Title: The effect of locomotion on early visual contrast processing in humans

Abbreviated title: No effect of locomotion on human surround suppression

Authors:

Benjamin, A.V.[*1]

Wailes-Newson, K [*1]

Ma-Wyatt, A[2]

Baker, D.H. [1]

Wade, A.R. [1]

Affiliations:

1: University of York, UK

2: University of Adelaide, Australia

[*] Both authors contributed equally to this work

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ABSTRACT

Most of our knowledge about vision comes from experiments in which stimuli are presented to immobile human subjects or animals. In the case of human subjects, movement during psychophysical, electrophysiological or neuroimaging experiments is considered to be a source of noise to be eliminated. Animals used in visual neuroscience experiments are typically restrained and, in many cases, anaesthetized.

In reality however, vision is often used to guide the motion of awake, ambulating organisms. Recent work in mice has shown that locomotion elevates visual neuronal response amplitudes (Erisken et al., 2014; Fu et al., 2014; Lee et al., 2014; Mineault et al., 2016; Niell and Stryker, 2010) and reduces long-range gain control (Ayaz et al., 2013). Here we use both psychophysics and steady-state electrophysiology to ask whether similar effects of locomotion on early visual processing can be measured in humans.

Our psychophysical results show that brisk walking has little effect on subjects' ability to detect briefly-presented contrast changes and that co-oriented flankers are, if anything, more effective masks when subjects are walking. Our electrophysiological data were consistent with the psychophysics, indicating no increase in stimulus-driven neuronal responses whilst walking and no reduction in surround suppression.

In summary we find evidence that early contrast processing is altered by locomotion in humans but in a manner that differs from that reported in mice. The effects of locomotion on very low-level visual processing may differ on a species-by-species basis and may reflect important differences in the levels of arousal associated with locomotion.

Significance Statement

Mice are the current model of choice for studying low-level visual processing. Recent studies have shown that mouse visual cortex is modulated by behavioural state: V1 neurons in locomoting mice tend to be more sensitive and less influenced by long-range gain control. Here we test these effects in humans by measuring psychophysical detection thresholds and EEG responses while subjects walk on a treadmill. We find no evidence of increased contrast sensitivity or reduced surround suppression in walking humans. Our data show that fundamental measurements of early visual processing differ between humans and mice and have important implications for recent work on the link between arousal, behaviour and vision in these two species.

Introduction

Recent work in head-fixed mouse models has demonstrated that locomotion is linked with changes in early visual processing. Many labs report that locomoting mice exhibit increased responsivity in primary visual cortex (Fu et al., 2014; Niell and Stryker, 2010; Polack et al., 2013) while there is also evidence for a locomotion-associated reduction in surround suppression (Ayaz et al., 2013) and locomotion-dependent visual plasticity (Kaneko et al., 2017; Kaneko and Stryker, 2014). These measurements are broadly consistent with the more general observations that sensory neuronal responses are dependent not just on stimulus strength but also on behavioural state, arousal and attention (Haider et al., 2013; Harris and Thiele, 2011; Lauritzen et al., 2010; McGinley et al., 2015; Motter, 1993; Posner and Petersen, 1990; Reimer et al., 2014). However, the underlying mechanisms linking locomotion to visual sensitivity in mice are unclear, as are the implications for human vision. Some labs do report modulations of early human visual processing during periods of acute exercise changes but these are at the level of featural tuning (Bullock et al., 2016) while the effects on low-level contrast sensitivity are more ambiguous (Bullock et al., 2015). Moreover, these effects are observed not during locomotion *per se* but during intense bouts of exercise on a stationary bicycle. To our knowledge, the most striking effect of true locomotion on human vision to date has been the observation of a locomotion-related motion aftereffect whose cause has never been fully explained (Pelah and Barlow, 1996) but which must act at a level above simple contrast processing in V1.

If locomotion alters early contrast representations in humans it would have profound implications for our understanding of natural scene processing. Orientation-selective surround suppression (Cavanaugh et al., 2002; DeAngelis et al., 1994; Nelson and Frost, 1978) has been hypothesized to play a critical role in scene segmentation by increasing neuronal responses at the boundaries of different texture patches (Knierim and van Essen, 1992; Lamme, 1995; Nothdurft et al., 2000; Rossi et al., 2001). The discovery of a significant reduction in surround suppression during locomotion would therefore raise the possibility that scene segmentation is altered (and potentially impaired) while subjects are navigating their environment. Similarly, a locomotion driven change in neuronal gain would reshape or reposition the contrast sensitivity function with implications for the discrimination of both low- and high-contrast edges as well as the computation of speed which is known to be contrast-dependent (Stocker and Simoncelli, 2006; Thompson, 1982).

Here we measure two aspects of early contrast processing (neuronal sensitivity and surround suppression) in locomoting humans. These measurements are made using two sensitive and complementary methods: psychophysical contrast discrimination and steady-state EEG to provide both perceptual and direct neuronal measures of contrast processing. The locomotion of the participants (on a treadmill) was varied across repetitions of the experiment. We then asked if we were able to measure changes in either responsivity or orientation-dependent surround suppression between the locomotion and static conditions. We compare our findings with those from the mouse literature with particular reference to the interaction between arousal and locomotion states in humans and mice.

Methods

General experimental design

We performed behavioral and electrophysiological (SSVEP) experiments to measure neuronal response amplitude and long-range, spatially-tuned gain control in human subjects. 13 subjects (4 female, mean age 26) took part in the behavioural experiment, 13 subjects (10 female, mean age 24) took part in the SSVEP experiments and 12 subjects (8 female, mean age 24) took part in the pupilometry experiment. Nine subjects took part in all experiments. All experimental protocols were approved by the ethics committee of the University of York Psychology Department.

All measurements were collected under two conditions: A '*locomotion'* or '*walking*' condition (while subjects walked on a motorized treadmill) and a '*static'* condition while they straddled the moving treadmill belt (width=60cm). Psychophysical subjects also participated in a third '*target moves*' condition to test the potential effects of retinal motion.

The same treadmill (Confidence Fitness, 'GTR Power Pro') was used in all experiments and ran constantly at a preset speed of 5Km/h which is equivalent to a brisk walk.

