked, units of alcohol and cups of coffee consumed per day.

The International Physical Activity Questionnaire (IPAQ) (Long Form, www.ipaq.ki.se*)* was administered to establish baseline levels of physical activity. This instrument has previously been used to monitor levels of physical activity across a broad range of countries and has been shown to produce valid and repeatable data.[54,55] Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters, squared and rounded to the nearest tenth.

The Rockport one-mile walk protocol[56] was used as a general-purpose estimate of cardiorespiratory fitness. Participants were required to wear the heart rate monitor and complete a 1-mile walk as quickly as possible without running. The estimate of the maximal oxygen consumption (VO2max) was calculated using a gender-specific formula that takes into consideration weight, age, heart rate and time to complete the walk.

Psychophysical measurements

For vertically oriented Vernier stimuli, on each trial the upper or lower line (randomly chosen) was placed at the centre of the monitor. The upper line was then positioned to the left or right, relative to the lower line, in random order from trial to trial. Vernier stimuli were presented for 200 ms and participants were asked to indicate whether the upper Vernier line was displaced to the left or to the right of the lower line via a keyboard response. Auditory feedback was given at the end of each trial, and was related to the actual position of the upper line: if the upper line was displaced to the left of the lower line, a low-pitched tone (frequency = 300 Hz) was played. Physical displacement of the upper line in the opposite direction was associated with a high-pitched tone (frequency = 800 Hz). The next stimulus was displayed immediately after the participants made their response. The horizontal separation of the two Vernier lines was varied within a 3-down, 1-up staircase procedure, where the step size was adjusted after each reversal (1st = 4 pixels; 2nd = 3 pixels; 3rd = 2 pixels; 1 pixel thereafter). Each block terminated after 60 trials and thresholds were estimated as the mean of the last four reversals. The experimental conditions were specifically chosen to match those of an earlier study by Astle *et al.*[57]

Vernier thresholds were also measured for horizontally oriented stimuli. Here, observers were asked to judge whether the line on the left was displaced upwards or downwards relative to the other line element. Again, auditory feedback related to the physical offset of the left line relative to the right was provided after each trial. Otherwise, the experimental procedure and method for threshold estimation was identical to the vertically orientated stimuli. A peripheral Vernier task was chosen because thresholds are known to be limited by cortical magnification,[58] and the elevated alignment thresholds found in the normal periphery permit greater opportunity for learning to take place. Previous work has demonstrated substantial amounts of learning for this particular task.[57]

Experimental design

Each participant was asked to complete seven sessions (*Figure 1*), each lasting no more than 60 min.

Session 1

During the first session, the four health and physiological measures outlined above were collected to ensure that for each participant we had information on their general health, routine levels of physical activity and aerobic fitness. An opportunity to try the psychophysical task for no more than 15 trials was given to participants prior to collection of baseline Vernier alignment thresholds. Baseline threshold estimates for the trained orientation (vertical) and untrained Vernier orientation (horizontal) were based on the results of at least three blocks (i.e. a minimum of 180 trials). Where more than three blocks were collected, the standard deviation of the last four reversals was used to select the three blocks that yielded the most stable threshold estimates.

Three participants withdrew from the study after session 1. The remaining participants were then allocated to either the active (N = 18, mean age: 24.5 +/−3.4) or the inactive control group (N = 19, mean age: 28.1 +/−8.5) using a free online minimisation tool (www.qminim.sourceforge.net). Minimisation is routinely used in clinical trials to allocate participants to different treatment arms in order to reduce