Experiment 1 – Psychophysics

Stimuli were presented on a Multisync CRT monitor (Mitsubishi Corp, Tokyo) running at 100Hz under the control of an OSX 10.9 computer (Apple Inc, Cupertino) running Psykinematix V1.4 (Kybervision, Japan). The monitor was positioned at a distance of 110cm from the subjects and centered vertically at face level. Spectral and gamma calibration was performed using a Spyder4 colorimeter, cross checked with a fiber-optic photospectrometer (Jaz, Oceanoptics, Dumoulin, Fl). All stimuli were presented on a mean-gray background with luminance of 94 cd/m^2. Responses were registered using an OSX-compatible USB gamepad (Logitech, Lausanne) fixed to the handle of the treadmill.

Subjects performed a set of contrast discrimination/detection judgements using stimuli similar to those described in Wade (Wade, 2009) and Petrov, Carandini and McKee (Petrov et al., 2005). A pair of 'probe' Gabor patches (σ= 1.5°, spatial frequency = 2cpd) were presented simultaneously for 200ms, 5° to the left and right of a fixation marker. One of the probes had a 'pedestal' contrast **C**, the other had a contrast **C**+Δ**C** and the subject's task was to indicate which probe (left or right) had the higher contrast. For each pedestal level (0, 1, 2, 5 and 10%), the magnitude of Δ**C** was determined using a Bayesian adaptive staircase procedure (Kontsevich and Tyler, 1999) to obtain a threshold at 78% correct. Staircases for all pedestal levels were interleaved and six repetitions of each threshold were obtained for each subject. Motion conditions (walking / stationary / target moves) were interleaved at random and each condition lasted around nine minutes.

To eliminate uncertainty about the spatial location of the probes (Petrov et al., 2006) a thin gray circle was present around the probe locations throughout the experiment. Similarly, to eliminate uncertainty about the temporal location of the stimuli, their

onset was cued by a subtle change in the shape of the fixation point 200ms before stimulus onset. Subjects received audio feedback (high or low tones to indicate correct or incorrect responses) throughout the experiments.

To measure the effects of surround suppression, we measured thresholds for isolated probes and also for probes placed in the center of annular 'surrounds' containing high contrast (90%) gratings. A gap of one grating wavelength (1λ) was present between the probe and the surround to minimize the contribution of isotropic precortical 'overlay masking' (Petrov et al., 2005) and the outer radius of the annulus was 6°. Because cortical surround suppression is tuned for orientation, we measured the effects of surround gratings in two configurations: collinear and orthogonal with the probe Gabor.

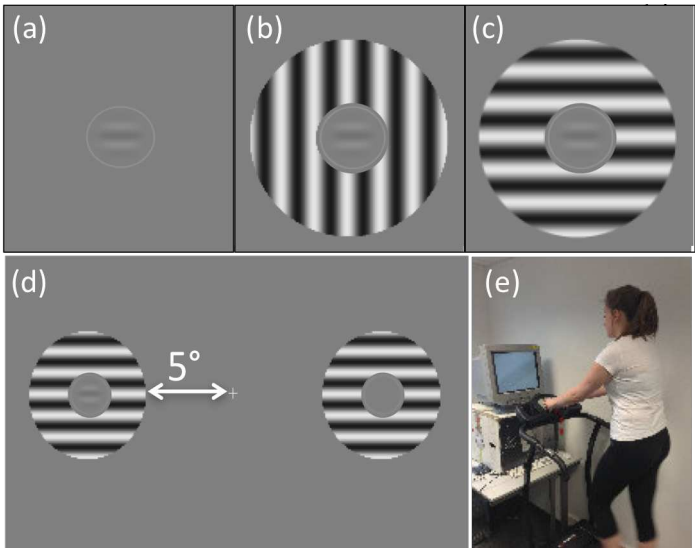

Figure 1 Stimulus configurations (a) No mask, (b) Orthogonal mask (c) Collinear mask. Stimuli were presented in a spatial 2AFC paradigm at +- 5° from fixation for 200ms at a time (d). Subjects indicated the position of the central probe with the highest contrast while either standing on a powered treadmill (e) or straddling the active treadmill belt.

In addition to the '*locomoting'* and '*static'* conditions, a third '*static/target moving*' or *'s/tm'* condition was generated in an attempt to simulate the effects of locomotion on retinal image position. In this '*s/tm*' condition, both sets of probe+surround drifted rapidly (30°/s) in the same, randomly-chosen direction for the duration of the 200ms presentation. We included this condition as a conservative test of the effect of retinal image motion and blurring. In total, we measured discrimination/detection thresholds for 15 different combinations of surround type (3) and contrast (5) for each of three locomotion conditions.

Experiment 2 – Steady State Visually Evoked Potentials

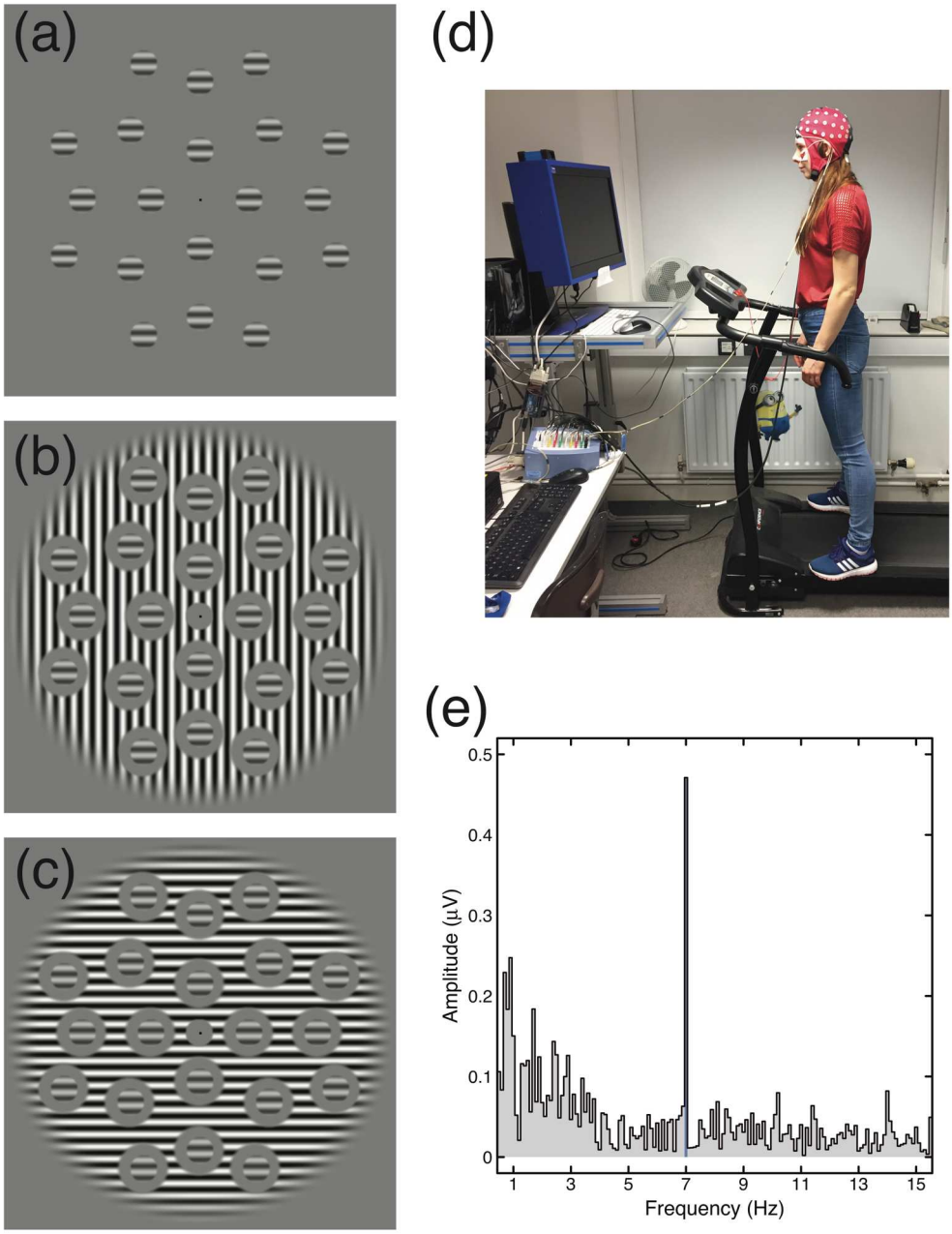

Figure 2 Example stimuli, photograph of experimental set-up, and example Fourier spectrum. (a) shows the matrix of target stimuli, which were rotated about the central fixation by a random amount on each trial. (b) shows the target stimuli with an orthogonal surround mask. (c) shows the target stimuli with a collinear surround mask. The phase alignment between target and mask is arbitrary, as the drifting mask meant that the relative phases of the two stimuli changed over time. (d) is a photograph of the experimental set-up, including the treadmill and a participant wearing an EEG cap. (e) shows an example Fourier spectrum taken from the stationary condition for the highest target contrast tested with no mask. A strong, well-isolated response is evident at the target frequency of 7Hz.

The stimuli used in the steady-state visually evoked potential (SSVEP) experiment were conceptually similar to those used in Experiment 1 but modified to optimize the evoked neuronal signal. Stimuli were generated in using the Psychophysics toolbox running on an OSX 10.10 computer (Apple Inc, Cupertino) and displayed on a

calibrated ViewPixx monitor (VPixx Technologies, Montreal) running at a framerate of 120Hz with a mean background luminance of 84 cd/m^2.

The 'probe' Gabors had a spatial frequency of 2cpd and a diameter of 1.2°, windowed by a raised cosine envelope. These frequency tagged probes were presented at a range of fixed contrast levels with three types of surround (no surround, collinear surround and orthogonal surrounds). The probes appeared and disappeared ('on/off') at a fixed frequency (7Hz sinusoidal flicker) and therefore generated a phase-locked response at 7Hz in the EEG record over visual cortex with additional second harmonic transients at 14Hz. When present, the high-contrast sine wave grating surround (96% contrast, 2cpd) drifted at a speed of 3 degrees per second. Drifting gratings are effective surround masks (Xiao and Wade, 2010) but do not generate a coherent frequency-locked response in SSVEP (Norcia et al., 2015).

To maximize the EEG response, multiple probe patches (N=20) were present on screen at any moment, arranged in a hexagonal grid with a diameter of 20° (Figure 2a). Absolute stimulus orientation was randomised on each trial to avoid local adaptation aftereffects, but the relative orientation of target and surround was controlled according to condition (collinear or orthogonal). The offset between the edge of the target gratings and the inner edge of the mask was one full grating cycle (0.5°).

EEG data were recorded at 1kHz using an ANT Neuroscan EEG system with a 64-channel Waveguard cap. Stimulus onset was recorded on the EEG trace using low-latency digital triggers sent over a parallel cable from the ViewPixx device. The first 1s of each 11s trial was discarded to remove onset transients, and a fast Fourier transform was taken of the EEG trace from the remaining 10s, giving a frequency resolution of 0.1Hz. We performed coherent averaging across trials within a condition for each participant, and then averaged the absolute amplitude values across participants. To calculate signal-to-noise ratios (SNRs) we averaged the amplitudes in the 10 frequency bins adjacent to the signal frequency (from 6.5-6.9Hz and from 7.1-7.5Hz in 0.1Hz steps) and divided the amplitude in the signal bin by this average.

As in the psychophysical experiments, responses were recorded under two randomized, interleaved conditions: 'static' and 'locomoting' (brisk walking at 5 km/h) in blocks of approximately 9 minutes.

Experiment 3 – Pupillometry

Systemic arousal in both humans and mice can be correlated with both neurophysiological and behavioural changes (Bradley et al., 2008; McGinley et al., 2015; Murphy et al., 2011). To measure the effects of treadmill walking on arousal we used a head-mounted, infra-red illuminated, video-based eyetracker (Pupil Labs AG, Berlin) to measure pupil sizes in subjects (N=12) performing the psychophysical task in both stationary and walking conditions in a randomized order using room illumination conditions identical to those in Experiment 1. The eye tracker software 'Pupil Capture' collected 10 minutes of samples at 120Hz and pupil size and confidence measures for both left and right eye were recorded. Data from the first half of each measurement block were discarded to remove artefacts due to residual light adaptation and mechanical 'settling' of the eyetracker on the head. A separate measurement was conducted to measure maximum pupil size in perceptual darkness (with infra-red pupil illuminations) to ensure that the pupil was not fully-dilated in the psychophysics task under dim illumination.