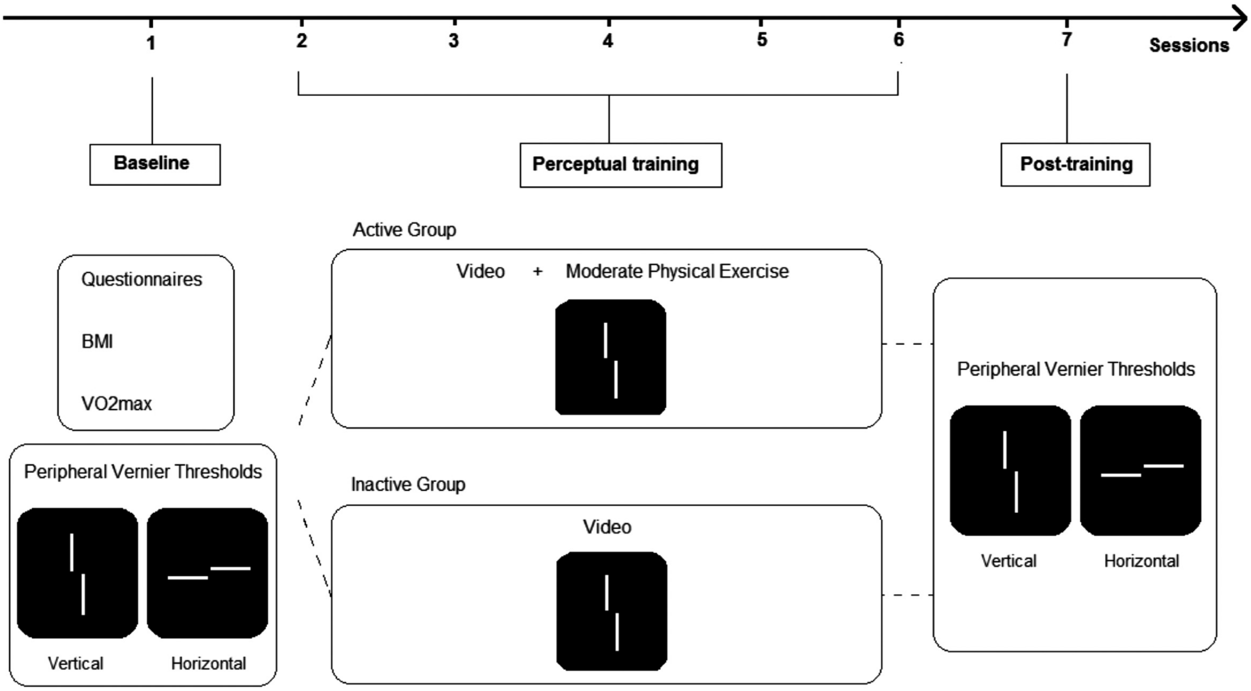

Figure 1. Schematic representation of experimental sequence. This shows the tasks performed by each participant group during the different phases of the experiment: baseline (session 1), perceptual training (sessions 2–6), and post-training (session 7). For all participants, peripheral Vernier thresholds, for both vertically and horizontally oriented stimuli, were measured in sessions 1 and 7. During sessions 2–6, the *active* group engaged in a period of moderate physical exercise while watching a video coupled to their progress around a cycling route and then trained on the peripheral Vernier alignment task at a single orientation (vertical); the *inactive* group watched the same video but did not engage in any physical exercise, followed by identical training on the Vernier alignment task (vertical). Each session was carried out on a different day. Wherever possible, sessions were completed on consecutive days, where this was not possible there was no more than a 3-day gap between sessions.

the influence of known confounding or prognostic factors. This process ensured the groups were balanced for age, gender, IPAQ score, BMI, VO2max, health related habits, and importantly, starting threshold for the vertically oriented Vernier stimuli. This latter factor is known to be a key determinant of the magnitude of visual perceptual learning.[57,59] Full details of participant characteristics are provided in Tables S1 and S2.

Session 2-6 (Perceptual Training)

Active group. Participants were required to wear the heart rate monitor and complete 30 min of physical activity on the cycle simulator. This composed a 5-min warm-up, 20-min of exercise (at between 60%–70% of the average maximum heart rate for a person of that age) and a 5-min cool down. During the physical exercise period, participants viewed a real life video of a bike route shown on a screen directly in front of them. Two sounds produced by the heart rate monitor helped participants to exercise at the required intensity: a high tone was played when heart rate increased above the target range of the participant, and a low tone was played when heart rate decreased below the target range. Immediately after the physical exercise period, participants completed two blocks of the Vernier alignment task at the trained orientation (vertical). A rest period (max 5-min) was provided between the blocks, if required.

Inactive group. Participants were seated on a chair in front of the screen and watched a 30-min long video of the same route sequence used for the active condition. Although participants were exposed to the same visual information, they were not engaged in any physical activity. At the end of the video, they were asked to complete two blocks of the Vernier task at the same trained stimulus orientation (vertical).

Session 7 (Active and Inactive group)

During the final session, each participant completed a minimum of three blocks for both the trained (vertical) and untrained (horizontal) orientation on the Vernier alignment task.

This experimental arrangement allowed us to compare the influence of a period of physical activity on visual perceptual learning. The visual stimulation and perceptual training sequence was identical for both groups. By measuring thresholds for trained and untrained orientations, we can establish whether physical activity enhanced the magnitude of perceptual learning (trained orientation) or increased its generalisation to new stimulus arrangements (untrained orientation). Furthermore, as we had access to data from a previous experiment that used exactly the same training task and retinal location, we were able to compare the data to ask whether the additional visual stimulation delivered to the *inactive* group during sessions 2-6 (optic flow only) had any additional influence on perceptual learning. Both physical activity and optic flow have been implicated in animal studies as factors that promote recovery of visual function.[51]

Analysis and statistics

Unpaired t-tests together with the Scaled JZS Bayes Factor (BF)[60,61] were used to assess differences between and within groups. Where BF < 0.33 is considered “substantial evidence” in favour of the null hypothesis, BF > 3 is considered “substantial evidence” in favour of the alternative hypothesis, and BF > 10 is considered “strong evidence” in favour of the alternative hypothesis. Finally, BF > 30 be considered “very strong evidence” in favour of the alternative hypothesis.

The ratios between pre-training thresholds and thresholds obtained at each subsequent training session were computed for the active and the inactive groups. These ratios underwent a mixed analysis of variance (ANOVA) with group (active vs inactive) as a between-subject factor and session as a within-subject factor. Post-hoc analysis for each group included within-subject polynomial contrasts and between- and within-subjects t-tests.

The amount of transfer (pre-post training ratios of the untrained orientation) and differences in transfer between groups were assessed with a mixed ANOVA with stimulus (trained vs untrained) as a within-subject factor and group as a between subject factor, on the ratios between pre- and post-training thresholds. In addition, we performed single-sample and between-subjects t-tests.

Results

No statistically significant difference was found between groups for any of the baseline measurements: thresholds for the trained stimuli ($t_{35} = -0.19$, $p = 0.85$, BF = 0.32), BMI ($t_{35} = 0.17$, $p = 0.86$, BF = 0.32), IPAQ scores ($t_{35} = 0.09$, $p = 0.92$, BF = 0.32) and VO2max ($t_{35} = -0.52$, $p = 0.6$, BF = 0.35). Therefore, any differences in the magnitude of perceptual learning between active and inactive groups are likely to reflect changes in cortical plasticity, rather than other confounding factors.