Measurements were analyzed off-line using Matlab (Mathworks, Natick, MA) and R (R Development Core Team, 2008) and only pupil diameters with a confidence rating greater than .95 (Max=1) were retained. Because the absolute mean pupil size depends on many factors including the angle of the eye-tracking camera and the proximity to the head, we present all data in units of screen pixels and assess the difference between walking and stationary conditions. We performed within-subjects t-tests on raw pupil diameter measures from left and right eyes independently and a paired t-test on the entire group.

Statistical analyses

We fit our psychophysical and neurophysiological data assuming an underlying neuronal response function that has the form of a hyperbolic ratio function (see Eq 3) (Albrecht and Geisler, 1991).

$$R = R_0 \frac{c^n}{(c^n+\sigma)} \qquad [E1]$$

In the case of our psychophysical data, we assumed that the thresholds were proportional to the first derivative of this hyperbolic ratio function which we computed analytically. This model is common in the psychophysical literature and rests on the assumption that detection or discrimination is limited by a single, late noise source (Boynton et al., 1999; Itti et al., 2000; Nachmias and Sansbury, 1974). In the case of the neuronal data we fit the parameters of the hyperbolic ratio function directly.

To obtain error bounds for our fits and avoid the use of parametric statistics, we used permutation methods to bootstrap the model parameters by resampling data points from our 13 subjects with replacement and re-computing model fits a total of 10,000 times (Efron and Tibshirani, 1993) using the Matlab function *bootci*. The error bounds shown in Figure 3 and 6 are derived from these bootstraps and indicate the 95% confidence intervals. Similarly, in Figures 4 and 7, the boxplots show the range of the bootstrapped parameters with the notches indicating the 95% confidence intervals.

Sample sizes

Niell and Stryker (Niell and Stryker, 2010) reported that motion increased population activity by approximately 300% - both for spontaneous gamma power and for measures of individual stimulus-driven neuronal responses (spikes/second). If such large effects were present in our EEG data (where we also measure neuronal responses to high contrast gratings) then we would expect to measure significant ($p<.001$) walking-driven SNR differences for the high contrast, unmasked probes with a sample size of no more than three subjects – even assuming a two-fold increase in overall noise (Lenth, 2001; Rosner, 2011). Ayaz et al report a more modest reduction in the amount of surround suppression that they measure in locomoting animals (Ayaz et al., 2013). Their population average suppression index (defined as the normalized difference in response between an optimal stimulus and one suppressed by the surround) decreased by a factor of around 40% (from 38% to 23%) when their mice were locomoting.

We acknowledge that the relationship between population average responses of neuronal activity as measured by single units and scalp-level EEG is not direct – but nevertheless we observe that our EEG measurements of R_{max} are reduced by approximately 25% between static/unmasked and static/suppressed suggesting that our baseline suppression index would be comparable to that seen in the Ayaz paper. Again, using realistic estimates of noise we calculated that we would require no more than four subjects to detect this level of change at the $p<.001$ level and we estimate that our actual sample sizes (13 subjects) had enough power to identify effects less than half the size of the magnitudes reported in the single unit literature.

Results

Experiment 1 - Psychophysics

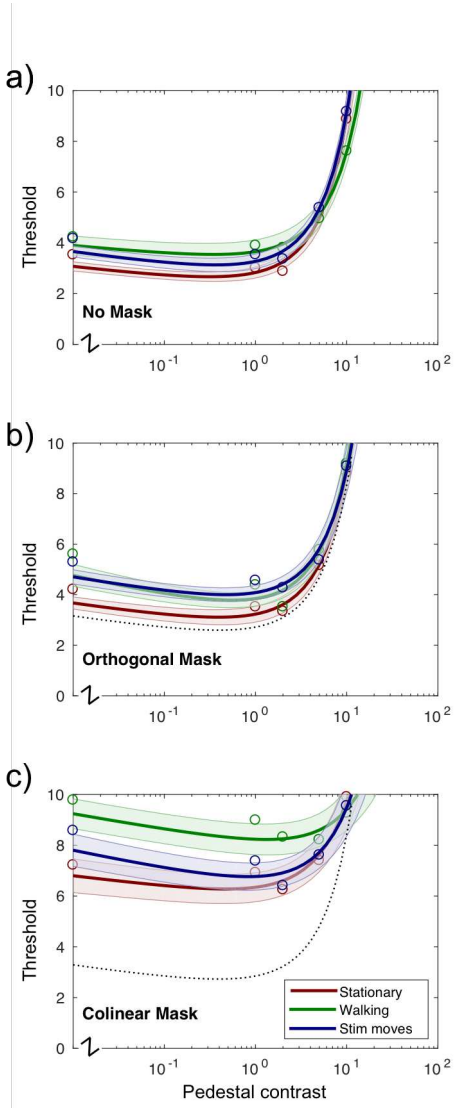

Figure 3 Detection/discrimination thresholds measured at five different pedestal levels. Orthogonal masks (b) generate almost no change in threshold compared to the unmasked condition (a) while collinear masks (c) raise thresholds significantly. Notably, colinear masking is significantly higher in the walking (green) condition. Unmasked / stationary thresholds are replotted as dashed black lines in (b) and (c) for comparison.

Figure 3 shows threshold data for all combinations of locomotion condition and surround type. Thresholds for the unmasked condition are shown in 3a. These exhibit a classic 'dipper' shape (Foley and Legge, 1981; Nachmias and Sansbury, 1974) with the lowest threshold occurring at a pedestal level of approximately half the detection threshold. Thresholds in the stationary condition (red line) are slightly lower than the other two conditions - for example, probe detection thresholds (zero pedestal) in the 'No mask' condition increase from 3.8% to 4.2% ($p<.001$) when subjects are walking. However, in general, unmasked thresholds for 'stationary', 'walking' and 'stimulus moves' conditions are strikingly similar suggesting that subjects are able to perform the task well under all conditions, that walking *per se* does not impose a significant attentional or fixational penalty and that in this experiment, subjects can compensate for relatively large amounts of retinal motion (Westheimer and McKee, 1975). Walking also does not appear to *increase* sensitivity to unmasked targets which might be expected to lead to reduced thresholds or a leftward shift in the curve.