To determine whether perceptual training led to learning, we compared thresholds for the vertically-oriented Vernier stimulus before (pre-) and after (post-) training. We also estimated the time course of threshold changes during the training period. *Figure 2* shows the ratios between pre-training thresholds and thresholds subsequently obtained in each training session, plotted separately for the active (A) and the inactive (B) group. Ratios <1 represent improvements in alignment thresholds. Both groups show substantial improvements in performance; the mean ratio in session 7 (±1standard error of the mean - SEM) was 0.7 (±0.06) and 0.6 (±0.09) for the active and the inactive group, respectively.

A mixed ANOVA with training session as a within-subjects factor and group as a between-subjects factor showed a significant effect of session ($F_{6,210} = 8.41$, $p < 0.001$, $\eta_p^2 = 0.19$), but no effect of group ($F_{1,35} = 1.39$, $p = 0.25$, $\eta_p^2 = 0.04$), nor any interaction between group and session ($F_{6,210} = 1.41$, $p = 0.21$, $\eta_p^2 = 0.01$). This suggests a similar improvement in performance across sessions in both groups. In fact, improvements in performance from the first to the last session were significant for both groups (active group $t_{17} = 4.63$, $p < 0.001$, BF = 130.39; inactive group $t_{18} = 4.49$, $p = 0.001$, BF = 111.47), but there was no statistical difference in post-hoc ratios at session 7 (that is, in the amount of learning between the groups, $t_{35} = -1.04$, $p = 1$, BF = 0.48).

Polynomial contrasts revealed that the decrease in threshold across sessions were best interpolated by a linear function for both the active ($F_{1,17} = 36.7$, $p < 0.001$, $\eta_p^2 = 0.68$) and inactive groups ($F_{1,18} = 8.46$, $p < 0.01$, $\eta_p^2 = 0.32$), although a cubic fit was also significant for the inactive group ($F_{1,18} = 7.26$, $p < 0.05$). The slopes describing the rate of decrease in thresholds in the two groups were also similar ($t_{35} = -0.47$, $p = 0.64$, BF = 0.34). However, numerically the mean slope was larger in the inactive (0.31) group with respect to the active (0.26) group. Taken together, these data suggest that physical activity undertaken by the active group did not increase the magnitude of learning, nor the rate of learning, relative to the inactive group. We found no significant relationship between the magnitude of learning and any measures of baseline fitness.

To ascertain whether physical exercise influenced the transfer of learned improvements to an untrained stimulus orientation, alignment thresholds were compared for horizontally oriented stimuli, measured only on the first and the final sessions. The data presented in *Figure 3* show that the untrained orientation (UT) performance improved with a ratio of 0.9 (±0.06) and 0.7 (±0.07) for the active and the inactive group respectively. A mixed ANOVA with stimulus (trained vs untrained) as a within-subject factor and group as a between-subject factor on the ratio between pre- and post-training thresholds, showed a significant effect of the stimulus ($F_{1,35} = 6.12$, $p < 0.05$, $\eta_p^2 = 0.15$). This indicates that the amount of improvement differed between trained and untrained stimulus orientations, but no difference between active and inactive group ($F_{1,35} = 1.29$, $p = 0.26$, $\eta_p^2 = 0.03$), nor any interaction ($F_{1,35} = 2.87$, $p = 0.99$, $\eta_p^2 = 0.08$) was observed. In fact, while the untrained orientation showed a smaller but significant improvement between pre- and post-training thresholds (active group: $t_{17} = 2.74$, BF = 4.01; inactive group: $t_{18} = 3.91$, BF = 36.15), again we found no statistical difference in transfer between groups ($t_{35} = -1.23$, $p = 0.23$, BF = 0.57). Therefore, physical exercise exerted no discernible influence between the two groups on the transfer of learning to untrained stimulus orientations. The small improvement for the untrained (horizontal) orientation is likely the result of taking two repeated measurements and reflects a combination of procedural and rapid perceptual learning.[62] There is some evidence of this in the training data of the inactive group, where thresholds show a rather dramatic drop between sessions 1 & 2, and a more gradual improvement thereafter. This effect is much less pronounced in the data from the active group, where we observed a more regular reduction in threshold across sessions.

To determine whether visual stimulation alone enhances learning, we compared the performance of the subjects

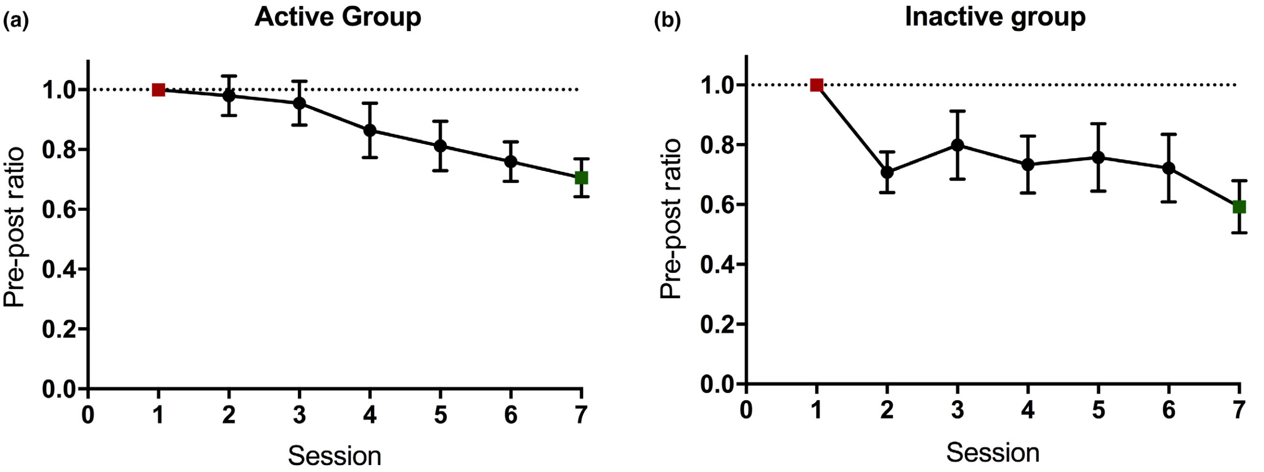

Figure 2. Magnitude and time course of perceptual learning. The figure shows the mean improvement for the active (a) and the inactive (b) group across training sessions. Data are normalised for each participant to their initial threshold. Error bars represent ±1 standard error of the mean (SEM).

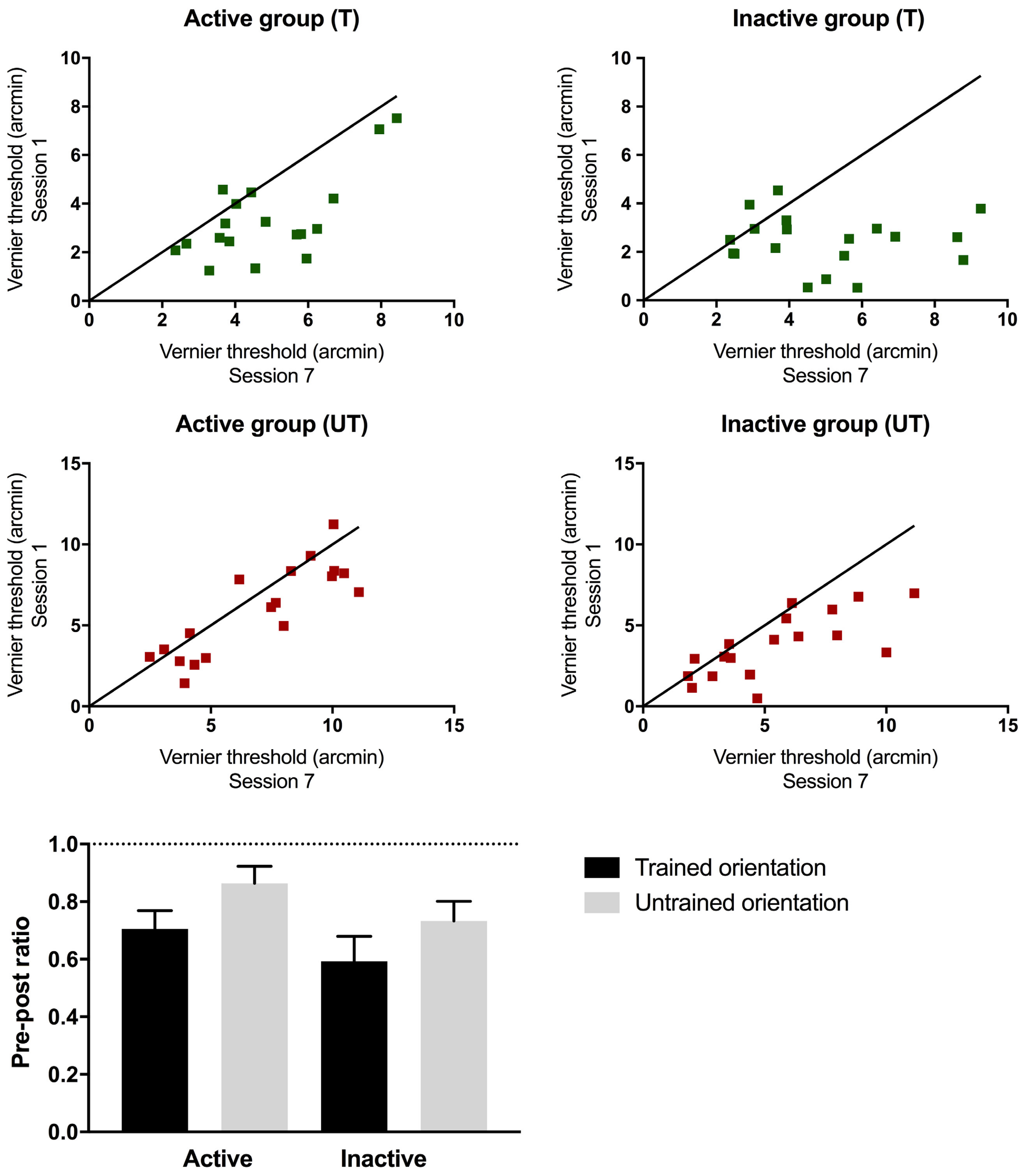

Figure 3. Improvements in performance for trained and untrained stimuli orientation. Scatter plots show improvements in Vernier alignment threshold for trained (green) and untrained (red) stimulus orientations for the active and the inactive groups. The identity line indicates where data would lie had no perceptual learning occurred. The summary bar graph shows improvement ratios for trained (black) and untrained (grey) stimulus orientations for each group.

tested here with another group of participants from an earlier study that used the same experimental conditions.[57] First we confirmed that there were no differences in Vernier starting thresholds (one-way ANOVA ($F_{2,45} = 0.30$, $p = 0.74$) across groups. Comparing the time course of learning of the three groups (*Figure 4*), we found a