Panel 3b shows thresholds measured for the 'orthogonal mask' condition. The unmasked, stationary thresholds are replotted as a dotted line for reference. Thresholds are slightly elevated in this condition but the effects are small and consistent with those seen in other studies of surround suppression (e.g. (Petrov et al., 2005).

Panel 3c shows thresholds measured in the 'colinear mask' condition where targets are suppressed by a co-oriented annular surround. These thresholds are significantly higher than those measured in either the 'no

mask' or 'orthogonal mask' conditions - consistent with the idea that we are measuring a suppressive, long-range, orientation-tuned (and therefore cortical) phenomenon.

Notably, Detection / discrimination thresholds measured during the conlinear locomotion condition (3b, green line) are *higher*, not lower than those measured when subjects are either stationary or viewing moving targets (red, blue lines). In brief, walking appears to increase, not decrease psychophysical surround suppression. While unmasked thresholds are also slightly higher in the 'locomoting' condition, surround suppression is also increased significantly by walking when the effect is computed as a multiple of the unmasked threshold contrast.

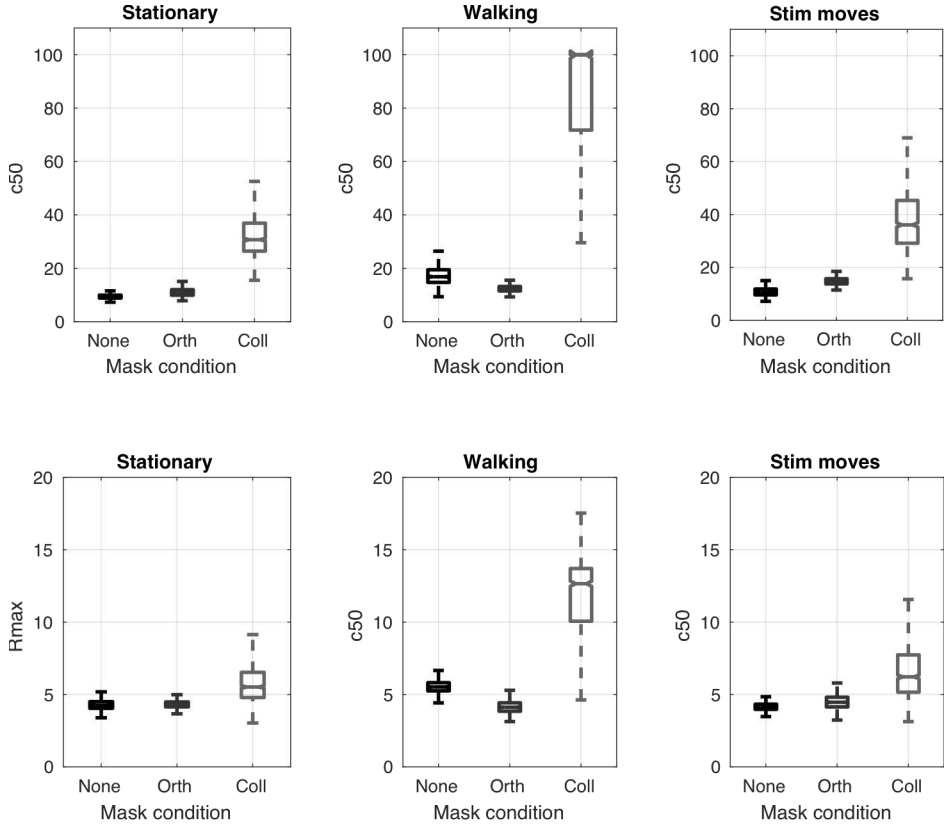

Figure 4 Bootstrapped parameters for hyperbolic ratio functions fitted to psychophysical data. Locomotion causes a significant increase in both the semisaturation constant (C_{50}) and a small but still significant increase in the predicted maximum response rate (R_{max}). Notches indicate 95% confidence intervals.

Figure 4 shows the bootstrapped parameter fits for c_{50} (the semi-saturation constant) and R_{max} (the maximum amplitude) under different surround and locomotion conditions. Interestingly, estimates of both parameters are significantly larger for the *walking* collinear condition than for the *stationary*- or *target moves* collinear conditions. This indicates that while the suppressive effects of contrast gain control appear to be, if anything, amplified in the walking condition (c_{50} is larger, implying that sensitivity is reduced), response gain (as measured by R_{Max}) may also be altered

in a manner that increases the maximum response level of the neuronal population at the highest contrast levels.

Experiment 2 - SSVEP

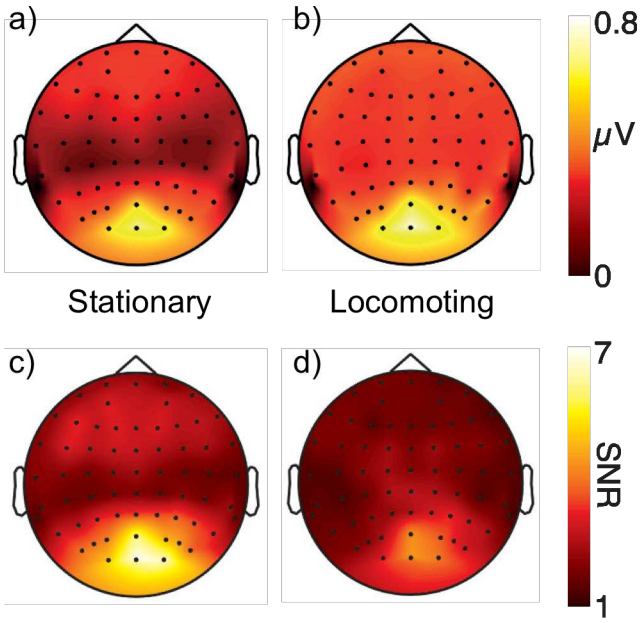

Figure 5 Grand average responses at the first harmonic of the stimulus modulation rate for isolated (unmasked) probes. Panels a) and b) show the raw amplitude at the tag frequency F1 while panels c) and d) show the ratio of F1 to the average amplitude of the local side bins (SNR). Although raw amplitude is higher in the locomotion condition, this is due to an increase in broadband noise and not an increase isolated to the SSVEP signal frequency.