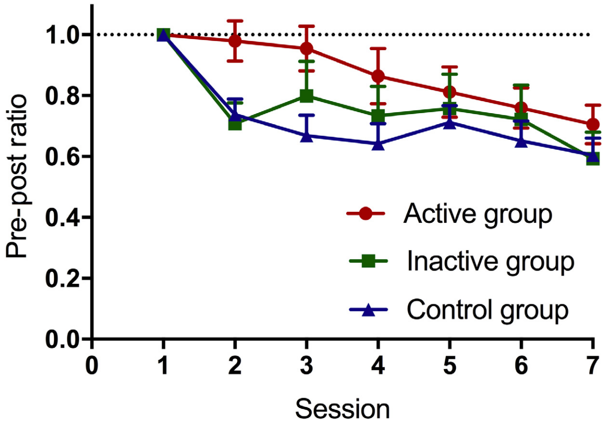

Figure 4. Characteristics of learning compared across three groups. Performance from the active and inactive groups are compared with a control group from a previous study by Astle and colleagues.[57] Data are normalised for each group to their starting thresholds. There was no statistical difference in the amount of learning between any of the groups.

significant improvement in performance across sessions ($F_{6,270} = 13$, $p < 0.001$, $\eta_p^2 = 0.22$), but no significant interaction between session and group ($F_{12,270} = 1.29$, $p < 0.22$, $\eta_p^2 = 0.05$), indicating that the pattern of learning was not influenced by either physical exercise, nor by visual stimulation from the video. Post-hoc polynomial contrasts indicate that learning curves were again well described by a linear function. The slope parameter did not differ between groups (range: -0.04 to -0.05; $F_{2,45} = 0.13$, $p = 0.87$).

Discussion

The key finding of this study is that perceptual training over a period of seven sessions produced similar levels of improvement in Vernier alignment threshold for a trained stimulus orientation in both the active and inactive groups. This result is entirely consistent with a large body of work that has demonstrated significant threshold reductions (or perceptual learning) across a broad range of visual tasks.[46] Critically, although the task generated large amounts of learning, there were no specific benefits associated with either the addition of an exercise schedule or congruent visual stimulation.

Animal models suggest that locomotor activity plays an important role in gating plasticity in the adult visual cortex. For example, neurons in rodent primary visual cortex show a dramatic increase in firing rate (almost two-fold) as the animal transitions from a stationary position to running.[63] These increases are not associated with changes in the spontaneous level of activity and are not mirrored in earlier neural structures such as the thalamus, suggesting that changes in responsiveness do not result from peripheral effects at the level of the eye. Instead, modified neural responsiveness due to locomotion involves the activation of vasoactive intestinal peptide (VIP) neurons in the primary visual cortex, which in turn inhibit somatostatin (SST) inhibitory neurons, thereby disinhibiting excitatory pyramidal neurons and allowing them to respond more strongly to visual stimuli for which they are selective.[64] These findings have established a key circuit for cortical gain control and provides an important link between locomotion and adult visual plasticity. Interestingly, the enhancement of V1 responses in mice during running occurs regardless of visual input; the same effect is seen when mice run in the dark.[64] More recent work in the mouse cortex suggests that locomotion also improves stimulus discriminability by reducing correlated noise across the active population.[65] If cycling regulated the gain of cortical responses via a similar circuit in humans, then one might expect to see enhanced learning. However, this would be predicated on the assumption that the neural mechanisms determining positional sensitivity would benefit from enhanced responses in the primary visual cortex, and that plasticity associated with the change in behavioural state persists for some time after the activity has ceased.

Benjamin *et al.*[66] recently reported a straight test of the link between enhanced locomotion-based activity and visual sensitivity. They measured subjects' ability to detect contrast changes while walking at a steady speed (5 km/h) on a motorised treadmill. Both psychophysical and electrophysiological measurements failed to reveal any enhancement associated with brisk walking. In fact, additional measures of surround suppression suggested that when the target was surrounded by a collinear mask, thresholds were actually elevated.[66] The divergence in results between humans and mice was attributed to species-specific differences in the link between locomotion and arousal; both are tightly coupled in mice and it may be the latter that drives the increases in neuronal responsiveness.[67] This explanation would appear to be broadly consistent with the finding that locomotion-based changes in neural responsiveness in mouse cortex are not linked to visual input.[64]

A direct link between visual input and locomotor activity was revealed in a study looking at functional rescue from visual deprivation in adult mice. Recovery was observed when visual stimulation and locomotion were combined, but not for either condition in isolation.[51] In support, other work has identified neural populations in mouse cortex that integrate locomotion and visual input[68] or register sensorimotor mismatches between these signals.[69] Taken together, the form of plasticity which drives recovery from visual deprivation in adult mice, involves circuits that require the co-activation of visual and locomotor systems.[51] It was for this reason that we sought to ensure that the visual stimulation experienced was congruent with the physical activity subjects were asked to undertake. During the active state, the large-field optic flow generated by the cycling simulator was consistent with natural cycling. The cycling simulator was set up in a dark room to try to limit access to other conflicting cues such as ground flow and static objects in the peripheral field. After cycling, there were no reports of any perceptual distortions of walking velocity that readily occur when visual information and locomotor activity are decoupled – for example, when running on a treadmill.[70] However, we did not incorporate all cues to egomotion, such as auditory signals or tactile information from air resistance. Despite our careful attempts to match visual information to the physical activity, we did not observe any additional effects on visual perceptual learning.

Physical exercise is thought to play an important role in visual homeostatic plasticity.[28] Lunghi and Sale found that short-term monocular adaptation, over a period of just a few hours, induced a shift in ocular dominance measured using a binocular rivalry task.[28] Interestingly, the shift was reliably modulated by introducing moderate levels of physical activity. Subjects were asked to cycle intermittently (for periods of about 10 min), while keeping their heart rate at around 120 beats per minute. Then they measured the extent to which the deprived eye dominated during rivalrous perception after patch removal. It was found that exercise, as compared to passively watching a movie, substantially altered the homeostatic response, boosting the magnitude of the ocular dominance shift in favour of the previously deprived eye. They speculated that the enhanced ocular dominance shift brought about by exercise was likely mediated by changes in the excitation/inhibition balance in the primary visual cortex.[28] It has previously been proposed that perceptual learning alongside other interventions such as dark-exposure,[25-27] environmental enrichment[23,24] and transcranial electrical or magnetic stimulation[15-21] exert their influence on visual plasticity by altering the excitation/inhibition imbalance in the visual cortex[2]. If true, then we might expect to see some interaction between perceptual learning and physical activity in line with that observed by Lunghi & Sale[28]. However, there are key differences between the studies. First, Lunghi & Sale measured the subjective perceptual experience of their subjects using the rivalrous interaction between eyes. Our measures, in contrast, were monocular. Second, we used a different period of physical exercise: 30-min versus 10-min of intermittent cycling. Other studies have attempted to replicate the findings of Lunghi & Sale using different binocular tasks, where the input from the eyes must be combined[71] and using similar exercise regimes[72]. Unfortunately, the effects have not generalised to these conditions, suggesting that they may be quite specific to situations where the visual input to the two eyes is discrepant.

Other studies, which have looked at the effects of exercise on both the magnitude and transfer of perceptual learning, have produced contradictory results. Perini *et al.*[49] investigated the effect of a single bout of aerobic exercise on both perceptual and motor learning. They found that physical activity of moderate intensity was sufficient to facilitate learning in both sensory and motor domains. This improvement was attributed to a process of synaptic strengthening, promoting what they refer to as 'associative plasticity'. Our own data from session 2 - where only a single exercise session has taken place - is inconsistent with this. Rather than observing greater improvement with physical activity, at this time point the gains are more modest in the active relative to inactive group. Further, by the end of training we found no difference between the two groups. The training effects found in session 7 are more consistent with the recent study conducted by Connell *et al.*[50] Although their training period was shorter and the training task used was based on discriminating the direction of motion, they reported no enhancement in either the rate or magnitude of learning when coupled with exercise[50]. In fact, when the exercise preceded the measurement of discrimination thresholds, they reported that the learning falls to about half that produced by either no exercise, or exercise delivered after the behavioural assessments. Over the full duration of training, and using groups balanced for a number of potentially confounding factors, we found that the rate and magnitude of learning was identical, irrespective of undertaking physical activity. Here, we have not tested explicitly whether the order of exercise versus training makes any difference to the outcome. In terms of the transfer of learning to untrained configurations, our results are in broad agreement with Connell *et a*l.[50] Training effects generalise to new orientations, albeit to a lesser degree. The fact that transfer is not complete suggests that changes in oculomotor control mechanisms (e.g. improved fixation or accommodation) do not account for the learning effects observed across the training sessions. But, as with the trained condition, the learning effect is not moderated by the subject undertaking exercise.

We find that the mechanisms which underpin the pronounced plasticity associated with perceptual learning are not modulated further by periods of visual stimulation or physical activity across the course of learning. This statement relates to a situation where essentially normal visual function is further refined by training, and may not apply to circumstances where cortical dysfunction limits visual performance. It could also be the case that combined effects are more pronounced at particular points in development, and are thus age-dependant in their expression. Clearly, more work is needed to clarify what environmental factors affect brain plasticity, when they act, and how different manipulations might be combined to produce new settings that reveal synergistic effects.