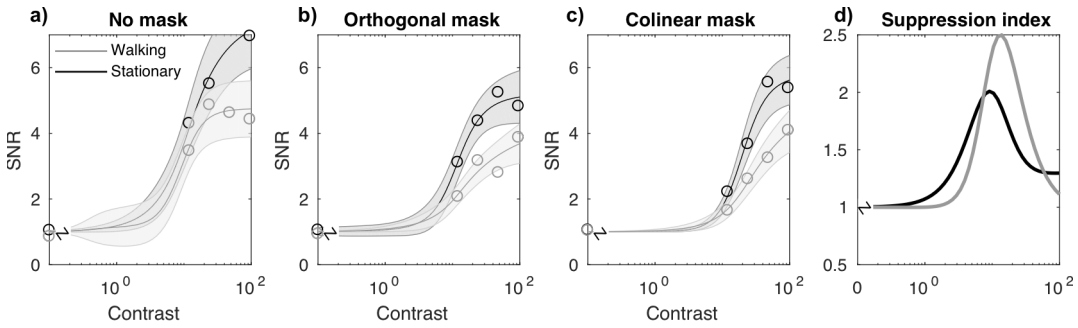

Figure 6 Signal to noise (SNR) ratios as a function of stimulus contrast under different mask conditions. Surrounds cause a reduction in sensitivity (increase in C_{50}) and maximum response level (R_{max}) with the collinear surround generating the largest changes. SNR is lower overall in the walking condition due to an increase in broadband noise. Panel (d) shows a suppression index computed as the ratio of the SNRs in 'No mask' and 'Colinear mask' conditions. There is no evidence of an increase in raw signal SNR (panel a), and no evidence of a reduction in tuned surround suppression (panel c) in the locomoting condition (panel d).

Figure 5 shows the average response to unmasked probes combined across all subjects. As expected, the dominant response is centered on Oz consistent with a source in early visual cortex. Panels a) and b) show the raw response amplitudes in the stationary and locomotion conditions respectively. Amplitudes are higher overall in the locomotion condition but this could reflect either a higher neuronal response restricted to the stimulus frequency or a generally increased response in the EEG signal due to broadband noise. Panels c) and d) show SNR rather than raw amplitude and confirm that SNR drops in the locomoting condition compared to the stationary condition. There is therefore no evidence that active walking increases neuronal responses to the frequency-tagged probe.

Figure 6 shows hyperbolic contrast response functions of the form described in E1 fitted to the population SNR data from all 13 subjects with bootstrapped 95% error bounds. Consistent with the data from Figure 5, overall SNR is lower in the locomoting condition (quantified in the fits below). Both conditions show evidence of orientation tuned surround suppression: the lines in (6c) tend to lie to the right and below of the corresponding lines in (6a). There is no overt reduction in the size of the surround suppression during the locomoting condition – if anything the suppression index (computed as the ratio of SNRs in the unmasked and collinear mask conditions) is higher for walking than for stationary observers on average (6d).

This is confirmed by examining the distribution of the bootstrapped fit parameters (Figure 7): The semisaturation constant 'c_{50}' for unmasked probes is very similar to that computed for psychophysical data – around 10% suggesting that our EEG measurements provide a reliable estimate of behavioral sensitivity. It is not possible to compare R_{max} values in the psychophysical and SSVEP experiments directly due to the change in measurement units. Evidence of orientation-tuned surround suppression is provided by the fact that c_{50} for collinear surrounds is reliably higher than for the

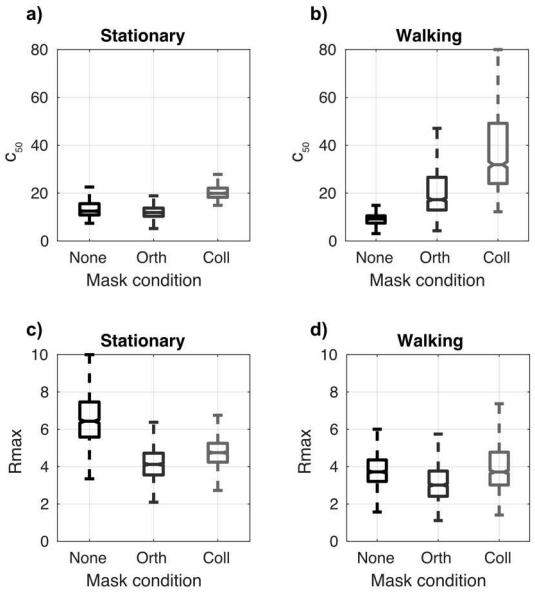

Figure 7. Parameter fits for SSVEP contrast response functions. In the stationary condition, orientation-tuned surround suppression increases c_{50} (reducing sensitivity). In the walking condition this effect is increased. Overall, R_{max} is reduced slightly in the walking/locomotion condition.

unmasked stimulus or orthogonally-masked stimulus for both stationary and locomoting conditions. Consistent with the psychophysical data, collinear-masked c_{50} is *higher* in the locomoting condition than it is in the static condition ($p<.001$), not lower as we would expect if surround suppression was reduced. R_{max} also shows a statistically significant reduction overall ($p<.001$) in the locomoting condition indicating that the SNR has not improved overall (see Discussion).

Experiment 3 – Pupillometry

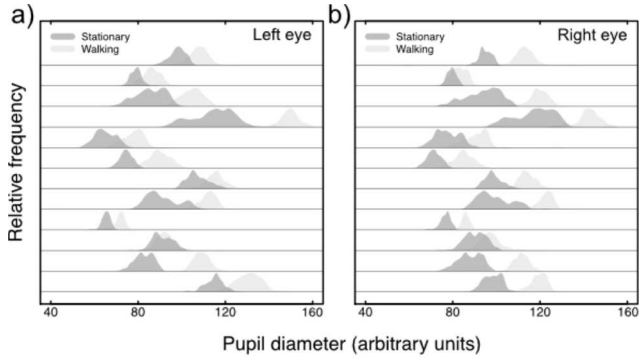

Figure 8 Pupil diameters measured in stationary (dark gray) and walking (light gray) conditions. Data from left and right eyes plotted separately in (a) and (b) and each row shows data from a different subject. All subjects had larger pupil diameters in the walking condition (mean diameter increase of 16%, area

Pupil sizes measured in both eyes were significantly larger (35% increase in area on average, $p<.001$) in the walking compared to the stationary conditions (See Figure 8). This size increase was not an artefact of increased noise generated by head movement during locomotion: we explicitly chose only measurements from frames with a high confidence rating (>95%) indicating an error-free fit while visual inspection of individual frames showed no evidence of motion blur or distortion. Similarly, task difficulty (as assessed by raw unmasked detection thresholds) was not significantly greater in the walking compared to the stationary condition (See Figure 4).