Conflict of interest

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

References

1. McGraw PV, Webb BS & Moore DR. Introduction. Sensory learning: from neural mechanisms to rehabilitation. *Philos Trans R Soc Lond B Biol Sci* 2008; 364(1515): 364279–364283.
2. Bavelier D, Levi DM, Li RW, Dan Y & Hensch TK. Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J Neurosci* 2010; 30(45): 14964–14971.
3. Gilbert CD, Sigman M & Crist RE. The neural basis of perceptual learning. *Neuron* 2001; 31(5): 681–697.
4. Dosher B & Lu ZL. Visual perceptual learning and models. *Annu Rev Vis Sci* 2017; 15(3): 343–363.
5. Sasaki Y, Nanez JE & Watanabe T. Advances in visual perceptual learning and plasticity. *Nat Rev Neurosci* 2010; 11 (1): 53–60.
6. Ehninger D, Li W, Fox K, Stryker MP & Silva AJ. Reversing neurodevelopmental disorders in adults. *Neuron* 2008; 60 (6): 950–960.
7. Levi DM & Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res* 2009; 49(21): 2535–2549.
8. Campana G & Maniglia M. Improving visual deficits with perceptual learning. *Front Psychol* 2015; 21(6): 491.
9. Stryker MP & Loewel S. Amblyopia: new molecular/pharmacological and environmental approaches. *Vis Neurosci* 2018; 35: E018.
10. Bear MF & Singer W. Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 1986; 320 (6058): 172–176.
11. Boroojerdi B, Battaglia F, Muellbacher W & Cohen LG. Mechanisms underlying rapid experience-dependent plasticity in the human visual cortex. *Proc Natl Acad Sci* 2001; 98 (25): 14698–14701.
12. Iwai Y, Fagiolini M, Obata K & Hensch TK. Rapid critical period induction by tonic inhibition in visual cortex. *J Neurosci* 2003; 23(17): 6695–6702.
13. Silingardi D, Scali M, Belluomini G & Pizzorusso T. Epigenetic treatments of adult rats promote recovery from visual acuity deficits induced by long-term monocular deprivation. *Eur J Neurosci* 2010; 31(12): 2185–2192.
14. Vetencourt JF, Tiraboschi E, Spolidoro M, Castrén E & Maffei L. Serotonin triggers a transient epigenetic mechanism that reinstates adult visual cortex plasticity in rats. *Eur J Neurosci* 2011; 33(1): 49–57.
15. Camilleri R, Pavan A, Ghin F, Battaglini L & Campana G. Improvement of uncorrected visual acuity and contrast sensitivity with perceptual learning and transcranial random noise stimulation in individuals with mild myopia. *Front Psychol* 2014; 29(5): 1234.
16. Camilleri R, Pavan A & Campana G. The application of online transcranial random noise stimulation and perceptual learning in the improvement of visual functions in mild myopia. *Neuropsychologia* 2016; 1(89): 225–231.
17. Campana G, Camilleri R, Pavan A, Veronese A & Lo Giudice G. Improving visual functions in adult amblyopia with combined perceptual training and transcranial random noise stimulation (tRNS): a pilot study. *Front Psychol* 2014; 9(5): 1402.
18. Herpich F, Melnick MD, Agosta S, Huxlin KR, Tadin D & Battelli L. Boosting learning efficacy with noninvasive brain stimulation in intact and brain-damaged humans. *J Neurosci* 2019; 39(28): 5551–5561.
19. Moret B, Camilleri R, Pavan A *et al*. Differential effects of high-frequency transcranial random noise stimulation (hf-tRNS) on contrast sensitivity and visual acuity when combined with a short perceptual training in adults with amblyopia. *Neuropsychologia* 2018; 1(114): 125–133.
20. Spiegel DP, Byblow WD, Hess RF & Thompson B. Anodal transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. *Nerorehabil Neural Repair* 2013; 27(8): 760–769.
21. Thompson B, Mansouri B, Koski L & Hess RF. Brain plasticity in the adult: modulation of function in amblyopia with rTMS. *Curr Biol* 2008; 18(14): 1067–1071.
22. Baroncelli L, Braschi C, Spolidoro M, Begenisic T, Sale A & Maffei L. Nurturing brain plasticity: impact of environmental enrichment. *Cell Death Differ* 2010; 17(7): 1092–1103.
23. Baroncelli L, Bonaccorsi J, Milanese M *et al*. Enriched experience and recovery from amblyopia in adult rats: impact of motor, social and sensory components. *Neuropharmacology* 2012; 62(7): 2388–2397.
24. Sale A, Vetencourt JF, Medini P *et al*. Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat Neurosci* 2007; 10 (6): 679–681.
25. Duffy KR & Mitchell DE. Darkness alters maturation of visual cortex and promotes fast recovery from monocular deprivation. *Curr Biol* 2013; 23(5): 382–386.
26. He HY, Ray B, Dennis K & Quinlan EM. Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nat Neurosci* 2007; 10(9): 1134–1136.
27. Fong MF, Mitchell DE, Duffy KR & Bear MF. Rapid recovery from the effects of early monocular deprivation is enabled by temporary inactivation of the retinas. *PNAS* 2016; 113(49): 14139–14144.