Discussion

We examined the effects of locomotion on long-range, orientation-tuned gain control using both behavioural and electrophysiological methods. The data from the locomotion condition clearly differed from those collected under static conditions but we saw no evidence for an increase in either spontaneous firing rate or sensitivity when walking. Instead, we measured very little effect of walking on detection/discrimination thresholds when targets are unmasked or surrounded by an orthogonal grating and significantly *increased* thresholds in the presence of a collinear surround. Our EEG data were equally clear: walking reduced the SNR of our responses slightly overall (possibly due to the introduction of broadband noise) and sensitivity (as measured by c_{50}) decreased significantly for collinear-masked targets, and to some extent for targets with orthogonal masks while the responses to unmasked targets were essentially unchanged. Walking seemed to have little effect on

unmasked sensitivity and *increased*, rather than *decreased* surround suppression in both experiments.

Robust changes in cortical visual sensitivity linked to locomotion have been measured in mice (Ayaz et al., 2013; Fu et al., 2014; Lee et al., 2014; Niell and Stryker, 2010; Polack et al., 2013; Reimer et al., 2014; Saleem et al., 2013): While locomotion does not affect responses in the LGN or input layers (Niell and Stryker, 2010), neurons in layer 2/3 of mouse visual cortex are relatively depolarized during locomotion (Polack et al., 2013) leading to higher spontaneous firing rates and increased visual sensitivity. One potential mechanism is that locomotion acts in a top-down manner through a two-layer network regulating visual gain control: stimulating neurons that subsequently inhibit a second class of inhibitory interneurons (Fu et al., 2014; Pfeffer et al., 2013). The same mechanism may contribute to the finding that the suppressive effects of extraclassical receptive fields are also reduced in locomoting animals (Ayaz et al., 2013).

Recent work has also shown that locomotion and arousal are usually tightly coupled in mice: high levels of arousal in mice often induce running behavior and running mice tend to be highly aroused. When the physiological effects of arousal are isolated, it can be shown that arousal that leads to an increase in neuronal sensitivity (McGinley et al., 2015; Reimer et al., 2014) even in the absence of locomotion. In support of this, recent work by Vinck et al has shown specifically that sensitivity increases in mouse visual cortex due to arousal can be dissociated from an increase in baseline firing rate due to locomotion (Vinck et al., 2015).

Our failure to find robust increases in neuronal sensitivity in locomoting humans might be explained by the behavioural and cognitive differences between people and mice. Humans are not *necessarily* aroused by brisk walking and in our experiments walking speed was fixed by the treadmill rather than being determined by the arousal state of the subjects. We note that the effects of exercise on neuronal feature selectivity and intracortical excitability that have been reported to date (Bullock et al., 2015, 2016; Neva et al., 2017) required 'somewhat hard' acute pedaling exercise of a type that the subjects in our own paper did not engage in.

Perhaps surprisingly therefore, our pupillometry measurements suggest that brisk walking did generate some level of arousal in our subjects – the increase of approximately 34% in mean pupil area is almost identical to the increase caused by a transition from 'rest' to 'low intensity exercise' measured by Bullock *et al* in their 2016 paper (Bullock et al., 2016)– a change that the same group reports as causing a small but significant increase in mean P1 amplitude over occipital cortex in high-frequency non-target trials (Bullock et al., 2015). We note that Bullock *et al* reported the most significant behavioural and electrophysiological results when contrasting the 'rest' and 'high intensity' exercise conditions while most of the differences that they measure in pupil size occurred between the 'rest' and 'low intensity' conditions. It is possible therefore that pupil size is a highly non-linear measure of exercise-driven arousal. While the relatively gentle exercise that our subjects engaged in may have been sufficient to generate mild arousal as indexed by pupil size, it may not have been energetic enough to cause measureable increases in neuronal responses.

Humans and mice may also differ in the level of neuronal modulation that can be driven by attention. Desynchronized states observed during active behaviour in mouse visual cortex may be similar to attention-driven modulation in primates (Harris and Thiele, 2011) but it is possible that in our studies attentional drive was consistently high because subjects were able to direct their attention to the task regardless of the locomotion state. Could a constitutively high level of neuronal activity driven by attention have masked more subtle modulations linked to locomotion or arousal? We believe this is unlikely. The effects of attention on psychophysical contrast response functions are difficult to measure in humans (because attention is intrinsically linked to the psychophysical task) but when they are measured at a population level with EEG, early visual areas exhibit a moderate but significant increase in response but not contrast gain that is selective for neurons tuned to the stimulus (Lauritzen et al., 2010; Verghese et al., 2012). There would seem to be no reason why changes in sensitivity should be masked by such a modulation and, strikingly, we measured a significant *reduction* in SNR R_{max} for the unmasked probe during our EEG locomotion condition indicating that we are able to measure a changes in this parameters but that these changes are not in the direction predicted by mouse studies. Similarly, we measured a significant increase in C_{50} for the collinear masking condition when subjects were walking, again showing that this parameter was unlikely to have been driven to saturation by attentional effects. Nevertheless, it is possible that attention was masking activity in a sub-population of neurons which would otherwise have been modulated by locomotion – further studies using EEG and a distractor task will be required to dissociate these effects fully.

Not all animal work finds a correlation between alertness and contrast sensitivity. Cano *et al* (Cano et al., 2006) and Zhuang *et al* (Zhuang et al., 2014) for example, report a range of changes in layer 4 of the rabbit visual cortex correlated with alertness including an increase in response gain and neuronal firing reliability but no change in contrast sensitivity. While our stimuli were different to those used by this group (specifically, we used flickering rather than drifting gratings), our psychophysical model fits are consistent with their findings, suggesting a locomotion-driven increase in R_{max}. Although our EEG data (which largely reflect activity in V1) do not show such an effect, it is nevertheless possible that the mouse visual system is modulated by locomotion or arousal in a manner that is simply different to that found in other mammals. We believe that it would be valuable to measure the effects of locomotion on some of the other parameters studied in rabbits – in particular orientation tuning for moving stimuli.

Two other potential confounds relate to the motion of the head during the locomotion condition:

First, it is possible that head motion generates retinal slip causing the images to move across the retina slightly during each presentation. There is some evidence that retinal 'blur' can degrade acuity at velocities above 3°/s (Westheimer and McKee, 1975). While the effect of retinal motion is more complex than a simple temporal integration (Burr, 1980), it is possible that center/surround stimuli are less well-segregated in locomoting subjects and therefore overlap to some degree. This, in turn, might introduce a second, largely precortical, and therefore untuned 'overlay' masking effect (Petrov et al., 2005). We tested for the effects of poor image stabilization in the psychophysical experiments by introducing a third condition in which the images

move rapidly during the 200ms that they are presented. Thresholds in this condition were not significantly elevated relative to the 'static' condition (Figure 3) and, most importantly, there was no significant increase in untuned masking from the orthogonal mask condition. This is likely to be a conservative test for retinal slip: The motion of the stimuli was both brief (and therefore untrackable) and random (and therefore unpredictable) while motion on the retina introduced by imperfect fixation while walking would have a predictable motion trajectory. We therefore believe that retinal slip is not responsible for the increase in tuned surround suppression that we observed in the locomoting condition.

Finally, head motion also contributed to broadband instrument noise in the EEG signal. Could this have masked a spectrally-localized increase in signal amplitude? Our data suggest not. Broadband noise increases the signal amplitude across all temporal frequencies but the effect is strongly mitigated in SSVEP recordings because of the high level of signal averaging: noise is phase randomized and therefore averages rapidly to zero across multiple presentations. In comparison, the signal generated by the flickering stimulus is phase locked and is therefore unaffected by averaging across time bins. In our data, the mean response at the tagged input frequency was 0.47μV in the stationary condition and 0.53μV in the walking condition – an increase in magnitude of approximately 0.06μV. However, in comparison, the mean sideband amplitude increased from 0.03 to 0.19μV – an increase of approximately 0.13μV. We expect broadband noise to be approximately equal across neighbouring frequency bins. Our data therefore suggests that, if anything, the evoked signal amplitude *decreased* when subjects were locomoting and the increase in raw amplitude at 7Hz was due to broadband noise (hence the apparent decrease in SNR seen in Figure 6 and the corresponding decrease in R_{max} in Figure 7). Our results indicate that very low-level visual processing is not necessarily altered by locomotion in humans. But it is also clear that periods of treadmill running can recalibrate the perception of egomotion in humans (Pelah and Barlow, 1996) – presumably through a normalization mechanism that combines information about optic flow and motor function. The error-minimization mechanisms that drive this normalization must be activated immediately when visual information fails to match that expected from the locomotion state (as in our experiments) and experiments with flow-fields in more complex simulations have revealed signals relating to this sensory combination in mouse primary visual cortex (Keller et al., 2012; Saleem et al., 2013). We therefore hypothesise that it might be possible to measure large EEG signals relating to these errors in future experiments that present optic flow stimuli to locomoting subjects – ideally in a head-mounted display system that eliminated extraneous cues to egomotion.

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Legends

Figure 1 Stimulus configurations (a) No mask, (b) Orthogonal mask, (c) Collinear mask. Stimuli were presented in a spatial 2AFC paradigm at +- 5° from fixation for 200ms at a time (d). Subjects indicated the position of the central probe with the highest contrast while either standing on a powered treadmill (e) or straddling the active treadmill belt.

Figure 2 Example stimuli, photograph of experimental set-up, and example Fourier spectrum. (a) shows the matrix of target stimuli, which were rotated about the central fixation by a random amount on each trial. (b) shows the target stimuli with an orthogonal surround mask. (c) shows the target stimuli with a collinear surround mask. The phase alignment between target and mask is arbitrary, as the drifting mask meant that the relative phases of the two stimuli changed over time. (d) is a photograph of the experimental set-up, including the treadmill and a participant wearing an EEG cap. (e) shows an example Fourier spectrum taken from the stationary condition for the highest target contrast tested with no mask. A strong, well-isolated response is evident at the target frequency of 7Hz.

Figure 3 Detection/discrimination thresholds measured at five different pedestal levels. Orthogonal masks (b) generate almost no change in threshold compared to the unmasked condition (a) while collinear masks (c) raise thresholds significantly. Notably, colinear masking is significantly higher in the walking (green) condition.

Figure 4 Bootstrapped parameters for hyperbolic ratio functions fitted to psychophysical data. Locomotion causes a significant increase in both the semisaturation constant (C50) and a small but still significant increase in the predicted maximum response rate (Rmax).

Figure 5 Grand average responses at the first harmonic of the stimulus modulation rate for isolated (unmasked) probes. Panels a) and b) show the raw amplitude at the tag frequency F1 while panels c) and d) show the ratio of F1 to the average amplitude of the local side bins (SNR). Although raw amplitude is higher in the locomotion condition, this is due to an increase in broadband noise and not an increase isolated to the SSVEP signal frequency.

Figure 6 Signal to noise (SNR) ratios as a function of stimulus contrast under different mask conditions. Surrounds cause a reduction in sensitivity (increase in C50) and maximum response level (Rmax) with the collinear surround generating the largest changes. SNR is lower overall in the walking condition due to an increase in broadband noise. Panel (d) shows a suppression index computed as the ratio of the SNRs in 'No mask' and 'Colinear mask' conditions. There is no evidence of an increase in raw signal SNR (panel a), and no evidence of a reduction in tuned surround suppression (panel c) in the locomoting condition

Figure 7. Parameter fits for SSVEP contrast response functions. In the stationary condition, orientation-tuned surround suppression increases c50 (reducing sensitivity).

In the walking condition this effect is increased. Overall, Rmax is reduced slightly in the walking/locomotion condition.

Figure 8 Pupil diameters measured in stationary (dark gray) and walking (light gray) conditions. Data from left and right eyes plotted separately in (a) and (b) and each row shows data from a different subject. All subjects had larger pupil diameters in the walking condition (mean diameter increase of 16%, area increase of 34%, $p<.001$).