28. Lunghi C & Sale A. A cycling lane for brain rewiring. *Curr Biol* 2015; 25(23): R1122–R1123.
29. Gibson EJ. Perceptual learning. *Annu Rev Psychol* 1963; 14 (1): 29–56.
30. Li R, Polat U, Makous W & Bavelier D. Enhancing the contrast sensitivity function through action video game training. *Nat Neurosci* 2009; 12(5): 549.
31. Li J, Thompson B, Deng D, Chan LY, Yu M & Hess RF. Dichoptic training enables the adult amblyopic brain to learn. *Curr Biol* 2013; 23(8): R308–R309.
32. Momi D, Smeralda C, Sprugnoli G *et al*. Thalamic morphometric changes induced by first-person action videogame training. *Eur J Neurosci* 2019; 49(9): 1180–1195.
33. Polat U. Making perceptual learning practical to improve visual functions. *Vision Res* 2009; 49(21): 2566–2573.
34. Hillman CH, Erickson KI & Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci* 2008; 9(1): 58–65.
35. Pierson WR & Montoye HJ. Movement time, reaction time and age. *J Gerontol* 1958; 13(4): 418–421.
36. Spirduso WW. Reaction and movement time as a function of age and physical activity level. *J Gerontol* 1975; 30(4): 435–440.
37. El-Sayes J, Harasym D, Turco CV, Locke MB & Nelson AJ. Exercise-induced neuroplasticity: a mechanistic model and prospects for promoting plasticity. *The Neuroscientist.* 2019; 25(1): 65–85.
38. McAllister AK, Katz LC & Lo DC. Neurotrophins and synaptic plasticity. *Annu Rev Neurosci* 1999; 22(1): 295–318.
39. Neeper SA, Gómez-Pinilla F, Choi J & Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 1996; 726(1–2): 49–56.
40. van Praag H, Shubert T, Zhao C & Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 2005; 25(38): 8680–8685.
41. Radak Z, Toldy A, Szabo Z *et al*. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem Int* 2006; 49(4): 387–392.
42. O'Callaghan RM, Ohle R & Kelly ÁM. The effects of forced exercise on hippocampal plasticity in the rat: a comparison of LTP, spatial-and non-spatial learning. *Behav Brain Res* 2007; 176(2): 362–366.
43. Kramer AF & Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn Sci* 2007; 11(8): 342–348.
44. Hötting K & Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev* 2013; 37(9): 2243–2257.
45. Fine I & Jacobs RA. Comparing perceptual learning across tasks: a review. *J Vis* 2002; 2: 190–203.
46. Sagi D. Perceptual learning in vision research. *Vision Res* 2011; 51(13): 1552–1566.
47. Ahissar M, Nahum M, Nelken I & Hochstein S. Reverse hierarchies and sensory learning. *Phil Trans R Soc Lond B Biol Sci* 2009; 364(1515): 285–299.
48. Woods RL & Thomson WD. Effects of exercise on aspects of visual function. *Ophthalmic Physiol Opt* 1995; 15(1): 5–12.
49. Perini R, Bortoletto M, Capogrosso M, Fertonani A & Miniussi C. Acute effects of aerobic exercise promote learning. *Sci Rep* 2016; 6(1): 1–8.
50. Connell CJ, Thompson B, Green H, Sullivan RK & Gant N. Effects of regular aerobic exercise on visual perceptual learning. *Vision Res* 2018; 1(152): 110–117.
51. Kaneko M & Stryker MP. Sensory experience during locomotion promotes recovery of function in adult visual cortex. *Elife* 2014; 26(3): e02798.
52. Kaneko M, Fu Y & Stryker MP. Locomotion induces stimulus-specific response enhancement in adult visual cortex. *J Neurosci* 2017; 37(13): 3532–3543.
53. Peirce JW. PsychoPy—psychophysics software in Python. *J Neurosci Methods* 2007; 162(1–2): 8–13.
54. Craig CL, Marshall AL, Sjöström M *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35(8): 1381–1395.
55. Hagströmer M, Oja P & Sjöström M. The International Physical Activity Questionnaire (IPAQ): a study of concurrent and construct validity. *Public Health Nutri* 2006; 9(6): 755–762.
56. Kline CJ, Porcari JP, Hintermeister R *et al*. Estimation of from a one-mile track walk, gender, age and body weight. *Med Sports Exerc* 1987; 19: 253–259.
57. Astle AT, Li RW, Webb BS, Levi DM & McGraw PV. A Weber-like law for perceptual learning. *Sci Rep* 2013; 29(3): 1158.
58. Levi DM, Klein SA & Aitsebaomo AP. Vernier acuity, crowding and cortical magnification. *Vision Res* 1985; 25(7): 963–977.
59. Fahle M & Henke-Fahle S. Interobserver variance in perceptual performance and learning. *Invest Ophthalmol Vis Sci* 1996; 37(5): 869–877.
60. Jeffreys H. *Theory of probability*, 3rd edn, Oxford University Press: Oxford, UK, 1961.
61. Rouder JN, Speckman PL, Sun D, Morey RD & Iverson G. Bayesian t tests for accepting and rejecting the null hypothesis. *Psychon Bull Rev* 2009; 16(2): 225–237.
62. Hawkey DJ, Amitay S & Moore DR. Early and rapid perceptual learning. *Nat Neurosci* 2004; 7(10): 1055.
63. Niell CM & Stryker MP. Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 2010; 65(4): 472–479.
64. Fu Y, Tucciarone JM, Espinosa JS *et al*. A cortical circuit for gain control by behavioral state. *Cell* 2014; 156(6): 1139–1152.
65. Dadarlat MC & Stryker MP. Locomotion enhances neural encoding of visual stimuli in mouse V1. *J Neurosci* 2017; 37 (14): 3764–3775.
66. Benjamin AV, Wailes-Newson K, Ma-Wyatt A, Baker DH & Wade AR. The effect of locomotion on early visual contrast processing in humans. *J Neurosci* 2018; 38(12): 3050–3059.

67. Vinck M, Batista-Brito R, Knoblich U & Cardin JA. Arousal and locomotion make distinct contributions to cortical activity patterns and visual encoding. *Neuron* 2015; 86(3): 740–754.
68. Saleem AB, Ayaz A, Jeffery KJ, Harris KD & Carandini M. Integration of visual motion and locomotion in mouse visual cortex. *Nat Neurosci* 2013; 16(12): 1864–1869.
69. Keller GB, Bonhoeffer T & Hübener M. Sensorimotor mismatch signals in primary visual cortex of the behaving mouse. *Neuron* 2012; 74(5): 809–815.
70. Pelah A & Barlow HB. Visual illusion from running. *Nature* 1996; 381(6580): 283.
71. Zhou J, Reynaud A & Hess RF. Aerobic exercise effects on ocular dominance plasticity with a phase combination task in human adults. *Neural Plast* 2017; 2017: 4780876.
72. Finn AE, Baldwin AS, Reynaud A & Hess RF. Visual plasticity and exercise revisited: no evidence for a "cycling lane". *J Vis* 2019; 19(6): 1–10.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Characteristics, health-related measures and starting Vernier alignment thresholds (vertically oriented stimulus) for the active group

Table S2. Characteristics, health-related measures and starting Vernier alignment thresholds (vertically oriented stimulus) for the inactive group